Genentech, Inc.

Rituximab SC (rituximab/hyaluronidase)
BLA 761064

ADVISORY COMMITTEE BRIEFING MATERIALS
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LIST OF ABBREVIATIONS

AE	Adverse event
ARR	Administration-related reaction
AUC	Area under the curve
BLA	Biologics License Application
BOR	Best overall response
BSA	Body surface area
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
C_{max}	Maximum serum concentration
CR	Complete response
CRi	Complete response with incomplete bone marrow recovery
CRR	Complete response rate
CRu	Unconfirmed complete response
CR30	Complete response rate at 30 months
C_{trough}	Minimum serum concentration before next dose or minimum serum concentration within a dosing interval
CTSQ	Cancer Treatment Satisfaction Questionnaire
DFS	Disease-free survival
DLBCL	Diffuse large B-cell lymphoma
EFS	Event-free survival
EFS24	Event-free survival rate at 24 months after diagnosis
EU	European Union
FL	Follicular lymphoma
FLIPI	Follicular lymphoma international prognostic index
GMR	Geometric mean ratio
HCP	Healthcare professional
HR	Hazard ratio
IND	Investigational New Drug
IPI	International prognostic index
IRC	Independent review committee
ITT	Intent-to-treat
IV	Intravenous
iwCLL	International Workshop on CLL
LDH	Lactate dehydrogenase
mAb	Monoclonal antibody
NCA	Non-compartmental analysis
NHL	Non-Hodgkin's lymphoma
ODAC	Oncologic Drugs Advisory Committee
ORR	Overall response rate
OS	Overall survival
PD	Pharmacodynamics
PFS	Progression-free survival
PFS24	Progression-free survival rate at 24 months after diagnosis
PK	Pharmacokinetics
PPQ	Patient Preference Questionnaire
PR	Partial response
PRO	Patient-reported outcome
q1w	Every 1 week
q2m	Every 2 months
q3m	Every 3 months

q3w	Every 3 weeks
q4w	Every 4 weeks
RASQ	Rituximab Administration Satisfaction Questionnaire
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone
R-CVP	Rituximab, cyclophosphamide, vincristine, and prednisolone
R-FC	Rituximab, fludarabine, and cyclophosphamide
rHuPH20	Recombinant human hyaluronidase
RND	Randomized patient population
SAE	Serious adverse event
SC	Subcutaneous
SOC	System organ class
U	Units
US	United States
USPI	United States Prescribing Information

1. EXECUTIVE SUMMARY

Overview

Rituximab (referred throughout this document as **RITUXAN®** or **rituximab IV**) is a monoclonal antibody designed to target and eliminate CD20-expressing B-cells. It was the first anti-cancer therapeutic antibody ever approved and has transformed outcomes for patients suffering from a variety of B-cell blood cancers, including certain types of non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL). However, associated with long-term survival benefit from rituximab is the burden of receiving multiple rounds of treatment over the course of many years. In the United States, rituximab is only available as an intravenous (IV) infusion. Treatment is delivered in a series of time-consuming administrations that range from 1.5 to 4 hours each and can create significant burden for patients, caregivers and healthcare providers.

A faster and more convenient rituximab delivery method could offer meaningful benefits for patients who may receive treatment for many years as well as healthcare providers who treat many patients daily. Therefore, a new formulation of rituximab was developed for subcutaneous (SC) injection that can be administered in minutes instead of hours. Rituximab subcutaneous (referred throughout this document as **rituximab SC**) has been marketed in the European Union (EU) under the brand name MabThera® (solution for SC injection) or MabThera since 2014 and is approved in approximately 50 other countries worldwide.

This new formulation was evaluated in a clinical development program comprised of five randomized, controlled clinical trials across a variety of B-cell cancers. The studies evaluated how changing the medicine's delivery impacted its levels in the blood (pharmacokinetics, PK), efficacy and safety of rituximab SC, as well as patient-reported outcomes and healthcare provider opinions. No new safety signals related to this new administration method were observed in these clinical trials or reported during real-world experience in over 34,000 people treated with rituximab SC in countries where it is approved.

Because the monoclonal antibody in rituximab SC and RITUXAN is identical, it was possible to design clinical studies that linked the safety and efficacy profile of rituximab SC to the well-established profile of RITUXAN, which is based on extensive clinical trial evidence as well as 20 years of clinical practice treating more than 4.4 million people with blood cancers. Collectively, the findings presented in this document represent a substantial body of evidence supporting the approval of this new administration method across the full range of blood cancer indications currently approved for RITUXAN.

Rituximab Subcutaneous

Rituximab SC was developed as a ready-to-use, fixed-dose formulation provided in single-dose vials that does not require dose calculation or dilution. It was designed to simplify the administration of rituximab and could reduce the burden to patients and healthcare systems compared to rituximab IV. Rituximab SC consists of the identical

monoclonal antibody as RITUXAN and was formulated with recombinant human hyaluronidase (rHuPH20). The rHuPH20 component facilitates the delivery of a relatively large volume of medicine, making the subcutaneous (under the skin) route of rituximab administration feasible.

History of Rituxan

Improved survival rates for a variety of B-cell blood cancers coincided with the introduction of RITUXAN, which has been widely recognized as improving the natural history of these diseases. RITUXAN continues to be a standard of care for the treatment of people with B-cell blood cancers (NCCN Guidelines), and was recently classified as an essential medicine by the World Health Organization.

Since initial approval by the U.S. Food and Drug Administration (FDA) in November 1997, RITUXAN has been approved across a wide range of indications, including follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL) and CLL. It has a well-established safety and efficacy profile, which is based on extensive clinical trial evidence (including eight randomized, Phase III studies across multiple indications) as well as 20 years of clinical practice.

Challenges of Intravenous Administration

RITUXAN is administered as an IV infusion that requires precise dose calculation based on patient body surface area (BSA) as well as dilution in an infusion bag. Treatment with RITUXAN requires the insertion of a small tube into a vein (venous catheter) and takes place at a clinical infusion center. The infusions themselves routinely take between 1.5 and 4 hours, not counting the additional time needed for preparation prior to administration and observation after the infusion is complete. Like other infusions, the time commitment and psychological impact of multiple infusions can result in a significant burden to patients.

Rituximab SC was specifically designed to address the challenges associated with IV administration. Most importantly, this new administration method is quick and efficient (requiring only 5-7 minutes), which dramatically reduces the time currently required for IV administration. The benefit would likely be substantial for patients in the United States who may receive treatment for many years and for healthcare providers who treat many patients daily. Rituximab SC is not intended to replace RITUXAN, but rather to provide an alternative option for patients and their physicians.

Co-Formulation of Rituximab and rHuPH20

Rituximab SC is a co-formulation of two extensively studied molecules, and is considered as a single biological product by the FDA. It consists of the identical monoclonal antibody from RITUXAN (rituximab) with rHuPH20. The rHuPH20 component is a necessary part of this co-formulation because of the relatively large volume of rituximab required for SC injection (10-15 mL) compared to the typical 1-2 mL volumes associated with other SC injections. The protein biochemistry of rituximab limits

further concentration, making it impossible to achieve therapeutic doses of rituximab SC with typical SC injection volumes.

rHuPH20 acts locally to depolymerize hyaluronan, a gel-like substance found in the subcutaneous layer of the skin. This results in decreased resistance to fluid flow and increased dispersion and absorption of injected medicines and fluids, allowing for a larger volume to be injected with limited swelling or pain. rHuPH20 is transiently acting, not systemically absorbed, has no long-term local effects, and has no impact on the safety or effectiveness of rituximab. rHuPH20 has a half-life in skin of less than 30 minutes. Hyaluronan levels in subcutaneous tissue return to normal within 24 to 48 hours because of the rapid biosynthesis of hyaluronan.

Animal-derived hyaluronidase has been used for decades to aid in drug delivery. rHuPH20 is the human recombinant form and is available as a standalone FDA-approved drug, Hylenex® recombinant (hyaluronidase human injection). Since 2005, HYLENEX has been administered to over 1.3 million patients.

Rituximab SC Development Program

The clinical development program for rituximab SC had three key areas of focus:

1) Robust pharmacokinetics to demonstrate non-inferior exposure of rituximab,
2) Confirm efficacy and safety is consistent between the two routes of administration,
3) Evaluation of patient and healthcare provider preference and satisfaction for the SC route of administration.

The extensive development program consisted of five randomized, controlled clinical trials (SparkThera, SABRINA, SAWYER, MabEase, PrefMab) designed to support the full range of oncology indications included in the RITUXAN label. The studies included more than 1500 patients with FL, DLBCL, or CLL treated with rituximab SC in combination with chemotherapy and/or as a single agent.

A PK approach was used to select and confirm fixed doses of rituximab SC corresponding to each of the approved RITUXAN doses. It was critical to achieve rituximab levels in the blood at least as high with rituximab SC as those achieved with rituximab IV, given the well-established safety and efficacy profile of rituximab IV for the serious and life-threatening diseases it is approved to treat. Therefore, the PK-based clinical studies focused on showing non-inferiority of rituximab SC exposure to that of rituximab IV.

This robust global clinical development program in B-cell blood cancers also evaluated the safety and efficacy of the SC route of administration, as well as healthcare provider opinions and patient preference in a large patient-reported outcomes trial.

Dose Finding and Confirmation

The PK-based clinical bridging approach used in this development program was possible because the monoclonal antibody in rituximab SC and IV is identical and because the PK and pharmacodynamics (PD) of RITUXAN are well understood. The approach was based on decades of scientific knowledge on rituximab's mechanism of action, particularly the binding and occupancy on the surface of target B-cells required for its anti-B-cell action (i.e., depletion of B-cells). Based on these scientific considerations, achieving non-inferior rituximab exposure would lead to comparable saturation of the target sites (i.e., binding to nearly all of the CD20-expressing B-cells), resulting in analogous efficacy. Importantly, the rituximab exposure would have to be non-inferior even at its lowest or trough level. Therefore, the primary endpoint for non-inferior exposure was the lowest concentration of medicine in the blood between doses (C_{trough}). The more conventional endpoint for evaluating exposure, area under the curve (AUC), was also evaluated as a key secondary endpoint.

The guiding principle for the use of these endpoints was that rituximab exposures at least as high (statistically non-inferior) as those achieved with approved rituximab IV doses would result in at least the same degree of target saturation and therefore the same anti-B-cell activity, independent of the route of administration. The standard regulatory lower bound of the 90% confidence interval (i.e., 0.8) for the ratio of geometric mean exposures for SC relative to IV was used to confirm non-inferiority of exposure. In addition, clinical efficacy and safety data were collected as further evidence that the overall benefit/risk is consistent between the SC and IV routes of administration.

Three controlled, randomized studies cumulatively established the consistency of PK and PD for rituximab via the SC and IV routes of administration. SparkThera, SABRINA, and SAWYER demonstrated statistically non-inferior exposure (C_{trough}) with rituximab SC 1400 mg and 1600 mg doses compared to the established 375 mg/m^2 and 500 mg/m^2 doses approved for RITUXAN in the treatment of NHL and CLL, respectively. The exposures were also non-inferior at the different dose schedules established for the various indications (FL induction and maintenance, DLBCL, and CLL). Higher overall doses were needed for rituximab SC to compensate for reduced bioavailability (approximately 65% compared with rituximab IV). This is consistent with the expected bioavailability for other monoclonal antibodies administered via SC route of administration (Richter 2012). The results from the key secondary endpoint, AUC, also showed comparable exposure for rituximab SC relative to rituximab IV. PD results support the PK findings and confirm that rituximab SC achieves similar and consistent durable B-cell depletion as well as recovery following completion of rituximab treatment in both NHL and CLL patients compared with rituximab IV.

Assessment of Efficacy of Rituximab SC

In addition to the PK results, data from three controlled randomized studies (SABRINA [FL], MabEase [DLBCL], SAWYER [CLL]) demonstrated consistent efficacy of rituximab SC and rituximab IV across all pre-specified primary and secondary endpoints, as measured by response rates and time-to-event endpoints including progression-free survival (PFS) and overall survival (OS).

The three studies showed no evidence of a clinically meaningful difference in PFS between the treatment groups. Findings from PFS sensitivity analyses in both studies, as well as the consistency of results across all time-to-event endpoints, support the robustness of the primary PFS analysis.

Based on subgroup analyses, there was no impact of fixed dosing on clinical benefit in patients with a relatively higher BSA who were treated with rituximab SC, as measured by overall response rates and PFS compared with patients treated on a BSA-adjusted basis with RITUXAN.

The entirety of the data shows comparable short and long-term efficacy for rituximab SC and rituximab IV, across diseases (FL, DLBCL, CLL). Efficacy of rituximab SC was not only consistent with rituximab IV in these studies, but also consistent with the performance of rituximab IV in earlier studies that established its effectiveness in B-cell blood cancers.

Assessment of Safety of Rituximab SC

The overall safety evaluation of rituximab SC is based on 1579 patients who received at least one injection of rituximab SC at any dose across the five studies. Overall, the safety profile of rituximab SC is considered acceptable, manageable, and consistent with that of RITUXAN.

There were no unexpected toxicities and the overall safety of rituximab SC was similar to RITUXAN, despite the fact that patients treated with rituximab SC received a higher median cumulative dose of rituximab compared to those treated with RITUXAN.

The most common adverse events with rituximab SC and RITUXAN across the clinical studies were in line with the established safety profile for RITUXAN. Events that occurred with a higher incidence in the SC arm compared with the IV arm were reflective of the change in the route of administration and included mostly mild to moderate administration-related reactions and local cutaneous reactions.

Some numerical differences between treatment groups in severe or serious AEs were apparent in the NHL combination chemotherapy analysis population, with higher incidence in the rituximab SC arm, while the overall safety profile in the rituximab monotherapy clinical setting and in the CLL setting was well balanced between the

treatment groups. These differences did not result in an increased rate of discontinuations or deaths due to adverse events.

Patients with low BSA, who experience a relatively higher exposure to rituximab with fixed dosing, appeared to have a higher incidence of severe or serious adverse reactions (neutropenia and febrile neutropenia) compared with patients treated on a BSA-adjusted basis in the combination chemotherapy setting. However, there was no apparent clinical impact of the higher incidence of these events in the SC arm, and the safety profile of rituximab SC in low BSA patients is considered acceptable and manageable. Neutropenia and infections are well-known risks and were well managed in the combination therapy clinical setting with no overall impact on the benefit/risk profile of rituximab SC. There were no noticeable differences in severe or serious adverse reactions by BSA subgroups in the monotherapy clinical setting.

Immunogenicity was extensively monitored, and the potential of rituximab SC to induce an immune response appears to be low and consistent with that observed in patients receiving rituximab IV. There was no suggestion of clinical consequences (worsening of efficacy or safety profile) in patients who developed anti-rituximab antibodies. The incidence of anti-rHuPH20 antibodies was in the range seen following rHuPH20 exposure in other trials (Rosengren 2015), and no neutralizing antibodies were observed.

Since 2014, rituximab SC has been approved in the EU and 50 additional countries worldwide, and ongoing post-marketing experience based on over 34,000 patients has been consistent with the safety profile from the clinical program. No new safety signals have been detected.

Overall, the comprehensive safety database of over 1500 patients with different diseases diseases (FL, DLBCL, CLL) treated with rituximab SC across the five clinical studies, as well as over 34,000 patients treated in the post-marketing setting globally, demonstrates that rituximab SC has a safety profile consistent with that of RITUXAN in the treatment of B-cell blood cancers.

Patient-Reported Outcomes and Healthcare Professional Opinions

An important component of the clinical program was to evaluate the impact of this new route of administration on patient-reported and healthcare professional-reported measures. Patient-reported outcome endpoints were evaluated in PrefMab (FL/DLBCL) and MabEase (DLBCL), and healthcare professional opinions were examined in SABRINA (NHL) and SAWYER (CLL).

In the dedicated patient preference study, PrefMab, patients overwhelmingly preferred rituximab SC over rituximab IV because of less time in the clinic, greater comfort during administration, less emotional distress while receiving treatment, and lower levels of injection site pain. Furthermore, doctors and nurses consistently responded that rituximab SC was more convenient than rituximab IV and could lead to time-savings

when used in routine clinical practice. This is particularly important for community oncologists and nurses and could potentially relieve strain on infusion centers.

Benefit/Risk

A robust clinical development program that included five studies with more than 1,500 patients demonstrated PK non-inferiority, consistent clinical efficacy and safety outcomes, and patient preference for rituximab SC versus rituximab IV. Additionally, experience from over 34,000 patients treated with rituximab SC in the real-world setting to date provides further evidence of safety and shows no meaningful differences compared to the known safety profile of RITUXAN established over the course of 20 years of clinical practice. Rituximab SC is an important option that should be available to patients in the United States. The entirety of the data demonstrates positive benefit/risk and supports full approval of the rituximab SC for the full range of oncology indications that are currently approved for RITUXAN.

2. INTRODUCTION

On March 29, 2017, the Oncologic Drugs Advisory Committee (ODAC) is being convened to provide their recommendations to the FDA on the application for rituximab subcutaneous (SC), a new co-formulation of the established monoclonal antibody rituximab (RITUXAN) used in the treatment of hematologic malignancies and a recombinant human hyaluronidase used as a permeation enhancer.

As described in this document, rituximab SC was developed as an option to simplify and shorten administration relative to RITUXAN, which is administered by intravenous (IV) infusion, thereby reducing the treatment burden for patients. At the same time, it was anticipated that faster, easier administration of rituximab will potentially relieve strain on infusion centers and ultimately allow more patients access. Rituximab SC is a ready-to-use, fixed-dose co-formulation provided in a single-dose vial, not requiring dose calculation or dilution. The administration time is reduced from hours to around 5-7 minutes.

The formulation was optimized for SC injection by co-formulating rituximab with recombinant human hyaluronidase (rHuPH20), an FDA-approved enzyme that transiently depolymerizes hyaluronan at the injection site, increasing the volume that can be administered via the SC route and facilitating drug delivery into the systemic circulation (permeation enhancer).

Based on its mechanism of action and available data, the enzyme rHuPH20 facilitates dispersion and absorption of the antibody rituximab in the co-formulation but has no other role or activity beyond permeation enhancement.

Development of rituximab SC was founded on the knowledge and experience established with RITUXAN over the course of 20 years of clinical practice since first approval in 1997. Rituximab SC was developed using a pharmacokinetics (PK)-based

clinical bridging approach with the underlying scientific consideration that achieving serum rituximab exposures at least as high as those achieved with approved RITUXAN doses would result in the same degree of target saturation and therefore consistent efficacy, independent of the route of administration. Once the doses were established for rituximab SC, data on clinical safety and effectiveness were generated to demonstrate consistency between rituximab SC and RITUXAN.

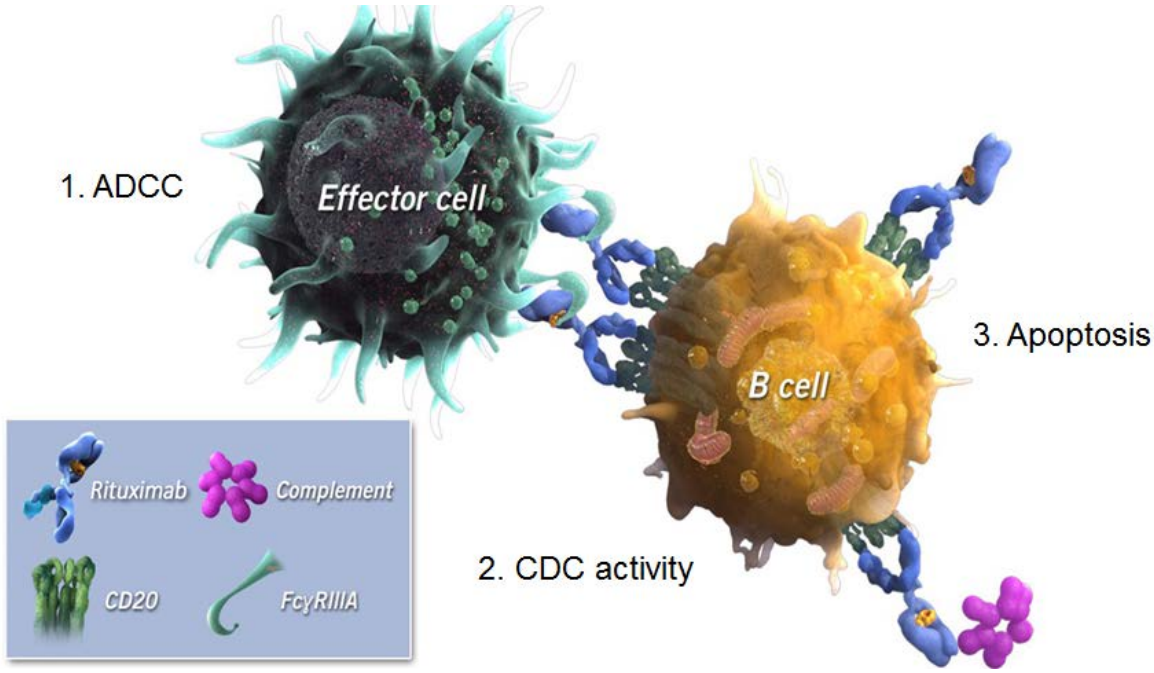
This briefing book outlines the approach used by the Sponsor (Roche/Genentech) to develop rituximab SC by applying PK-based clinical bridging to first demonstrate statistically non-inferior PK exposure levels of the same rituximab antibody at the clinically established doses and schedules approved with RITUXAN, and subsequently gather evidence of consistent efficacy and safety between the SC and IV routes of administration. This document also summarizes the data gathered from over 1500 patients with various B-cell malignancies treated with rituximab SC across five randomzied, controlled clinical studies in the development program. The entirety of the data presented in the BLA supports approval of the co-formulation of this life-saving drug for the treatment of B-cell malignancies. The SC route offers an important option and should be available for patients in the United States.

2.1 OVERVIEW OF RITUXAN AND RATIONALE FOR DEVELOPMENT OF RITUXIMAB SC

Rituximab is a chimeric murine/human monoclonal antibody (mAb) that binds to cluster of differentiation 20 (CD20) protein, a hydrophobic transmembrane protein on the cell surface of pre-B- and mature B-lymphocytes. In particular, CD20 is present on the malignant B-lymphocytes in the majority of patients with mature B-cell lymphomas and leukemias. The binding and occupancy of rituximab to its target, CD20, on B-lymphocytes eliminates these cells via a number of different possible mechanisms, including antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and induction of apoptosis (Reff 1994; Shan 2000; Cartron 2004) (Figure 1). The mechanism of action of rituximab has been extensively studied and is well understood.

The PK of rituximab following IV administration have been well characterized and support that the target sites of CD20 on malignant B-cells are saturated at steady state at the exposures attained following administration of the approved dosing regimens (see Section 3.1.1 for a discussion). Establishing the SC route of administration for rituximab is based on the scientific consideration, described above, that achieving a non-inferior rituximab exposure would lead to comparable saturation of the target sites resulting in analogous efficacy.

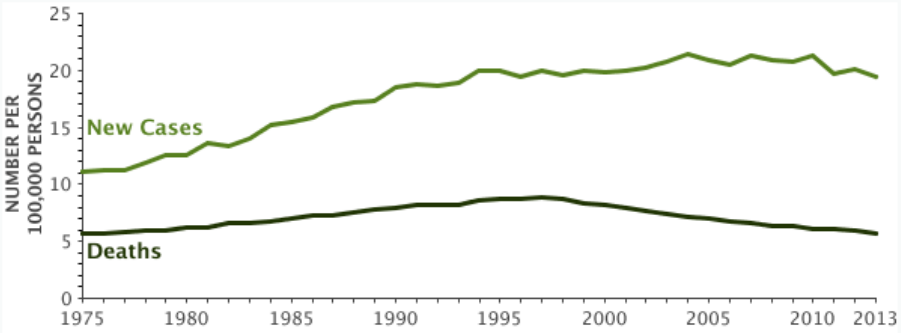
Figure 1 Mechanism of Action of Rituximab



Adapted from Mössner 2010.

