# FDA Briefing Document

# Oncologic Drugs Advisory Committee Meeting

# BLA 761064
# Rituximab and hyaluronidase injection, for subcutaneous use
# Applicant: Genentech, Inc.

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the rituximab and hyaluronidase BLA to this Advisory Committee in order to gain the Committee's insights and opinions regarding the effectiveness and safety of the proposed drug product for the proposed oncologic indications. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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**Table of Abbreviations**

| | |
|---|---|
| AE | adverse events |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| AST | aspartate aminotransferase |
| AUC | area under the curve |
| BLA | biologic license application |
| BSA | body surface area |
| CHOP | cyclophosphamide, doxorubicin, vincristine, prednisolone |
| CLL | chronic lymphocytic leukemia |
| CR | complete response |
| CrCl | creatinine clearance |
| CRi | complete response with incomplete bone marrow recovery |
| CRu | complete response unconfirmed |
| $C_{trough}$ | trough concentration |
| CTSQ | Cancer Therapy Satisfaction Questionnaire |
| CVP | cyclophosphamide, vincristine, prednisolone |
| DFS | disease-free survival |
| ECOG | Eastern Cooperative Oncology Group |
| EFS | event-free survival |
| DLBCL | diffuse large B-cell lymphoma |
| FC | fludarabine and cyclophosphamide |
| FDA | Food and Drug Administration |
| FL | follicular lymphoma |
| FLIPI | Follicular Lymphoma International Prognostic Index |
| GMR | geometric mean ratios |
| HIV | human immunodeficiency virus |
| IPI | International Prognostic Index |
| IV | intravenous |
| iwCLL | International Workshop on CLL |
| LDH | lactate dehydrogenase |
| mg | milligrams |
| mL | milliliters |
| NHL | Non-Hodgkin lymphoma |
| ORR | overall response rate |
| OS | overall survival |
| PK | pharmacokinetic |
| PPQ | patient preference questionnaire |
| PR | partial response |
| PFS | progression free survival |
| Q2M | every 2 months |
| Q3M | every 3 months |
| RASQ | Rituximab Administration Satisfaction Questionnaire |

| | |
|---|---|
| SAE | serious adverse events |
| SD | stable disease |
| SC | subcutaneous |
| ULN | upper limit of normal |
| U/mL | units per milliliter |

## 1. Introduction

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)**
TRADENAME (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 *TRADENAME*™ 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)**
TRADENAME (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)**
TRADENAME (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.

*FDA Comment: At the time of completion of this briefing document, TRADENAME is still pending for the rituximab and hyaluronidase drug product.*

Rituxan® is an intravenously administered CD20-directed cytolytic antibody approved for the treatment of patients with NHL (Non-Hodgkin lymphoma) and CLL[1] .

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 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/m$^2$ intravenous (IV) rituximab dose and a 1600 mg SC dose to represent the 500 mg/m$^2$ 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<br>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<br>Stage 1: dose-finding single SC injection<br>Stage 2: Dose confirmation of 1600 mg SC dose | Non-inferiority of $C_{trough}$ SC vs IV |
| BP22333/ SparkThera | FL | Phase 1b<br>Stage 1: dose finding single SC injection<br>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 |

This briefing document addresses four areas of consideration: clinical pharmacology considerations and pharmacokinetic bridging, efficacy, safety, and patient preference of rituximab SC compared to rituximab IV.

## 2. Background and Development Pathway

### 2.1 Rituximab SC Background

Rituximab is a monoclonal antibody that binds CD20 and induces B-cell lysis. Rituximab IV has been approved and marketed for oncology indications such as NHL and CLL[1] . The initial oncology approval occurred in 1997.

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[2] . 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

In the current submission, the Applicant has co-formulated two previously approved drugs, for which effectiveness and of safety and has been established for the individual components. The Applicant has proposed to use a PK bridging strategy for the development of rituximab SC. Such development approach is consistent with FDA Guidance on "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" [3], which states the following:

> "In certain cases, effectiveness of an approved drug product for a new indication, or effectiveness of a new product, may be adequately demonstrated without additional adequate and well-controlled clinical efficacy trials. Ordinarily, this will be because other types of data provide a way to apply the known effectiveness to a new population or a different dose, regimen or dosage form."

This approach has been used in the development and approval of modified-release dosage forms and different doses, regimens, or dosage forms of the same product. When being applied to different doses, regimens, or dosage forms, the above FDA Guidance states that "it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of PK data without an additional clinical efficacy trial". In the current application, PK data, together with a well-defined PK-efficacy relationship, are used to bridge the established safety and efficacy results of rituximab IV to rituximab SC.

The use of PK data to bridge the effectiveness to a new formulation, dosing regimen, or dosage form is common in the life cycle management of small molecular drugs. For example, PK data was used as a bridge for the approval of the following drugs:

- The intravenous formulation of temozolomide [NDA022277], was approved by leveraging safety and efficacy data from temozolomide capsules[4]
- The extended release formulation of carvedilol (carvedilol phosphate) [NDA 022012] was approved by leveraging efficacy data from carvedilol immediate-release tablets[5]
- Nitroglycerin powder [NDA 208424] was approved by leveraging efficacy data from nitrolingal pumpspray[6] and
- The IV route of administration for asparaginase *Erwinia chrysanthemi* [BLA 125359] was approved by leveraging efficacy data from intramuscular route of administration[7].

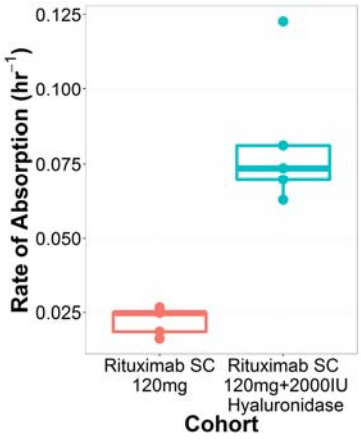
The development of rituximab SC is based on the predicate that rituximab SC is "a different dose, regimen, or dosage form" of rituximab IV and that PK data can be used to bridge the two different formulations of the same molecular entity provided the role of hyaluronidase is to serve as an adjunct to 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 |

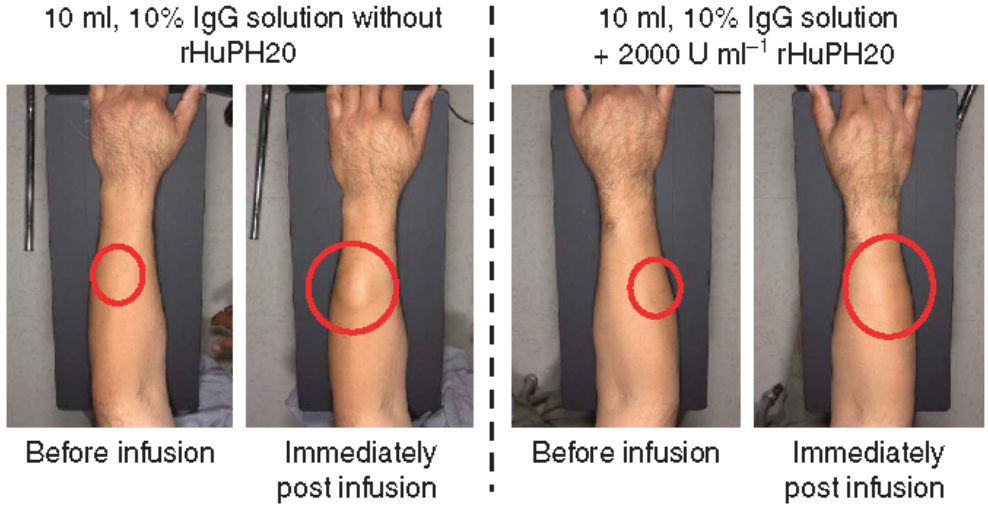
One major difference between rituximab SC and rituximab IV is the inclusion of hyaluronidase in the rituximab SC formulation. In order to justify the inclusion of this adjuvant, the Applicant conducted a proof of concept study in minipigs. As shown in Figure 1, co-administration of rituximab SC with hyaluronidase increased the absorption rate of rituximab 3-fold.

**Figure 1 Absorption rate of rituximab SC 120 mg in minipigs with and without 2000 U/mL hyaluronidase**




SC injections are generally limited to 2.5 mL due to concerns regarding injection pain. Shpilberg et al showed in Figure 2 that hyaluronidase allows the rapid absorption of a relatively large volume (10 mL) when administered subcutaneously[8] . As shown in Figure 2, very little injection site swelling was observed when a 10 mL Immunoglobulin G (IgG) solution was administered subcutaneously with hyaluronidase. However, a large injection site swelling was observed when the solution was administered subcutaneously without hyaluronidase (Figure 2).

**Figure 2 Injection site swelling after the SC administration of 10 mL of 10% IgG solution with and without hyaluronidase**

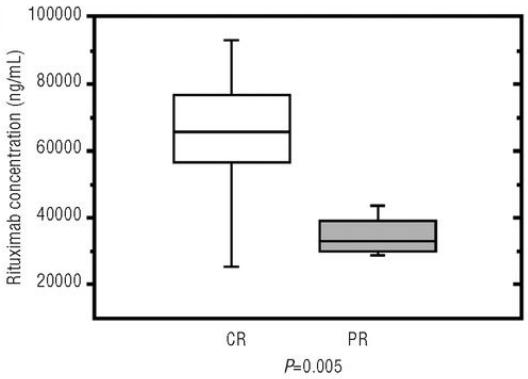



Source: Shpilberg O et al. Br J Cancer 2013;109:1556-61.

## 2.2 Rituximab SC Development

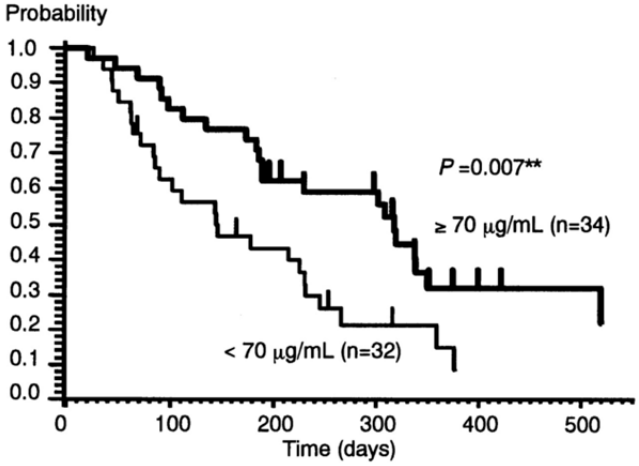
In the development of rituximab SC, the Applicant has changed the dose, dosing regimen, and dosage form relative to the previously approved intravenous formulation product. For the purposes of PK bridging, trough rituximab concentrations are considered as the key exposure metric. For chronically administered drugs, the area under the curve (AUC) and trough concentrations ($C_{trough}$) often correlated with safety and efficacy. As shown in Figure 3 and Figure 4, $C_{trough}$ is highly correlated with efficacy [9-11]. Therefore, the $C_{trough}$ of rituximab following IV dose can serve as a reference threshold in assessing the required $C_{trough}$ following rituximab SC.

**Figure 3 Association of rituximab trough levels with quality of remission [complete response (CR) vs. partial response (PR)].**




Source: Ulrich Jäger et al. Haematologica 2012;97:1431-1438

**Figure 4 Relationship between serum rituximab levels and progression-free survival.**




Source: Igarashi et al. Ann Oncol. 2002;13(6):928-943

## 3. Studies conducted to support development of Rituximab SC

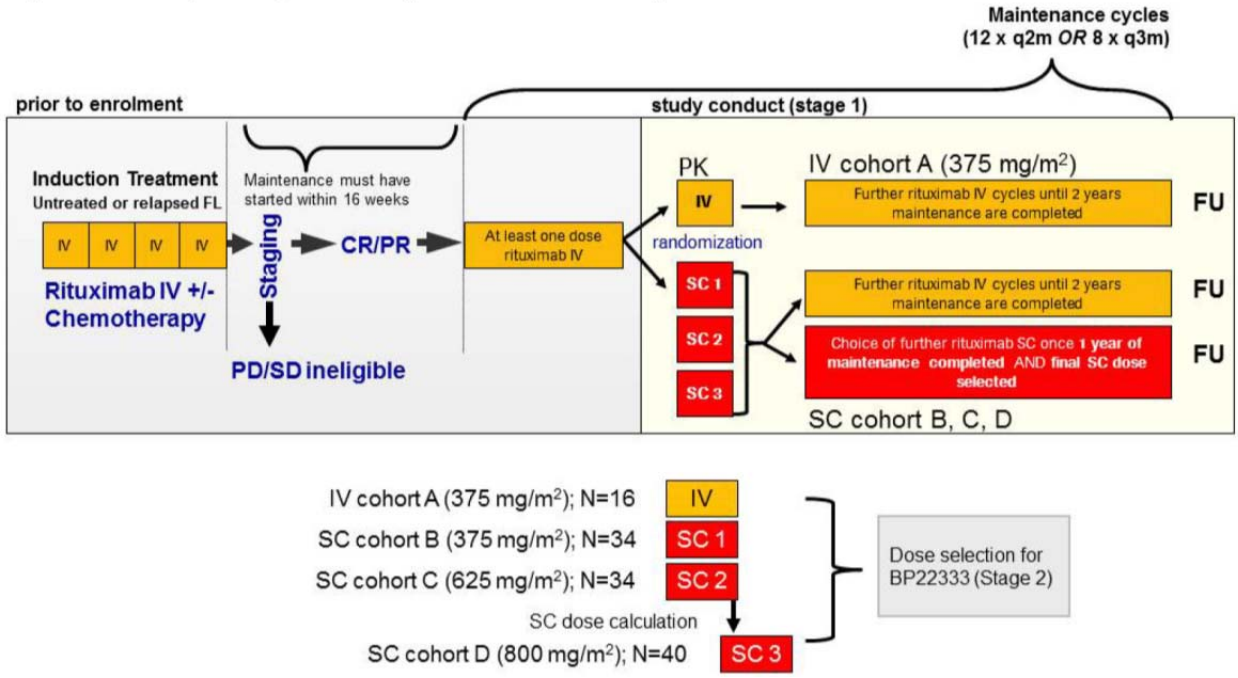
The clinical development of rituximab SC consisted of five clinical trials. There were two Phase 3 trials – Study BO22334/SABRINA conducted in frontline FL and Study MO28107/MabEase conducted in frontline DLBCL. These two Phase 3 trials were supported by Study BO25341/ SAWYER conducted in patients with previously untreated CLL, Study BP22333/SparkThera conducted in the maintenance treatment of FL and Study MO28457/PrefMab which was conducted in patients with previously untreated DLBCL or FL with the primary objective of patient preference. All clinical trials were conducted outside the U.S. All patients who took part in rituximab SC clinical trials received rituximab IV as their first dose.

### 3.1 BP22333/SparkThera

Study BP22333 or SparkThera, entitled "A Two-Stage Phase Ib Study To Investigate the Pharmacokinetics, Safety, and Tolerability of Rituximab Subcutaneous Formulation in Patients with Follicular Lymphoma as Part of Maintenance Treatment", was a two-stage clinical trial in patients with FL in the maintenance setting.

The primary objective of Stage 1 was to determine a rituximab SC dose that would yield a serum $C_{trough}$ comparable to rituximab IV. Stage 1 consisted of 4 cohorts with a randomization of 1:2:2:2 as shown in Figure 5. The primary endpoint for Stage 1 was the evaluation of rituximab $C_{trough}$ levels after IV or SC administration.