RITUXAN (rituximab IV) is the standard of care for the majority of B-cell malignancies (e.g., follicular lymphoma [FL] and diffuse large B-cell lymphoma [DLBCL], the most common subtypes of non-Hodgkin lymphoma [NHL]; and chronic lymphocytic leukemia [CLL]) (NCCN Guidelines) and was classified as an essential medicine by the World Health Organization in 2015. Since approval in 1997, rituximab (RITUXAN/MabThera) has been used in 4.4 million patients. Rituximab has changed the natural history of these hematologic malignancies. Whether administered as a single agent or in combination with chemotherapy, rituximab IV has been shown to prolong progression-free survival (PFS), and in some indications overall survival (OS), in patients suffering from various B-cell malignancies (Dreyling 2014; Tilly 2015; Eichhorst 2015). A downward trend in mortality rates from the mid-1990s coincided with the introduction of rituximab IV in clinical practice (Fisher 2005; Sehn 2005; Molina 2008; Keating 2010; Vidal 2011) (Figure 2).

Figure 2 Non-Hodgkin's Lymphoma: New Cases, Deaths and 5-Year Relative Survival



Year	1975	1980	1985	1990	1995	2000	2004	2008
5-Year Relative Survival	45.8%	49.1%	52.4%	49.7%	51.9%	63.8%	70.1%	72.5%

SEER 9 Incidence & U.S. Mortality 1975-2013, All Races, Both Sexes. Rates are Age-Adjusted.
Source: https://seer.cancer.gov/statfacts/html/nhl.html (last accessed, February 01, 2017).

Rituximab has a well-established safety profile from extensive experience in clinical trials and the post-marketing setting. The main risks associated with rituximab treatment of NHL and CLL are related to the biologic nature of the drug and to its B-cell-depleting mechanism of action. The most important identified risks described for rituximab IV include infusion-related reactions (IRRs), neutropenia, and infections.

Establishing SC delivery of rituximab was expected to simplify and shorten its administration relative to IV infusion, thereby reducing the treatment burden for patients. At the same time, it was anticipated that faster, easier administration of rituximab will potentially relieve strain on infusion centers and ultimately allow more patients access to this life-saving drug. Rituximab SC is a ready-to-use, fixed-dose co-formulation provided in single-dose vials, not requiring dose calculation or dilution. The administration time is reduced from several hours to around 5-7 minutes.

2.2 RITUXIMAB SC PRODUCT DEVELOPMENT

The new formulation was optimized for SC injection by co-formulating the same rituximab antibody as found in RITUXAN with the permeation enhancer rHuPH20. Fixed (flat) dosing was introduced to simplify drug preparation and administration and to reduce the potential risk of dosing errors. These aspects are discussed in further detail below.

2.2.1 Rituximab SC Formulation Development

The rituximab antibody in the SC formulation is identical to the anti-CD20 monoclonal antibody as found in the marketed RITUXAN formulation, concentrate for IV infusion

containing 10 mg/mL rituximab. The relatively large volume of solution required to deliver therapeutic doses of rituximab using the existing formulation (e.g., ~70 mL for a 70-kg NHL patient, without factoring for reduced bioavailability via SC dosing [Richter 2012]) precluded use of the concentrate for SC injections. To deliver therapeutic doses with an acceptable SC-injectable volume of 1-2 mL would require rituximab concentrations of more than 350 mg/mL, a protein concentration which would be challenging with regards to manufacturability due to the very high viscosity. To support development of rituximab for SC administration, the concentration of rituximab was increased 12-fold (120 mg/mL). The volumes projected for SC injection of therapeutic doses with this concentrated formulation still exceeded feasible SC-injectable volumes and required addition of rHuPH20 (recombinant human hyaluronidase), an established permeation enhancer to the formulation to facilitate administration of SC injection volumes of 10-15 mL (see Section 2.2.2 for a description of the enzyme).

The manufacturing processes for rituximab SC and rituximab IV drug substances are identical with the exception of the last formulation step, which enables a higher concentration of rituximab to be reached in the SC product. The manufacturing process for rituximab SC drug product includes the addition of rHuPH20 to the rituximab SC drug substance. The finished drug product contains rituximab at a concentration of 120 mg/mL and rHuPH20 at a concentration of 2000 U/mL (approx. 17-18 μg/mL, corresponding to 0.23-0.27 mg protein per single-dose vial). rHuPH20 comprises only 0.02% of the total protein content in rituximab SC. No interaction between rituximab and rHuPH20 in the rituximab SC drug product was identified. Extensive side-by-side stability studies of rituximab with and without rHuPH20, stored under normal and stress conditions, did not reveal any detrimental interaction between rituximab and rHuPH20. It was concluded that combination of rHuPH20 and rituximab has no impact on the quality of either molecule.

2.2.2 rHuPH20 – Permeation Enhancer

Injectable hyaluronidase products have been in clinical use in the United States for over 60 years and are used to increase the tissue dispersion and absorption of other injected drugs (Bookbinder 2006; Frost 2007). Historically, the most common use of hyaluronidase has been in ophthalmology in conjunction with ocular surgery to increase the dispersion and absorption of local regional anesthetics (Frost 2007). Early forms of hyaluronidase were derived from extracts of bovine and ovine testes. In contrast to the animal-derived hyaluronidases, rHuPH20 is a highly purified recombinant human protein (Bookbinder 2006) and has lower potential for immunogenicity.

rHuPH20 depolymerizes the gel-like hyaluronan, resulting in a decreased resistance to fluid flow and a transient increase in permeability of the local subcutaneous tissue (Bookbinder 2006). This allows for co-administered monoclonal antibodies to disperse through the subcutaneous tissue matrix and results in more of the antibody reaching the systemic circulation, compared to SC administration without rHuPH20 (Shpilberg and

Jackisch 2013; Bittner 2014). It facilitates increased flow rates and increased delivery volumes compared with SC administration without rHuPH20 (Bookbinder 2006; Haller 2007).

rHuPH20 increases the SC dispersion and absorption of rituximab (Bittner 2014); see Appendix 2 for a description of results from nonclinical studies. The effects of rHuPH20 on the SC injection site are transient (half-life in skin of < 30 minutes) and reversible. Hyaluronan is rapidly restored by resynthesis in the subcutaneous tissue within 24 to 48 hours after hyaluronidase treatment (Morrow 2011). Similar to previous clinical experience with the mAb trastuzumab (Herceptin; Wynne 2013), there is no evidence of rHuPH20 systemic exposure at the doses used with rituximab SC (see Section 5.3).

rHuPH20 was established as safe and effective in enhancing dispersion and absorption of fluids and drugs administered subcutaneously and was approved by the FDA in December 2005 as Hylenex® recombinant (hyaluronidase human injection). Since approval, the estimated cumulative patient exposure to HYLENEX is over 1.3 million (based on vials sold; data on file at Halozyme Therapeutics Inc.).

Subcutaneous injections of rHuPH20 alone or in combination with hydration fluids (lactated Ringer's and normal saline) and co-injected drugs and biological products (ceftriaxone, morphine, insulin and insulin analogs, immunoglobulin G [IgG], and adalimumab) were generally well tolerated in all clinical study populations, including healthy subjects, dehydrated pediatric subjects, hospice and palliative care subjects, subjects with type 1 and 2 diabetes mellitus, and subjects with rheumatoid arthritis.

Most adverse events (AEs) were mild, transient injection site reactions (erythema, pain, bruising, pruritus, burning, tenderness, edema, induration, irritation, paresthesia, numbness, and rash), and have been reported in less than 0.1% of patients receiving hyaluronidase (HYLENEX USPI).

Moderate injection site reactions, which have occurred less frequently, include burning, erythema, pain, and numbness. Mild to moderate headache was also commonly reported. Adverse events have otherwise generally reflected the adverse reaction profiles of the co-administered drug or have been associated with the rapid introduction of a relatively large volume of fluid into the SC space. Volumes up to 1000 mL of lactated ringers solution was infused following subcutaneous administration of HYLENEX.

Furthermore, repeat administration of rHuPH20 has been used safely in the clinic in combination with other therapeutic agents, such as insulin for diabetes mellitus (up to 21 times per week for 12 weeks), human immunoglobulin for primary immunodeficiency (up to 600 mL volumes every 3-4 weeks for 3 years), and trastuzumab for breast cancer (5 mL every 3 weeks for 1 year), and has been well tolerated (Rosengren 2015; Wasserman 2016).

2.2.3 Fixed (Flat) Dosing

An additional consideration for the development of SC dosing of rituximab was the shift from body surface area (BSA) dosing with rituximab IV to a fixed-dose product. A fixed dosing approach was desirable to facilitate drug preparation without the need to calculate the dose, per patient, thus lowering the potential risk of dosing errors as compared with BSA-adjusted dosing. The use of body-size-adjusted dosing in oncology is largely historical and a product of many years of experience with chemotherapeutic agents that have, by virtue of their mode of action, a narrow therapeutic window. BSA dosing with rituximab was based on this historical concept, as it was the first mAb established as an anti-cancer therapeutic agent. For mAbs that have a wide therapeutic window, such as rituximab, it is possible to adopt a different approach to treat oncology patients (Bai 2012). There are several examples since the development of RITUXAN more than 20 years ago where monoclonal antibodies have been developed using a fixed dosing approach, such as obinutuzumab (Gazyva) for the treatment of B-cell malignancies, pertuzumab (Perjeta) for breast cancer, atezolizumab (Tecentriq) for urethral carcinoma, an nivolumab (Opdivo) for non-small cell lung cancer.

The rationale to employ fixed dosing for rituximab SC was initially supported by a published simulation study comparing the performance of body size-based and fixed dosing in reducing PK and/or pharmacodynamic (PD) variability in adults for 12 unique mAbs, including rituximab (Wang 2009). Overall, PK variability did not differ remarkably between the fixed and body size-based dosing approaches across the 12 antibodies studied, including RITUXAN, supporting the approach of fixed dosing for rituximab SC. These findings were subsequently confirmed by results from the three PK-based clinical bridging studies with rituximab SC which demonstrated comparable variability in exposure with rituximab SC flat dosing and rituximab IV BSA-adjusted dosing (Section 5.1.3).

In moving from a BSA-adjusted dosing scheme to a fixed dosing approach, the distribution of drug exposure in the patient population may potentially change, with expected lower exposure in high BSA patients and higher exposure in low BSA patients. Therefore, the selected fixed dose of rituximab SC needed to be high enough to ensure sufficient drug exposure over the entire BSA range to ensure clinical benefit in patients with high BSA, while maintaining an acceptable safety profile in patients with low BSA. Rituximab is considered to have a wide therapeutic window with several dose escalation studies demonstrating no acute dose limiting toxicities up to doses of 2250 mg/m^2 (approximating 4320 mg for a cancer patient with BSA of 1.92 m^2; Maloney 1994; Coiffier 1998; Keating and O'Brien 2000; O'Brien 2001). Based on this, it was considered unlikely that any differences in exposure expected after fixed dosing of rituximab SC compared with BSA-adjusted rituximab IV administration would result in a greater risk of adverse reactions.

The clinical program was thus designed to ensure adequate rituximab exposure was achieved with the SC doses selected and that these doses were well tolerated and effective across the BSA entire range.

2.3 TARGET INDICATIONS

Rituximab SC was developed for the treatment of the same B-cell malignancies as indicated for RITUXAN. The proposed indication language for rituximab SC is as follows and is exactly the same as the approved RITUXAN oncology indications:

TRADENAME™ (rituximab/hyaluronidase) for subcutaneous injection is a co-formulation of rituximab (a CD20-directed cytolytic antibody) and recombinant human hyaluronidase (rHuPH20), indicated for the treatment of patients with:

- **Follicular Lymphoma (FL)**
  - Relapsed or refractory, follicular lymphoma as a single agent.
  - Previously untreated follicular lymphoma 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), follicular lymphoma as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy.
- **Diffuse Large B-cell Lymphoma (DLBCL)**
  - Previously untreated diffuse large B-cell lymphoma in combination with cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) or other anthracycline-based chemotherapy regimens.
- **Chronic Lymphocytic Leukemia (CLL)**
  - previously untreated and previously treated CLL, in combination with fludarabine and cyclophosphamide (FC).

2.4 DOSAGE & ROUTE OF ADMINISTRATION

The proposed dosage and administration for rituximab SC is:

- NHL (FL/DLBCL): *TRADENAME*™ 1400 mg rituximab and 2000 U/mL hyaluronidase (11.7 mL solution in a single-dose vial) for subcutaneous injection
- CLL: *TRADENAME*™ 1600 mg rituximab and 2000 U/mL hyaluronidase (13.4 mL solution in a single-dose vial) for subcutaneous injection

Based on extensive experience with rituximab, the highest risk of experiencing an infusion-related reaction is generally observed at Cycle 1 with the first exposure to rituximab. Most of these reactions are successfully managed by slowing or temporarily stopping the infusion, which would not be possible if the first administration of rituximab was delivered as a subcutaneous injection. Therefore, for patient safety, the proposed dosing is to administer rituximab IV at Cycle 1 to manage these reactions, and to administer rituximab SC at subsequent cycles. All of the clinical studies within the

rituximab SC program were conducted with the first dose of rituximab given intravenously for this reason. This also underlines another reason why rituximab SC is considered an option, and not intended to replace RITUXAN, as the first dose of the rituximab schedule is given in IV.

The proposed labeling information pertaining to dosing contains the following recommendations:

> All patients must receive at least one full dose of intravenous RITUXAN before starting treatment with *TRADENAME*™ for subcutaneous injection due to the higher risk of infusion-related reactions during the first infusion. *TRADENAME*™ for subcutaneous injection should only be used in subsequent treatment cycles.

2.5 REGULATORY HISTORY

Rituximab 1400 mg solution for SC injection was first approved in the EU on 21 March 2014 for the treatment of patients with NHL and has since been approved in approximately 50 other countries. Recently, in May 2016, rituximab 1600 mg for SC injection gained its first approval in the EU for patients with CLL.

Roche/Genentech has received feedback from FDA regarding the filing of the BLA for rituximab SC. The regulatory pathway was clarified in June 2015 when the FDA Office of Combination Products determined that rituximab SC is considered a single biological entity (Public Health Service Act under section 351(i)).

A Type B pre-Investigational New Drug (IND)/pre-BLA meeting was held with FDA in September 2015. The FDA recognized the potential benefit of the availability of a SC rituximab formulation and advised that PK bridging data would need to be supplemented with clinical data to support a BLA submission. The Agency provided guidance on additional clinical pharmacology and clinical data necessary to support a submission, and asked the Sponsor to outline a proposal that included providing substantial evidence of efficacy and safety for review.

Roche/Genentech subsequently proposed a robust clinical package including data from 1500 patients treated with rituximab SC and providing longer follow-up for efficacy and safety that was discussed during a Type B, pre-BLA meeting with FDA in February 2016.

As a result, the Sponsor filed the application for rituximab SC as a BLA for a single-entity biological product in August 2016 including the clinical data package agreed with the FDA. The BLA for rituximab SC (761064) was accepted for review by FDA in October 2016. The advisory committee has been convened to provide guidance to the FDA on the evidence supporting the rituximab SC formulation.

3. RATIONALE FOR CLINICAL DEVELOPMENT PROGRAM FOR RITUXIMAB SC

Development of rituximab SC was based on the knowledge and experience established over the course of 20 years with rituximab IV, since approval in 1997, and applied a PK-based clinical bridging approach with safety and efficacy to establish the fixed rituximab SC dosing regimens across NHL and CLL indications.

Clinical development of rituximab SC comprised three key components:

1. PK-based clinical bridging to demonstrate non-inferior exposure of rituximab,
2. Confirm efficacy and safety is consistent between the two routes of administration,
3. Evaluation of patient preference and satisfaction for the SC route of administration.

3.1 PK-BASED CLINICAL BRIDGING

Establishing the SC route of administration for rituximab was based upon the cumulative available information on PK and PD characteristics relating to rituximab's mechanism of action and its long established clinical benefit/risk profile following IV administration. Following administration, rituximab exerts its activity upon binding to its target, CD20, on malignant B-cells leading to depletion of these cells and therapeutic effect (see Section 2.1).

The rituximab SC PK-based clinical development was based on the scientific consideration that achieving similar systemic concentrations of rituximab will lead to the same mechanistic effect regardless of route of administration. Therefore, by achieving a non-inferior rituximab exposure comparable saturation of the target sites would be obtained resulting in analogous efficacy. Establishing appropriate rituximab SC fixed doses was based on considerations associated with a change in route of administration from IV to SC including bioavailability of the SC route, the need to achieve non-inferior exposures in the systemic circulation compared to the approved doses for IV administration to NHL and CLL patients across the range of BSA to result in consistent efficacy, and the knowledge gained on rituximab PK from the extensive experience with rituximab IV including use of a well-established mechanistic population PK model (see below).

3.1.1 Rituximab IV PK

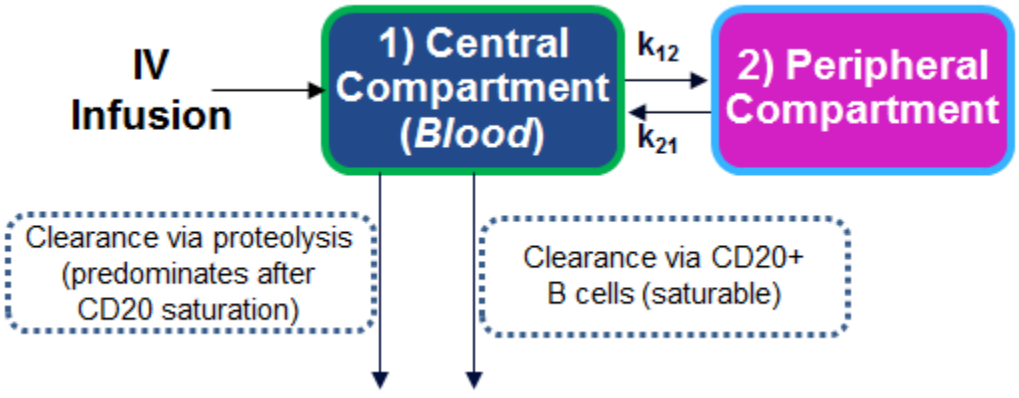
The PK of rituximab IV has been investigated throughout its clinical development and has been well described following various doses and schedules across multiple B-cell malignancies.

Rituximab binds with high affinity to the CD20 antigen target on the surface B-cells. Following this binding, rituximab exerts its clinical effect through depletion of the B-cells through mechanisms of CDC, ADCC, and/or induction of direct cell death by apoptosis (Figure 1). This process will also clear rituximab from the circulation and is saturable as

it is limited by the number of target binding sites on B-cells and/or number of remaining B-cells. Therefore, the expected maximal effect will occur at rituximab exposures which saturate the target sites and/or eliminate target B-cells over time given the persistence of tumor cells in hematologic malignancies (Li 2012). Rituximab is also cleared by endogenous, non-saturable proteolytic processes that are independent of target binding. These two clearance processes are typically observed with antibodies that bind receptors on cell surfaces and undergo the phenomenon of target-mediated drug disposition (TMDD). Like for other biological systems, a model describing rituximab pharmacokinetics has be constructed which can be used to gain information on the depletion of accessible target cells (i.e., malignant B cells). This model provides insight into the rituximab drug-target interaction and its link between exposure, target saturation and/or elimination of target cells, and response (Figure 3). Similar PK characteristics of TMDD and PK models have been widely described for other mAbs that target receptors on cell surfaces, including the other anti-CD20 mAbs obinutuzumab (Gazyva) and ofatumumab (Arzerra) (Wang 2008; Mager and Jusko 2001; Gibiansky 2014; Struemper 2014).

The model depicted in Figure 3 has been widely used and validated during the development of rituximab IV in multiple indications. Following infusion into the systemic circulation (i.e., central compartment), rituximab IV distributes to tissues (i.e., peripheral compartment), including to sites of action, and is removed from the systemic circulation by a combination of a time-varying, CD20 target-mediated clearance component representing the binding and elimination of target B-cells (i.e., the TMDD pathway) which saturates over time as malignant B-cells are eliminated from the body; and a constant linear clearance component related to the endogenous proteolytic processes of IgGs (Figure 3).

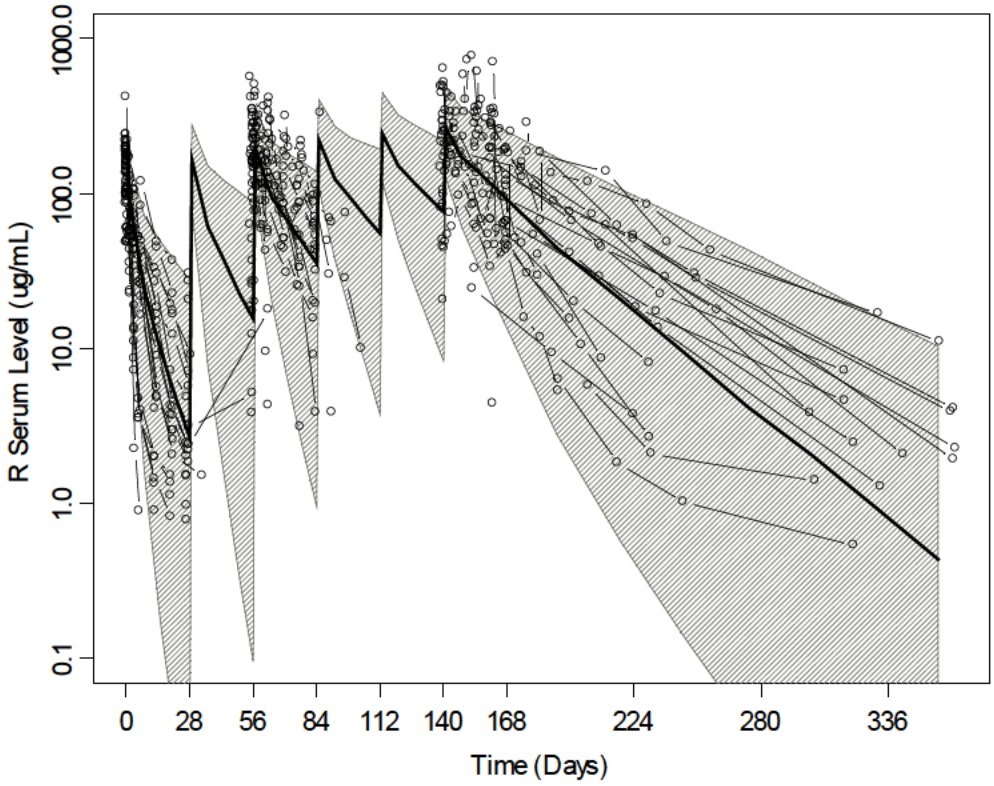
Figure 3 Model Describing Rituximab IV PK



Modified from Li 2012.

This established model can be applied to populations of patients and the parameters derived for different malignancies (e.g., NHL versus CLL) to derive an estimate of rate and extent of accessible tumor depletion. For example, an actual model fit with historical CLL data from the REACH study in relapsed/refractory CLL is included below (Figure 4; Li 2012). The established rituximab PK model has been shown to adequately predict the full concentration-time profile of rituximab IV over time (Figure 4).