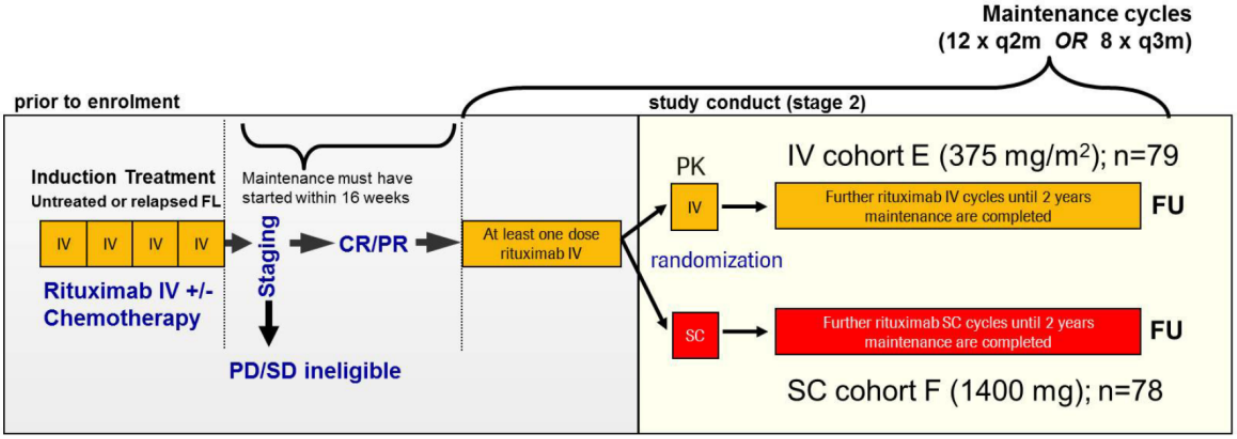
**Figure 5 Study Design for Stage 1 of BP22333/SparkThera**




[Source: Roche Clinical Study Report Protocol BP22333 page 23]

The primary objective for stage 2 was to compare $C_{trough}$ of rituximab IV and rituximab SC. In stage 2, patients with FL, who received one dose of rituximab IV in the maintenance setting, were randomized 1:1 to treatment with either rituximab IV 375 mg/m$^2$ or rituximab SC 1400 mg for 24 months. A schematic of the study dosing in shown in Figure 6. Patients were stratified by the maintenance regimen used, every 2 months (Q2M) or every 3 months (Q3M). The primary endpoint for stage 2 was the evaluation of the rituximab $C_{trough}$ level after rituximab IV or rituximab SC administration.

**Figure 6 Study Design Stage 2 of BP22333/SparkThera**



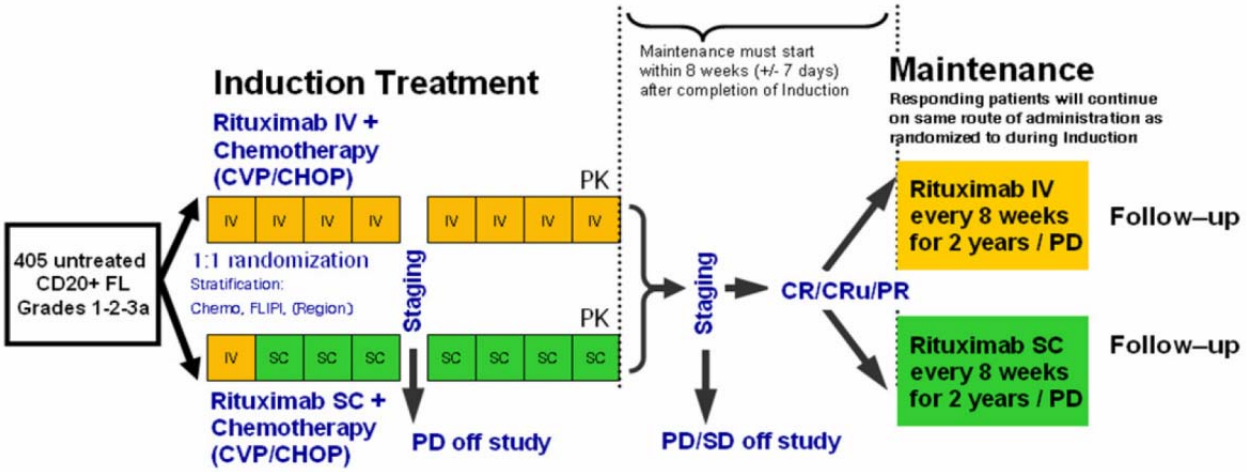

CR: complete response; FU: follow-up; IV: intravenous; PD: progressive disease; PK: pharmacokinetic; PR: partial response; SC: subcutaneous; SD: stable disease.
[Source: Roche Clinical Study Report Protocol BP22333 page 24]

### 3.2 BO22334/SABRINA

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".

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 7, 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 7 Trial Design for BO22334 SABRINA for stage 1 and stage 2**




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

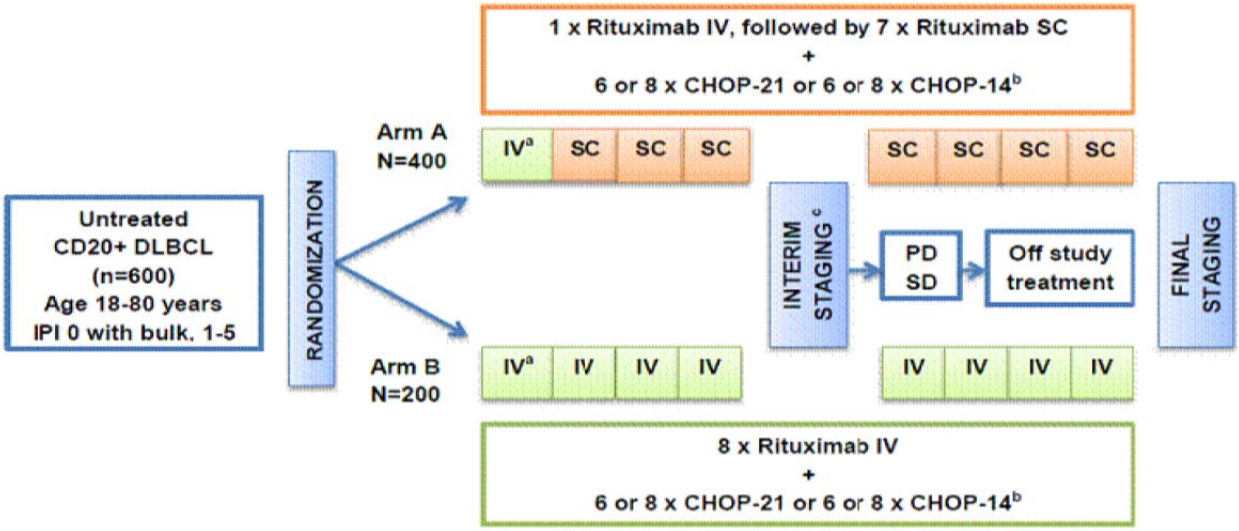
As shown in Figure 7, the rituximab SC arm consisted of the first cycle of rituximab IV 375 mg/m$^2$ followed by 7 cycles of rituximab SC 1400 mg both combined with a total of 8 cycles of CHOP or CVP chemotherapy. A cycle was defined as 3 weeks. Patients with at least a PR were to receive rituximab SC maintenance which was rituximab SC monotherapy every 8 weeks for 24 months. The rituximab IV arm was 8 cycles of rituximab IV 375 mg/m$^2$ 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/m$^2$ 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 $C_{trough\ SC}/C_{trough\ IV}$ cycle 7 of induction treatment every 3 weeks. The primary endpoint for Stage 2 was the estimated ORR consisting of CR, CRu, and PR at the completion of induction.

### 3.3 MO28107/MabEase

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 8, 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 8 Trial Design for DLBCL (Trial MO28107/MabEase)**




[Source: Roche Clinical Study Report MO28107 page 29]

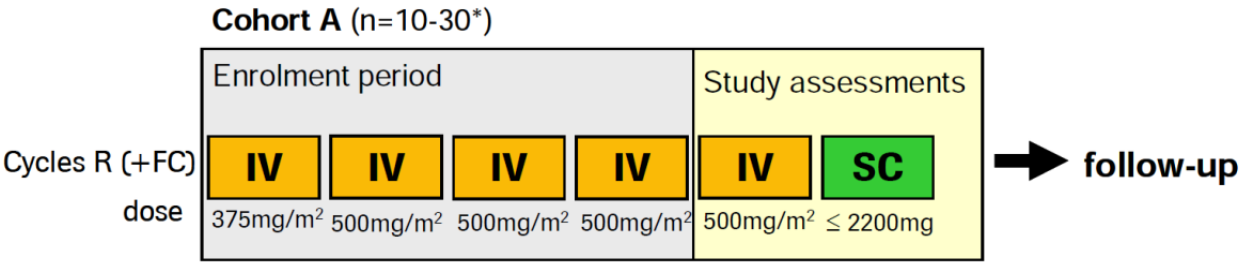
Patients were randomized 2:1 to the rituximab SC arm or the rituximab IV arm. Patients randomized to the rituximab SC arm received rituximab SC at a fixed dose of 1400 mg in Cycles 2 to 8 after the first cycle with rituximab IV 375 mg/m$^2$. Patients randomized to the rituximab IV arm received rituximab IV 375 mg/m$^2$. 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).

### 3.4 BO25341/SAWYER

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/m$^2$, doses 2 to 5 were rituximab IV 500 mg/m$^2$, 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 9.

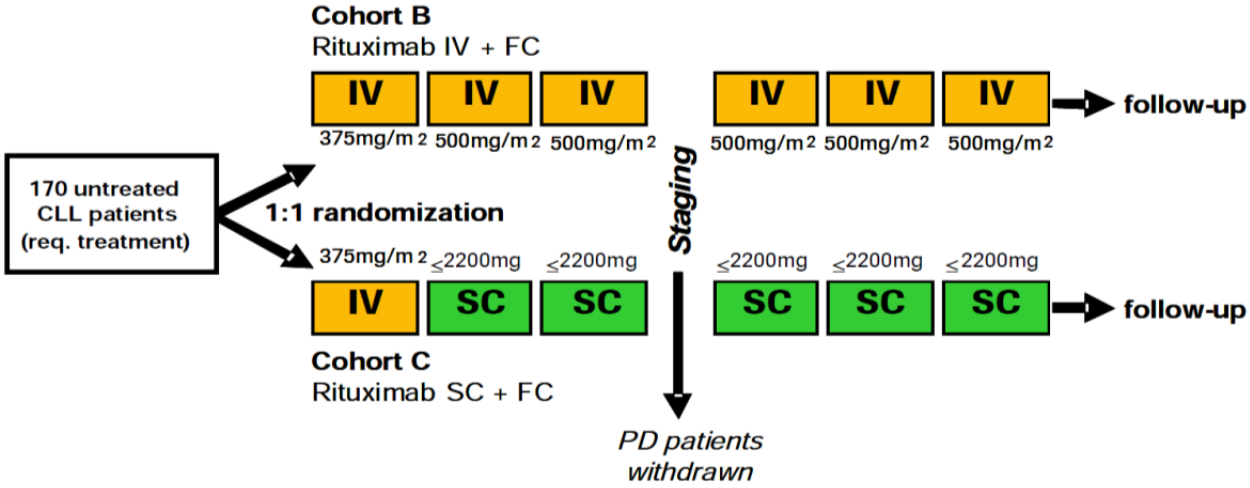
**Figure 9 Trial Design for CLL – Part A (BO25341/SAWYER)**




[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 10.

**Figure 10 Trial Design for CLL – Part B (BO25341/SAWYER)**



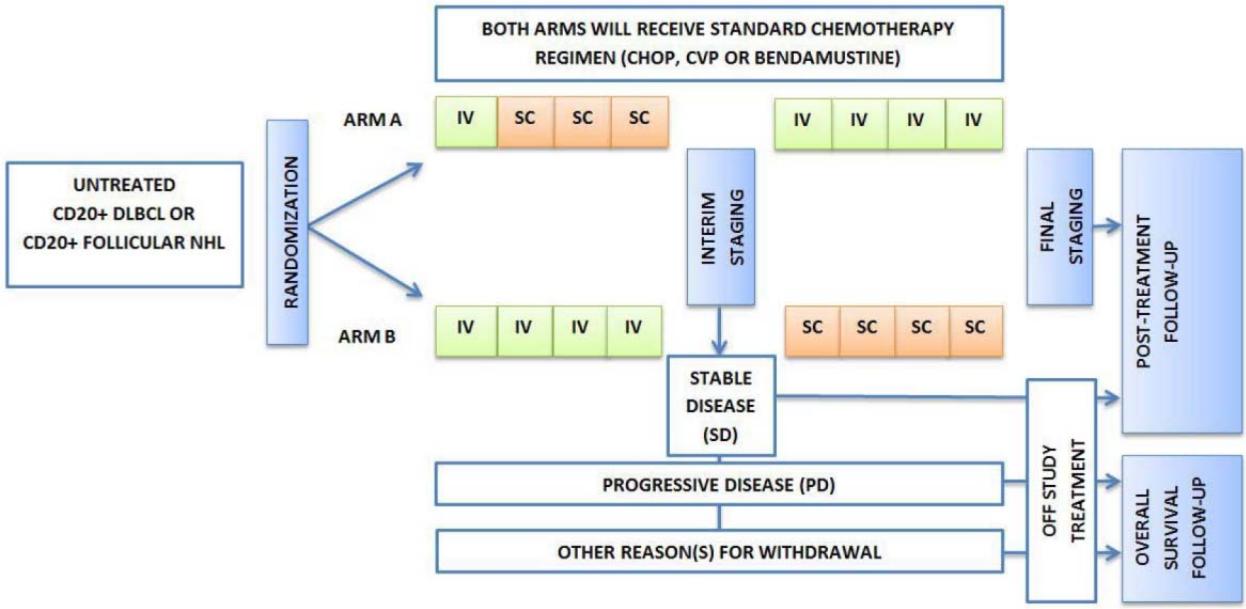

[Source: Roche Clinical Study Report- Protocol BO25341 page 43]

As shown in Figure 10, 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/m$^2$ for cycle 1 followed by rituximab IV 500 mg/m$^2$ for doses 2-6. For the rituximab SC arm, for first cycle was rituximab IV 375 mg/m$^2$, 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).

### 3.5 MO28457/PrefMab

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-postive 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 11. Patients received rituximab SC at a fixed dose of 1400 mg and received rituximab IV at a dose of 375 mg/m$^2$. 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 11 Trial Design for Patient Preference Study (MO28457/PrefMab)**




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

## 4. PK Bridging Strategy in Development of Rituximab SC

PK data to support the clinical development of rituximab SC was collected from three clinical studies in patients with FL and CLL (Table 3). Two of the three studies had dose selection and dose confirmation components. The first dose selection study was conducted in patients with FL and compared the labeled rituximab IV 375 mg/m$^2$ dose with rituximab SC doses to select a rituximab SC dose of 1400 mg for the treatment of patients with NHL. A second dose selection was conducted in patients with CLL and compared the rituximab IV 500 mg/m$^2$ dose to rituximab SC doses to select a dose of 1600 mg for the treatment of patients with CLL. The non-

inferiority of rituximab $C_{trough}$ following rituximab SC doses relative to rituximab IV doses were then evaluated in the dose confirmation studies.

**Table 3 Studies conducted to support development of rituximab SC**

| Study (Population) | Objective per Study Stage | |
|---|---|---|
| | Dose Selection Stage | Dose Confirmation Stage |
| BP22333 (FL) | Identify a SC dose that yielded comparable $C_{trough}$ to the IV dose | Demonstrate $C_{trough}$ non-inferiority of SC dose when given every 2 or 3 months |
| BO22334 (FL) | Not Applicable | Demonstrate $C_{trough}$ non-inferiority of 1400 mg SC compared to 375 mg/m$^2$ IV |
| BO25341 (CLL) | Determine a SC dose that yielded comparable $C_{trough}$ to IV dose | Demonstrate $C_{trough}$ non-inferiority of 1600 mg SC compared to 500 mg/m$^2$ IV |

When assessing the adequacy of the PK data provided to demonstrate the efficacy of rituximab SC by leveraging data from rituximab IV, the Food and Drug Administration (FDA) review evaluated the following questions:

- Do the proposed rituximab SC doses of 1400 and 1600 mg provide adequate systemic exposures relative to exposures obtained following rituximab IV doses of 375 and 500 mg/m$^2$?
- Do the proposed fixed doses of rituximab SC 1400 and 1600 mg provide adequate systemic exposures across all body surface area (BSA) sizes for their respective indications?
- Do differences in $C_{trough}$ between rituximab SC and rituximab IV lead to differences in safety?

## 4.1 Do the proposed rituximab SC doses of 1400 and 1600 mg provide adequate systemic exposures relative exposures obtained following rituximab IV?

*Non-Hodgkin's Lymphoma*

#### 4.1.1.1 Dose Selection and Confirmation

The initial selection of an appropriate dose for NHL was evaluated in the maintenance phase of treatment of patients with previously untreated and relapsed/refractory FL, who had received rituximab-containing induction therapy, achieved at least a partial response PR, and received at least one cycle of rituximab IV in maintenance (Stage 1 of Study BP22333). In this study, patients were administered rituximab IV 375 mg/m$^2$ IV, or rituximab SC 375 mg/m$^2$, 650 mg/m$^2$, or 800 mg/m$^2$ to determine which SC dose would yield comparable $C_{trough}$ to that observed following rituximab IV 375 mg/m$^2$. Additional details on the design of Study BP22333 are provided in Section 3.1.

The geometric means of the $C_{trough}$ and the geometric mean ratios (GMR) of the SC to IV dosing regimen $C_{trough}$ are shown in Table 4.

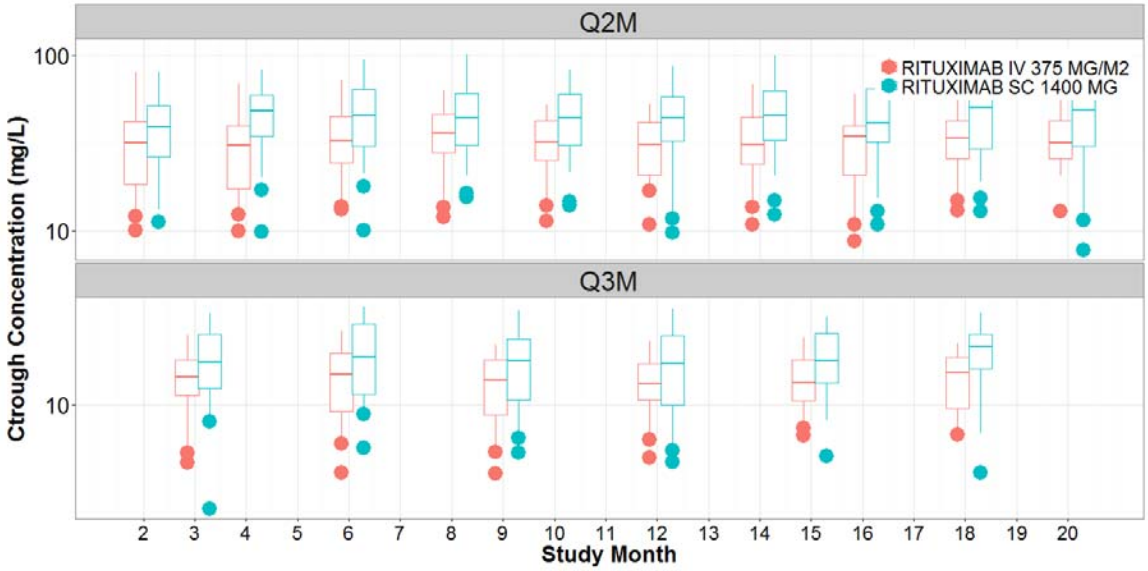
**Table 4 Geometric mean (%CV) of the $C_{trough}$ by regimen and dosing schedule and SC to IV geometric mean ratio (90% CI) for Study BP22333 (Stage 1)**

| Dosing Schedule | Regimen | N | Geometric mean (CV%) | GMR for SC/IV (90% CI) |
|---|---|---|---|---|
| Every 2 months | 375 mg/m$^2$ IV | 9 | 38.1 (69) | |
| | 375 mg/m$^2$ SC | 17 | 18.1 (85) | 0.475 (0.279 – 0.81) |
| | 625 mg/m$^2$ SC | 17 | 35.6 (51) | 0.933 (0.588 – 1.48) |
| | 800 mg/m$^2$ SC | 21 | 39.3 (80) | 1.03 (0.625 – 1.70) |
| Every 3 months | 375 mg/m$^2$ IV | 6 | 14.2 (44) | |
| | 375 mg/m$^2$ SC | 15 | 11.7 (56) | 0.823 (0.546 – 1.24) |
| | 625 mg/m$^2$ SC | 13 | 12.4 (65) | 0.871 (0.558 – 1.36) |
| | 800 mg/m$^2$ SC | 17 | 16.8 (86) | 1.18 (0.735 – 1.90) |

Based on the findings from stage 1, the 800 mg/m$^2$ SC dose, for both the Q2M and Q3M, was shown to achieve equal or greater rituximab $C_{trough}$ relative to the 375 mg/m$^2$ IV dose. Using modeling and simulation approaches, the body surface area (BSA)-based dose of 800 mg/m$^2$ SC was converted to a fixed 1400 mg SC dose. The 1400 mg dose of rituximab SC was then evaluated in the maintenance phase of the treatment in patients with FL (Stage 2 of BO22333).

In Stage 2 of BO22333, patients were randomized to receive rituximab SC 1400 mg or rituximab IV 375 mg/m$^2$ every 2 or 3 months. As shown in Figure 12 and Table 5, for the Q2M and Q3M regimens, the $C_{trough}$ in rituximab SC 1400 mg arm was consistently higher than that in the rituximab IV 375 mg/m$^2$ arm.

**Figure 12 Comparisons of the $C_{trough}$ after the administration of rituximab SC 1400 mg and rituximab IV 375 mg/m$^2$ over time by dosing schedule**



Note for above figure: The horizontal line represents the median, the top and bottom of the box represent the 25 and 75 percentile, the top and bottom line represent the 5 and 95 percentile and the circles represent the values lower than the 5 percentile.

**Table 5 Geometric mean (%CV) of the observed $C_{trough}$ by regimen and dosing schedule and the SC to IV geometric mean ratio (90% CI) for Study BO22333 (Stage 2) at Maintenance Cycle 2**

| Dosing Schedule | Regimen | N | Geometric mean (%CV) | GMR for SC/IV (90% CI) |
|---|---|---|---|---|
| Q2Months | 375 mg/m$^2$ IV | 37 | 30.2 (57) | |
| | 1400 mg SC | 41 | 36.6 (54) | 1.21 (0.98 – 1.50) |
| Q3Months | 375 mg/m$^2$ IV | 34 | 14.5 (56) | |
| | 1400 mg SC | 34 | 19.0 (65) | 1.32 (1.03 – 1.68) |

4.1.1.2 Dose Confirmation.

The rituximab SC 1400 mg dose was confirmed in Study BO22334, a two-stage, phase III study designed to investigate the PK, efficacy, and safety of rituximab SC in combination with CHOP or CVP chemotherapy in induction followed by maintenance with rituximab as monotherapy in patients with previously untreated FL. In this study, patients were randomized to receive rituximab IV 375 mg/m$^2$ or rituximab SC 1400 mg starting from Cycle 2. In the induction phase, patients received 8 cycles of chemotherapy including rituximab every 3 weeks. Additional details on the design of Study BO22334 are provided in Section 3.2.

In order to evaluate the impact of the rituximab SC dose over time, the geometric mean ratio (GMR) of the SC to IV $C_{trough}$ were calculated and are shown in Figure 13 and Table 6, respectively.

**Figure 13 The change in the SC/IV $C_{trough}$ Geometric Mean Ratio (90% CI) over time for Study BO22334**

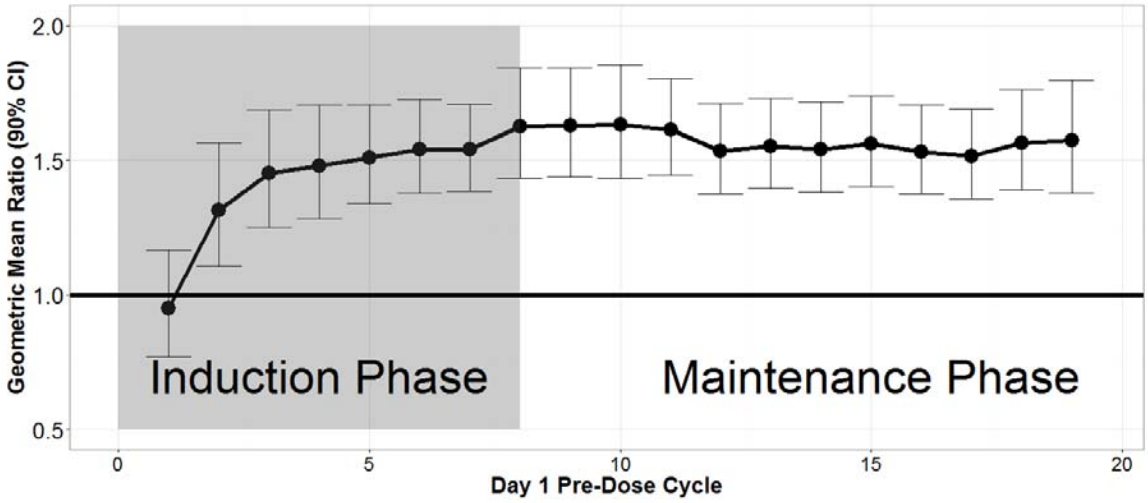


**Table 6 Geometric mean (%CV) of the $C_{trough}$ for the SC and IV arm and the SC to IV geometric mean ratio (90% CI) for Study BO22334 – predose Cycle 7 (Induction Phase) and pre dose Cycle 18 (Maintenance Phase)**

| Phase | Cycle | Rituximab IV | | Rituximab SC | | GMR for SC/IV (90% CI) |
|---|---|---|---|---|---|---|
| | | N | Geometric mean (%CV) | N | Geometric mean (%CV) | |
| Induction | 7 | 185 | 78.7 (68.6) | 175 | 121 (52) | 1.53 (1.39 – 1.71) |
| Maintenance | 18 | 143 | 28.6 (57.1) | 132 | 44.8 (62) | 1.58 (1.39 – 1.76) |

As shown in Figure 13 and Table 6, the geometric mean ratios for SC/IV $C_{trough}$ and 90% CI of the $C_{trough}$ were higher than 1 over the duration of the study indicating that rituximab SC leads to consistently higher $C_{trough}$ relative to rituximab IV, supporting the rituximab SC 1400 mg dose.

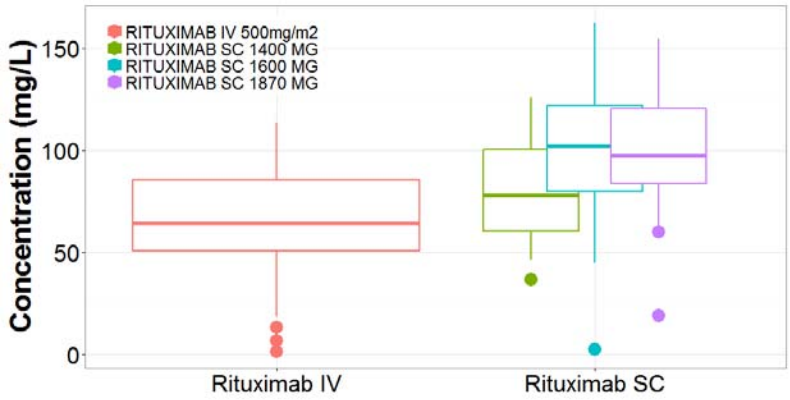
*Chronic Lymphocytic Leukemia (CLL)*

4.1.1.3 Dose Selection and Confirmation

The dose for evaluation in CLL was initially evaluated in the Stage 1 of Study BPO25341, which 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 CLL". In Stage 1, patients received rituximab IV 375 mg/m$^2$ in Cycle 1; in cycles 2-5, patients were assigned to receive either rituximab IV 500 mg/m$^2$, rituximab SC 1400 mg, 1600 mg, or 1870 mg. Pre-dose Cycle 5 and Cycle 6 $C_{trough}$ were then evaluated. Additional details on the design of Study BO25431 are provided in Section 3.4.

The geometric means of the $C_{trough}$ 28 days after the last rituximab IV dose and after the rituximab SC dose and the geometric mean ratios (GMR) are shown in Figure 14 and Table 6, respectively.

**Figure 14 Comparisons of $C_{trough}$ 28 days after the administration of rituximab IV 500 mg/m$^2$ and rituximab SC 1600 mg for Study BO25341 (Stage 1)**



Note for above figure: The horizontal line represents the median, the top and bottom of the box represent the 25 and 75 percentile, the top and bottom line represent the 5 and 95 percentile and the circles represent the values lower than the 5 percentile.

**Table 7 Geometric Mean (%CV) 28 days after the last rituximab IV dose and after the rituximab SC dose and the geometric mean ratios (90% CI) for Study BO25341 (Stage 1)**

| Dose | 28 days after 500 mg/m$^2$ IV | 28 days post SC dose | GMR for SC/IV (90% CI) |
|---|---|---|---|
| | Geometric mean (%CV) | Geometric mean (%CV) | |
| 1400 mg (n=16) | 59.2 (45) | 77.5 (38) | 1.31 (1.17 – 1.46) |
| 1600 mg (n=17) | 49.6 (117) | 83.8 (96) | 1.69 (1.30 – 2.19) |
| 1870 mg (n=22) | 61.7 (46) | 93.6 (44) | 1.52 (1.41 – 1.64) |

Given that rituximab SC 1600 mg did not result in an appreciable difference in $C_{trough}$ compared to rituximab SC 1870 mg, the rituximab SC 1600 mg dose was selected for the dose confirmation part of Study BO23451.

#### 4.1.1.4 Dose Confirmation

The rituximab SC 1600 mg dose was confirmed in Stage 2 of Study BO25431. Patients enrolled in this Stage were randomized to receive rituximab SC 1600 mg or rituximab IV 500 mg/m$^2$ in Cycles 2 to 6, after an initial dose of rituximab IV 375 mg/m$^2$ in Cycle 1. In order to evaluate the impact of the rituximab SC dose over time, the geometric mean ratio of the SC to IV $C_{trough}$ were calculated and are shown in Figure 15 and Table 8, respectively.