Figure 4 Rituximab Concentration-Time Profiles for Relapsed/Refractory CLL Patients Receiving Rituximab IV Doses of 500 mg/m^2



Solid line is predicted median serum concentration. Open circles are observed patient data. Grey shaded area represents the 5th-95th percentile.
Source: Li 2012.

The rituximab time-varying (target-mediated) clearance was demonstrated in the initial, pivotal phase III single-agent trial of rituximab IV which showed a decrease in apparent half-life of rituximab from the first infusion to the fourth infusion. Berinstein et al. (1998) postulated that the change in half-life was most likely related to elimination of circulating CD20-positive B-cells (i.e., target malignant B-cells), which serve to clear serum antibody with the initial infusions of rituximab. Thus, as rituximab binds CD20 on the surface of B-cells, it was found that the time-dependent change in half-life reported by the authors was due to a reduction of the time-varying (target-mediated) clearance of rituximab reflecting the elimination of the malignant B-cells over time. Approved

rituximab IV dosing regimens have ensured elimination of the target CD20-positive malignant B-cells during the course of treatment. Population PK analyses have confirmed that with the approved dosing regimens, the time-varying (target-mediated) clearance component becomes negligible at steady state, suggesting near-complete saturation on B-cells.

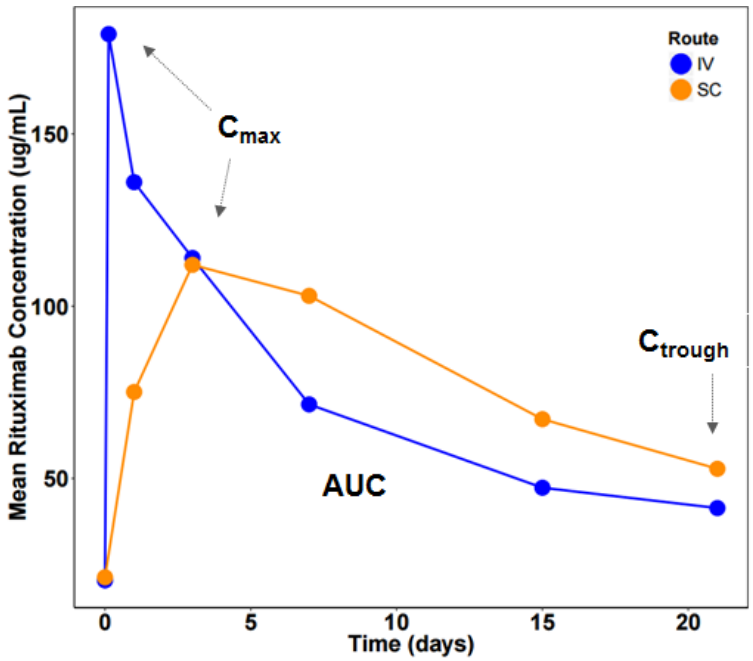
The same model was used for the rituximab SC development with minor refinements to account for the absorption from the subcutaneous compartment into the systemic circulation.

3.1.2 Relevant Measures of Rituximab Exposure for PK-based Clinical Bridging

The PK-based clinical bridging approach for rituximab SC was designed to confirm that selected SC doses would achieve non-inferior exposure to those achieved with approved rituximab IV dosing regimens. Based on the considerations in Section 3.1.1, this approach can therefore demonstrate similar observed rituximab exposure in the blood to maintain rituximab target-site saturation and therefore efficacy consistent with the long established rituximab IV experience with the approved 375 mg/m^2 and 500 mg/m^2 doses used in NHL and CLL, respectively.

In terms of measure of exposure, changes in route of administration, and particularly the need for absorption of rituximab from the subcutaneous injection site to reach the systemic circulation following SC administration, lead to distinct pharmacokinetic profiles (Figure 5). Therefore, it was important to consider the most clinically relevant exposure measures for bridging between rituximab IV and SC routes of administration.

Figure 5 Mean Concentration-Time Profile for Rituximab Following IV and SC Administration



Based on observed data from Cycle 2 in the SABRINA study in previously untreated FL patients.

C_{max} values were not appropriate for comparisons between rituximab IV and rituximab SC. C_{max} via the IV route is instantaneous at the end of the infusion and is an arbitrary measure before equilibration occurs between the different blood, tissue, and lymphatic compartments, whereas C_{max} via the SC route occurs after approximately 2-3 days. (Figure 5). Furthermore, rituximab C_{max} did not appear to clearly correlate with response or outcomes (Tobinai 2004).

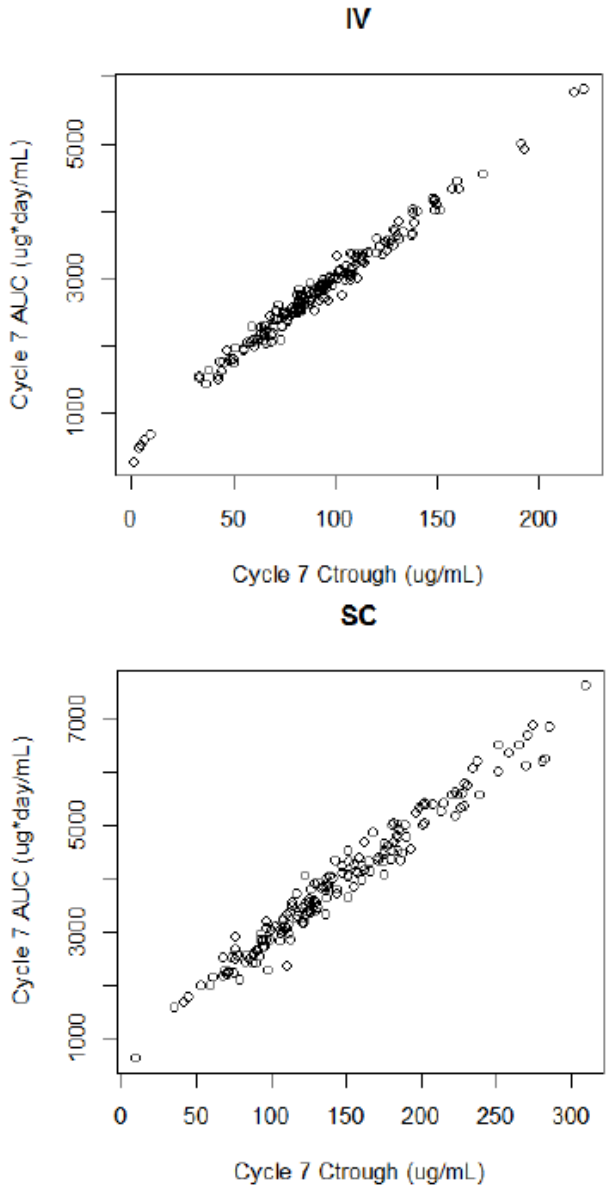
C_{trough} and AUC at steady-state, were therefore considered as exposure parameters for comparison.

C_{trough}, following multiple dosing with rituximab, was selected as the primary PK endpoint in the PK-based clinical bridging studies for rituximab SC. C_{trough} reflects the scientific considerations described in Section 3.1.1 and represents the minimum concentration of rituximab in the dosing interval which is available for binding to its target, and therefore can be used as a reference to maintain target saturation of B-cells. Multiple investigations, both nonclinical and clinical, including the Sponsor's historical data, support associations between rituximab exposure and clinical outcome and are described in detail in Appendix 1. Indeed, rituximab C_{trough} correlated with response rates in FL and DLBCL and was shown to correlate with remission quality and PFS (Yin 2010; Tobinai 2004; Jäger 2012).

Relationships between C_{trough} and clinical outcomes have also been established for other mAbs across disease states (e.g., trastuzumab [Herceptin], trastuzumab-emtansine [Kadcyla], tocilizumab [Actemra], infliximab [Remicade], and adalimumab [Humira]) (Wang 2014; Levi 2013; Abdallah 2016; Ternant 2015).

AUC following multiple doses was chosen as a secondary endpoint. AUC provides information regarding the exposure over time during the entire treatment cycle (dosing interval, τ), and therefore could contribute to the anti-B-cell action by rituximab. As, with C_{trough}, AUC has also been shown to correlate with response rates in FL and DLBCL (Tobinai 2004). AUC is shown to be highly correlated with C_{trough}, the primary exposure endpoint, in the completed clinical studies for both IV and SC routes of administration (Figure 6; see also Section 5).

Figure 6 Correlation Between Model-Estimated AUC and C_{trough} Following IV and SC Administration



Based on data from the SABRINA study in previously untreated FL patients.

3.1.3 Selection of the C_{trough} Non-Inferiority Margin for PK-Based Clinical Bridging

Given the significant morbidity and mortality associated with the approved indications for rituximab IV (NHL and CLL), the confirmed long-term benefit with rituximab treatment and its well-established and manageable safety profile, a focus of the rituximab SC clinical development program was to demonstrate that rituximab exposures for clinically

established doses and dosing intervals were at least as high with rituximab SC as those achieved with rituximab IV.

Consequently, the PK-based clinical studies were powered to demonstrate non-inferiority for the primary PK endpoint, C_{trough}, of rituximab SC versus rituximab IV, with formal Type I error control. A non-inferiority margin of 0.8 was applied to the lower limit of the two-sided 90% confidence interval (CI) of the geometric mean ratio (GMR) of C_{trough} SC/IV to establish non-inferior C_{trough} in the dose-confirmation studies. The rationale for the 0.8 non-inferiority margin relied on the standard lower bound recommended in regulatory guidance documents for demonstration of bioequivalence for PK bridging (FDA Bioavailability and Bioequivalence Guidance March 2014). An upper bound for the confidence interval was not applied in the dose-confirmation studies due to the established wide therapeutic window of rituximab (see Section 2.2.3). A Type I error of 5% was allocated to this one-sided approach to testing (equivalent to 10% two-sided), thus the 90% confidence interval was used to demonstrate the non-inferiority of rituximab SC when compared with rituximab IV.

3.2 EVIDENCE OF COMPARABLE CLINICAL OUTCOMES

By achieving serum rituximab exposures not inferior throughout the treatment cycle to those achieved with approved rituximab IV doses, at least the same degree of target saturation and pharmacologic activity (B-cell depletion) and therefore analogous efficacy was expected, regardless of the route of administration. Since the PK (dose confirmation) studies were powered to demonstrate C_{trough} non-inferiority for rituximab SC relative to rituximab IV with Type I error control applied to the primary PK endpoint, there was no formal statistical testing for efficacy. The clinical program was designed to provide evidence that the overall benefit/risk profile of rituximab in the treatment of B-cell malignancies is consistent between the SC and IV routes of administration.

Efficacy was demonstrated using an estimation-based approach across three randomized, controlled studies evaluating rituximab SC versus rituximab IV in three indications (FL, DLBCL, and CLL) and measured by tumor response rates at the end of induction (immunochemotherapy) treatment, time-to-event endpoints (progression-free survival [PFS], event-free survival [EFS], overall survival [OS]), and further exploratory endpoints (Table 1). A complete examination of all endpoints, including subgroup analyses, across all studies was necessary to thoroughly assess short- and long-term efficacy with rituximab SC. Demonstration of consistent efficacy between IV and SC routes of administration across the studies for all endpoints was considered adequate to rule out clinically meaningful differences in efficacy between the SC and IV routes of administration.

Safety was an important objective across the clinical development program (Table 1). As both formulations contain the same antibody, rituximab, the safety profile was not expected to differ substantially except for those adverse effects related to the change in the route of administration to SC (i.e., local cutaneous reactions with rituximab SC).

Furthermore, as outlined earlier, no specific safety concerns were anticipated in regard to the presence of rHuPH20 as a permeation enhancer in the co-formulation. Nevertheless, even with the extensive knowledge of rituximab IV, its well-established safety profile, and its wide therapeutic window, the safety evaluation across the rituximab SC clinical studies was rigorously conducted and included special attention to unique adverse events that would be observed following a SC injection. A variety of analyses were conducted to evaluate the potential for safety concerns, including subgroup analyses exploring the impact of BSA, to rule out clinically meaningful differences in safety between the SC and IV routes of administration.

4. OVERVIEW OF THE CLINICAL DEVELOPMENT PROGRAM

Rituximab SC was developed as a new option to simplify and shorten administration of rituximab therapy, thereby reducing the treatment burden for patients. Five randomized, controlled clinical trials were conducted including over 1500 patients treated with the rituximab SC with various B-cell malignancies. The program comprised three key components:

1) PK-based clinical bridging to demonstrate non-inferior exposure of rituximab (SparkThera, SABRINA, and SAWYER studies),
2) Confirm efficacy and safety is consistent between the two routes of administration,
3) Evaluation of patient preference and satisfaction for the SC route of administration (PrefMab and MabEase studies).

The program was primarily designed to evaluate the effects of the change in the route of administration on the overall benefit/risk profile of rituximab for the treatment of B-cell malignancies. Demonstration of PK non-inferiority and consistent safety and efficacy with rituximab SC would support the proposal to grant the same indications in B-cell malignancies for which RITUXAN has been approved. Additional patient benefit with rituximab SC was also evaluated in a dedicated patient-reported outcomes trial.

PK-based clinical bridging to the established NHL and CLL doses and schedules approved for RITUXAN was evaluated in first-line (1L) FL and 1L CLL populations, with the rationale that demonstrated non-inferior C_{trough} for a given dose could be applied to other schedules and indications that use the same dose. Therefore, results from SABRINA Stage 1 in 1L FL could be applied to relapsed/refractory (R/R) indolent lymphoma where patients are also treated with rituximab at the NHL dose. Similarly, results from SAWYER Stage 2 in 1L CLL could be applied to the R/R CLL population also treated with rituximab at the CLL dose.

Ultimately, the three components of the clinical development program are inter-linked and should be considered in their entirety, and the robustness of the overall package and the entirety of data assessed along with the results from individual studies.

4.1 OVERVIEW OF THE STUDIES

An overview of the designs and objectives of the five key rituximab SC studies is presented in Table 1 which also outlines the key data supporting approval of rituximab SC.

A total of 2227 patients were treated across the five randomized, controlled clinical trials, 1579 of whom received at least one injection of rituximab SC.

The majority of the studies (SABRINA, MabEase, PrefMab, SAWYER Stage 2) enrolled previously untreated adult patients with histologically confirmed, CD20-positive disease requiring treatment, while the SparkThera and SAWYER Stage 1 studies enrolled patients partway through the course of treatment. All previously untreated patients received rituximab IV at Cycle 1 via the IV route of administration in order to manage any infusion reactions upon the first exposure to rituximab; those randomized to receive SC treatment were administered rituximab SC from the second cycle.

The SparkThera study included both relapsed and previously untreated FL patients who entered the study having received induction treatment and at least one cycle of rituximab IV in the FL maintenance (rituximab monotherapy) setting.

Across the four other studies, rituximab was combined with standard-of-care chemotherapy approved for use with rituximab IV. Of note, the SABRINA study featured both induction and maintenance treatment, which is the approved standard of care for patients with FL.

The rituximab IV and rituximab SC arms of the studies were well-balanced with regard to demographic factors and baseline stratification characteristics, and the study populations were overall similar to those included in earlier pivotal trials of RITUXAN in these diseases.

A detailed synopsis of each study, including design, evaluation criteria, and overview of the patient population included, can be found in Appendix 2.

Table 1 Overview of Clinical Studies Evaluating Rituximab SC

Study	Disease State/ Number of Patients as Randomized	Study Design	Treatment and Treatment Duration	Objective(s)/ Study Endpoints	Evidence Supporting Rituximab SC			
					PK/PD	Efficacy	Safety	PRO
SparkThera	FL maintenance (both previously treated and relapsed) n = Stage 1: 108 SC, 16 IV; Stage 2: 78 SC, 79 IV	Phase Ib two-stage randomized adaptive study: Stage 1: dose finding single SC injection 375/675/800 mg/m^2; Stage 2: dose confirmation 1400 mg SC q2m/q3m in maintenance treatment of FL	Stage 2: q2m/q3m R maintenance: C2-8 or C2-12: 1400 mg SC vs. 375 mg/m^2 IV treatment duration~18-20 months	**Primary**: non-inferior rituximab C_{trough} SC vs IV **Secondary:** safety, B cells, immunogenicity	✓		✓	
SABRINA	1L FL induction and maintenance n = 205 SC, 205 IV	Phase III two-stage, randomized study of rituximab SC 1400 mg vs rituximab IV 375 mg/m^2 in previously untreated CD20+ FL grade 1, 2, 3a, induction (6 months) followed by maintenance (2 years)	q3w induction: R-CHOP or R-CVP C2-8[a]: 1400 mg SC vs. 375 mg/m^2 IV q2m R maintenance: C9-20: 1400 mg SC vs. 375 mg/m^2 IV treatment duration~2.5 years	**Primary PK** (Stage 1): non-inferior rituximab C_{trough} SC vs IV **Primary Efficacy** (Stage 2): ORR at end of induction **Secondary:** Efficacy (CRR at end of induction, PFS, EFS, OS, CR30); Safety, B cells, immunogenicity; Convenience/ resource-saving questionnaires	✓	✓	✓	
SAWYER	1L CLL n = Stage 1: 64 SC; Stage 2: 88 SC, 88 IV	Phase Ib two-stage, randomized study: Stage 1: dose-finding single SC injection 1400/1600/1870 mg; Stage 2: dose-confirmation 1600 mg SC q4w	Stage 2: q4w R-FC induction: Cycles 2-6[a]: 1600 mg SC vs. 500 mg/m^2 IV treatment duration~6 months	**Primary:** non-inferior rituximab C_{trough} SC vs IV **Secondary:** Safety, B cells, immunogenicity; Convenience/resource-saving/preference questionnaires; Efficacy (ORR at end of treatment, MRD, PFS, EFS, OS)	✓	✓	✓	

Table 1 Overview of Clinical Studies Evaluating Rituximab SC (cont.)

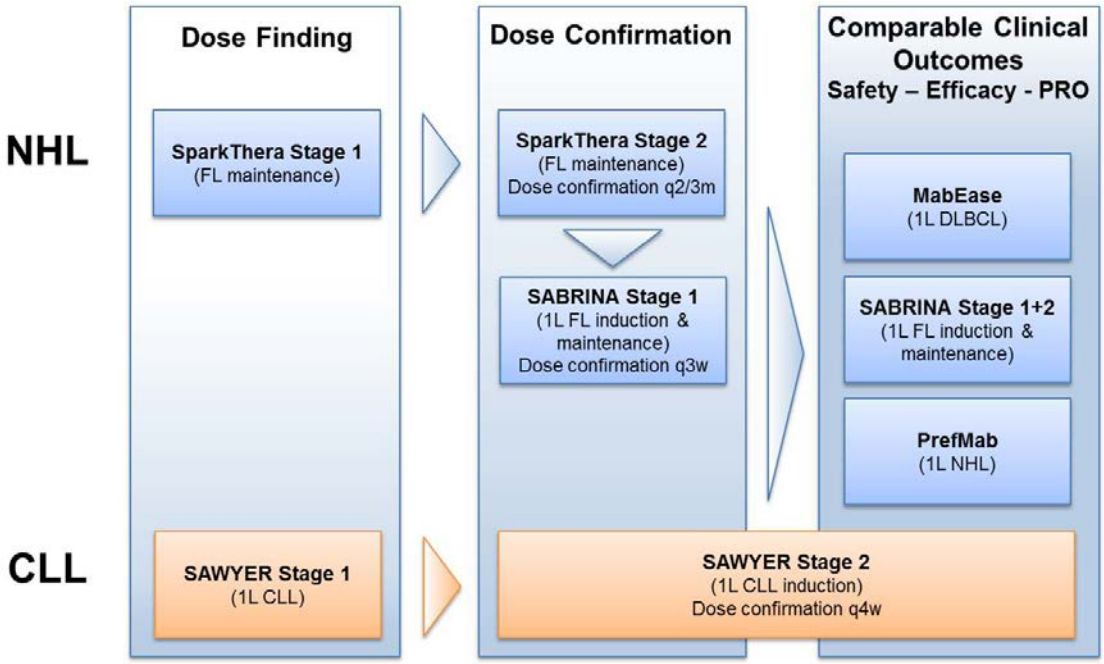
Study	Disease State/ Number of Patients as Randomized	Study Design	Treatment and Treatment Duration	Objective(s)/ Study Endpoints	Evidence Supporting Rituximab SC			
					PK/PD	Efficacy	Safety	PRO
MabEase	1L DLBCL n = 381 SC, 195 IV	Phase IIIb randomized study investigating efficacy of rituximab SC 1400 mg vs rituximab IV 375 mg/m^2 in previously untreated CD20+ DLBCL	q2w/q3w induction: R-CHOP-14 or R-CHOP-21 C2-8[a]: 1400 mg SC vs. 375 mg/m^2 IV treatment duration~4-6 months	**Primary:** CR at end of treatment **Secondary:** Efficacy (EFS, DFS, PFS, OS); PRO (patient satisfaction questionnaire); Safety, immunogenicity		✓	✓	✓
PrefMab[a]	1L FL or DLBCL n = 372 Arm A, 371 Arm B	Phase IIIb randomized crossover study evaluating patient preference for rituximab IV or rituximab SC during immunochemotherapy for previously untreated CD20+ DLBCL or FL	q2w/q3w/q4w induction: R plus CHOP, CVP, or B Arm A: C2-4[a]: 1400 mg SC; C5-8: 375 mg/m^2 IV Arm B: C2-4[a]: 375 mg/m^2 IV; C5-8: 1400 mg SC treatment duration ~4-8 months	**Primary:** PRO (dosing route preference) **Secondary:** Safety, immunogenicity; Efficacy (CRR at end of treatment, EFS, DFS, PFS, OS)			✓	✓

1L: first-line; C: cycle of therapy; CLL: chronic lymphocytic leukemia; CR30: complete response rate at 30 months; CRR: complete response rate; DFS: disease-free survival; DLBCL: diffuse large B-cell lymphoma; EFS: event-free survival; FL: follicular lymphoma; NHL: non-Hodgkin's lymphoma; ORR; overall response rate; OS: overall survival; PFS: progression-free survival; PRO: patient-reported outcome.
a: Patients were randomized to receive either rituximab SC at Cycles 2-4 (after the first cycle rituximab IV) or rituximab IV at Cycles 1-4. After the fourth cycle, patients were crossed over to the alternative route of administration for the remaining four cycles.

4.2 SEQUENTIAL APPROACH TO DEVELOPMENT

The clinical development program was executed in a sequential manner (Figure 7): first, the doses of rituximab SC expected to be non-inferior to the established NHL and CLL rituximab IV doses were determined; second, the identified doses of rituximab SC were confirmed across the clinically established dose schedules based on statistically non-inferior C_{trough} compared with rituximab IV; third, the program was expanded to support consistent efficacy and safety of rituximab SC and rituximab IV, and evaluate patient-reported outcomes associated with the two routes of administration.

Figure 7 Overview of the Clinical Development Program



1L: first-line; CLL: chronic lymphocytic leukemia; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; NHL: non-Hodgkin's lymphoma; PRO: patient-reported outcomes; q2/3m: once every 2/3 month dosing; q3/4w: once every 3/4 week dosing.

Dose Finding and Confirmation

A sequential approach was adopted to select and confirm the rituximab SC doses which correspond to the approved IV doses in NHL (375 mg/m^2) and CLL (500 mg/m^2) across the three PK studies (Figure 7):

SparkThera: A two-stage phase Ib study to investigate the pharmacokinetics, safety, and tolerability of rituximab SC in patients with follicular lymphoma as part of maintenance treatment

SparkThera Stage 1 evaluated several BSA-adjusted doses of rituximab SC in order to determine a dose of rituximab SC that would yield non-inferior C_{trough} compared with the approved IV dose in NHL.