**Figure 15 Geometric mean ratio (90% CI) over time for 1600 mg SC vs. the 500 mg/m$^2$ IV doses (Study BO25341 – Stage 2)**

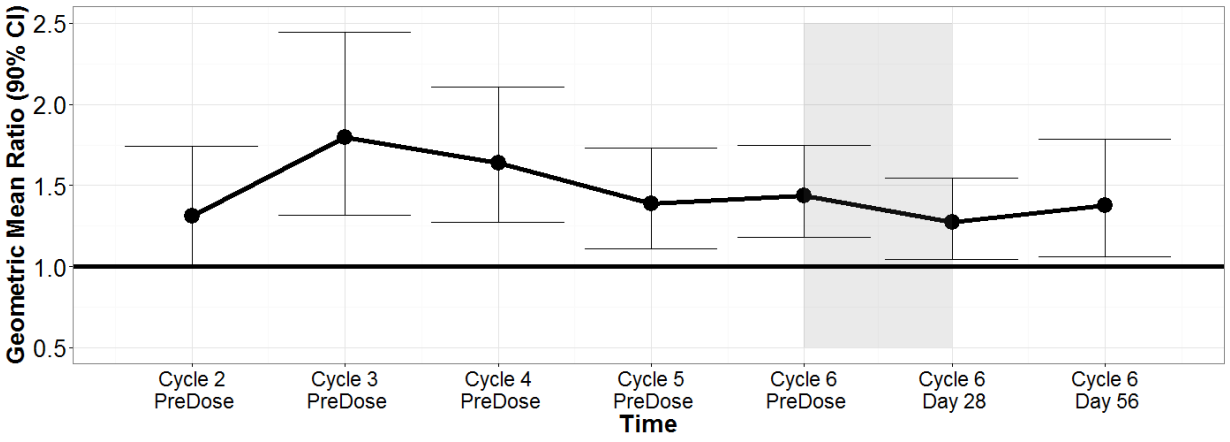


**Table 8 Geometric mean (%CV) of the $C_{trough}$ for the SC and IV arm and the SC to IV geometric mean ratio (90% CI) for Study BO25341 after Cycle 2**

| Cycle | Sample Day | Rituximab IV | | Rituximab SC | | GMR for SC/IV (90% CI) |
|---|---|---|---|---|---|---|
| | | N | Geometric mean (%CV) | N | Geometric mean (%CV) | |
| 2 | Pre dose | 72 | 2.40 (102) | 75 | 3.15 (105) | 1.31 (0.99 – 1.74) |
| 3 | Pre dose | 76 | 15.7 (124) | 80 | 28.1 (108) | 1.79 (1.32 – 2.44) |
| 4 | Pre dose | 74 | 33.6 (105) | 78 | 55.1 (80) | 1.64 (1.28 – 2.10) |
| 5 | Pre dose | 72 | 52.5 (88) | 78 | 72.8 (73) | 1.39 (1.11 – 1.73) |
| 6 | Pre dose | 72 | 60.2 (76) | 74 | 86.5 (66) | 1.44 (1.18 – 1.44) |
| | 28 days Post dose | 71 | 75.9 (71) | 72 | 96.6 (71) | 1.27 (1.04 – 1.55) |
| | 56 days Post dose | 72 | 34.1 (100) | 72 | 47.1 (87) | 1.38 (1.06 – 1.79) |

As shown in Figure 15 and Table 8, the geometric mean ratios for SC/IV and 90% CI of the $C_{trough}$ were consistently higher than 1 over the duration of the study indicating that the $C_{trough}$ after the SC administration was consistently higher than after IV dosing.

### 4.2 Do the proposed fixed doses of rituximab SC 1400 and 1600 mg provide adequate systemic exposures across all BSA sizes for their respective indications

Given that BSA-based dosing allows individualization of doses based on BSA, a transition to fixed dosing could lead to under- or over-dosing of patients in the extremes of the BSA spectrum. As shown in Figure 16 using data from Study BO22334, the distribution of rituximab $C_{trough}$ across BSA sizes appears to be consistent following Rituxmab IV 375 mg/m$^2$. The solid black line represents the median $C_{trough}$ after the IV dose. However, as expected, the $C_{trough}$ following the rituximab SC 1400 mg dose was consistently equal or higher than that observed after the rituximab IV dose, with a gradual decrease with increasing BSA. The FDA concludes that rituximab 1400 mg SC will lead to fairly consistent $C_{trough}$ across all BSA sizes relative to 375 mg/m$^2$ rituximab IV. As shown in Figure 17, similar results were observed for the rituximab SC 1600 mg dose compared to the rituximab IV 500 mg/m$^2$ dose.

**Figure 16 Relationship between observed Ctrough and body surface area for rituximab IV 375 mg/m2 and rituximab SC 1400 mg**

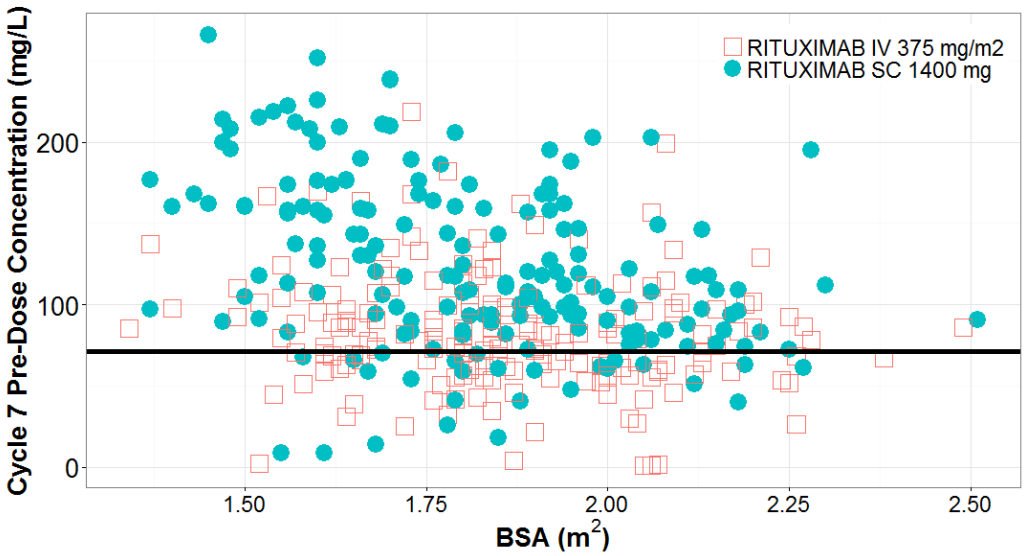
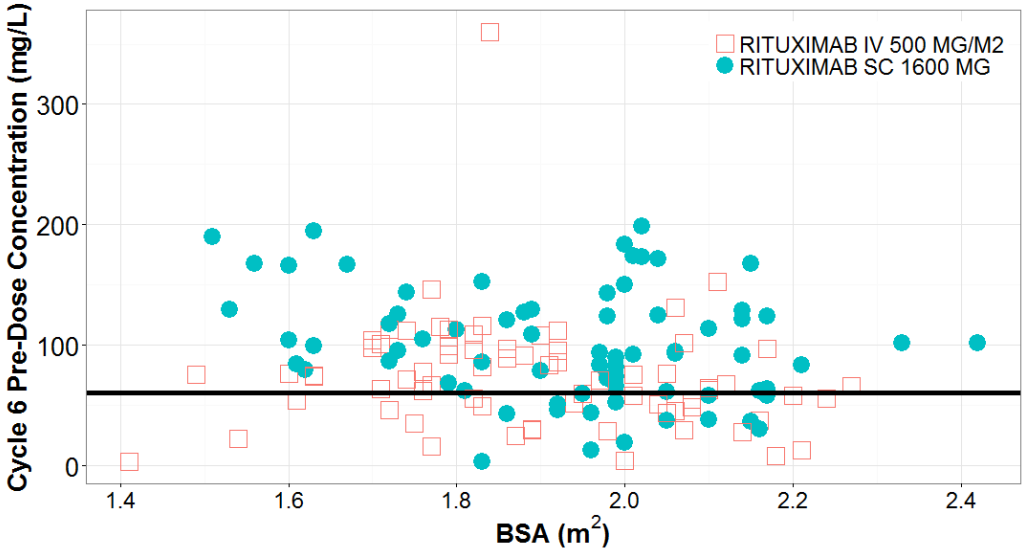



**Figure 17 Relationship between observed $C_{trough}$ and body surface area for rituximab IV 500 mg/m$^2$ and rituximab SC 1600 mg**



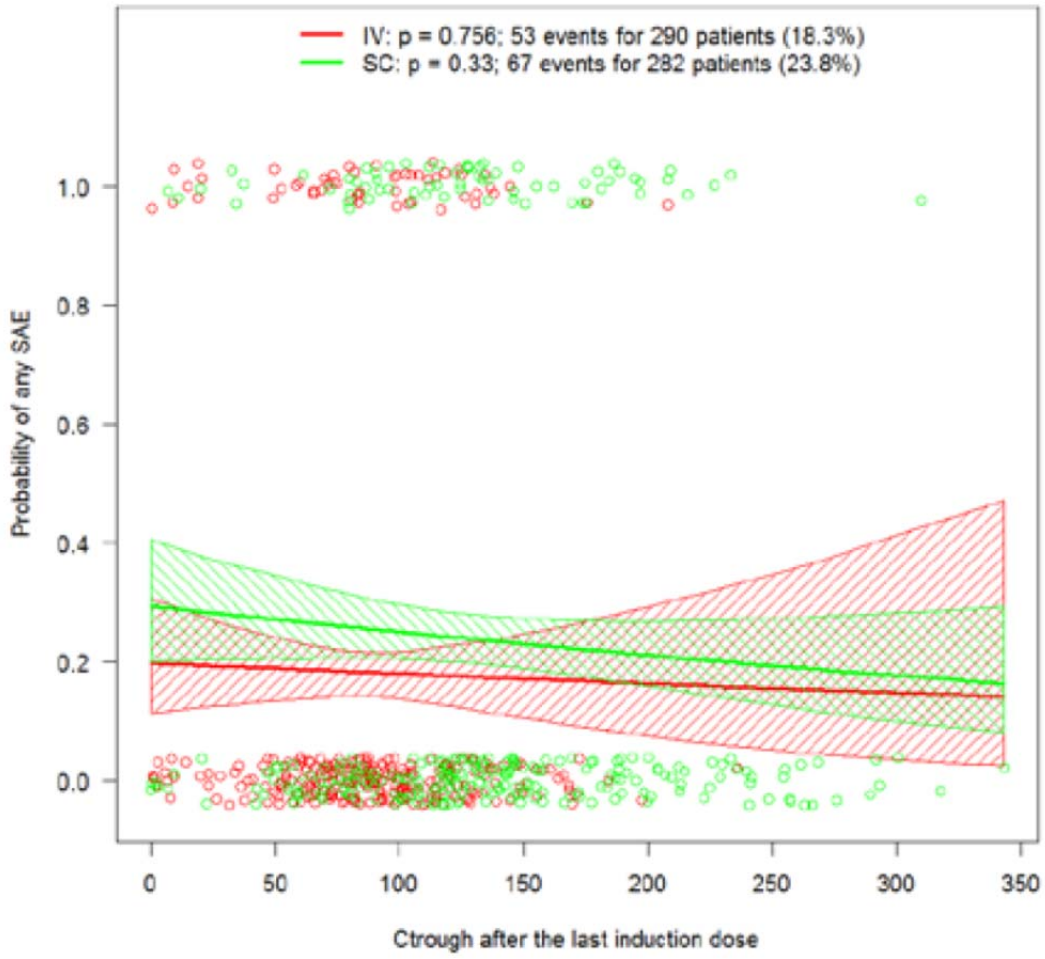

### 4.3 Do differences in $C_{trough}$ between rituximab SC and rituximab IV lead to differences in safety?

Neutropenia, serious adverse events (SAE), and adverse events (AE) ≥ Grade 3 were identified as potentially clinically important safety endpoints to be considered with higher rituximab

exposures. As such, the impact of exposure on these safety endpoints were explored by evaluating the relationship between $C_{trough}$ and each of these safety endpoints in patients with FL using data from Study BO22334 and in patients with CLL using data from Study BO23541. These exposure-response relationships for safety were evaluated using a logistic regression model.

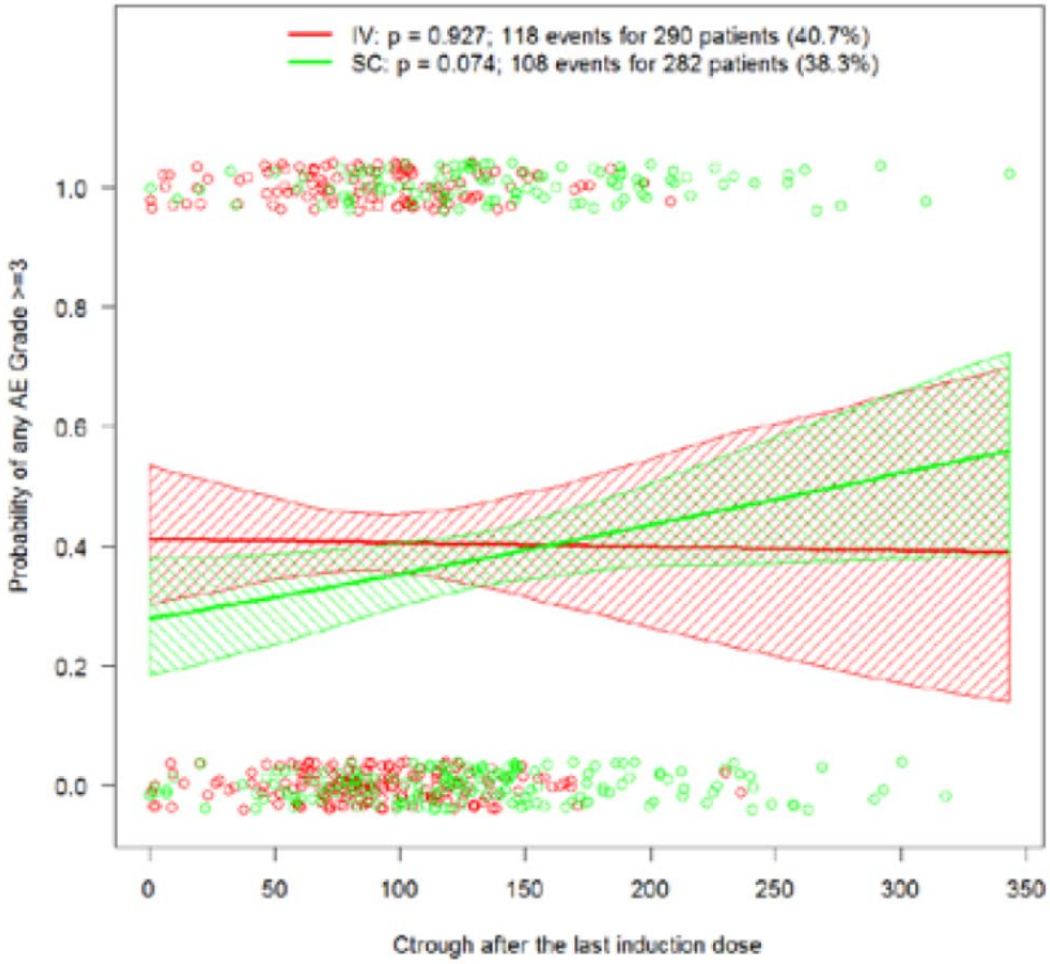
Based on the univariate evaluations relating exposure to each of the safety endpoints, no significant relationships was observed between $C_{trough}$ and each of the safety endpoints (See Figure 18 and Figure 19) in patients with NHL and CLL.

**Figure 18 Relationship between probability of any SAE and $C_{trough}$ during induction period (From cycle 1 until end of induction)**




Source: Applicant's Response to FDA Information Request 04Jan2017

**Figure 19 Relationship between probability of any AE Grade ≥ 3 and $C_{trough}$ during induction period (From cycle 1 until end of induction)**




Source: Applicant's Response to FDA Information Request 04Jan2017

## 5. Clinical Efficacy and Safety

For safety and efficacy, the objective was to describe the data and to determine if efficacy is compromised, or if safety risk is increased by the use of rituximab SC compared to rituximab IV. Three clinical trials will be discussed: BO22334/SABRINA in patients with FL, MO28107/MabEase in patients with DLBCL and BO25341/SAWYER in patients with CLL. From an efficacy perspective, none of the studies had pre-specified hypotheses testing on the efficacy endpoints. The studies were not powered for the clinical efficacy endpoints either. For each study, there are multiple secondary endpoints; however, no adjustment for multiplicity is carried out.

The evaluation of safety is descriptive. While the difference in safety events between the two arms is discussed, this is not meant to imply statistical significance. An area of concern this

safety evaluation does not address is long term safety. Rituximab IV is typically given with each subsequent regimen or line of chemotherapy. Patients, over the course of their disease, may receive multiple courses of rituximab. The trials discussed are all in the first line indication. None of the trials discussed address the potential longer term risks if multiple courses of rituximab SC are given.

### 5.1 Follicular Lymphoma

The safety and efficacy of rituximab SC was described in trial BO22334 or SABRINA. As discussed previously (Section 3.2), the same design was used in the two stages with more extensive PK sampling in stage 1. For safety and efficacy, the two stages were analyzed together.

*Patient Population*

The patient population was ≥18 year of age with histologically confirmed CD20-positive follicular lymphoma grade 1, 2, or 3a according to WHO classification. Patients with 3b follicular lymphoma, transformation to high-grade, presence of CNS disease (lymphoma or lymphomatous meningitis) or other types of NHL were excluded. Patients could not have received prior treatment. Other pertinent inclusion and exclusion criteria are below.

Inclusion (summarized)

- Tumor biopsy within 6 months available for central review. Tissue samples > 6 months old were acceptable if certain criteria were met.
- One of the following signs or symptoms requiring treatment
    - Bulky disease defined as a nodal or extranodal (except spleen) mass ≥ 7 cm in its greatest diameter
    - B-symptoms
    - Elevated serum lactate dehydrogenase (LDH) or β2-microglobulin
    - Involvement of at least 3 nodal sites (each with a diameter greater than 3 cm)
    - Symptomatic spleen enlargement
    - Compressive syndrome
    - Pleura/peritoneal effusion
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
- Life expectancy of 6 months or more
- Adequate hematologic function within 28 days unless related to lymphoma infiltration of the bone marrow
    - Hemoglobin ≥ 8.0 g/dL
    - Absolute neutrophil count (ANC) ≥ 1.5 x $10^9$/L
    - Platelet count ≥ 100 x $10^9$/L

Exclusion criteria (summarized)

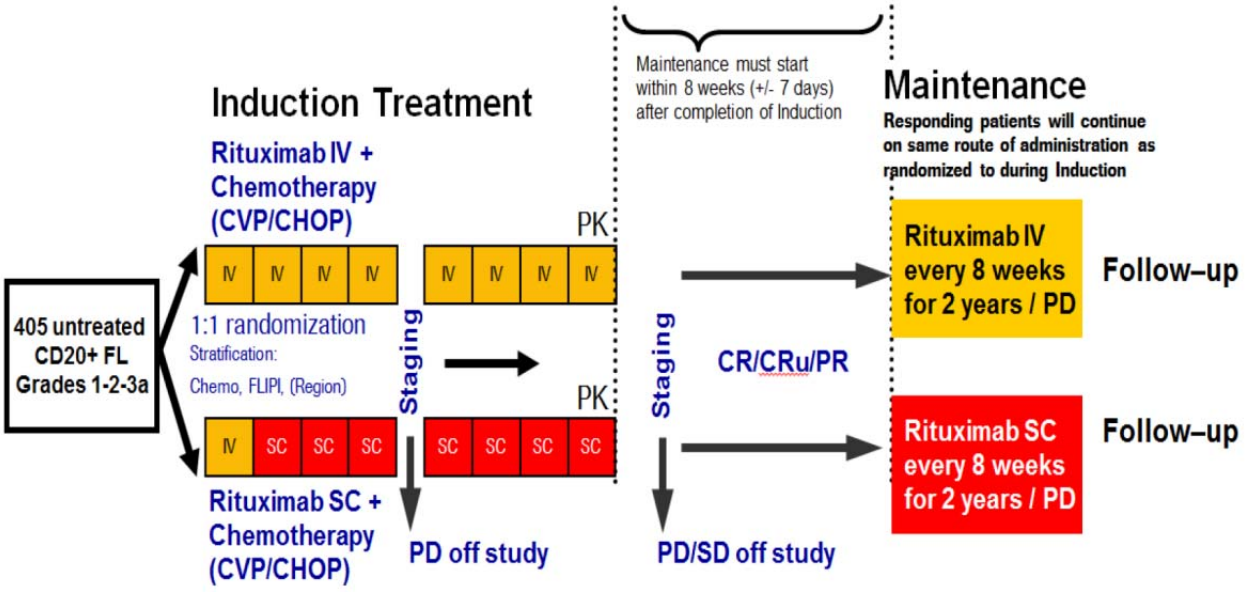
- Corticoid therapy during the last 4 weeks, unless the dose was below 20 mg/day prednisone equivalent
- Presence or history of malignancies other than FL
- Any of the following abnormal laboratory values
  - Serum creatinine >2 mg/dL
  - Total bilirubin > 1.5 x upper limit of normal (ULN) with an exception for patients with Gilbert's disease
  - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 x ULN (or > 5 x ULN if liver involvement)
- Active hepatitis B virus or hepatitis C virus or history of hepatitis B virus infection
- Known human immunodeficiency virus (HIV) disease
- Known active bacterial, viral, fungal or mycobacterial, or any major episode of infections requiring hospitalization or treatment with IV antibiotics within 4 weeks of start of study medication, or oral antibiotics within 2 weeks prior to start of study medication
- Organ transplantation including stem cell transplantation
- Uncontrolled concomitant diseases which could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina) or pulmonary disease (including obstructive pulmonary disease and history of symptomatic bronchospasm)

*Trial Design*

As discussed previously (Section 3.2), the trial was a two-stage, international, multicenter, randomized, controlled, open-label trial to evaluate PK, efficacy, and safety. Patients received induction treatment of rituximab in combination with CHOP or CVP followed by maintenance treatment with rituximab monotherapy. The randomization ratio was 1:1 and randomization was stratified by selected chemotherapy (CHOP or CVP), FLIPI score (low-risk, intermediate-risk, or high-risk), and region, (Europe and North America, South and Central America, and Asia).

Patients randomized to the rituximab SC arm received the first dose of rituximab IV. Patients were to receive 8 cycles of induction therapy with an interim assessment after 4 cycles. Patients with CR, CRu, PR or SD at the interim assessment were to continue with induction treatment. Patients receiving CHOP as the backbone had two options, 6 cycles of R-CHOP with the last two cycles of induction being rituximab only or 8 cycles of R-CHOP. After induction, patients with CR, CRu or PR, were to continue rituximab maintenance every 8 weeks for 2 years. The rituximab IV dose of 375 mg/m$^2$ in this trial was compared to rituximab SC 1400 mg. The schema for the trial is displayed in Figure 20.

**Figure 20 Trial Design in Follicular Lymphoma (trial BO22334/SABRINA)**




[Source: Clinical Study Report Hoffmann-La Roche Ltd Protocol BO22334 page 39]

Statistical Evaluation

The primary endpoint in the study was investigator-assessed objective response rate (ORR). ORR was defined as CR, CRu and PR in each treatment arm at the end of completion of induction treatment.

The secondary endpoints are CRR (CR and CRu) at the end of completion of induction treatment, ORR and CRR at the end of 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.

*Demographics*

The mean age of the patient population was 56.5 years with range of 28 to 86. There was an imbalance in gender in the two treatment groups with the rituximab IV arm 51.7% male and the rituximab SC arm 41.5% male. The majority of the patient population was white at 79.0%, 5.1% Asian, 0.2% black, 1.0% American Indian/Alaska native and 6.6% other. A total of 63.9% received CHOP as the chemotherapy regimen and 36.1% received CVP. Chemotherapy regimen was a stratification factor and was balanced between the two arms. Approximately half of the patients, 53.9% were Ann Arbor stage IV at entry, otherwise 31.2% were stage III, 11.2% were stage II and 3.4% were stage I. Other disease characteristics are listed in Table 9.

**Table 9 Disease Characteristics for FL trial BO22334/SABRINA**

| | Rituximab IV N=205 | Rituximab SC N=205 |
|---|---|---|
| Follicular lymphoma grade | | |
| 1 | 22.0% | 32.7% |
| 2 | 53.2% | 45.4% |
| 3 | 4.4% | 4.4% |
| 3a | 20.5% | 17.1% |
| Total number of risk factors | | |
| High risk (≥3) | 46.3% | 43.9% |
| Intermediate risk (=2) | 32.2% | 35.6% |
| Low risk (0-1) | 21.5% | 20.5% |

*Primary Endpoint*

The results for the primary endpoint are presented in Table 10. 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 risk ratio is 0.99 with a 95% confidence interval of 0.92 to 1.08. The risk 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 10 Primary Endpoint Result for FL**

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

*Secondary Endpoints*

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 11 (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 risk ratio is 1.00. For ORR at the end of the maintenance period, the difference between two arms is -0.2% with a 95% confidence interval of -9.2% to 8.8%. The estimated risk 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 risk 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 11 Secondary Endpoint Results for FL**

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

The results of time-to-event secondary endpoints of PFS, EFS and OS are presented in Table 12. As shown in Figure 21 and Figure 22, 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 12 . The number of events in the rituximab SC arm is smaller than in the rituximab IV arm for each of PFS, EFS, and OS.

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.

**Table 12 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% |

**Figure 21 Kaplan Meier PFS for FL**

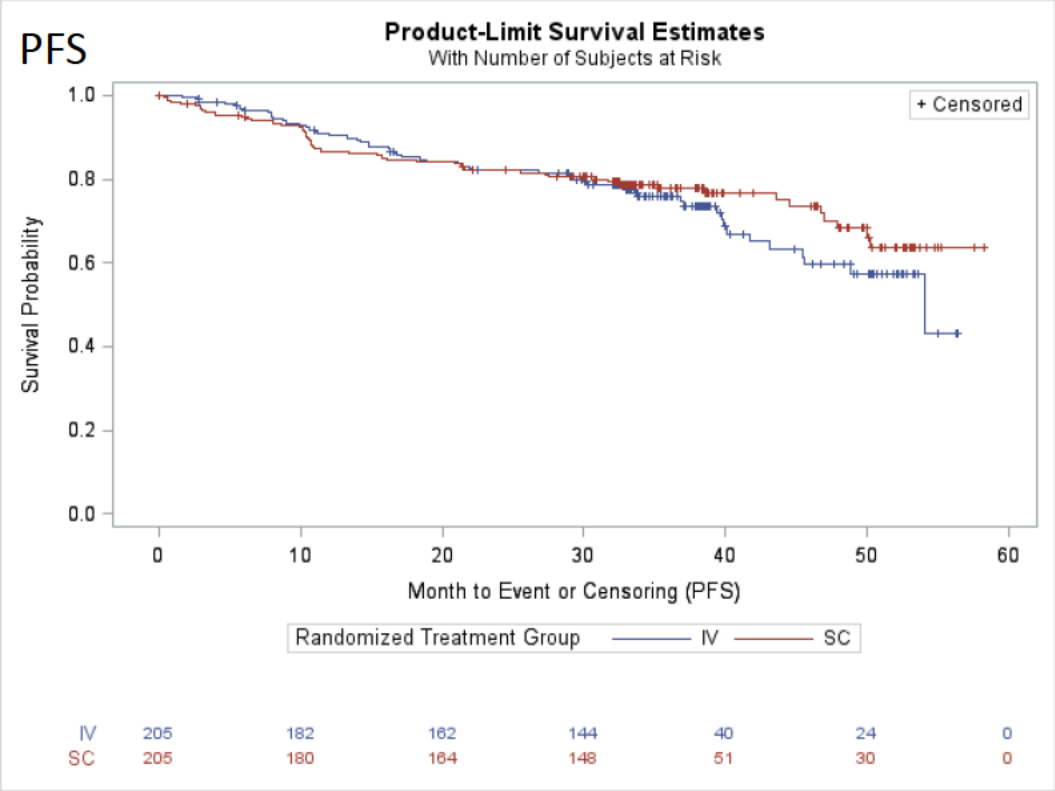
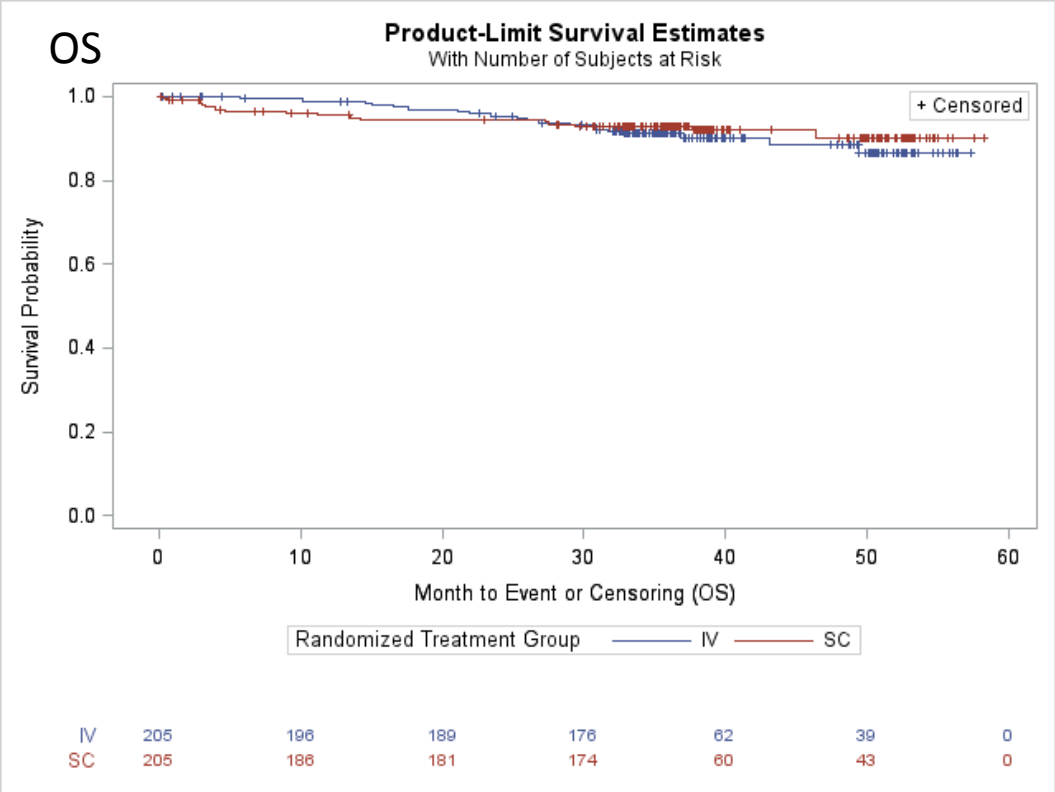


**Figure 22 Kaplan Meier for OS for FL**




*Safety Evaluation*

The ITT population consisted of 205 patients in each arm. The safety population was defined as patients who received at least one dose of rituximab IV or SC, analyzed as treated. Six patients randomized to rituximab SC withdrew after cycle 1 (the first cycle for all patients is rituximab IV), and were analyzed in the rituximab IV arm for the safety population. One patient in the rituximab IV arm and 2 patients in the rituximab SC arm discontinued prior to receiving rituximab. Thus, the safety population was 210 for rituximab IV and 197 for rituximab SC for this trial.