- PK data from the dose-finding cycle were integrated into a reference population PK model developed using the NHL population (Levi 2008), and model-based simulations were used to predict serum C_{trough} and AUC values for a range of fixed rituximab SC doses.
- A fixed dose of 1400 mg rituximab SC was selected for further evaluation in the NHL induction (SABRINA Stage 1) and FL maintenance settings (SparkThera Stage 2). Model-based simulations were also used to determine the starting dose of rituximab SC (1870 mg) in CLL (SAWYER Stage 1).

SparkThera Stage 2 subsequently confirmed C_{trough} non-inferiority of 1400 mg rituximab SC versus rituximab IV 375 mg/m^2 given as monotherapy every 2 months or every 3 months (FL maintenance schedule).

SABRINA: A two-stage randomized phase III study to investigate the pharmacokinetics, efficacy, and safety of rituximab SC versus rituximab IV in combination with CHOP or CVP in patients with previously untreated follicular lymphoma followed by maintenance treatment with rituximab SC or rituximab IV

SABRINA Stage 1 confirmed C_{trough} non-inferiority of 1400 mg rituximab SC versus rituximab IV 375 mg/m^2 given every 3 weeks in combination with chemotherapy (FL induction and DLBCL schedule) based on observed PK data.

SABRINA Stage 2 was opened to enrolment only after PK non-inferiority of the rituximab SC dose was confirmed in Stage 1 induction. Stage 2 was primarily designed to compare the effects on efficacy and safety of the switch to the SC route of administration, as measured by overall response rates at the end of induction (primary endpoint). Response rates at the end of maintenance and time to event endpoints (PFS, event-free survival [EFS], and overall survival [OS] from randomization) were also evaluated. All patients had PK sampling for C_{trough}.

SAWYER: An adaptive, comparative, randomized, parallel-group, multicenter, phase Ib study of rituximab SC versus rituximab IV both in combination with FC chemotherapy in patients with previously untreated CLL

SAWYER Stage 1 initially evaluated the 1870 mg starting dose of rituximab SC in CLL identified from modeling and simulation following SparkThera Stage 1 and subsequently alternative doses to identify a rituximab SC dose that would yield non-inferior C_{trough} compared with the approved IV dose in CLL.

- PK data from the dose-finding cycle were integrated into the reference population PK model developed using the CLL population (Li 2012), and model-based

simulations were used to predict serum C_{trough} and AUC values for a range of fixed rituximab SC doses.

- A dose of 1600 mg rituximab SC was selected for further evaluation in CLL (SAWYER Stage 2).

SAWYER Stage 2 evaluated C_{trough} non-inferiority of 1600 mg rituximab SC versus 500 mg/m^2 rituximab IV given every 4 weeks (q4w) in combination with chemotherapy (CLL schedule) based on observed PK data. Stage 2 was also designed to compare the effects on efficacy and safety of the switch to the SC route of administration.

Assessment of Efficacy

The primary comparison of efficacy after SC and IV administration was conducted in the phase III studies SABRINA (1L FL) and MabEase (1L DLBCL, described below) and supported by data from the phase Ib study SAWYER Stage 2 (1L CLL):

MabEase: A comparative, randomized, parallel-group, multicenter, phase IIIb study to investigate the efficacy of rituximab SC versus rituximab IV both in combination with CHOP (R-CHOP) in previously untreated patients with CD20-positive DLBCL

The MabEase study in first-line DLBCL was initiated after PK non-inferiority of the rituximab SC dose in NHL was confirmed in SABRINA Stage 1 induction. MabEase was designed to estimate the efficacy of rituximab administered SC or IV in combination with CHOP, as measured by the primary endpoint of complete response rate (CR/CRu) approximately one month after the end of rituximab-based treatment based on investigator assessment. Time-to-event endpoints (EFS, PFS, and OS from randomization) were also evaluated.

Assessment of Safety

The overall safety evaluation of rituximab SC is based on the four studies described above (SparkThera, SABRINA, SAWYER, MabEase) and a fifth study, PrefMab (1L FL/DLBCL), described below. Specifically, the randomized controlled SparkThera Stage 2, SABRINA, MabEase, and SAWYER Stage 2 studies allowed comparison of the safety profile of rituximab SC with that of RITUXAN. The PrefMab study, which features a crossover design, is used to support the overall safety profile of rituximab SC in NHL.

Patient-Reported Outcomes and Healthcare Professional Opinions

As rituximab SC was specifically developed to ease the burden on patients and healthcare providers, an important component of the program was to evaluate the impact of this new route of administration on patient-reported and HCP-reported measures. The PrefMab study (1L FL/DLBCL, described below) was specifically designed to investigate patient preference of rituximab administration (SC vs IV). Additionally, patient satisfaction of treatment was evaluated in the PrefMab and

MabEase (1L DLBCL) studies, and healthcare professional opinions were examined in the SABRINA (FL) and SAWYER (CLL) studies.

PrefMab: A randomized, open-label, multicenter study to evaluate patient preference with SC administration of rituximab versus IV rituximab in previously untreated patients with CD20+ DLBCL or CD20+ FL grades 1, 2, or 3a in combination with chemotherapy

The PrefMab study in first-line FL and DLBCL was initiated after PK non-inferiority of the rituximab SC dose in NHL was confirmed in SABRINA Stage 1 induction. PrefMab featured a crossover design whereby patients were randomized to receive either rituximab SC at Cycles 2-4 (after the first cycle rituximab IV) or rituximab IV at Cycles 1-4. After the fourth cycle, patients were crossed over to the alternative route of administration for the remaining four cycles. The primary objective of this study was to evaluate the proportion of patients indicating an overall preference via a Patient Preference Questionnaire (PPQ) for either the SC or the IV route of rituximab administration.

Further details of endpoints and methodology are provided in the following sections together with results.

5. CLINICAL PHARMACOLOGY RESULTS

The key findings from the clinical pharmacology evaluations are summarized below and presented in more detail in subsequent subsections. In addition, a detailed description of results from the completed population PK analyses is provided in Appendix 4:

- Rituximab SC demonstrated a statistically non-inferior exposure (C_{trough}) compared with the established rituximab IV BSA-adjusted dose in NHL and CLL.
  - Rituximab SC 1400 mg demonstrated non-inferior exposure (C_{trough}) compared with the established rituximab IV BSA-adjusted dose (375 mg/m^2) at 3-weekly, 2-monthly, and 3-monthly dosing intervals established in NHL.
  - Rituximab SC 1600 mg demonstrated non-inferior exposure (C_{trough}) compared with the established rituximab IV BSA-adjusted dose (500 mg/m^2) at the 4-weekly dosing interval established in CLL.
  - The lower limits of the two-sided 90% CI for the key secondary endpoint, AUCτ(SC)/AUCτ(IV) GMR, were also above the lower bound of 0.8, supporting non-inferior exposure of the rituximab SC dose over the given dosing interval
  - Subgroup analyses show that the fixed 1400 mg and 1600 mg doses of rituximab SC ensure non-inferior exposure to rituximab in all patients across the entire BSA range, including patients with high BSA.

- For the once-weekly dosing regimen, modeling and simulation predicted that weekly dosing with rituximab SC 1400 mg as monotherapy for 4 weeks would result in non-inferior C_{trough} and AUC compared with rituximab IV 375 mg/m^2.

- Rituximab SC has a similar PD effect (B-cell depletion and repletion/recovery) as rituximab IV. The pattern and durability of B-cell depletion and recovery over time was similar for the SC and IV groups.
- There was no evidence of systemic exposure to rHuPH20 following administration of rituximab SC.

5.1 RITUXIMAB PHARMACOKINETICS

5.1.1 Rituximab Pharmacokinetics Assessments

Extensive clinical pharmacology evaluations were conducted in the SparkThera (FL maintenance), SABRINA (FL induction and maintenance,) and SAWYER (CLL) studies to characterize and compare the pharmacokinetics of rituximab following IV and SC administration to support the overall comparability between the two routes of administration.

Rituximab PK sampling was conducted in all three PK-based clinical bridging studies to support identification and confirmation of fixed SC doses to demonstrate non-inferior rituximab exposure following rituximab SC relative to rituximab IV route of administration.

For SparkThera, blood samples for rituximab PK analyses were drawn at prespecified timepoints during the first cycle after randomization (predose, 8, 24, 48 hours and Days 3,8, 17 (Stage 1) or 22 (Stage 2), 42 (q3m), 57 (q2m), 63 (q3m) and 85 (q3m) postdose for SC administration and predose, end of infusion, and 24 hours and Days 8, 17 (Stage 1) or 22 (Stage 2), 42 (q3m), 57 (q2m), 63 (q3m) and 85 (q3m) postdose for IV administration), predose at all subsequent cycles, as well as following completion of maintenance treatment on a three-monthly basis until the last follow-up visit, 9 months after the last dose of maintenance treatment.

For Stage 1 of SABRINA, blood samples for rituximab PK analyses were drawn intensively at Cycle 2 and Cycle 7 following SC or IV administration and additional predose samples were collected prior to each cycle of induction for the two routes of administration. During Stage 2, blood samples for rituximab PK were taken within 2 hours predose at Cycles 1-8. Further PK assessments in both stages were performed within 2 hours predose at maintenance cycles (Cycles 9-20) and then every 12 weeks ($\pm$7 days) after the last rituximab administration for 96 weeks or until undetectable rituximab levels (rituximab washout).

For Stage 1 of SAWYER, blood samples for rituximab PK analyses were drawn pre- and post-rituximab IV infusion on Day 1 at Cycle 5 (IV) and on Days 2, 5, 11, and 15. At Cycle 6 (SC), blood samples were drawn predose rituximab SC injection on Day 1 and

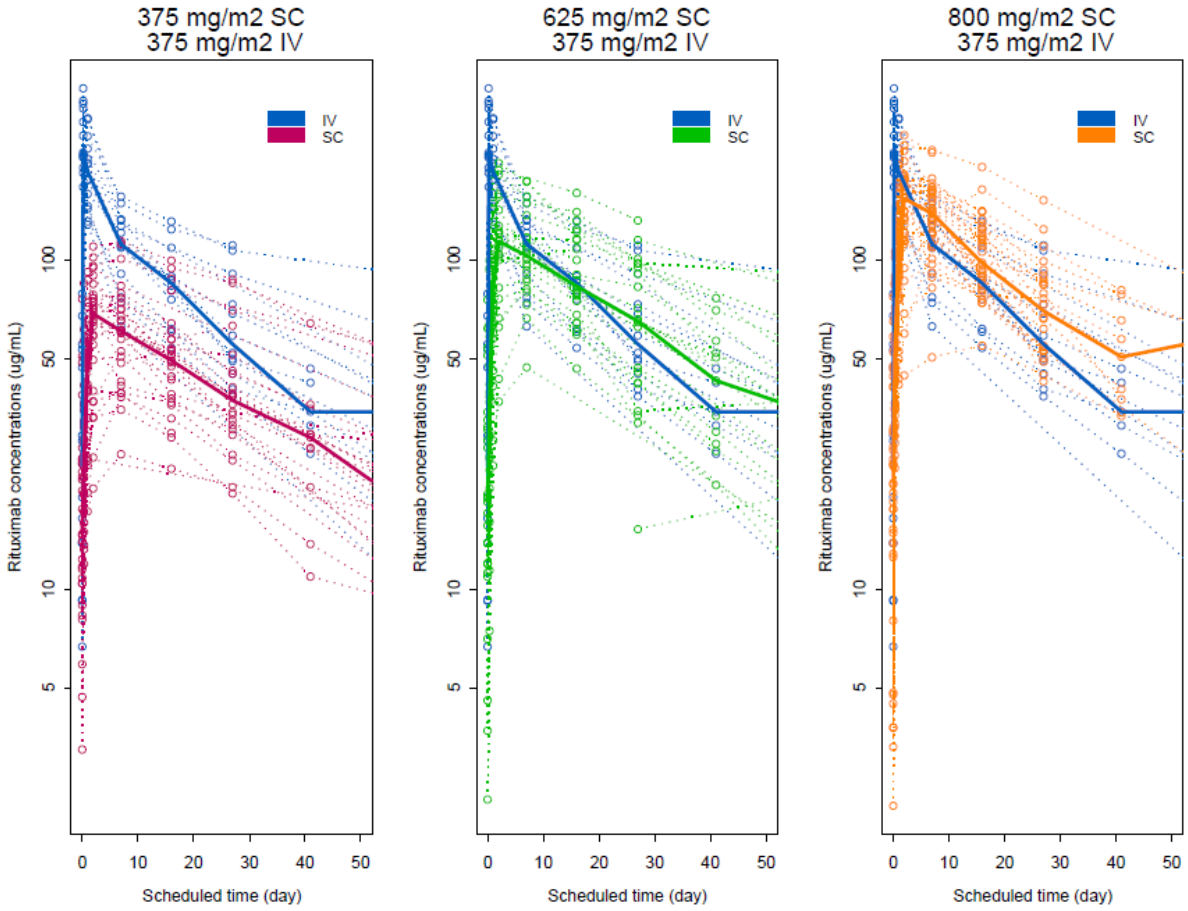
on Days 2, 3, 5, 11, 15, 29, and 57. For Stage 2, blood samples for rituximab PK were drawn intensively at Cycle 1 and Cycle 6 following SC or IV administration and additional predose samples were collected prior to each cycle of treatment for the two routes of administration.

The primary PK endpoint in the three PK-based clinical bridging studies was to demonstrate C_{trough} non-inferiority for rituximab SC relative to rituximab IV with Type I control applied to the primary PK endpoint. A key secondary endpoint was to investigate AUC following SC administration relative to IV administration. All PK analyses were based on patients for whom PK assessments were available; patients were analyzed according to treatment received.

5.1.2 Dose Finding and Selection

SparkThera Stage 1 was the dose-finding study to determine the rituximab SC dose corresponding to the established rituximab IV dose of 375 mg/m^2 to treat patients with NHL (for study design details, see Section 4.2). Observed PK data from the first cycle of IV/SC treatment on study, at maintenance Cycle 2 or later, indicated that a rituximab SC dose between 625 mg/m^2 and 800 mg/m^2 would lead to non-inferior mean C_{trough} and comparable mean AUC_T relative to rituximab IV 375 mg/m^2 (Figure 8).

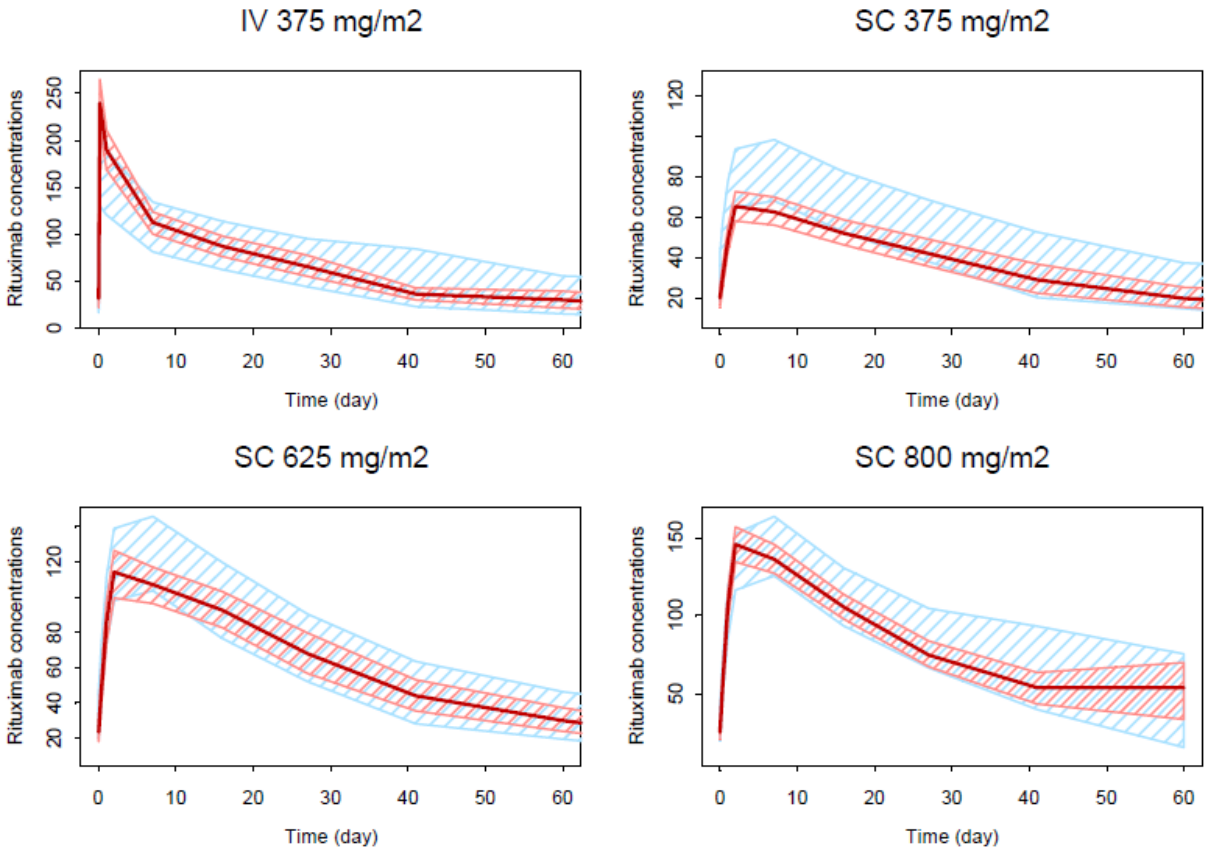
Figure 8 Observed Individual and Median Rituximab Concentration-Time Profiles for 375mg/m^2 IV Rituximab and 375, 625, and 800 mg/m^2 SC Rituximab from SparkThera (FL) Stage 1 (Dose Finding)



The dotted lines represent the individual patient time course profiles. The solid lines represent the median time course profile for each route of administration.
Adapted from Salar 2014.

Observed PK data from the dose-finding cycle were integrated into the reference population PK model previously developed using a NHL population treated with rituximab IV (Section 3.1.1). In the model enriched with PK data from rituximab IV and SC from Stage 1, a first-order process was used to describe the absorption phase following SC administration. The absolute bioavailability of the SC formulation was estimated at 65%, therefore a higher dose of rituximab SC was needed to compensate for the reduced systemic bioavailability after SC administration. The previously established PK model in NHL patients enriched with data from SparkThera was able to adequately predict the full time course of observed rituximab concentrations following IV and SC routes of administration (see visual predictive check; Figure 9).

Figure 9 Visual Predictive Check Illustrating the Overlay of Observed and Simulated Rituximab Serum Concentrations over Time Following Administration of IV and SC Doses in SparkThera (FL)



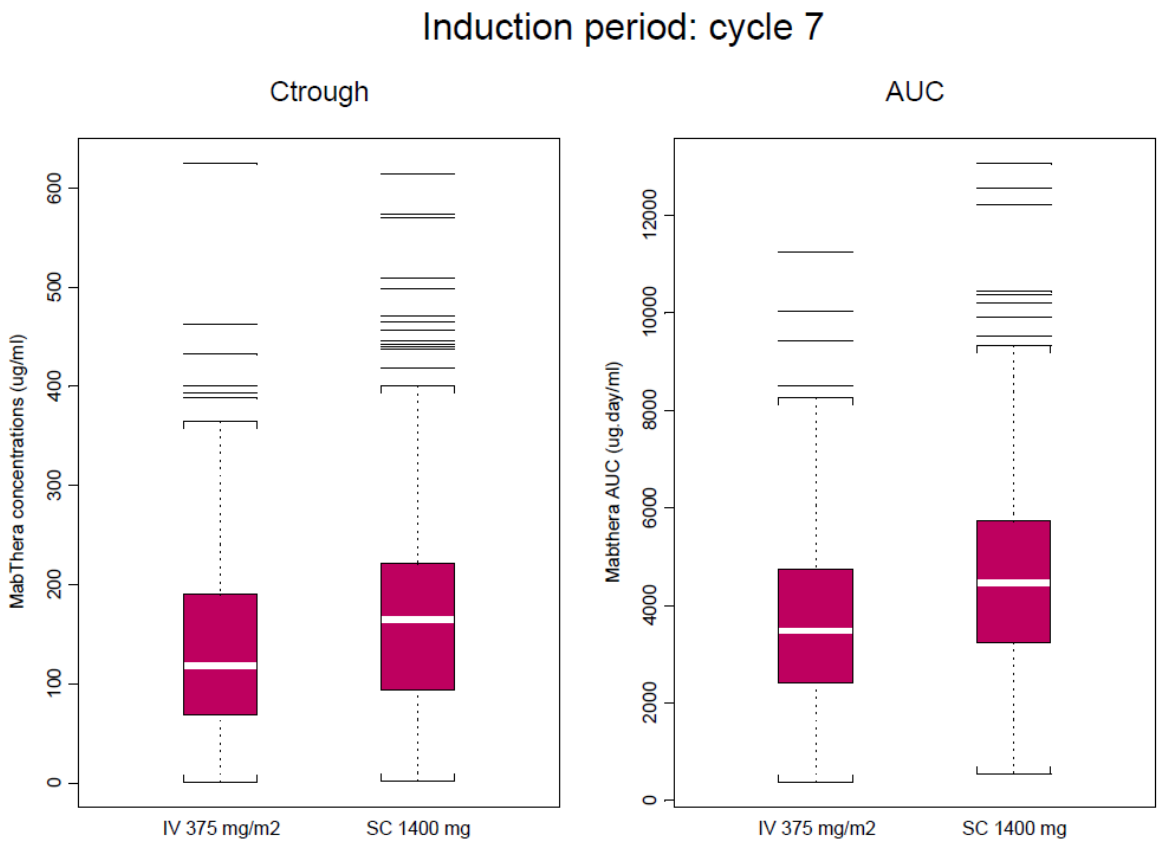
The shaded blue and red areas represent the 95th confidence interval of the simulated and observed median concentration-time course profile, respectively. The red line represents the observed median value of the concentration time-profile.
The *y* axis shows rituximab serum concentrations; the *x* axis shows time (days).

After qualification, the model was used to simulate the fixed dose of rituximab SC that would result in non-inferior C_{trough} compared with rituximab IV 375 mg/m2 during q3w induction or q2m or q3m maintenance. The analysis was based on a BSA distribution of 1.92 m^2±0.24 m^2 (mean ± SD) (Sacco 2010) and conducted under the assumption that patients in the SC group received SC drug in the induction setting followed by SC drug in the maintenance setting. Model-based simulations were used to predict serum C_{trough} and AUC values for a range of fixed rituximab SC doses from 1100 mg to 1400 mg. C_{trough} was modeled for the induction Cycle 7 and maintenance Cycle 2 timepoints.

Based on the model, a fixed dose of 1400 mg was expected to achieve C_{trough} values non-inferior to those with rituximab IV 375 mg/m^2 when administered in the maintenance setting in NHL with a q2m or q3m schedule and in the induction setting with a q3w dose schedule (see Figure 10 for induction setting). The fixed dose of 1400 mg rituximab SC was also expected to achieve AUC_T values comparable to those with rituximab IV

375 mg/m^2 in both settings (see Figure 10 for induction setting). Importantly, the 1400 mg dose was expected to ensure adequate exposure in all patients across the entire BSA range (up to 2.4 m^2). This dose was selected for evaluation in a head-to-head study design with rituximab IV to confirm C_{trough} non-inferiority at the q2m and q3m dose schedules established with rituximab as monotherapy in the FL maintenance setting (i.e., SparkThera Stage 2) and at the q3w dose schedule established with rituximab in combination with chemotherapy for the treatment of DLBCL and FL induction (i.e., SABRINA Stage 1).