The majority of patients, 89.5% in the rituximab IV arm and 90.9% in the rituximab SC arm completed all eight cycles of induction treatment. A total of 69.0% in the rituximab IV arm and 69.5% in the rituximab SQ arm completed all 20 cycles.

Deaths within 30 days

A total of 3 patients (1.4%) on the rituximab IV arm and 4 patients (2.0%) on the rituximab SC arm died within 30 days of last dose. The causes of death on the rituximab IV arm were acute respiratory failure, myocardial infarction/pneumonia and infection/hepatic coma. The causes of

death on the rituximab SC arm were febrile neutropenia (2 patients), myocardial infarction, and congestive cardiac failure.

Nonfatal Treatment Emergent Adverse Events

Nonfatal TEAE (treatment emergent adverse events), limited to the worst grade per patient for the adverse event, that occurred in 10% or greater on either arm are displayed in Table 13. Five have a difference in overall incidence ≥5%. Of these, nausea, pneumonia, injection site erythema and cough were more common the rituximab SC arm and urinary tract infection was more common on the rituximab IV arm. For nonfatal TEAE grades 3-4, only neutropenia had a difference ≥5% and was more common on the rituximab SC arm. Given the difference in administration routes, the difference in injection site erythema is not unexpected. As demonstrated in the table, many of the differences between the arms were small.

**Table 13 TEAE for FL (trial BO22334/SABRINA)**

| | All grades (%) | | | Grades 3-4 (%) | | |
|---|---|---|---|---|---|---|
| | IV N=210 | SC N=197 | SC-IV | IV N=210 | SC N=197 | SC-IV |
| Blood and Lymphatic System Disorders | | | | | | |
| Neutropenia | 27.1 | 32 | 4.8 | 21.0 | 26.4 | 5.4 |
| Anemia | 12.4 | 15.2 | 2.9 | 0.0 | 4.6 | 4.6 |
| Leukopenia | 11 | 6.1 | -4.9 | 2.4 | 4.1 | 1.7 |
| Gastrointestinal Disorders | | | | | | |
| Constipation | 26.2 | 24.9 | -1.3 | 0.5 | 0.0 | -0.5 |
| Nausea | 21.9 | 31.5 | 9.6 | 0.0 | 0.0 | 0.0 |
| Diarrhea | 15.7 | 17.8 | 2.1 | 1.0 | 1.5 | 0.6 |
| Abdominal pain | 12.4 | 13.7 | 1.3 | 1.0 | 0.0 | -1.0 |
| Vomiting | 12.4 | 13.7 | 1.3 | 1.0 | 0.0 | -1.0 |
| General Disorders and Administration Site Conditions | | | | | | |
| Fatigue | 17.6 | 19.8 | 2.2 | 1.0 | 0.0 | -1.0 |
| Pyrexia | 15.7 | 14.7 | -1.0 | 0.5 | 0.5 | 0.0 |
| Asthenia | 12.9 | 17.3 | 4.4 | 0.0 | 1.0 | 1.0 |
| Injection site erythema | 0.0 | 13.2 | 13.2 | 0.0 | 0.0 | 0.0 |
| Infections and Infestations | | | | | | |
| Urinary tract infection | 13.3 | 7.6 | -5.7 | 0.5 | 1.0 | 0.5 |
| Upper respiratory tract infection | 10.0 | 14.7 | 4.7 | 0.0 | 0.5 | 0.5 |
| Nasopharyngitis | 10.0 | 9.6 | -0.4 | 0.0 | 0.0 | 0.0 |
| Pneumonia | 4.3 | 10.7 | 6.4 | 2.9 | 4.6 | 1.7 |
| Musculoskeletal and Connective Tissue Disorders | | | | | | |
| Back pain | 11.9 | 9.1 | -2.8 | 1.0 | 0.5 | -0.4 |
| Arthralgia | 9.5 | 12.7 | 3.2 | 0.0 | 0.5 | 0.5 |
| Nervous System Disorders | | | | | | |
| Peripheral neuropathy | 13.8 | 11.7 | -2.1 | 0.5 | 1.5 | 1.1 |
| Paraesthesia | 12.4 | 15.7 | 3.4 | 0.0 | 0.0 | 0.0 |

| | All grades (%) | | | Grades 3-4 (%) | | |
|---|---|---|---|---|---|---|
| | IV N=210 | SC N=197 | SC-IV | IV N=210 | SC N=197 | SC-IV |
| Headache | 8.6 | 13.2 | 4.6 | 0.0 | 0.0 | 0.0 |
| Respiratory, Thoracic and Mediastinal Disorders | | | | | | |
| Cough | 13.3 | 22.8 | 9.5 | 0.5 | 0 | -0.5 |
| Dyspnea | 7.6 | 10.7 | 3.0 | 1.9 | 1.0 | -0.9 |
| Skin and Subcutaneous Tissue Disorders | | | | | | |
| Pruritis | 11.4 | 9.1 | -2.3 | 0.5 | 0.0 | -0.5 |
| Alopecia | 10.5 | 14.2 | 3.7 | 0.5 | 0.5 | 0.0 |

Non-fatal SAE

Non-fatal SAE, that occurred in 3 or more patients on either arm, are displayed in Table 14. For the nonfatal SAE at the preferred term level, there are no nonfatal SAEs that occurred in more than 3 patients in either arm that have a greater than 2% difference between the two arms.

**Table 14 Nonfatal SAE for FL (BO22334/SABRINA)**

| | Nonfatal SAE all grades (%) | | |
|---|---|---|---|
| | IV N=210 | SC N=197 | SC-IV |
| Febrile neutropenia | 4.8 | 5.1 | 0.3 |
| Neutropenia | 1.9 | 3.1 | 1.1 |
| Constipation | 1.4 | 0.0 | -1.4 |
| Pyrexia | 2.4 | 3.1 | 0.7 |
| Pneumonia | 3.3 | 5.1 | 1.7 |
| Neutropenic sepsis | 1.9 | 0.5 | -1.4 |
| Sepsis | 0.0 | 1.5 | 1.5 |
| Pulmonary embolism | 1.9 | 0.5 | -1.4 |
| Dyspnea | 1.4 | 1.0 | -0.4 |

Laboratory Values

Hematologic, liver function and creatinine laboratory values limited to worst grade for each patient are displayed in Table 15. As demonstrated in Table 15, leukocyte count, neutrophil count, hemoglobin, platelets, ALT, AST and alkaline phosphatase are increased slightly in overall grade and in grades 3-4. The majority of these increases are small, although there is approximately a 7% increase in grades 3-4 leukocyte count and absolute neutrophil count.

**Table 15 Laboratory Values Follicular Lymphoma**

| | All grades (%) | | | Grades 3-4 (%) | | |
|---|---|---|---|---|---|---|
| | IV N=210 | SC N=197 | SC-IV | IV N=210 | SC N=197 | SC-IV |
| Leukocyte count | 71.0 | 74.1 | 3.1 | 11.0 | 18.3 | 7.3 |
| Neutrophil count | 64.8 | 68.0 | 3.2 | 30.0 | 37.6 | 7.6 |

| | All grades (%) | | | Grades 3-4 (%) | | |
|---|---|---|---|---|---|---|
| | IV N=210 | SC N=197 | SC-IV | IV N=210 | SC N=197 | SC-IV |
| Hemoglobin | 54.8 | 58.4 | 3.6 | 1.0 | 4.6 | 3.6 |
| Platelets | 16.7 | 19.3 | 2.6 | 1.9 | 3.0 | 1.1 |
| ALT | 31.4 | 35.5 | 4.1 | 0.0 | 1.5 | 1.5 |
| AST | 31.9 | 37.1 | 5.1 | 0.0 | 1.5 | 1.5 |
| Alkaline phosphatase | 20.5 | 23.9 | 3.4 | 0.0 | 1.0 | 1.0 |
| Bilirubin | 14.8 | 10.2 | -4.6 | 0.5 | 1.0 | 0.5 |
| Creatinine | 16.7 | 15.7 | -1.0 | 1.0 | 2.0 | 1.0 |

### 5.2 Diffuse Large B-Cell Lymphoma

The safety and efficacy of rituximab SC in the DLBCL population was evaluated MO28107/MabEase as previously discussed (Section 3.3). The primary objective of this trial was to determine the complete response rate (CR and CRu) one month after the end of treatment.

*Patient Population*

The trial population was patients aged 18-80 (both inclusive) with untreated histologically confirmed CD20-positive DLBCL according to the World Health Organization (WHO) classification system. Patients need an IPI score of 1-5 or a score of 0 with bulky disease defined as one lesion ≥ 7.5 cm. Patients with primary CNS lymphoma, blastic variant of mantle cell lymphoma, evidence of transformation to Burkitt's lymphoma, primary mediastinal DLBCL, primary effusion lymphoma, primary cutaneous DLBCL or primary DLBCL of the testis were excluded. Also excluded was transformed lymphoma or follicular lymphoma IIIB. Patients with prior therapy for DLBCL except biopsy or local irradiation were also excluded. Other pertinent inclusion and exclusion criteria are below.

Inclusion (summarized)

- At least one bi-dimensionally measurable lesion defined as ≥ 1.5 cm in its largest dimension
- Adequate hematologic function, unless related to bone marrow involvement by DLBCL
  - Hemoglobin ≥ 9 g/dL (No transfusions allowed within 2 weeks prior to start)
  - Absolute neutrophil count ≥ 1.5 x $10^9$/L
  - Platelet count ≥ 75 x $10^9$/L
- ECOG performance status ≤ 2

Exclusion criteria (summarized)

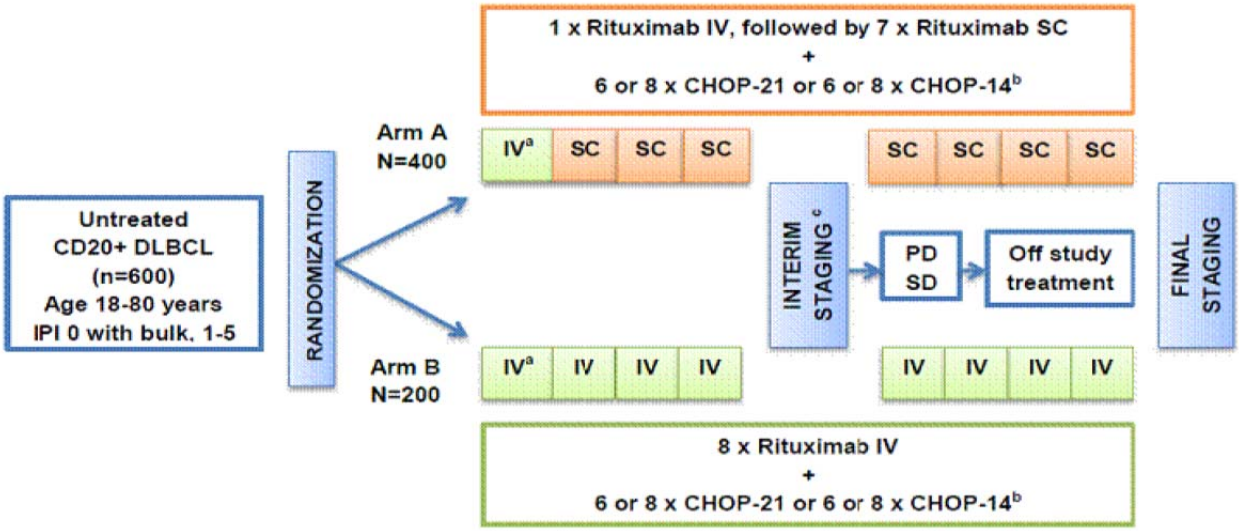
- History of other malignancy with some exceptions.
- Inadequate renal function defined as Cr > 1.5 x ULN (unless creatinine clearance (CrCl) normal) or calculated CrCl < 30 mL/min
- Inadequate hepatic function defined as any of the following:
  - ALT, AST, or alkaline phosphatase > 2.5 x ULN

  - total bilirubin ≥1.5 x ULN unless Gilbert's disease then patient eligible if total bilirubin ≤ 3.0 x ULN
- Known HIV disease
- Active or severe bacterial, viral, fungal, mycobacterial, parasitic or other infection or any major infection requiring IV antibiotics within 4 weeks prior to start
- Active hepatitis B virus or active hepatitis C virus. Patients with occult or prior hepatitis B infection with undetectable deoxyribonucleic acid may be included but followed closely. Patients positive for hepatitis C antibody are eligible if polymerase chain reaction testing for hepatitis C virus ribonucleic acid is negative. Prior treatment with cytotoxic drugs or rituximab for another condition or prior use of an anti-CD20 antibody
- Treatment with a monoclonal antibody within 3 months
- Ongoing corticosteroid use at a dose of >20 mg/day of prednisone or equivalent
- Life expectancy of less than 6 months

*Trial Design*

This was a phase IIIb, multi-center, international, open label trial in patients randomized 2:1 to rituximab SC + CHOP and rituximab IV + CHOP. Patients were stratified by age (<60 and ≥60 years), IPI risk category (low, low-intermediate, high-intermediate, and high), and chemotherapy regimen (CHOP-21 and CHOP-14). Patients were to receive 8 cycles of rituximab with 6 or 8 cycles of CHOP-21 or 6 or 8 cycles of CHOP-14. Response was assessed approximately one month after day 1 of the last cycle. An interim staging was done after 4 cycles. All patients received the first cycle with rituximab IV. The trial schema is displayed in Figure 23.

**Figure 23 Trial schema for DLBCL (trial MO28107/MabEase)**




[Source: Roche Clinical study Report MO28107 page 29]

Statistical Evaluation

The primary objective of the study is to estimate the efficacy of rituximab SC or IV in combination with CHOP as measured by CR/CRu approximately one month after the end of rituximab-based treatment. The primary endpoint of the study is complete response rate (CR/CRu) based on investigator's assessment according to the international working group response criteria at the end of the induction treatment (visit 10).

The secondary endpoints are PFS, EFS, DFS, and OS. PFS, EFS, and OS are defined similarly to BO22334 study. DFS is defined as the time from the date of the initial CR/CRu until the date of progression or death from any cause.

The ITT population was used as the primary analysis population. The applicant defined the ITT population as all randomized patients with completed baseline and at least one on-treatment efficacy assessment. In the FDA's definition, the ITT population includes all randomized patients. The results for this study will be presented in the ITT population by FDA's definition.