Figure 10 Distribution of predicted C_{trough} and AUC during Induction after IV 375 mg/m^2 or SC 1400 mg Rituximab Administration

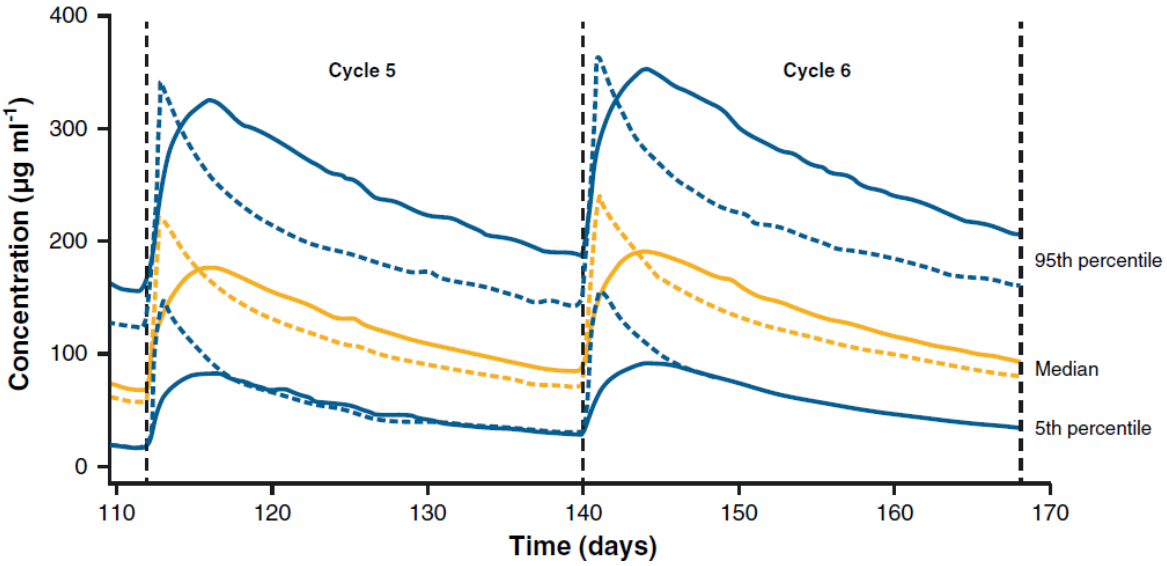


The rituximab (MabThera) concentrations are plotted versus a categorical covariate (IV 375 mg/m2 and SC 1400 mg) using a box and whisker plot. Median values of the continuous covariates are designated by white lines in the center of the boxes. Boxes indicate the inter-quartile range (IQR). Whiskers represent 1.5*IQR. Outliers are marked outside of the whiskers by short lines.

Model-based simulations using the NHL population PK model also predicted that a fixed dose of 1870 mg rituximab SC administered subcutaneously would be an appropriate starting dose in the CLL study SAWYER Stage 1 to select a rituximab SC dose that

would yield non-inferior C_{trough} relative to the established IV dose of 500 mg/m^2 administered with a q4w schedule, while avoiding unnecessary high exposures. A population PK analysis of the first 10 patients dosed at 1870 mg at Cycle 6 in SAWYER Stage 1 indicated that the dose was higher than needed to demonstrate C_{trough} non-inferiority, and hence two further sub-cohorts were enrolled, the first dosed at 1400 mg and the second at 1600 mg. PK data from patients dosed with rituximab SC in the dose-finding cycle in SAWYER Stage 1 were then integrated into the reference population PK model previously developed using a CLL population treated with rituximab IV (Li 2012). A fixed dose of 1600 mg was expected to achieve C_{trough} values non-inferior to those with rituximab IV 500 mg/m^2 (Figure 11; Assouline 2012). Importantly, the 1600 mg dose was expected to ensure adequate exposure in all patients across the entire BSA range (up to 2.4 m^2). The 1600 mg dose ensures that even the 5th percentile of exposures would were expected to be non-inferior to those achieved with the approved 500 mg/m^2 IV dose (Figure 11). This dose was selected for evaluation in a head-to-head study design with rituximab IV 500 mg/m^2 to confirm C_{trough} non-inferiority at the q4w dosing interval established with rituximab in combination with FC chemotherapy for the treatment of CLL (i.e., SAWYER Stage 2).

Figure 11 Model-Based Simulations: Concentration-Time Course for Rituximab SC 1600 mg and Rituximab IV 500 mg/m^2 During Cycles 5 and 6



Solid lines represent the 1600 mg SC median (yellow solid line) and 5th and 95th percentile (blue solid lines) of the simulations. The dotted lines represent the 375 mg/m^2 IV median (yellow dotted lines) and 5th and 95th percentile (blue dotted lines) of the simulations.
Adapted from Assouline 2012.

5.1.3 Dose Confirmation: C_{trough} Non-Inferiority

In SparkThera (NHL) Stage 2, observed PK data (i.e., collected PK samples) from 153 patients from the first cycle of rituximab treatment (1400 mg SC or 375 mg/m2 IV) on study were integrated into the NHL population PK model enriched with data from Stage 1, and model-based simulations were used to predict the PK parameters for each patient at Cycle 2 of maintenance treatment. Because of underlying crossover from IV to SC formulation and variability in the number of prior IV doses during maintenance therapy, a modeling approach was required to account for the residual concentrations from previous rituximab IV infusions as well as the different numbers of cycles of treatment that patients had received prior to entering the study. These values were used to calculate the C_{trough} and AUC values and the geometric mean ratios (GMRs) and corresponding 90% CIs for both q2m and q3m dose schedules used in FL maintenance for the primary analysis of C_{trough} non-inferiority of rituximab SC 1400 mg versus rituximab IV 375 mg/m^2.

In SABRINA (NHL) Stage 1, an interim PK futility analysis was performed after Cycle 7 C_{trough} was available for approximately 70 patients to confirm that the 1400 mg dose of rituximab SC did not require adjusting based on no clear evidence of futility of SC over IV; since the PK results did not cross the futility boundary, the study continued without modification. Observed PK data from 102 patients measured at Cycle 7 of induction treatment (predose Cycle 8, the last cycle of NHL immunochemotherapy) were analyzed using NCA for the primary analysis of C_{trough} non-inferiority of rituximab SC 1400 mg versus rituximab IV 375 mg/m^2 at the q3w dose schedule used in the FL and DLBCL induction setting.

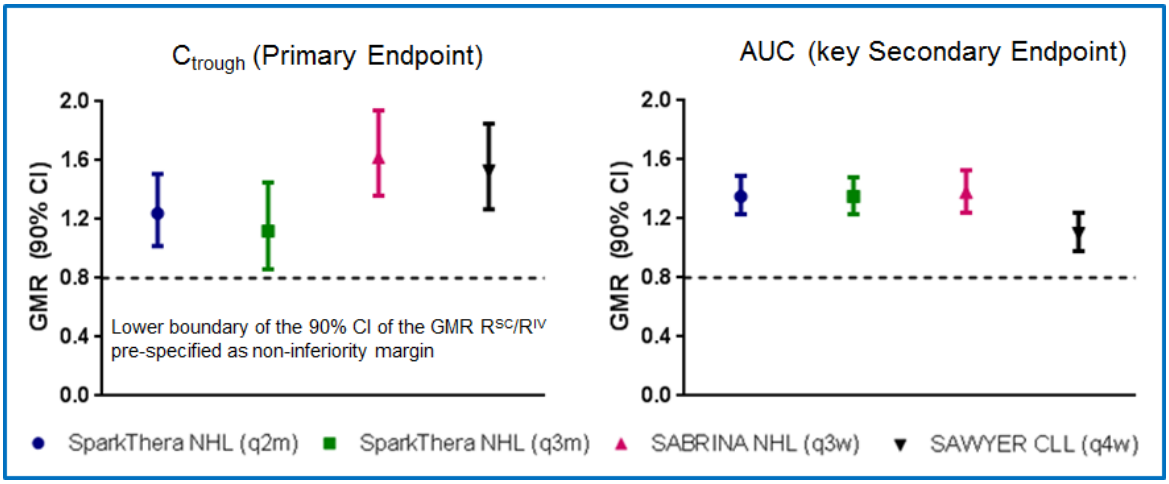
In SAWYER (CLL) Stage 2, observed PK data from 134 patients measured at Cycle 5 of treatment (predose Cycle 6, the last cycle of CLL immunochemotherapy) were analyzed using NCA methods for the primary analysis of C_{trough} non-inferiority of rituximab SC 1600 mg versus rituximab IV 500 mg/m^2 at the q4w dose schedule used in CLL.

All three dose-confirmation studies met their primary endpoint and demonstrated C_{trough} non-inferiority of the evaluated rituximab SC doses relative to the established rituximab IV doses at the dosing intervals most commonly used with rituximab in the treatment of B-cell malignancies, with lower bounds for the two-sided 90% CI of the respective GMR for C_{trough} SC/IV in each study greater than the prespecified non-inferiority boundary of 0.8 (Figure 12; Table 2). In addition, results from SABRINA Stage 1+Stage 2 demonstrated C_{trough} non-inferiority based on observed values at every cycle of induction and maintenance over the course of treatment (GMR C_{trough} SC/IV at Cycle 19: 1.58, 90% CI [1.38;1.80]), confirming both the primary endpoint results and results from SparkThera Stage 2 for the q2m maintenance regimen.

Additionally, the lower limits of the two-sided 90% CI for the GMR of the key secondary endpoint, AUC_T SC/IV were also above the lower bound of 0.8 (Table 3), supporting non-inferior exposures of the rituximab SC dose over the given dosing interval.

Variability in PK parameters was generally similar between the two routes of administration.

Figure 12 Summary of C_{trough} and AUC Comparisons (GMR [90% CI]) between SC and IV Doses in Confirmation Studies



q2m: once every 2 months; q3m: once every 3 months; q3w: once every 3 weeks; q4w: once every 4 weeks.
Figures illustrate the geometric mean ratio (GMR) and associated 90% confidence interval (CI) for the primary (C_{trough}) and key secondary (AUC) endpoint in the PK-based clinical bridging studies across populations and dosing schedules.

Table 2 Summary of C_{trough} Comparisons (GMR [90% CI]) between SC and IV Doses in Confirmation Studies

Dose interval	Treatment cycle of C_{trough} NI testing	Geometric mean rituximab C_{trough}/µg/mL (CV%) SC	IV	Geometric mean ratio $C_{trough(SC)}/C_{trough(IV)}$ [90% CI]
SparkThera (NHL) Stage 2		1400 mg	375 mg/m^2	
q2m[a]	Maintenance Cycle 2	32.2 (74.6%)	25.9 (52.5%)	1.24 [1.02;1.51]
q3m[a]		12.1 (100%)	10.9 (68%)	1.12 [0.86;1.45]
SABRINA (NHL) Stage 1		1400 mg	375 mg/m^2	
q3w[b]	Induction Cycle 7	134.6 (43.2%)	83.1 (36.7%)	1.62 [1.36;1.94]
SAWYER (CLL) Stage 2		1600 mg	500 mg/m^2	
q4w[b]	Cycle 5	97.5 (42.6%)	61.5 (63.9%)	1.53 [1.27;1.85]

Ctrough: trough (pre-dose) concentration; CV%: coefficient of variation; NI: non-inferiority; q2/3m: every 2/3 months; q3/4w: every 3/4 weeks.
a Estimated using a population PK approach. b Calculated using NCA of observed data.

Table 3 Summary of AUC_T Comparisons (GMR [90% CI]) between SC and IV Doses in Confirmation Studies

Dose interval	Treatment cycle of AUC measurement	Geometric mean rituximab AUC_T/µg • day/mL (CV%) SC	IV	Geometric mean ratio $AUC_{T(SC)}/AUC_{T(IV)}$ [90% CI]
SparkThera (NHL) Stage 2		**1400 mg**	**375 mg/m^2**	
q2m[a]	Maintenance Cycle 2	5430 (42.7%)	4012 (29.9%)	1.35 [1.23;1.49]]
q3m[a]		5320 (43%)	3947 (30.3%)	1.35 [1.23;1.48]
SABRINA (NHL) Stage 1		**1400 mg**	**375 mg/m^2**	
q3w[b]	Induction Cycle 7	3779 (33.7%)	2734 (28.0%)	1.38 [1.24;1.53]
SAWYER (CLL) Stage 2		**1600 mg**	**500 mg/m^2**	
q4w[b]	Cycle 6	4088 (34.6%)	3630 (32.8%)	1.10 [0.98;1.24]

AUC_τ: area under the serum concentration-time curve for dosing interval; CV%: coefficient of variation; q2/3m: every 2/3 months; q3/4w: every 3/4 weeks.
a Estimated using a population PK approach. b Calculated using observed data.

In summary, PK exposure non-inferiority was demonstrated for rituximab SC 1400 mg compared with rituximab IV 375 mg/m^2 at the 3-weekly, 2-monthly, and 3-monthly schedules approved for rituximab in the treatment of NHL, and rituximab SC 1600 mg compared with rituximab IV 500 mg/m^2 at the 4-weekly schedule approved for rituximab in the treatment of CLL.

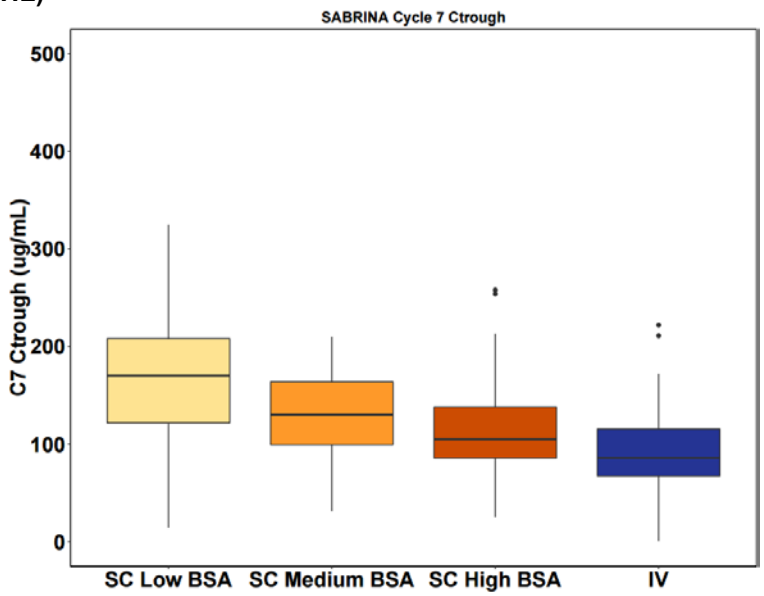
5.1.4 Analysis of PK Results in Subpopulations: Effect of BSA

Subgroup analyses of C_{trough} demonstrate that the fixed 1400 mg and 1600 mg doses of rituximab SC for NHL and CLL, respectively, ensure adequate exposure to rituximab in all patients across the entire BSA range, including patients with high BSA. Low/medium/high BSA subgroups were defined based on the 33rd and 66th percentiles of BSA for the sampling distribution of the patients who were enrolled in individual studies (BSA ranges and cut-offs for tertiles are provided in footnotes to tables presenting results by BSA subgroups). The range of BSA from the enrolled rituximab SC studies is consistent with the range of BSA from prior pivotal studies of rituximab IV.

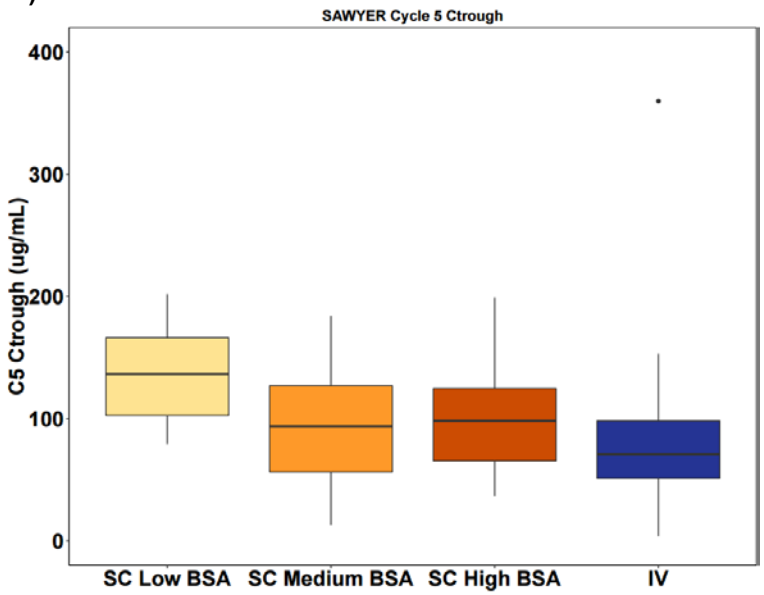
Results from low/medium/high BSA subgroups in SABRINA based on the Stage 1 + Stage 2 population confirm that while rituximab exposure decreases with increasing BSA, the fixed dose of 1400 mg rituximab SC provides rituximab exposures which are non-inferior to those achieved with rituximab IV 375 mg/m^2 over the entire BSA range (Figure 13). Similarly, results from BSA subgroups in SAWYER Stage 2 confirm that the fixed dose of 1600 mg rituximab SC provides rituximab exposures which are non-inferior to those achieved with rituximab IV 500 mg/m^2 over the entire BSA range.

Figure 13 Distribution of Observed C_{trough} by BSA Category and for All IV Data at Cycle 7 in SABRINA and Cycle 5 in SAWYER

SABRINA (1L NHL)



SAWYER (1L CLL)



SABRINA (BSA range 1.34-2.51 m^2): Low BSA $\leq$ 1.70 m^2, medium BSA between 1.70 and 1.90 m^2, and high BSA $\geq$ 1.90 m^2, based on sampling distribution of Stage 1 population and applied to PK analyses of Stage 1+2.
SAWYER Stage 2 (BSA range 1.41-2.42 m^2): Low BSA $\leq$ 1.81 m^2, medium BSA between 1.81 m^2 and 2.00 m^2, and high BSA $\geq$ 2.00 m^2.
The upper whisker extends from the hinge to the highest value that is within 1.5×IQR of the hinge, where IQR is the inter-quartile range, or distance between the first and third quartiles. The lower whisker extends from the hinge to the lowest value within 1.5×IQR of the hinge. Data beyond the end of the whiskers are outliers and plotted as points.

Results from the BSA subgroup analyses in the SABRINA (NHL) and SAWYER (CLL) studies confirm no risk of underexposure for patients with high BSA receiving rituximab SC 1400 mg or 1600 mg, respectively. Furthermore, modeling and simulation explored the impact of very high BSA in NHL patients from SABRINA. Results indicated that there appears to be minimal risk of underexposure for patients with a BSA up to 2.7 m^2 who are administered rituximab SC at a fixed dose of 1400 mg. Of note, patients with BSA > 2.7 m^2 appear to be rare based on data across several trials (SparkThera, SABRINA, MabEase and the IV studies M39021 [range, 1.26-2.36 m^2; Marcus 2008] and PRIMA [range, 1.19-2.67 m^2; Salles 2011]).

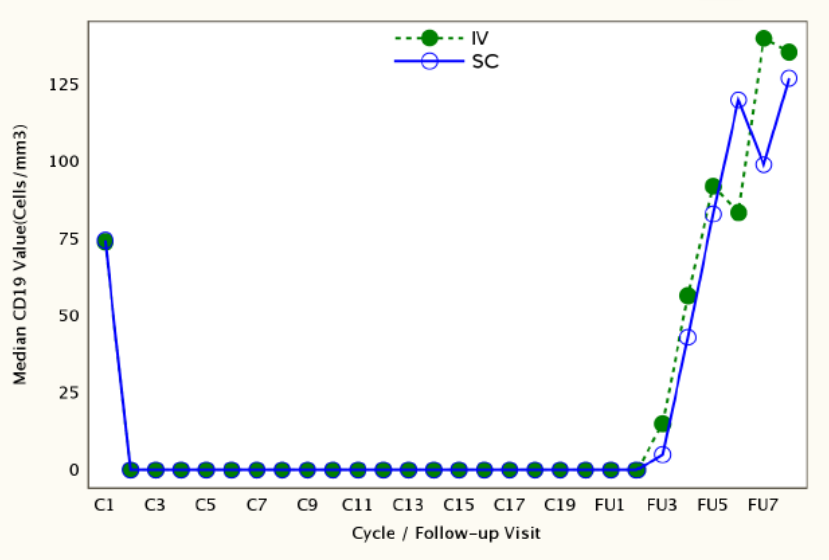
5.2 PHARMACODYNAMICS – B-CELL DEPLETION

The three PK-based clinical bridging studies also investigated the effect of rituximab on peripheral B-cells as the desired PD effect of rituximab. In the dose-finding study SparkThera (NHL), all patients were effectively B-cell-depleted at study entry during maintenance. In SABRINA (NHL) and SAWYER (CLL) studies, patients were previously untreated patients and hence had measurable B-cell levels pre-treatment (baseline). Investigations of B-cell depletion/repletion in SABRINA and SAWYER included visual examinations of the time course of B-cell depletion and repletion after stopping rituximab therapy based on samples collected in the studies across the two treatment arms (Figure 14).

Overall, rituximab SC and rituximab IV given at doses that demonstrate non-inferior exposure have a similar PD effect: the time course, pattern, and durability of B-cell depletion and recovery over time was consistent for both treatment groups in both NHL and CLL patients.

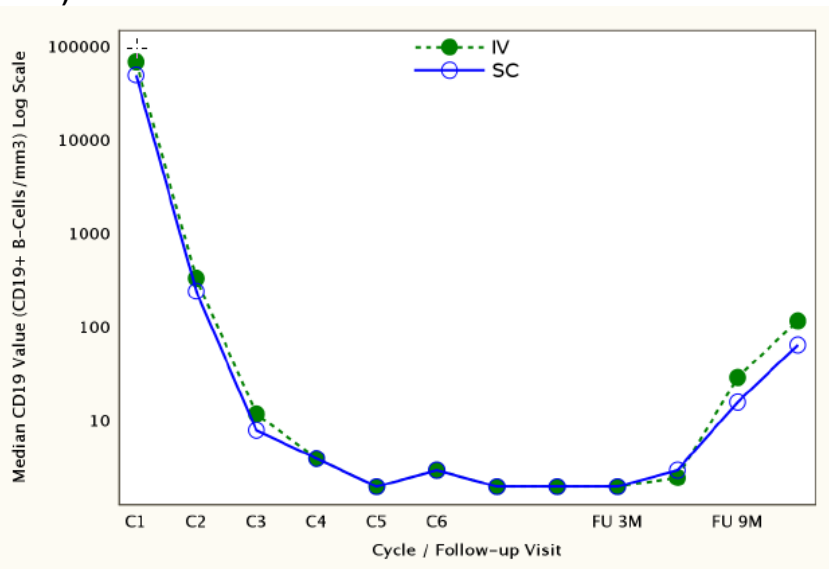
Figure 14 Time Course of B-Cell Depletion and Repletion Following Rituximab IV or SC Administration in NHL Population from SABRINA or CLL Population from SAWYER

SABRINA (1L NHL)



n	C1 (BL)	C3	C5	C7	C9	C11	C13	C15	C17	C19	FU 1	FU 3	FU 5	FU 7
IV	188	175	179	178	170	158	149	149	145	140	131	90	42	35
SC	168	175	176	173	161	158	141	140	142	138	127	107	50	45

SAWYER (1L CLL)



n	C1 (BL)	C2	C3	C4	C5	C6	FU 1M	FU 2M	FU 3M	FU 6M	FU 9M	FU 12M
IV	79	71	67	71	68	71	66	63	65	60	50	21
SC	80	73	67	69	67	63	63	67	67	68	45	18

BL: baseline; C: cycle of treatment; FU: follow-up visit; M: month.
Tables include number of evaluable patients for PD measurement at each cycle.

5.3 RHUPH20 PHARMACOKINETICS

Both phase Ib dose-finding/dose-confirmation studies (SparkThera and SAWYER) collected samples to measure rHuPH20 concentrations at the first cycle of rituximab SC. rHuPH20 PK sampling was conducted at the first cycle of rituximab SC in the SparkThera (FL) and SAWYER (CLL) studies to evaluate the potential for systemic exposure. Blood samples were collected for rHuPH20 PK at predose and at 30 minutes, 60 minutes, and 24 hours following the first injection of rituximab SC.

The results confirmed that there was no evidence of systemic exposure to rHuPH20 following administration of rituximab SC.

6. ASSESSMENT OF EFFICACY OF RITUXIMAB SC

6.1 EFFICACY EVALUATION

In the context of the PK-based clinical bridging approach and demonstrated PK non-inferiority of rituximab SC relative to rituximab IV with Type I error control, efficacy was evaluated with an estimation-based approach (i.e., point estimates and precision of confidence intervals). This was measured by response rates at the end of induction (immunochemotherapy) treatment, time-to-event endpoints (i.e., PFS and OS), and further exploratory endpoints across three randomized, controlled studies (SABRINA, MabEase, and SAWYER Stage 2) evaluating rituximab SC versus rituximab IV in three distinct disease states (1L FL, 1L DLBCL, and 1L CLL; Table 1). Demonstration of consistent efficacy between IV and SC routes of administration across all studies for all endpoints was considered appropriate to rule out clinically meaningful differences in efficacy between the SC and IV routes of administration.

The phase III efficacy studies SABRINA (1L FL) and MabEase (1L DLBCL) were designed based on precision for estimation of the primary endpoint of response rate; both studies included evaluation of PFS, EFS, and OS as key secondary endpoints. The phase Ib study SAWYER Stage 2 (1L CLL) was powered to demonstrate C_{trough} non-inferiority for rituximab SC relative to rituximab IV, with efficacy an important secondary objective to provide further supportive evidence of consistent efficacy across various endpoints.

In the FL study, SABRINA, overall response rate (ORR) at the end of induction treatment (comprising complete response [CR], unconfirmed complete response [CRu] and partial response [PR]) was selected as the primary efficacy endpoint. In the DLBCL study, MabEase, complete response rate (CRR: CR/CRu) was selected as primary endpoint. The CLL study (SAWYER Stage 2) included a comparison of tumor response rates comprising CR, complete response with incomplete bone marrow recovery (CRi), and PR.

Assessment of tumor response in the NHL studies (SABRINA and MabEase) was conducted by the investigator according to the International Working Group response criteria for NHL (Cheson 1999). In the CLL study (SAWYER Stage 2), tumor response was assessed by the investigator according to the International Workshop on CLL (iwCLL) guidelines (Hallek 2008).

The primary analysis of response rates at the end of immunochemotherapy in all studies was based on investigator assessments. Based on previously submitted registration studies of rituximab IV that have shown > 90% concordance rate between investigator and IRC assessments of response/progression (e.g., PRIMA study in FL maintenance) as well as reports of high concordance between investigator and IRC-assessed PFS in peer-reviewed articles (Stone 2011), it was considered that response based on investigator assessment is reliable and appropriate for the rituximab SC studies. Nevertheless, an independent review committee (IRC) was additionally used to assess response at the end of induction in the SABRINA study in FL to confirm the robustness of the results based on investigator assessments.

Progression-free survival (PFS), a clinically meaningful and standard endpoint for new drug approvals in FL, DLBCL, and CLL, together with EFS and OS were prespecified and analyzed across the three efficacy studies to support consistency of long-term efficacy between rituximab SC and rituximab IV.

All efficacy endpoints were analyzed in line with the intent-to-treat (ITT) principle, with patients assigned to treatment groups as randomized.

6.2 OVERVIEW OF EFFICACY OF RITUXIMAB SC

Results of the primary efficacy endpoints (response rates at the end of induction) and secondary time-to-event endpoints (PFS, OS) in both the SABRINA (1L FL) and MabEase (1L DLBCL) studies demonstrate consistent effectiveness of rituximab SC and rituximab IV (Table 4). With median follow-up of 37 months for SABRINA and 28 months for MabEase, the data from these studies are sufficiently mature to establish the efficacy of rituximab SC and rule out any clinically meaningful differences in efficacy upon switching to the SC route of administration.

The results of these studies are supported by tumor response data from the primary analysis of SAWYER Stage 2 (median follow-up 14 months) as well as time-to-event endpoints from an updated analysis (median follow-up 36 months).

Together, the three studies consistently demonstrate analogous efficacy for rituximab IV and rituximab SC as measured by short-term and long-term efficacy endpoints (Table 4, Figure 15). In view of the demonstrated statistically non-inferior C_{trough}, the entirety of data across all endpoints and across subpopulations across all studies support consistent efficacy with the switch from IV to the SC route of administration. Efficacy of rituximab SC was not only consistent with rituximab IV in the studies but also

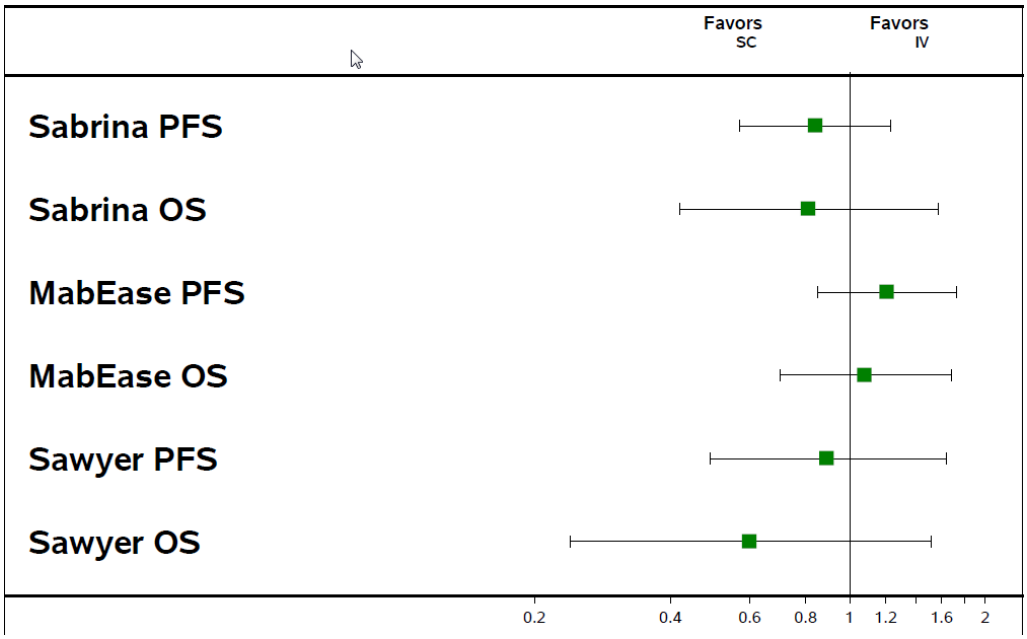
consistent with the performance of the rituximab IV experimental arm in earlier studies that established the effectiveness of RITUXAN in B-cell malignancies.

Table 4 Top Line Efficacy Results for SABRINA, MabEase, and SAWYER Stage 2 (ITT)

	SABRINA (1L FL)		MabEase (1L DLBCL)		SAWYER Stage 2 (1L CLL)	
	IV (N=205)	**SC** (N=205)	**IV** (N=195)	**SC** (N=381)	**IV** (N=88)	**SC** (N=88)
Overall response rate	84.9%	84.4%	71.8%	72.7%	80.7%	85.2%
End of induction 95% CI (%)	[79.2;89.5]	[78.7;89.1]	[65.5;78.1]	[68.2;77.2]	[70.9;88.3]	[76.1;91.9]
Difference	-0.49%		0.91%		4.55%	
95% CI (%)	[-7.7;6.8]		[-6.83;8.65]		[-7.2;16.3]	
p-value	0.8911		-		0.4227	
Complete response rate						
CR/CRu (or CR/CRi) at end of induction 95% CI (%)	32.2% [25.9;39.1]	32.2% [25.9;39.1]	42.1% [35.1;49.0]	47.0% [42.0;52.0]	33.0% [23.3;43.8]	26.1% [17.3;36.6]
Difference	0.00%		4.9%		-6.82%	
95% CI (%)	[-9.3;9.3]		[-3.6;13.5]		[-20.9;7.3]	
p-value	1.0000		0.261		0.3216	
Progression-free survival	0.84		1.23		0.89	
Hazard Ratio	[0.57;1.23]		[0.86;1.76]		[0.49;1.64]	
95% CI (%)	0.3696		0.280		0.7192	
p-value						
Event-free survival	0.91		1.14		0.76	
Hazard Ratio	[0.64;1.31]		[0.84;1.56]		[0.44;1.33]	
95% CI (%)	0.6192		0.509		0.3351	
p-value						
Overall survival						
Hazard Ratio	0.81		1.06		0.60	
95% CI (%)	[0.42;1.57]		[0.68;1.65]		[0.24;1.52]	
p-value	0.5398		0.717		0.2789	

SABRINA clinical cut-off January 11, 2016 (median observation time 37 months).
MabEase clinical cut-off December 31, 2015 (median observation time 28 months). Data are presented for the RND population defined in this study which corresponds to the conventional definition of ITT population. Overall response rates in MabEase were calculated post hoc as an exploratory endpoint.
SAWYER data cut for primary analysis (ORR at end of treatment) May 7, 2014 (median observation time 14 months); clinical cut-off for time-to-event endpoints March 10, 2016 (median observation time 36 months).
For time-to-event analyses, a hazard ratio below 1 implies a risk reduction for rituximab SC.

Figure 15 Forest Plot Showing PFS and OS Results Across Studies



6.3 SABRINA EFFICACY RESULTS (FL)

Efficacy results for the SABRINA study in FL (8 cycles of induction immunochemotherapy followed by 12 cycles of q2m maintenance) are presented for the pooled Stage 1 + 2 ITT population in the study, as pre-specified in the protocol, to allow a more precise estimation of the results.

The primary efficacy endpoint for Stage 2 of SABRINA was ORR at the end of induction, hence this endpoint was selected as the primary comparison of the pooled Stage 1+2 data. An IRC was additionally used to assess response at the end of induction in the study to verify the primary analysis. The IRC assessment of response at the end of induction was highly concordant with the investigator assessment (93% concordance rate).

Of 410 patients included in the analysis of ORR at the end of induction, 347 patients (84.6%) achieved a complete (CR or CRu) or partial response at the end/completion of induction treatment. The difference in ORR between arms was 0.49% (95% CI [−7.7;6.8]) (Table 5), demonstrating consistent efficacy between rituximab SC and rituximab IV.

Table 5 SABRINA Tumor Response Rate at End of Induction – Investigator Assessment (ITT Population)

	IV (N = 205)	SC (N = 205)
Responders[a]	174 (84.9%)	173 (84.4%)
Non-Responders	31 (15.1%)	32 (15.6%)
95% CI in Response Rates[b]	[79.2; 89.5]	[78.7; 89.1]
Difference in Response Rates	-0.49%	
95% CI for Difference in Response Rates[c]	[-7.7; 6.8]	
p-value (Chi-squared test)	0.8911	
Odds Ratio	0.96	
95% CI for Odds Ratio	[0.56; 1.65]	
Complete Response (CR and CRu)	66 (32.2%)	66 (32.2%)
95% CI for CR and CRu Rates[b]	[25.9;39.1]	[25.9;39.1]
Difference in CR and CRu Rates	0.00%	
95% CI for Difference in CR and CRu Rates[c]	[-9.3;9.3]	
p-value (Chi-squared test)	1.0000	
Odds Ratio	1.00	
95% CI for Odds Ratio	[0.66;1.51]	

[a] Patients with end of treatment response of CR, CRu, or PR.
[b] 95% CI for one sample binomial using Pearson-Clopper.
[c] Approximate 95% CI for difference of two rates using Hauck-Anderson method.

Subgroup analyses of ORR at the end of induction based on investigator assessment (Appendix 5, Table 1) support the primary analysis in the ITT population. Although there was some variability in the point estimates, 95% CIs were overlapping for all subgroups analyzed and the 95% CIs for differences in response rates between the IV and SC groups all included zero, including the high BSA subgroup (see Section 6.6). Overall, the results of the subgroup analyses are supportive of the primary analysis in the overall population and demonstrate consistent efficacy between the treatment groups.

The primary endpoint results are further supported by analogous response rates at the end of the maintenance period, where ORR was 78.1% (95% CI [71.3;83.9]) for the rituximab IV arm and 77.9% (95% CI [71.0;83.9]) for the rituximab SC arm. Point estimates for complete response (CR/CRu) were 56.2% (95% CI [48.6;63.6]) in the rituximab IV arm and 50.6% (95% CI [42.9;58.3]) in the rituximab SC arm.

PFS and OS Analyses

Results of PFS and OS in SABRINA based on a median follow-up of 37 months indicate that there is no evidence of a difference between the treatment arms with respect to long-term efficacy (Table 6).

Table 6 SABRINA Progression-Free Survival and Overall Survival (ITT Population)

	IV (N = 205)	SC (N = 205)
Progression Free Survival		
Number of patients with PFS event	57 (27.8%)	50 (24.4%)
Hazard Ratio[a]	0.84	
95% CI[a]	[0.57; 1.23]	
p-value[b]	0.3696	
Overall Survival		
Number of deaths	20 (9.8%)	16 (7.8%)
Hazard Ratio[a]	0.81	
95% CI[a]	[0.42; 1.57]	
p-value[b]	0.5398	

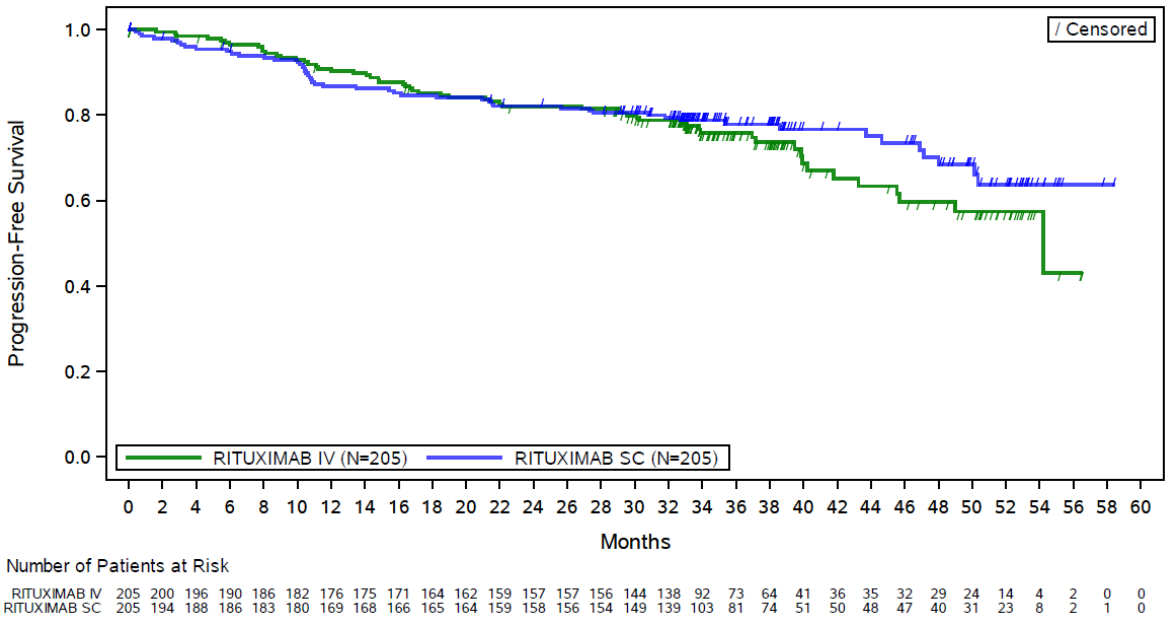
[a] Hazard ratios and corresponding 2-sided 95% confidence intervals estimated using an unstratified Cox model.
[b] Wald test p-value.

With median follow-up of 37 months, 57/205 patients (27.8%) in the rituximab IV arm and 50/205 patients (24.4%) in the rituximab SC arm had experienced a PFS event (disease progression/relapse or death from any cause).

Based on unstratified Cox analysis, the hazard ratio (HR) for PFS was 0.84 (95% CI [0.57;1.23], Wald test p-value 0.3696) indicating no evidence of a difference in PFS between the two arms. The Kaplan-Meier plot showed the curves for the IV and SC arms were largely overlapping up to approximately 36 months from randomization (Figure 16). The reverse Kaplan-Meier plot showed that the rate of censoring was low and consistent between treatment groups until shortly before 30 months, after which point the number of censored patients increased (Appendix 5, Figure 1). The PFS Kaplan-Meier curves are thus robust up to 30 months, which is consistent with median follow-up of 37 months. From Month 40 onwards, approximately 20% patients remained at risk, and beyond this Kaplan-Meier curves should be interpreted with caution (Pocock 2002). Median PFS appeared to be reached for the rituximab IV arm (54 months), however, this was based on a sharp drop at the right-hand tail of the Kaplan-Meier curve with only a few patients left at risk.

Results of PFS sensitivity analyses considering three different approaches for missing data were highly consistent with each other and further support the robustness of the primary PFS analysis (Appendix 5, Figure 2).

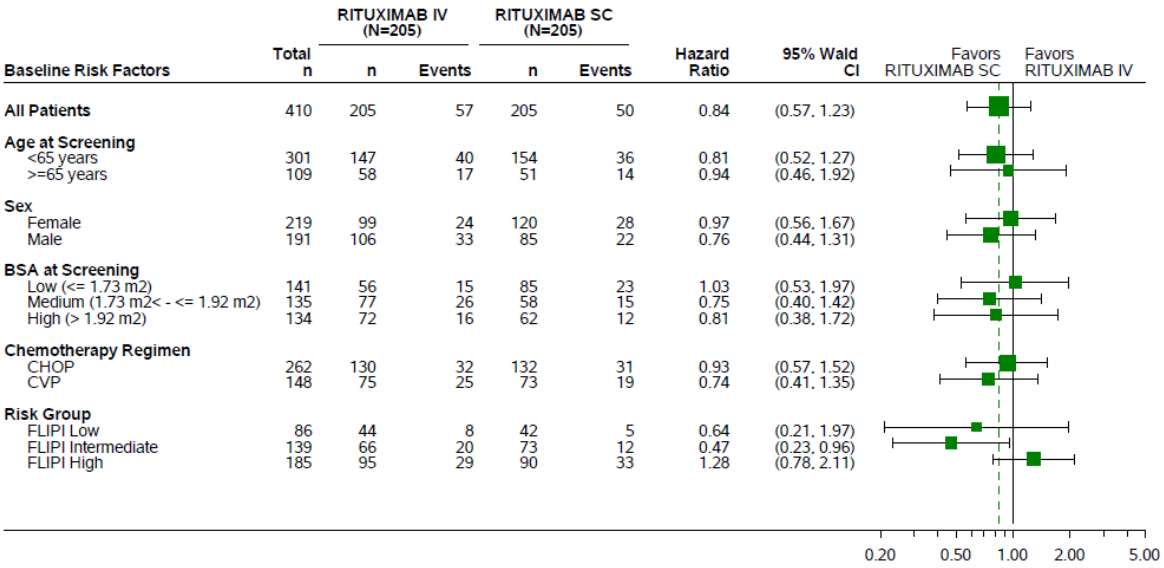
Figure 16 SABRINA (FL) Kaplan-Meier Plot of Progression-Free Survival (ITT Population)



PFS - day of randomization until 1st documented disease progression, relapse after response or death from any cause - investigator assessment. Censoring occurs at last response assessment.

In subgroup analysis of PFS (Figure 17), the 95% CIs for the PFS HRs included 1 for almost all subgroups, suggesting no evidence of a difference in PFS between the treatment arms within each subgroup. An apparent difference in the intermediate-risk follicular lymphoma international prognostic index (FLIPI) subgroup is considered a chance finding given the apparent lack of a difference between SC and IV groups for the low- and high-risk FLIPI subgroups and no apparent trend with increasing FLIPI risk category. The FLIPI categorization is based on the key prognostics factors in follicular lymphoma (Solal-Celigny 2004) and comprises five factors (age, Ann Arbor stage, hemoglobin level, number of nodal sites involved, and serum lactate dehydrogenase [LDH] levels).

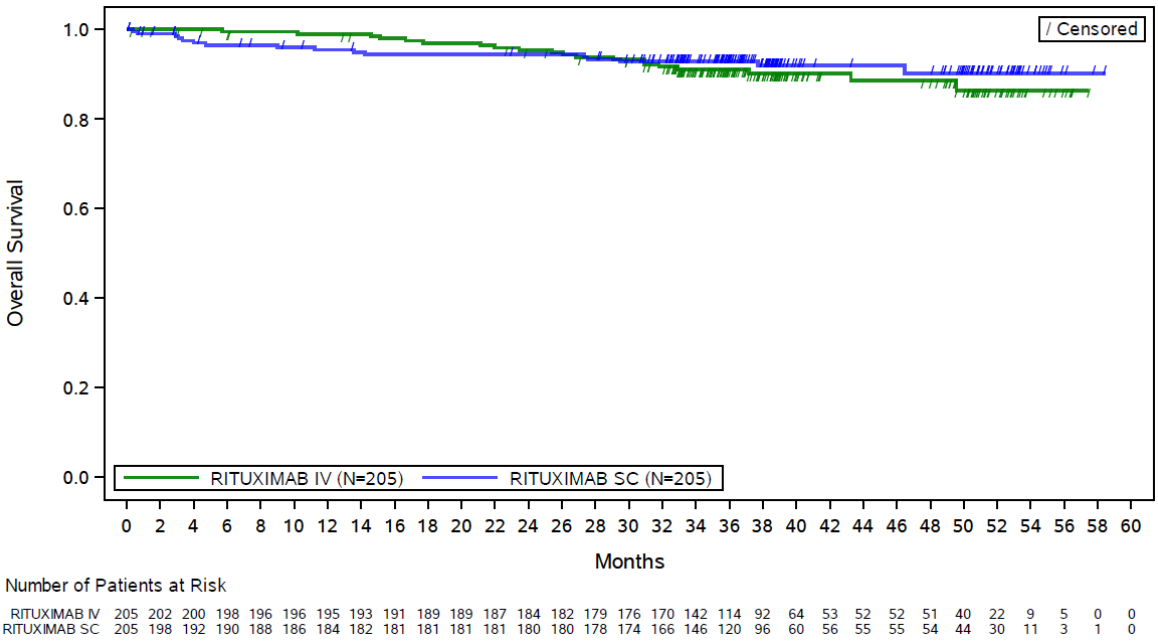
Figure 17 SABRINA (FL) Forest Plot for Progression-Free Survival (ITT Population)



BSA: body surface area (based on sampling distribution of Stage 1+2 population);
CHOP: cyclophosphamide, vincristine, doxorubicin, prednisolone; CVP: cyclophosphamide, vincristine, prednisolone; FLIPI: Follicular Lymphoma International Prognostic Index.
Hazard Ratio is calculated from unstratified Cox model.

Regarding overall survival, 20/205 patients (9.8%) in the rituximab IV arm and 16/205 patients (7.8%) in the rituximab SC arm had died from any cause at the time of the analysis. Based on the unstratified Cox analysis, the HR for OS was 0.81 (95% CI [0.42;1.57]; Wald test p-value 0.5398) (Figure 18).