*Demographics*

The two treatment arms were balanced in terms of age. The mean age of the study population was 60.6 years with a minimum age of 18 and a maximum age of 80. Overall, the majority of the patients (83.3%) were white. The remaining 5.9%, 6.8%, 0.2%, 3.8% were Asian, not applicable per local regulation, black, and other, respectively. The rituximab SC arm had 54.9% male subjects while the rituximab IV arm had 51.3% male subjects. The IPI risk category and chemotherapy regimen are displayed in Table 16.

**Table 16 Disease Demographics for DLBCL (MO28107/MabEase)**

| | 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 |

*Primary endpoint*

The primary endpoint results are presented in Table 17. 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 risk ratio is 1.12 favoring SC arm with a 95% confidence interval of 0.92 to 1.36.

**Table 17 Primary Endpoint DLBCL**

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

*Secondary endpoints*

The time-to-event secondary endpoints results are presented in Table 18. Kaplan-Meier curves of PFS and OS are included as Figure 24 and Figure 25 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 18. 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, $\geq 60$ 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 every14 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 18 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% |

**Figure 24 Kaplan Meier PFS plot for DLBCL**

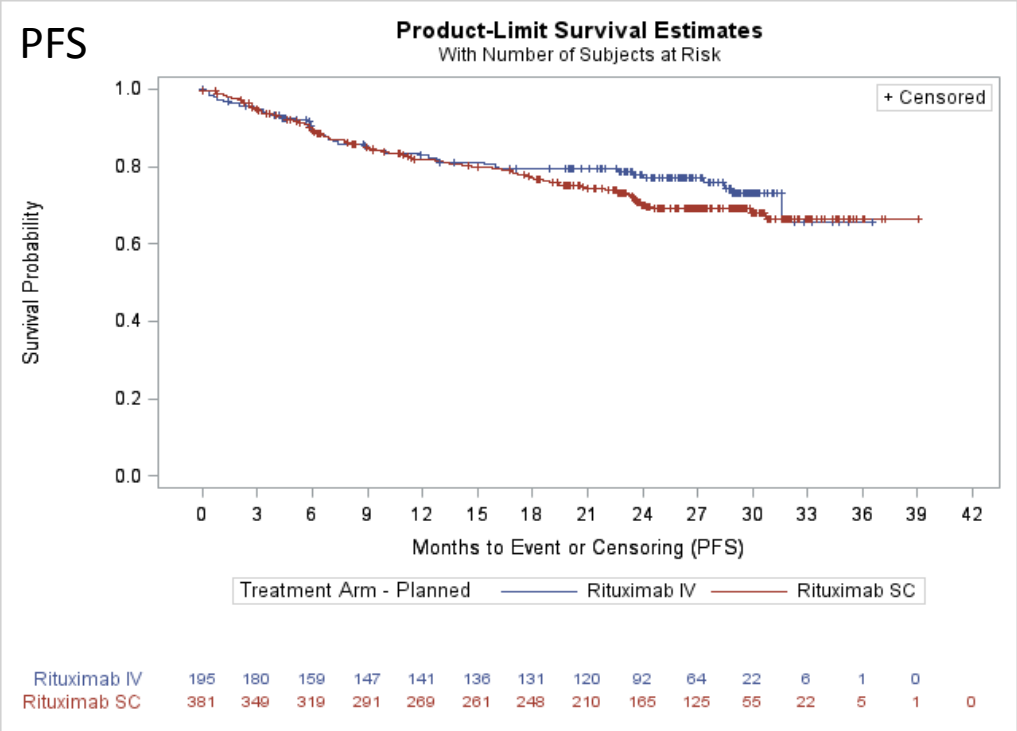
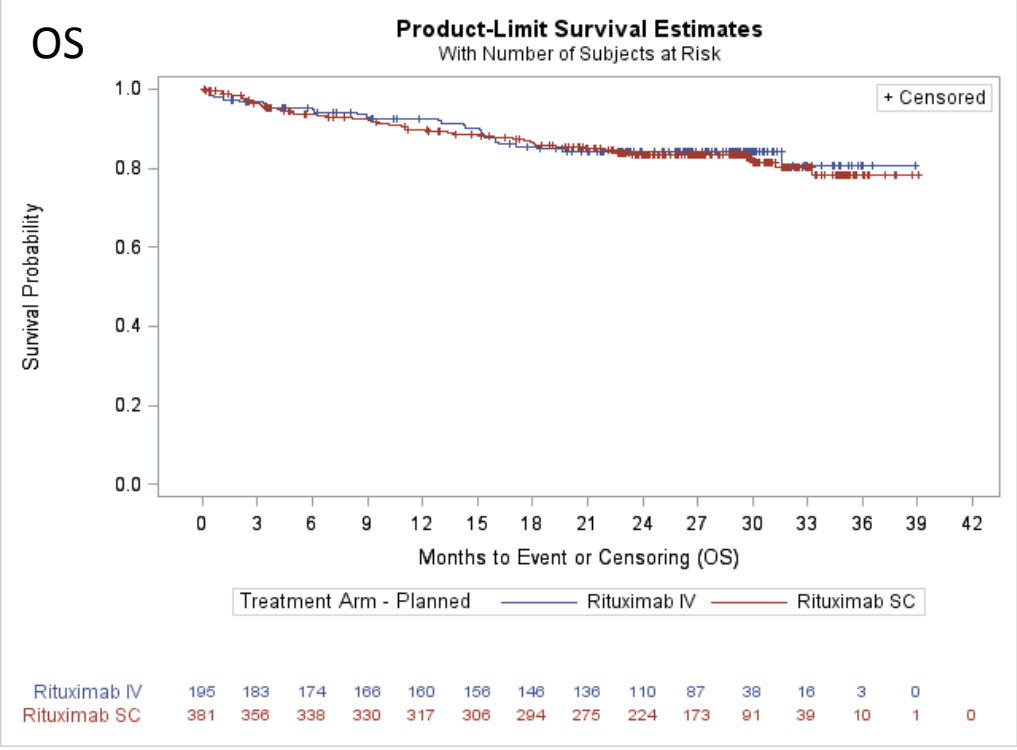



**Figure 25 Kaplan Meier OS plot for DLBCL**



*Safety*

The safety population was defined as patients who received at least one dose of study drug according to the treatment actually received. Four patients did not received any study drug and were not included in the safety population and nine patients randomized to the rituximab SC group only received the first dose of rituximab, which is given IV, and were included in the rituximab IV safety population. The safety population was 369 patients for rituximab SC and 203 patients for rituximab IV.

The exposure in terms of rituximab and CHOP cycles received was comparable between the two arms. The mean number of rituximab cycles was 7.0 for the rituximab IV arm and 7.4 for the rituximab SC arm. The mean number of CHOP cycles was 6.3 for the rituximab IV arm and 6.7 for the rituximab SC arm.

Deaths within 30 days

A total of 8 patients (3.9%) on the rituximab IV arm and 13 patients (3.5%) on the rituximab SC arm died within 30 days of last dose. The causes of death on the rituximab IV arm was septic shock , cardiac arrest (2 patients), febrile neutropenia, sudden death, myocardial infarction, respiratory failure, and epistaxis. The causes of death on the rituximab SC arm was disease progression, generalized peritonitis, respiratory infection, septic shock (2 patients), fatal acute diarrhea, pneumonia, lung infection, multi-organ failure, cardiac failure, acute heart failure, acute respiratory failure, and unknown.

Nonfatal Treatment Emergent Adverse Events

Nonfatal treatment emergent adverse events that occurred in >10% of patients on either arm is displayed in Table 19. One TEAE has a greater than 5% difference between the two arms, grade 3-4 neutropenia, which was more common on the rituximab SC arm. Of the 12 adverse events listed for all grades, 6 have a positive difference (higher in the rituximab SC arm) while 6 have a negative difference (higher incidence in the rituximab IV arm). In conclusion, there does not appear to be a major difference in adverse events at the preferred term level for this clinical trial.

**Table 19 Nonfatal TEAE for DLBCL (MO28107/MabEase)**

| | All grades (%) | | | Grades 3-4 (%) | | |
|---|---|---|---|---|---|---|
| | IV N=203 | SC N=369 | SC-IV | IV N=203 | SC N=369 | SC-IV |
| Blood and Lymphatic System Disorders | | | | | | |
| Neutropenia | 29.1 | 30.6 | 1.6 | 19.2 | 25.2 | 6.0 |
| Anemia | 20.7 | 23.0 | 2.4 | 3.9 | 5.2 | 1.2 |
| Febrile Neutropenia | 11.3 | 14.4 | 3.0 | 11.3 | 14.4 | 3.0 |
| Gastrointestinal Disorders | | | | | | |
| Nausea | 23.6 | 21.7 | -2.0 | 0.5 | 0.5 | 0.1 |

| | All grades (%) | | | Grades 3-4 (%) | | |
|---|---|---|---|---|---|---|
| | IV N=203 | SC N=369 | SC-IV | IV N=203 | SC N=369 | SC-IV |
| Constipation | 17.2 | 15.2 | -2.1 | 0.5 | 0.5 | 0.1 |
| Diarrhea | 10.3 | 14.1 | 3.8 | 1.5 | 1.4 | -0.1 |
| Vomiting | 8.4 | 11.4 | 3.0 | 0.5 | 0.8 | 0.3 |
| General and Administrative Side Conditions | | | | | | |
| Fatigue | 14.8 | 19.0 | 4.2 | 1.5 | 0.5 | -0.9 |
| Pyrexia | 12.8 | 12.7 | -0.1 | 0.0 | 0.3 | 0.3 |
| Asthenia | 11.8 | 11.1 | -0.7 | 1.0 | 0.5 | -0.4 |
| Investigations | | | | | | |
| Neutrophil count decreased | 14.3 | 13.8 | -0.5 | 11.3 | 10.8 | -0.5 |
| Nervous System Disorders | | | | | | |
| Peripheral Neuropathy | 11.8 | 11.9 | 0.1 | 0.0 | 0.8 | 0.8 |
| Respiratory Thoracic and Mediastinal Disorders | | | | | | |
| Cough | 9.4 | 11.4 | 2.0 | 0.0 | 0.3 | 0.3 |
| Skin and Subcutaneous Tissue Disorders | | | | | | |
| Alopecia | 23.6 | 23.6 | -0.1 | 0.0 | 0.0 | 0.0 |

Nonfatal Serious Adverse Events

Nonfatal SAE that occurred in over 3% of patients on either arm are displayed in Table 20. For the SAEs listed, there was approximately a 2% higher incidence of febrile neutropenia on the rituximab SC arm.

**Table 20 Nonfatal SAE for DLBCL (MO28107/MabEase)**

| | Nonfatal SAE all grades (%) | | |
|---|---|---|---|
| | IV N=203 | SC N=369 | SC-IV |
| Febrile neutropenia | 10.8 | 13 | 2.2 |
| Neutropenia | 4.9 | 4.9 | -0.0 |
| Pneumonia | 3.0 | 4.6 | 1.7 |

Laboratory Values

Pertinent laboratory values limited to worst grade per patient are displayed in Table 21. Overall, there was a slight increase for all grades for the laboratory values of leukocyte count, neutrophil count, hemoglobin, platelets, ALT, AST and creatinine, with the largest difference in hemoglobin, neutrophil count and creatinine. The differences between the two arms for grades 3-4 were not greater than 3% for the laboratory values listed.

**Table 21 Laboratory Values DLBCL (MO28107/MabEase)**

| | All grades (%) | | | Grades 3-4 (%) | | |
|---|---|---|---|---|---|---|
| | IV N=203 | SC N=369 | SC-IV | IV N=203 | SC N=369 | SC-IV |
| Leukocyte count | 61.6 | 64.2 | 2.6 | 18.2 | 20.6 | 2.4 |
| Neutrophil count | 13.3 | 18.4 | 5.1 | 4.9 | 7.0 | 2.1 |
| Hemoglobin | 47.8 | 61.0 | 13.2 | 5.9 | 6.0 | 0.1 |
| Platelets | 29.6 | 31.2 | 1.6 | 9.4 | 8.1 | -1.3 |
| ALT | 24.6 | 27.6 | 3.0 | 0.5 | 2.2 | 1.7 |
| AST | 24.6 | 26.8 | 2.2 | 2.0 | 1.1 | -0.9 |
| Bilirubin | 9.9 | 9.2 | -0.7 | 0.5 | 2.2 | 1.7 |
| Creatinine | 62.1 | 67.5 | 5.4 | 0.0 | 0.5 | 0.5 |

### 5.3 Chronic Lymphocytic Leukemia

The safety and efficacy of rituximab SC was described in trial BO25341/SAWYER. As discussed previously (Section 3.4), this trial was designed with two parts, the primary objective of part 1 was to confirm a selected SC rituximab dose that resulted in a $C_{trough}$ comparable to rituximab IV. In part 1, only one dose of rituximab SC in cycle 6 was given, and is not discussed further in this section. The primary objective for part 2 was to establish non-inferiority in $C_{trough}$ levels between the SC dose and the IV dose.

*Patient Population*

Patients in this trial were ≥18 years of age and had CD20-positive B cell CLL confirmed according to International Workshop on CLL(iwCLL) criteria and required treatment according to iwCLL criteria. Patients with transformation to an aggressive B-cell malignancy such as DLBCL, Richter's syndrome or prolymphocytic leukemia were excluded. Patients with previous treatment for CLL were excluded from part 2. Other pertinent inclusion and exclusion criteria are summarized below.