Figure 18 SABRINA (FL) Kaplan-Meier Plot of Overall Survival (ITT Population)



OS - day of randomization until death from any cause. Censoring occurs at date of last contact.

Importantly, a comparison of data from the SABRINA study with historical data from rituximab IV studies (Appendix 5, page 147), including the pivotal studies M39021 (Marcus 2008) and PRIMA (Salles 2011) described in the RITUXAN USPI, suggests that the rituximab IV (and rituximab SC) group in this study performed as expected based on both short-term and longer-term efficacy measures:

- End of induction response rates in the R-CVP groups in SABRINA (ORR 82.7% IV vs 78.1% SC) were similar to those reported for the R-CVP group in study M39021 (81%).
- End of maintenance response rates in SABRINA (ORR 78.1% IV vs 77.9% SC) were similar to those for the rituximab maintenance experimental arm in PRIMA (79%).
- The correlation of complete response rates at the end of maintenance (CR30) and PFS in SABRINA was highly consistent with that observed in earlier 1L FL trials, including PRIMA, M39021, and other RITUXAN trials in the induction and/or maintenance setting (Sargent 2015), supporting the robustness of the PFS results and comparability with historical data.

6.4 MABEASE EFFICACY RESULTS (DLBCL)

The primary efficacy endpoint in the MabEase study in 1L DLBCL (8 cycles of induction immunochemotherapy) was complete response rate at the end of induction, comprising CR and CRu, based on investigator assessment. Based on the all randomized patients (RND) population, corresponding to the conventional definition of an ITT population, point estimates and corresponding 95% CIs for complete response rates were overlapping for the treatment groups, demonstrating consistent efficacy for rituximab SC and rituximab IV (Table 7).

Table 7 MabEase (DLBCL) Complete Response Rates at the End of Induction Treatment (RND Population)

	IV (N = 195)	SC (N = 381)	SC-IV[a]	p-value[b]
CR/CRu Achieved				
Yes	82	179		
No	113	202		
Response Rate (%)	42.1	47.0	4.9	0.261
Response Rate (95% CI)	35.1-49.0	42.0-52.0	-3.6 to 13.5	

a Difference in response rates (rituximab SC minus rituximab IV).
b Based on the Wald $\chi 2$.

Subgroup analyses of complete response supported the primary analysis in the RND population. Despite some variability in the point estimates, 95% CIs for the difference in complete response rates all included zero indicating no evidence of a difference between IV and SC treatment groups (Appendix 5, Table 4). Overall, the results of the subgroup analyses are supportive of the primary analysis in the overall population.

PFS and OS Analyses

For MabEase, the prespecified analysis was based on the stratified Cox model using three randomization strata (age group, international prognostic index [IPI] risk category, and chemotherapy); an unstratified analysis was planned as supportive and the results were consistent with the stratified analysis.

Overall, results of PFS and OS based on a median follow-up of 28 months indicate efficacy that is consistent for rituximab SC and rituximab IV with respect to long-term efficacy (Table 8).

Table 8 MabEase (DLBCL) Progression-Free Survival and Overall Survival (RND Population)

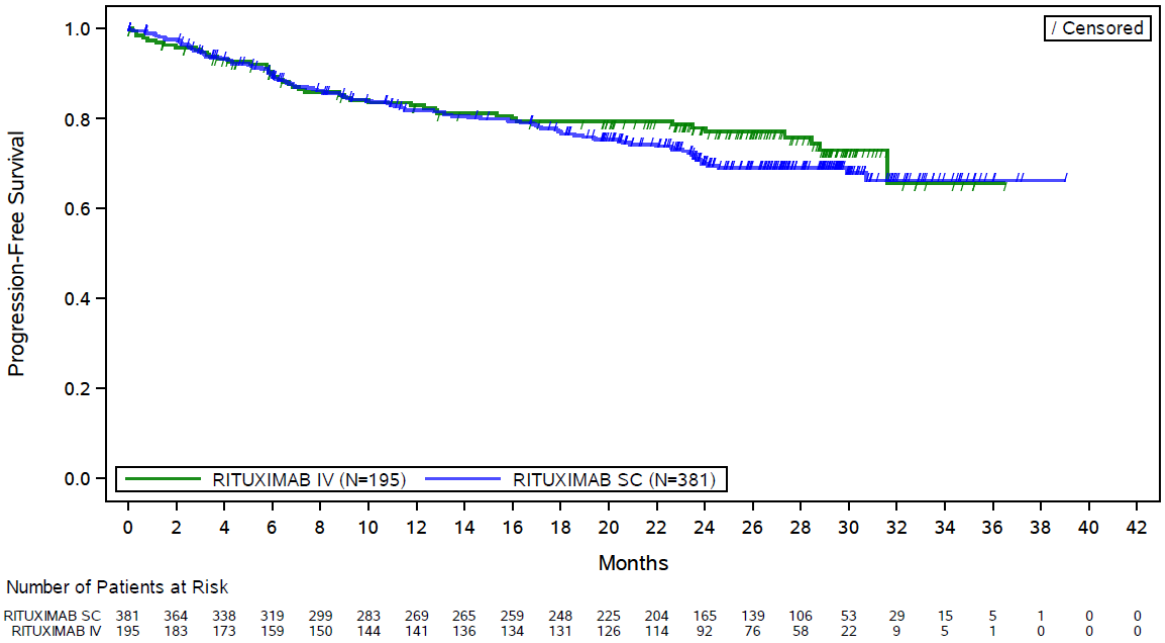
	IV (N = 195)	SC (N = 381)
Progression Free Survival		
Number of patients with PFS event	44 (22.6%)	104 (27.3%)
Hazard Ratio[a]	1.23	
95% CI[a]	[0.86; 1.76]	
p-value[b]	0.28	
Overall Survival		
Number of deaths	29 (14.9%)	63 (16.5%)
Hazard Ratio[a]	1.06	
95% CI[a]	[0.68; 1.65]	
p-value[b]	0.717	

[a] Hazard ratios and corresponding 2-sided 95% confidence intervals estimated using a stratified Cox model.
[b] Log-rank p-value.

With median follow up of approximately 28 months, 44/195 patients (22.6%) in the IV group and 104/381 patients (27.3%) in the SC group had progression of disease/relapse or died (stratified HR 1.23; 95% CI [0.86;1.76], log-rank p-value 0.280). Median PFS was not reached for either treatment group. The Kaplan-Meier curves are superimposed until 17 months (Figure 19). The reverse Kaplan-Meier plot (Appendix 5, Figure 3) showed that the rate of censoring was low and consistent between treatment groups until shortly before 21 months, after which point the number of censored patients increased greatly. The PFS Kaplan-Meier curves are thus robust up to 21 months, which is consistent with median follow-up of 28 months. The curves are superimposed again from approximately 32 months onwards (Figure 19).

Results of the unstratified Cox analysis (unstratified HR 1.21, 95% CI [0.85;1.73]) were consistent with the stratified PFS analysis. Results of PFS sensitivity analyses considering three different approaches for missing data were highly consistent with each other and further support the robustness of the primary PFS analysis (Appendix 5, Figure 4).

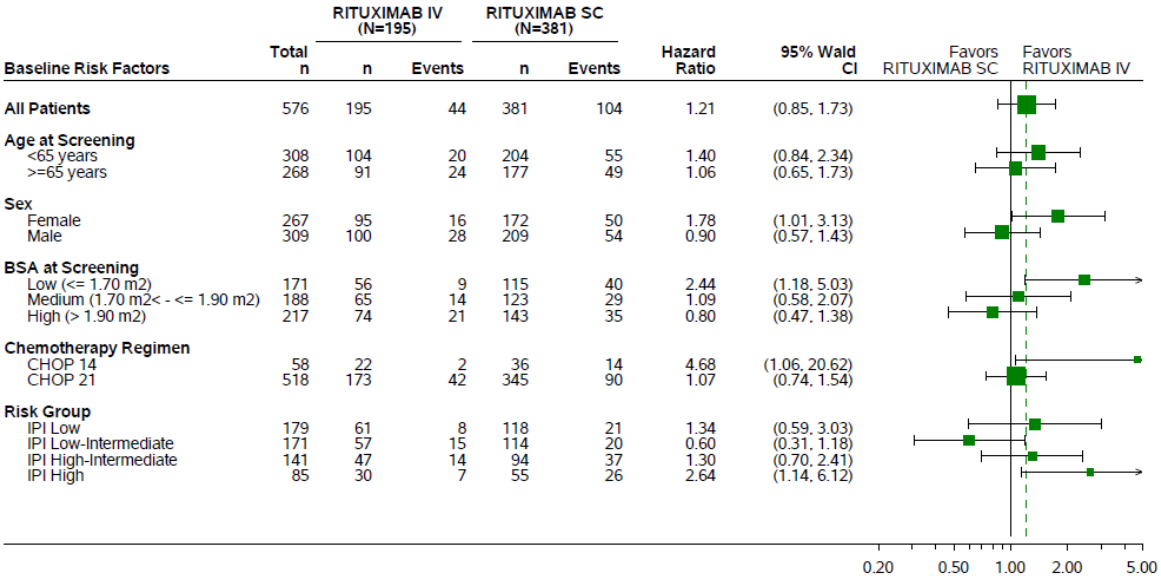
Figure 19 MabEase (DLBCL) Kaplan-Meier Plot of Progression-Free Survival (RND Population)



Time to event is calculated from randomization to first occurrence of progression of disease or death from any cause. Patients who have experienced none of these events at the time of analysis or who have been lost to follow-up will be censored at their last tumor or clinical assessment date.
Note: The curve for rituximab IV drops at approximately 32 months and is superimposed with the plot for rituximab SC.

In subgroup analysis of PFS (Figure 20), the 95% CIs for the PFS HRs included 1 for the majority of subgroups, suggesting no evidence of a difference in PFS between the treatment arms within each subgroup. Results in subgroups of IPI risk category high, CHOP-14, females, and low BSA appeared to favor rituximab IV, however, the low number of events in subgroups should be considered when interpreting the results. The IPI includes key prognostic factors identified for DLBCL (Shipp 1993) and comprises five factors (age, tumor stage, serum LDH concentration, ECOG performance status, and number of extranodal disease sites).

Figure 20 MabEase (DLBCL) Forest Plot for Progression-Free Survival (RND Population)

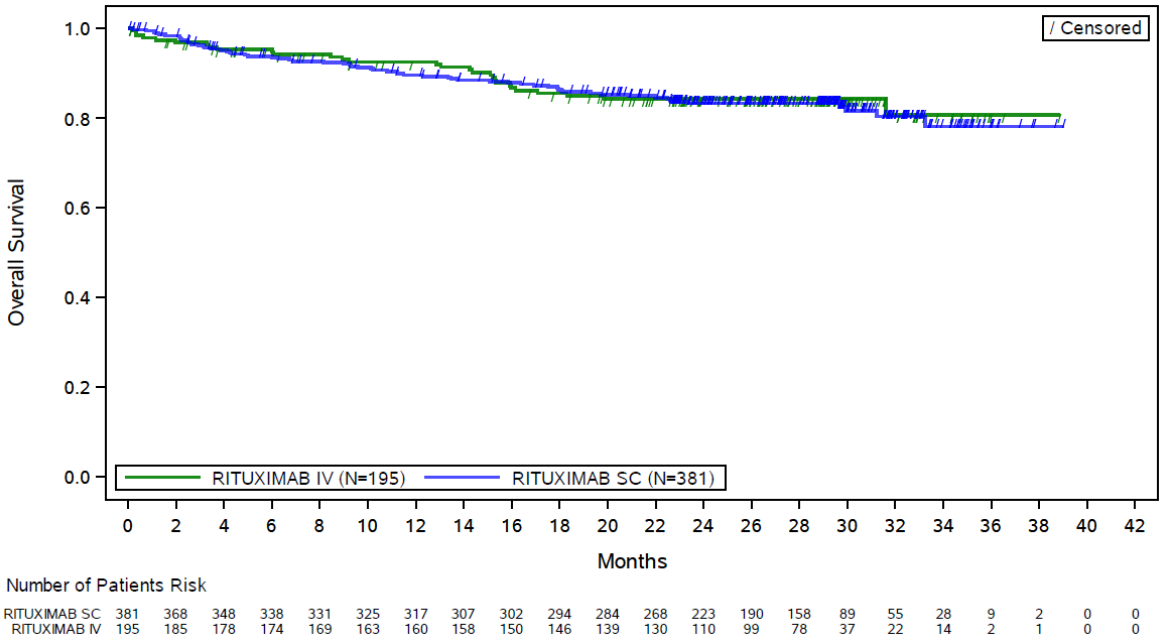


BSA: body surface area; CHOP: cyclophosphamide, vincristine, doxorubicin, prednisolone; IPI: International Prognostic Index.
Hazard Ratio is calculated from unstratified Cox model.

With EFS24 and PFS24 being considered a clinically relevant outcome for patients with previously untreated DLBCL (Maurer 2014), reflecting the proportion of patients remaining event/progression-free from diagnosis until 24 months follow-up, these endpoints were also analyzed in the MabEase study. Approximately 75% of patients had more than 2 years of follow-up or experienced an EFS/PFS event before 2 years of follow-up. Estimates of PFS24 were similar for the two treatment groups (47.2% IV and 43.3% SC) and similar to estimates of EFS24 (42.1% vs 39.6%), further supporting the consistency of the efficacy observed between rituximab SC and rituximab IV.

In regard to overall survival, 29/195 patients (14.9%) in the IV group and 63/381 patients (16.5%) in the SC group had died from any cause at the time of the analysis. The stratified HR for OS was 1.06 (95% CI [0.68;1.65], log-rank p-value 0.717). Median OS was not reached for either treatment group. The number of deaths remains too low to make definitive conclusions about OS at this time, however, the Kaplan-Meier curves for SC and IV arms overlap until 33 months (Figure 21).

Figure 21 MabEase (DLBCL) Kaplan-Meier Plot of Overall Survival (RND Population)



Time to event is calculated from randomization to death of any cause. Patients who have not died at the time of analysis or who have been lost to follow-up will be censored at the last known date they were alive - from the Survival Status page of the (e)CRF or latest clinical assessment if later than the dated survival page.

Importantly, a comparison of data from the MabEase study with historical data from rituximab IV studies (Appendix 5, page 153) further support that the rituximab IV (and rituximab SC) group in this study performed as expected based on both short-term (response rates) and longer-term efficacy measures (PFS). Comparisons with the pivotal studies described in the RITUXAN USPI that led to approval of RITUXAN in DLBCL are limited because of differences in study design and patient populations included, specifically regarding age and IPI risk categories, compared with MabEase. The study population in MabEase included previously untreated patients of all ages and all IPI risk categories and was more similar to patient population included in a large phase III UK NCRI study in 1L DLBCL (Cunningham 2013):

- Complete response (CR/CRu) rates at the end of treatment based on IWG 1999 guidelines were 63% for the R-CHOP-21 group and 58% for the R-CHOP-14 group in the UK NCRI study, which are also lower than those reported in the pivotal trials of RITUXAN (76%-86%) and more comparable to those observed in the MabEase study (43.9%-47.8% with R-CHOP-21; 27.3%-38.9% with R-CHOP-14; Table 4 in Appendix 5).
- With median follow-up of 46 months in the UK NCRI trial, 2-year PFS was 75% for both the R-CHOP-21 and R-CHOP-14 groups. In the MabEase study, with

median follow-up of 28 months, 70% of patients in the rituximab SC arm and 78% in the rituximab IV arm were estimated to be progression-free at 2 years.

6.5 SAWYER STAGE 2 EFFICACY RESULTS (CLL)

Tumor response rates at the end of treatment were assessed 3 months after the last cycle of treatment and reported at the primary analysis with median follow-up of 14 months. Time-to-event endpoints (PFS, EFS, and OS) were not analyzed at the time of the primary analysis due to insufficient events but were analyzed in an updated analysis with median follow-up of 36 months. Efficacy was analyzed for Stage 2 only which compared rituximab SC with rituximab IV.

Overall tumor response rates in the Stage 2 ITT population based on investigator assessments were similar in the rituximab IV (80.7%, 95% CI [70.9;88.3]) and rituximab SC arms (85.2%, 95% CI [76.1;91.9]). These results were comparable to those reported in a similar patient population treated with rituximab IV in combination with FC (ORR 86% and CRR 36% in the CLL8 study; Hallek 2010) which was the basis of approval of RITUXAN in 1L CLL (RITUXAN USPI).

Table 9 SAWYER (CLL) Stage 2: Summary of Tumor Response at the End of Treatment (ITT Population)

	IV (N = 88)	SC (N = 88)
Responders[a]	71 (80.7%)	75 (85.2%)
Non-Responders[b]	17 (19.3%)	13 (14.8%)
95% CI in Response Rates[c]	[70.9; 88.3]	[76.1; 91.9]
Difference in Response Rates	4.55	
95% CI for Difference in Response Rates[d]	[-7.2; 16.3]	
p-value (Chi-squared test)	0.4227	
Odds Ratio	1.38	
95% CI for Odds Ratio	[0.63; 3.05]	
Complete Response (CR and CRi)	29 (33.0%)	23 (26.1%)
95% CI for CR and CRi Rates[c]	[23.3; 43.8]	[17.3; 36.6]
Difference in CR and CRi Rates	-6.82	
95% CI for Difference in CR and CRi Rates[d]	[-20.9; 7.3]	
p-value (Chi-squared ted)	0.3216	
Odds Ratio	0.72	
95% CI for Odds Ratio	[0.38; 1.38]	

a Patients with end of treatment response of CR, CRi, or PR.
b Patients with Non-evaluated/missing response assessments are classified as non-responders.
c 95% CI for one sample binomial using Pearson-Clopper.
d Approximate 95% CI for difference of two rates using Hauck-Anderson method.

Results in subgroups (BSA, gender, C_{trough}) overall supported the primary analysis in the ITT population. Although there was some variability in ORR point estimates, the corresponding 95% CIs were overlapping for all subgroups and the 95% CIs for differences in response rates between the IV and SC groups included zero indicating no evidence of a difference between treatment groups (Appendix 5, Table 5).

With median observation time of 36 months in Stage 2, the results of the time-to-event analyses in Stage 2 show consistent efficacy across treatment arms (Table 10). The hazard ratios for PFS and OS each demonstrate a wide confidence interval crossing 1, indicating no substantial difference in benefit between treatment groups. Because of the low number of events at the time of the analysis, median survival times could not be estimated for either treatment arm for any of the time-to-event endpoints analyzed.

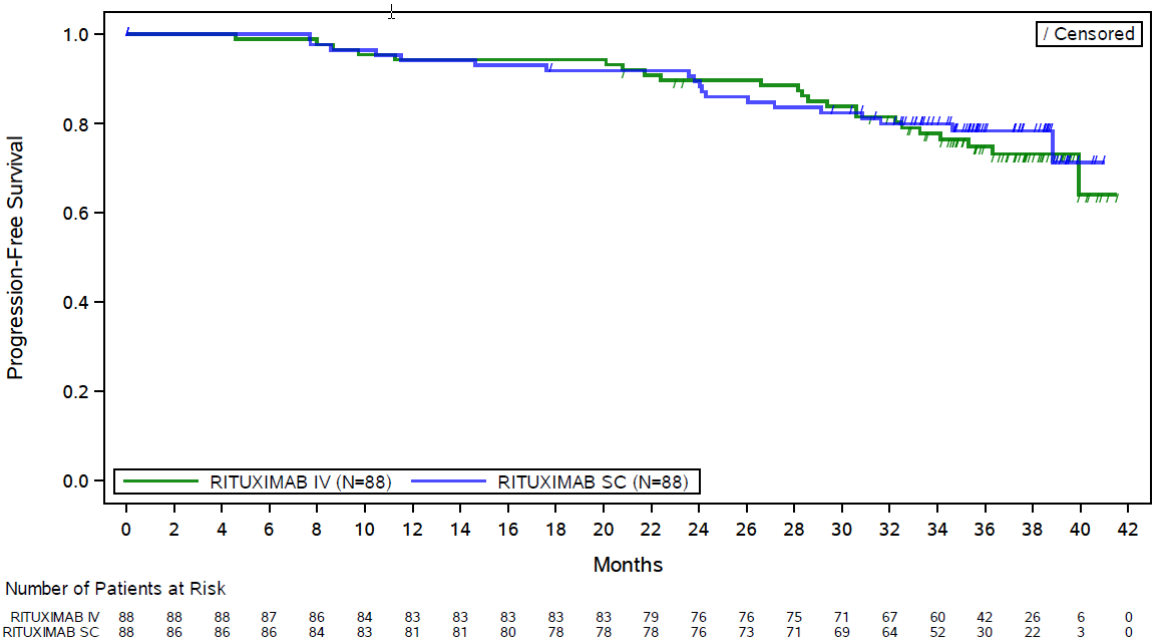
Table 10 SAWYER Stage 2: Time to Event Endpoints (ITT Population)

	IV (N = 88)	SC (N = 88)
Progression-free survival		
Number of patients with event	23 (26.1%)	19 (21.6%)
Hazard Ratio [95% CI] (unstratified Cox model)	0.89 [0.49;1.64]	
Wald test p-value	p=0.7192	
Overall survival		
Number of patients with event	12 (13.6%)	7 (8.0%)
Hazard Ratio [95% CI] (unstratified Cox model)	0.60 [0.24;1.52]	
Wald test p-value	p=0.2789	

Median observation time: 36 months.

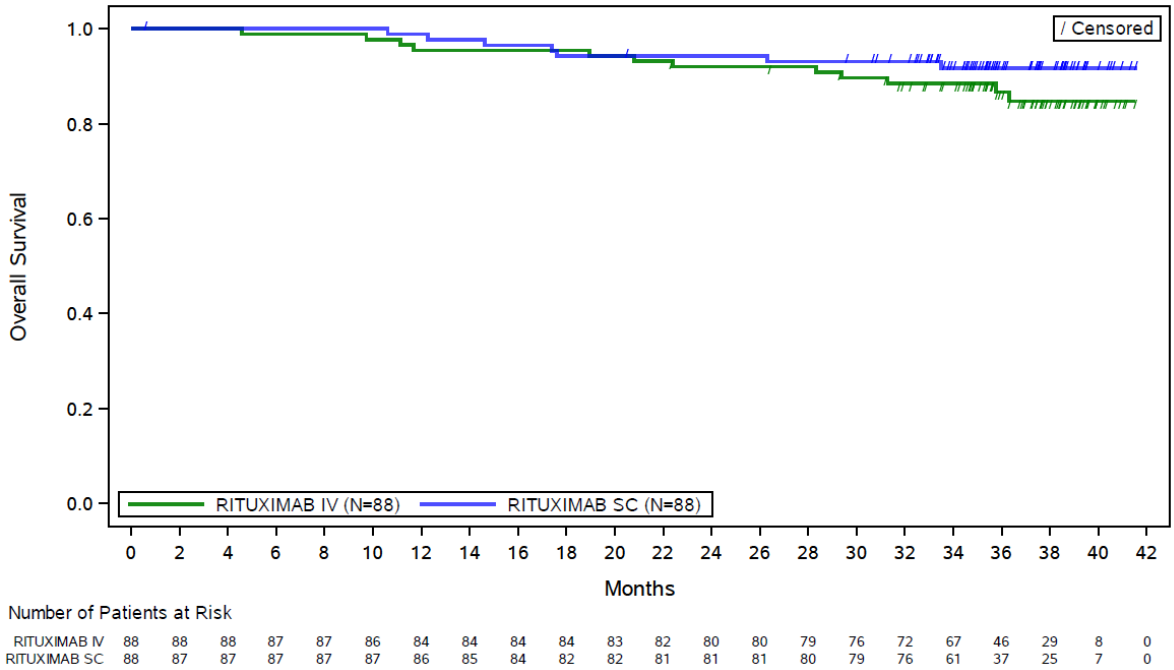
The respective Kaplan-Meier plots for PFS and for OS show similar and overlapping curves for the two treatment arms (Figure 22 and Figure 23).