Inclusion criteria (summarized)

- ECOG performance status of 0-1
- Life expectancy > 6 months

Exclusion criteria (summarized)

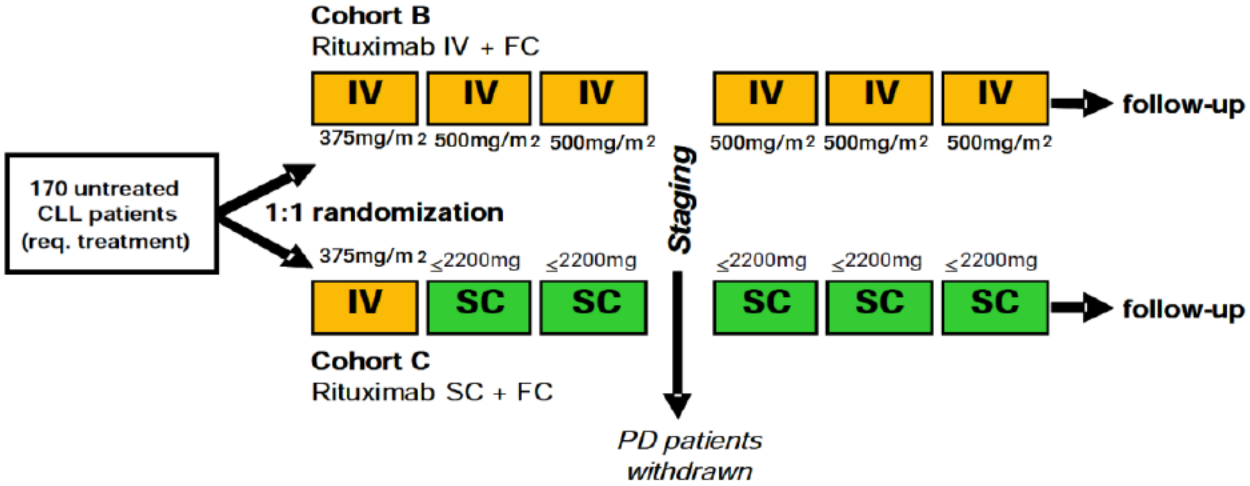
- History of other malignancy unless treated with curative intent and in remission for ≥5 years with some exceptions.
- Cumulative illness rating scale score > 6
- Hepatitis B seropositive unless due to vaccination

- Known HIV
- Clinically significant autoimmune cytopenia including Coombs positive hemolytic anemia
- Inadequate liver function:
  - alkaline phosphatase and transaminases > 2 x ULN
  - total bilirubin > 2 x ULN
- Inadequate renal function: creatinine clearance <70 ml/min calculated according to Cockcroft and Gault formula
- Concomitant disease requiring prolonged use of glucocorticoids (> 1 month) unless below 20 mg/day prednisone
- Active bacterial, viral, or fungal infection requiring systemic therapy
- Uncontrolled concomitant diseases, including significant cardiovascular disease (New York Heart Association class III or IV cardiac disease, myocardial infarction within 6 months, unstable arrhythmias, or unstable angina) or pulmonary disease (including obstructive pulmonary disease and history of symptomatic bronchospasm)
- Any patient with a history of malignancy with less than 5 years remission must be approved by the Roche Clinical Scientist

*Trial Design*

For part 2 patients with untreated CLL were randomized 1:1 to rituximab IV (cohort B) or rituximab SC (cohort C). Cohort A was part 1 and is not discussed here. Treatment was rituximab 375 mg/m$^2$ for the first cycle for both treatment arms combined with FC followed by rituximab IV 500 mg/m$^2$ + FC in the rituximab IV arm and rituximab 1600 mg SC + FC in the rituximab SC arm. Cycles were every 28 days for 6 cycles. Patients could receive FC either orally or intravenously. For fludarabine, the IV dose was 25 mg/m$^2$ IV days 1-3 or the oral regimens of 24 mg/m$^2$ days 1-5 or 30-40 mg/m$^2$ on day 1-3. Cyclophosphamide was 250 mg/m$^2$ IV on days 1-3 or 150 mg/m$^2$ orally on days 1-5 or 200-250 mg/m$^2$ orally on days 1-3. Patients were stratified by Binet stage (A, B or C) and route of chemotherapy (IV or oral). The schema for the trial is displayed in Figure 26.

**Figure 26 Trial Design for CLL (BO25341/SAWYER)**




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

Statistical Evaluation

The primary objective of the BO25341/SAWYER study is non-inferiority in $C_{trough}$ between rituximab SC over rituximab IV arm. Please refer to section 4.1.1.4 for the results. The secondary endpoint is response rate including complete response (CR), complete response with incomplete bone marrow recovery (CRi), and partial response (PR).

*Demographics*

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 22.

**Table 22 Baseline Characteristics CLL (Part 2 BO25341/SAWYER)**

| | 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 |

*Secondary efficacy endpoints*

The clinical efficacy of response rate is summarized in Table 23. 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 risk ratio is 1.06, favoring rituximab SC arm with a 95% confidence interval of 0.92 to 1.21.

**Table 23 Response Rate Results CLL**

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

The results of time-to-events endpoints are summarized in Table 24. 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 24 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] |

*FDA Comment: The time-to-event results in Table 24 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.*

*Safety Evaluation*

The ITT population was 176 patients. Two patients withdrew prior to study treatment and are not included in the safety population. Two patients randomized to rituximab SC only received the first cycle of treatment (first cycle for all patients is rituximab IV) and these patients are part

of the rituximab IV safety population. The safety population was 89 patients in the rituximab IV arm and 85 patients in the rituximab SC arm.

Deaths within 30 days of last dose

For part 2, no deaths occurred within 30 days of last dose.

Nonfatal TEAE

Nonfatal TEAE that occurred in >10% on either arm are displayed in Table 25. Nonfatal TEAE with a difference in all grades greater than 5% were neutropenia, pyrexia, injection site erythema, injection site pain, and erythema which were greater on the rituximab SC arm and asthenia and anemia which was greater on the rituximab IV arm. For grades 3-4 and the other nonfatal TEAE listed, the difference between the two arms was not greater than 5%.

**Table 25 Nonfatal TEAE >10% in either arm for CLL (part 2 BO25341/SAWYER)**

| | All grades (%) | | | Grades 3-4 (%) | | |
|---|---|---|---|---|---|---|
| | IV N=89 | SC N=85 | SC-IV | IV N=89 | SC N=85 | SC-IV |
| Blood and Lymphatic System Disorders | | | | | | |
| Neutropenia | 58.4 | 64.7 | 6.3 | 51.7 | 56.5 | 4.8 |
| Thrombocytopenia | 25.8 | 23.5 | -2.3 | 9.0 | 5.9 | -3.1 |
| Leukopenia | 15.7 | 18.8 | 3.1 | 12.4 | 14.1 | 1.8 |
| Anemia | 23.6 | 12.9 | -10.7 | 9.0 | 4.7 | -4.3 |
| Febrile neutropenia | 7.9 | 10.6 | 2.7 | 7.9 | 8.2 | 0.4 |
| Gastrointestinal Disorders | | | | | | |
| Nausea | 34.8 | 37.6 | 2.8 | 0.0 | 1.2 | 1.2 |
| Vomiting | 22.5 | 21.2 | -1.3 | 1.1 | 2.4 | 1.2 |
| Diarrhea | 11.2 | 11.8 | 0.5 | 3.4 | 0.0 | -3.4 |
| General Disorders and Administration Site Conditions | | | | | | |
| Pyrexia | 24.7 | 31.8 | 7.1 | 1.1 | 4.7 | 3.6 |
| Injection Site Erythema | 0.0 | 25.9 | 25.9 | 0.0 | 2.4 | 2.4 |
| Injection Site Pain | 0.0 | 16.5 | 16.5 | 0.0 | 1.2 | 1.2 |
| Chills | 10.1 | 12.9 | 2.8 | 1.1 | 0.0 | -1.1 |
| Fatigue | 10.1 | 10.6 | 0.5 | 0.0 | 0.0 | 0.0 |
| Asthenia | 16.9 | 8.2 | -8.6 | 2.3 | 1.2 | -1.1 |
| Infections and Infestations | | | | | | |
| Upper respiratory tract infection | 12.4 | 12.9 | 0.6 | 1.1 | 0.0 | -1.1 |
| Respiratory, Thoracic and Mediastinal Disorders | | | | | | |
| Cough | 11.2 | 12.9 | 1.7 | 0.0 | 0.0 | 0.0 |
| Skin and Subcutaneous Tissue Disorders | | | | | | |
| Erythema | 6.7 | 15.3 | 8.6 | 0.0 | 0.0 | 0.0 |
| Rash | 10.1 | 11.8 | 1.7 | 1.1 | 0.0 | -1.1 |

Nonfatal Serious Adverse Events

Nonfatal SAE that occurred in greater than 3% on either arm are displayed in Table 26. The incidence of febrile neutropenia and pyrexia were higher in the rituximab SC while neutropenia and anemia were higher in the rituximab IV arm.

**Table 26 Nonfatal SAE CLL >3% on either arm (part 2 BO25341/SAWYER)**

| | Nonfatal SAE all grades (%) | | |
|---|---|---|---|
| | IV N=89 | SC N=85 | SC-IV |
| Febrile neutropenia | 4.5 | 10.6 | 6.1 |
| Neutropenia | 10.1 | 1.2 | -8.9 |
| Anemia | 3.4 | 0.0 | -3.4 |
| Pyrexia | 1.1 | 3.5 | 2.4 |

Laboratory Values

Pertinent laboratory values for the CLL trial, limited to worst grade per patient, are displayed in Table 27. Laboratory values with a greater than 5% difference was neutrophil count all grades and grades 3-4, ALT all grades, and creatinine all grades which were increased on the rituximab SC arm and hemoglobin grades 3-4, and platelets grades 3-4, and bilirubin all grades, which were increased on the rituximab IV arm.

**Table 27 Laboratory Values for CLL (part 2 BO25341/SAWYER)**

| | All grades (%) | | | Grades 3-4 (%) | | |
|---|---|---|---|---|---|---|
| | IV N=89 | SC N=85 | SC-IV | IV N=89 | SC N=85 | SC-IV |
| Neutrophil count | 50.6 | 60.0 | 9.4 | 37.1 | 42.4 | 5.3 |
| Hemoglobin | 46.1 | 41.2 | -4.9 | 7.9 | 1.2 | -6.7 |
| Platelets | 53.9 | 50.6 | -3.3 | 14.6 | 7.1 | -7.5 |
| ALT | 29.2 | 36.5 | 7.3 | 2.2 | 0.0 | -2.2 |
| AST | 23.6 | 28.2 | 4.6 | 2.2 | 1.2 | -1.0 |
| Alkaline phosphatase | 13.5 | 12.9 | -0.6 | 0.0 | 0.0 | 0.0 |
| Bilirubin | 33.7 | 25.9 | -7.8 | 2.2 | 2.4 | 0.2 |
| Creatinine | 7.9 | 16.5 | 8.6 | 1.1 | 0.0 | -1.1 |

## 6. Patient Preference

The PrefMab (MO28457) study was designed to evaluate patient preference (measured by using the Patient Preference Questionnaire [PPQ]) of subcutaneous (SC) administration of rituximab versus intravenous (IV) rituximab in previously untreated patients with CD20-positive diffuse large B-cell lymphoma or CD20-positive follicular non-Hodgkin lymphoma grades 1, 2, or 3a. This study also evaluated patient satisfaction as secondary endpoints using two patient-reported outcome (PRO) instruments, Cancer Therapy Satisfaction Questionnaire (CTSQ) and Rituximab

Administration Satisfaction Question (RASQ). Table 28 provides a brief overview of each patient assessment. Additional information regarding the study design can be found in Section 3.5.

**Table 28 Patient Assessments in the PrefMab Study**

| Patient Assessment | Brief Description |
|---|---|
| Patient Preference Questionnaire (PPQ) | The PPQ is a 3-item self-reported questionnaire developed by the Applicant to assess patients' preference for a route of treatment administration (SC vs. IV). The three PPQ questions are:<br>**Question 1**: All things considered which method of administration did you prefer? (IV/SC/No preference)—Primary endpoint<br>**Question 2**: If you have a preference for one of the administration routes, how strong is this preference? (Very strong/Fairly strong/Not very strong)<br>**Question 3**: If you have a preference for one of the administration routes, what are the two main reasons for your preference?<br>The response scale varies for each question. Question 1 is measured on a categorical scale. Question 2 is rated on a 3-point verbal rating scale, whereas Question 3 includes a checklist of responses for patients to select two responses. Respondents are asked to reflect on their experience with both methods of administration and preference. |
| Cancer Treatment Satisfaction Questionnaire (CTSQ) | The CTSQ is a 16-item PRO instrument designed to measure treatment satisfaction in individuals with cancer. The CTSQ is comprised of three domains related to patients' satisfaction with cancer therapy: expectations of therapy, feelings about side effects, and satisfaction with therapy. Each item is rated on a 5-point verbal rating scale and assessed with a recall period of 4 weeks. The CTSQ is scored on a 0-100 point scale, where a lower score indicates greater dissatisfaction with treatment, and a higher score indicates greater satisfaction with treatment. |
| Rituximab Administration Satisfaction Questionnaire (RASQ) | The RASQ is a 20-item PRO instrument designed to measure "treatment satisfaction" (covering subconcepts of "overall preference/satisfaction", "convenience", "confidence", and "bothersomeness") and "impact of treatment administration" (covering subconcepts of "physical impact", "psychological impact," "impact on activities of daily life," and "impact on the interaction with health care providers"). The Applicant utilized two similar versions of the RASQ for each method of administration (RASQ-IV and RASQ-SC) in the PrefMab study. Sixteen items were rated on a 5-point verbal rating scale, two items were rated on a 3-point verbal rating scale, and one Yes/No item. Each item was assessed with a recall period based on the recall of their most recent SC or IV administration. The RASQ is scored on a 0-100 point scale, where a lower score indicates greater dissatisfaction with treatment, and a higher score indicates greater satisfaction with treatment. |

The PrefMab intent-to-treat (ITT) population consisted of 743 patients (372 in Arm A and 371 in Arm B), and was defined as all patients randomized into the study. The modified intent-to-treat (mITT) population, consisting of 645 patients (323 in Arm A and 322 in Arm B), was defined as all patients randomized into the study, who received both routes of administration, and who completed the primary question in the PPQ at either Cycle 6 or Cycle 8.

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).

Preference Results (PPQ Assessment)

After Cycle 6, 495 of 620 patients (79.8%) preferred rituximab SC (Cl: 76.5%, 82.9%). After Cycle 8, 477 of 591 patients (80.7%) preferred rituximab SC (CI: 77.3%, 83.8%): 77.1% in Arm A and 84.2% in Arm B, and the most common reasons preferring subcutaneous administration were:

- Requires less time in the clinic (reported by 69% of patients),
- Feels more comfortable during administration (37%),
- Feels less emotionally distressing (29%), and
- Lower level of injection site pain (16%).

(Responses are not mutually exclusive –Percentages add up to >100% because patients were asked to provide two answers to this question.)

Satisfaction Results (CTSQ and RASQ Assessments)

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 below.

**Table 29 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) |

Results from the RASQ, also administered at cycles 4 and 8, favored rituximab SC in four out of five domains.

**Table 30 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) |

Comparison of the efficacy and safety of rituximab SC versus IV were secondary objectives and were not formally compared. Using descriptive methodologies, there were no significant differences in efficacy and safety in the untreated DLBCL and FL populations.

Limitations in the design of the trial and instruments used include (1) long recall period (subjects were asked to compare current method of administration to the method they last received four cycles prior), (2) difficulty in gauging satisfaction of SC versus IV rituximab administration while subjects were receiving multi-agent IV chemotherapy simultaneously, and (3) lack of validation methods built into the trial to ensure that subjects adequately understood the instruments.

For the PPQ, these limitations may be mitigated by (1) the brevity of the preference questionnaire (three straightforward, face-valid questions) (2) language translation validation techniques, and (3) consistent preference results between cycle 6 and 8.

The satisfaction questionnaires (RASQ and CTSQ), specifically the development of these instruments, timing of the satisfaction instruments, and conflicting results between RASQ and CTSQ, limit the interpretability for patients and practitioners.

Although comparison of safety and efficacy between IV versus SC rituximab was not formally tested, there were no significant differences.

## 7. Conclusion

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.

FDA verified that rituximab SC achieved equal or higher $C_{trough}$ relative to rituximab IV in patients with FL, DLBCL, and CLL. The addition of hyaluronidase increased the absorption rate of rituximab. The fixed-dosing strategy lead to reasonably consistent $C_{trough}$ across all BSA sizes relative to BSA-based dosing of rituximab IV.

Although the clinical trials were not designed for efficacy hypothesis testing, the efficacy results between rituximab SC and rituximab IV are comparable.

There were no major differences in safety findings between rituximab SC and rituximab IV, with the exception of increase in administration site-related local reactions with rituximab SC. In addition, exposure-response analyses for safety did not show significant relationships between $C_{trough}$ and any of the safety endpoints evaluated.

Finally, results based on the PPQ instrument from the PrefMab clinical trial, demonstrate that 80% of the patients preferred rituximab SC over rituximab IV.

FDA requested discussion at ODAC 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).

## 8. REFERENCES

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