Figure 22 SAWYER (CLL) Stage 2: Kaplan-Meier Plot for PFS (ITT Population)



PFS - day of randomization until 1st documented disease progression, relapse after response or death from any cause - investigator assessment.

Figure 23 SAWYER (CLL) Stage 2: Kaplan-Meier Plot for OS (ITT Population)



OS - day of randomization until death from any cause.

6.6 ANALYSIS OF EFFICACY RESULTS IN SUBPOPULATIONS: EFFECT OF BSA

In moving from BSA-adjusted dosing with rituximab IV to a fixed dosing approach with rituximab SC, the selected fixed dose of rituximab SC needed to be high enough to ensure sufficient drug exposure over the entire BSA range and, in particular, in patients with high BSA (at risk of relative under-exposure) to ensure clinical benefit.

As demonstrated in Section 5.1.4, rituximab SC doses of 1400 mg and 1600 mg result in non-inferior exposures relative to rituximab IV across the entire BSA range, including high BSA subgroups. Rituximab SC also demonstrated a similar pharmacodynamic effect (B-cell depletion/recovery) to rituximab IV (Section 5.2).

BSA subgroup analyses of response rates at the end of induction in the three efficacy studies SABRINA (1L FL), MabEase (1L DLBCL), and SAWYER Stage 2 (1L CLL) (Appendix 5, Table 1, Table 4, Table 5, respectively), and PFS in the SABRINA and MabEase studies (Forest plots in Figure 17 and Figure 20, respectively), support the PK/PD findings that patients with high BSA are adequately exposed and that the clinical benefit with rituximab SC is consistent with that achieved with rituximab IV.

6.7 EXPOSURE-EFFICACY RELATIONSHIPS

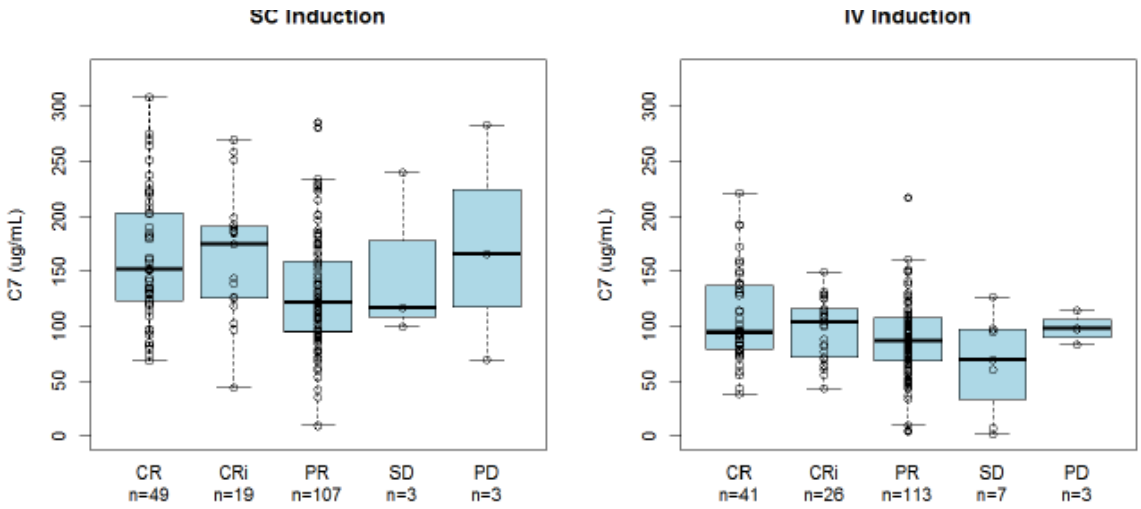
Exposure-response analyses were conducted based on data from SABRINA (FL) and SAWYER Stage 2 (CLL) to investigate the relationship between rituximab exposure and efficacy. The analyses utilized exposure measures derived from the developed and qualified population PK models (see Section 5.1.1).

6.7.1 SABRINA (FL)

For FL patients in SABRINA, graphical exposure-efficacy analyses investigated relationships of the observed values of B-cell counts, tumor size, and change of tumor size from baseline with the predicted rituximab C_{trough} at induction Cycle 7 (C7), the timepoint of the primary PK analysis (C_{trough} non-inferiority) in the study. Additionally, association of the observed ORR at the end of induction and at the end of maintenance with exposure in each treatment arm was assessed using graphical analyses. Results from these investigations demonstrated the following:

- Rituximab exposure and route of administration did not influence the time course of pharmacodynamic parameters (B-cell counts and tumor size). There were no differences in time-course of B-cell counts, tumor size, and change of tumor size from baseline between IV and SC treatment arms, and there were no relationships between these profiles and exposure for either treatment arm.
- Rituximab exposure and route of administration did not influence the clinical response of patients with FL following induction and maintenance treatment. There were no relationships between response (CR, CRu, PR, SD, or PD) during induction and maintenance and exposure, for either SC or IV treatment arms Figure 24.

Figure 24 Relationship between Predicted C_{trough} in Cycle 7 (C7) and Response Rate at the End of Induction by Treatment Arm in the SABRINA (FL) Study



The predicted exposure is plotted versus response at the end of Induction using a box and whisker plot. Median values are designated by black lines in the center of the boxes. Boxes indicate the inter-quartile range (IQR). Whiskers represent 1.5*IQR. Circles represent the individual values.

The exposure-response relationship for PFS in SABRINA was analyzed using a semi-parametric Cox proportional hazards (CPH) model. The exposure-PFS analysis using graphical displays and CPH model for patients with FL that received at least 7 rituximab doses indicated the following:

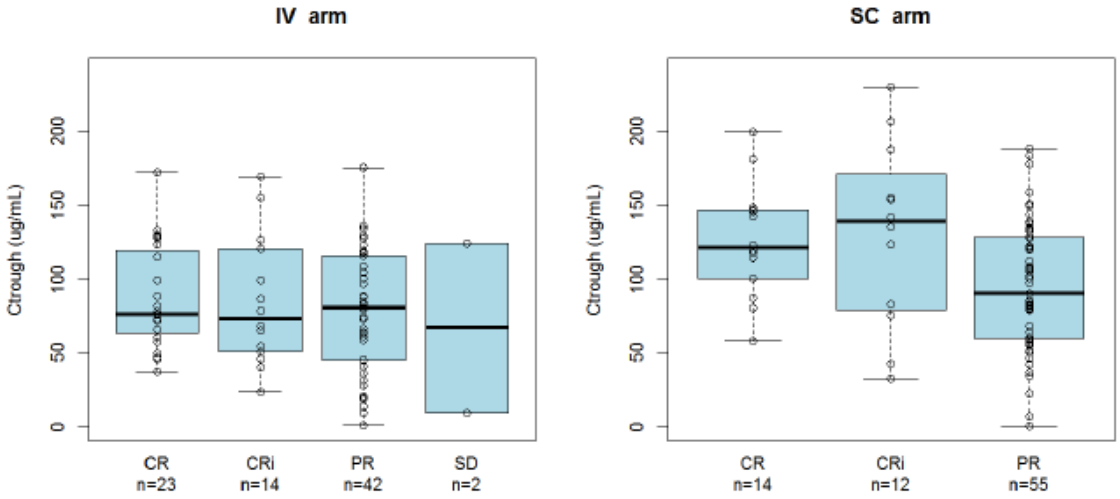
- There were no differences in PFS between the IV and SC arms and no evidence of exposure-response relationships among 363/371 patients (97.8%).
- In 8/371 patients (2.2%) with the lowest rituximab exposure (C_{trough}) at Cycle 7, risk of progression or death was approximately 12-fold higher compared with the patients with higher exposure. Of these 8 patients, 7 were from the IV arm and 1 was from the SC arm. Most of them had high B-cell counts, indicating high target expression that could explain lower exposure. Consistent with this hypothesis, all these patients had much higher initial clearance that declined slowly. Two of the 7 patients from the IV arm had anti-rituximab antibodies detected.
- Of all considered covariates, only tumor size at baseline had a statistically significant effect on PFS. Patients with higher tumor burden at baseline had an increased risk of progression or death compared to other patients.

6.7.2 SAWYER (CLL) Stage 2

For CLL patients in SAWYER Stage 2, graphical exposure-efficacy analyses investigated relationships between the observed values of B-cell counts and the association of the observed BOR with the predicted rituximab exposure (C_{mean} and C_{trough}) in each treatment arm. Results from those graphical exposure-efficacy analyses showed the following:

- For both treatments, there was a slight trend of stronger B-cell response in higher exposure groups however there were no differences between the treatment arms in nadir B-cell counts, while time to nadir appeared to be slightly shorter in the IV treatment arms.
- No clear relationships were identified between rituximab exposure and response in the two treatment arms (Figure 25).

Figure 25 Relationship between Best Objective Response Rate and Exposure by Treatment Arm in SAWYER (CLL) Stage 2



The predicted exposure is plotted versus best ORR values using a box and whisker plot. Median values are designated by black lines in the center of the boxes. Boxes indicate the inter-quartile range (IQR). Whiskers represent 1.5*IQR. Circles represent the individual values.

6.8 EFFICACY CONCLUSIONS

Data from the three controlled randomized studies in FL, DLBCL and CLL (SABRINA, MabEase, SAWYER, respectively) demonstrate consistent efficacy of rituximab IV and rituximab SC across all prespecified primary and secondary endpoints as measured by response rates and time-to-event endpoints (PFS, OS).

In the SABRINA (FL) and MabEase (DLBCL) studies, the 95% confidence intervals for the PFS HR include 1 and the p-values indicate no evidence of a difference in PFS between the treatment groups. Findings from PFS sensitivity analyses in both studies and the consistency of results across all time-to-event endpoints support the robustness of the primary PFS analysis.

Results from the SAWYER (CLL) study are also consistent for the two treatment groups and consistent across endpoints, further supporting the consistency of the observed efficacy for rituximab SC and rituximab IV as demonstrated in the SABRINA and MabEase studies.

Results among subpopulations across the three studies were consistent with the results in the overall population in each study. While there was some variability in point estimates of treatment effects, confidence intervals were overlapping in the majority of subgroups. In particular, subgroup analyses by BSA indicate there is no compromise in clinical benefit to patients with a high BSA receiving rituximab SC at a fixed dose as compared to those receiving rituximab IV at BSA-adjusted doses, supporting the C_{trough} analyses demonstrating adequate exposure to rituximab in all patients across the entire BSA range with the fixed-dose formulation (Section 5.1.4).

Exposure-response analysis of data from SABRINA (FL) and SAWYER Stage 2 (CLL) demonstrated that the majority of patients derived clinical benefit from rituximab independent of exposure and route of administration for the endpoints investigated and support the overall consistency of the efficacy profiles via either route of administration.

The entirety of data shows analogous short-term and long-term efficacy for rituximab SC and rituximab IV, across lymphoma (FL and DLBCL) and CLL. Efficacy of rituximab SC was not only consistent with rituximab IV in the studies but also consistent with the performance of rituximab IV in earlier studies that established the effectiveness of RITUXAN in B-cell malignancies.

7. ASSESSMENT OF SAFETY OF RITUXIMAB SC

7.1 SAFETY EVALUATION

Safety endpoints included all-grade adverse events (AEs), serious adverse events (SAEs), and administration-related reactions (ARRs; i.e., AEs that occurred during or within 24 h of administration and were assessed by the investigator to be related to rituximab).

The safety analysis focused on the comparison of safety between rituximab IV and rituximab SC from studies SABRINA (FL), MabEase (DLBCL), SparkThera Stage 2 (FL maintenance) and SAWYER Stage 2 (CLL), with the safety analysis populations in each study defined as patients who had received at least one dose of study drug (rituximab IV or SC) and patients analyzed as treated.

An integrated analysis of safety for “rituximab monotherapy” and “combination therapy” settings in NHL was conducted to provide a more robust safety evaluation within these patient groups and treatment settings, by pooling safety data across the three studies that assessed rituximab IV versus rituximab SC 1400 mg (SABRINA, MabEase, and SparkThera Stage 2):

- Combination therapy: Includes patients who received rituximab in combination with chemotherapy in the induction phase of SABRINA in FL and MabEase in DLBCL (979 patients treated, of whom 413 received rituximab IV and 566 received 1400 mg rituximab SC)
- Rituximab monotherapy: Includes patients who received rituximab as single agent in the FL maintenance phase of SABRINA and SparkThera Stage 2 (504 patients treated, of whom 255 received rituximab IV and 249 received 1400 mg rituximab SC)

The PrefMab (FL/DLBCL) study was not used in the safety integrated analysis because of its crossover design and thus the data were not suitable for pooling.

The SAWYER study was also not included in the integrated analysis of safety due to the different indication (CLL). Results from SAWYER Stage 2 which compares rituximab IV versus rituximab SC 1600 mg are presented in side-by-side fashion with the integrated analyses in NHL to support the overall safety profile of rituximab SC.

The three PK studies (SparkThera [FL maintenance], SABRINA [FL], and SAWYER [CLL]) included an extensive assessment of anti-rituximab antibodies and anti-rHuPH20 antibodies to compare the immunogenic potential of the new formulation and the SC route of administration versus rituximab IV.

7.2 OVERVIEW OF SAFETY OF RITUXIMAB SC

The overall safety evaluation of rituximab SC is based on 1579 patients who received at least one injection of rituximab SC at any dose across the five studies, including the dose-finding parts of the phase Ib studies. Of these, 1475 patients received one dose or more of rituximab SC at the final dose of 1400 mg (1373 patients with NHL) or 1600 mg (102 patients with CLL).

The median duration of rituximab exposure and number of cycles of rituximab received were similar between treatment arms in each study. The majority of patients completed the planned number of cycles of induction (immunochemotherapy) treatment in the SABRINA, MabEase, and PrefMab studies conducted in NHL (each 8 cycles) and in SAWYER Stage 2 (6 cycles) in CLL. As anticipated, patients in the rituximab SC treatment arms received a higher median cumulative dose of rituximab compared with patients in the rituximab IV treatment arms in line with BSA-based dosing with the IV product versus a fixed dosing regimen with the SC product (Appendix 6, Table 2).

There were no new clinically relevant safety signals observed with rituximab SC and the safety profile of rituximab SC was consistent with that of rituximab IV with the exception of administration-related reactions (ARRs, defined as any events reported within 24 h of study drug administration) and specifically local cutaneous injection site reactions which were reported more commonly in patients treated via the SC route. These ARR events were mostly mild or moderate (Table 11; see Section 7.5.1).

Some numerical differences between SC and IV treatment groups were noted for Grade ≥ 3 AEs and SAEs in the NHL combination chemotherapy clinical setting based on SABRINA induction (FL) and the MabEase study (DLBCL) data, while there were no numerical differences in severe of serious AEs observed in the rituximab monotherapy clinical setting based on SABRINA (FL) maintenance and SparkThera (FL) maintenance data (Table 11; see Section 7.3).

The difference in Grade ≥ 3 AEs between the two arms in the combination chemotherapy setting was mainly driven by a higher incidence of blood and lymphatic system disorders (specifically neutropenia AEs) and infection and infestations in the rituximab SC arm. The difference in SAEs was mainly driven by a slightly higher incidence of serious infections and infestations in the rituximab SC arm. Infections and neutropenia are well known and manageable risks in patients treated with rituximab in particular in combination with chemotherapy and are therefore not unexpected in this clinical setting. The numerical differences observed between SC and IV treatment groups for Grade ≥ 3 AEs and SAEs in the NHL combination chemotherapy analysis population did not result in imbalances in treatment discontinuation or AEs leading to deaths, and did not have any impact on the safety profile of the SC formulation in NHL patients which is considered acceptable, manageable, and similar to the IV formulation.

In the NHL rituximab monotherapy setting, based on SABRINA maintenance and SparkThera Stage 2 data, the overall safety profile was consistent between the treatment groups, with events of infections, neutropenia, and febrile neutropenia balanced between the IV and SC arms. The overall safety profile observed in SAWYER Stage 2 in CLL patients was similar for the rituximab SC and IV treatment arms and was as expected for this patient population (Table 11; see Section 7.4).

Table 11 Top Line Safety Results for Rituximab SC in NHL and CLL Populations (SAP)

	NHL (Rituximab SC 1400 mg)				CLL (Rituximab SC 1600 mg)	
	Combination Chemotherapy (SABRINA induction, MabEase)		Rituximab Monotherapy (SABRINA maintenance, SparkThera Stage 2)		Rituximab + FC Chemotherapy (SAWYER Stage 2)	
	IV (N=413)	SC (N=566)	IV (N=255)	SC (N=249)	IV (N=89)	SC (N=85)
	No. (%) of Patients		No. (%) of Patients		No. (%) of Patients	
Any AE	380 (92)	533 (94)	208 (82)	202 (81)	81 (91)	82 (96)
Grade ≥ 3 AEs	208 (50)	322 (57)	73 (29)	67 (27)	63 (71)	59 (69)
SAEs	120 (29)	204 (36)	55 (22)	48 (19)	29 (33)	25 (29)
Deaths	42 (10)	65 (11)	14 (5)	9 (4)	4 (4)	5 (6)
AEs leading to deaths	19 (5)	34 (6)	9 (4)	3 (1)	2 (2)	2 (2)
AEs leading to treatment discontinuation	25 (6)	34 (6)	9 (4)	14 (6)	7 (8)	9 (11)
Administration-related reactions	131 (32)	192 (34)	8 (3)	50 (20)	40 (45)	37 (44)
AEs classified as Infections and infestations (SOC)	170 (41)	262 (46)	136 (53)	123 (49)	44 (49)	48 (56)
Neutropenia	112 (27)	171 (30)	20 (8)	25 (10)	52 (58)	55 (65)
Febrile neutropenia	37 (9)	67 (12)	2 (1)	2 (1)	7 (8)	9 (11)

AE: adverse events; CLL: chronic lymphocytic leukemia; NHL: non-Hodgkin's lymphoma; IV: intravenous; SAE: serious adverse event; SC: subcutaneous; SOC: system organ class.

The following subsections describe safety results by treatment setting (NHL combination and monotherapy, and CLL). Supporting summary tables for all-grade AEs, Grade ≥ 3 AEs, SAEs, AEs leading to death, and AEs leading to treatment discontinuation are provided in Appendix 6.

Selected adverse events (ARRs, infections, and neutropenia) are described in Section 7.5.

Subgroup analyses of any grade AEs, Grade ≥ 3 AEs, and SAEs by low/medium/high BSA are summarized in Section 7.6. Results of an exposure-safety analysis conducted to investigate the relationship between exposure and key safety endpoints using pooled data across IV and SC treatment arms in NHL and CLL populations is summarized in Section 7.7.

Results of immunogenicity testing are described in Section 7.8.

Finally, the post-marketing experience from over 34,000 patients treated with rituximab SC since approval in 2014 is summarized in Section 7.10.

7.3 OVERVIEW OF SAFETY IN NHL (COMBINATION CHEMOTHERAPY AND RITUXIMAB MONOTHERAPY)

Overall, there were no new clinically relevant safety signals observed with rituximab SC 1400 mg in the NHL combination chemotherapy setting or in the rituximab monotherapy setting and the safety profile of rituximab SC was consistent with that of rituximab IV with the exception of local cutaneous reactions, which were more commonly reported in patients treated via the SC route. Some numerical differences between SC and IV treatment groups were noted for Grade ≥ 3 AEs and SAEs in the combination therapy population only, but the overall benefit/risk profile of rituximab SC remains positive and consistent with rituximab IV in the NHL population.

7.3.1 Combination Chemotherapy (NHL Induction Setting)

In the combination therapy analysis based on SABRINA induction (FL) and the MabEase study (DLBCL), the safety profile was generally consistent between the rituximab IV and SC arms, with the exception of local cutaneous reactions which were reported with higher incidence in the SC arm. Local cutaneous reactions were mainly of Grade 1 or 2 severity, are expected with the SC route of administration, and do not impact the overall benefit/risk profile of rituximab SC. No new clinically relevant safety signals were noted.

The incidence of all-grade AEs was balanced between the rituximab IV and SC arms (92% vs 94%) in the combination therapy setting. The most frequently reported AEs in each arm were neutropenia, nausea, constipation, and anemia, AEs known to be associated with the chemotherapy regimens administered.

The most frequent Grade ≥ 3 AEs in either arm were neutropenia, febrile neutropenia, and neutrophil count decreased. The most frequent SAEs in either arm were febrile neutropenia, pneumonia, neutropenia, and pyrexia.

Grade ≥ 3 AEs and SAEs were reported with a slightly higher incidence in the rituximab SC arm (57% for Grade ≥ 3 AEs; 36% for SAEs) compared with the rituximab IV arm (50% and 29%, respectively). The difference in Grade ≥ 3 AEs between arms was mainly driven by a higher incidence of Blood and lymphatic system disorders (34% SC vs 28% IV, specifically neutropenia AEs) and Infections and infestations (13% SC vs 8% IV) in the rituximab SC arm. In both IV and SC arms, the highest incidence of Grade ≥ 3 AEs, neutropenia, and febrile neutropenia was observed at Cycle 1 of induction combination therapy, with a slightly higher incidence noted already for the SC arm even though all patients received the IV formulation at this cycle.

The difference in SAEs was mainly driven by a slightly higher incidence of serious infections and infestations in the rituximab SC arm (13% SC vs 8% IV). Neutropenia and infections are known and manageable risks in patients treated with rituximab in combination with chemotherapy. The incidence of treatment discontinuations due to events of neutropenia and infections was low and similar for the SC and IV arms (1/413 patients in IV vs 3/566 patients in SC for neutropenia [< 1% each]; and 6/413 patients [1%] in IV vs 9/566 patients [2%] in SC for infections). Furthermore, none of the events of neutropenia led to death, and the incidence of infections leading to death was balanced (2%) between the IV and SC arms.

When looking into subgroup analyses of severe and serious AEs by BSA, similar imbalances in regard to SAEs and Grade ≥ 3 AEs were also apparent in patients with low BSA (lower tertile) treated with rituximab SC. These findings were explored with a logistic regression analysis to investigate whether the higher incidence of severe or serious AEs could potentially be associated with baseline demographic factors (including BSA), and whether there was a differential treatment effect within these factors. The results indicate a consistent association between BSA and risk of SAEs or Grade ≥ 3 AEs in both rituximab SC and IV groups in the combination therapy population. Details of BSA subgroup analyses and exploratory logistic regression analyses are presented in Section 7.6.

The overall incidence of death in the combination therapy analysis population was 11% and balanced across the rituximab SC and IV arms (10% in the rituximab IV arm and 11% in the rituximab SC arm). The incidence of deaths due to AEs (the most frequent cause of death) was similar in both treatment arms (5% IV vs. 6% SC), with infections and cardiac disorders the most common events leading to death. All AEs leading to patient deaths were each reported in 1% or less of patients in either treatment arm. Pneumonia was the most common AE leading to death.

The incidence of AEs that led to treatment discontinuation was well balanced between the rituximab IV and SC arms (6% each). All AEs that led to treatment discontinuation were each reported in ≤ 1% of patients. The most common AE leading to discontinuation was septic shock (3/413 patients in IV vs. 2/466 in SC).

7.3.2 Rituximab Monotherapy (FL Maintenance Setting)

In the rituximab monotherapy analysis based on SABRINA maintenance and SparkThera Stage 2 data from the FL maintenance setting, the safety profile was similar for the rituximab IV and SC arms, and the incidences of AEs of any grade, Grade ≥ 3 AEs, and SAEs were generally consistent between the two treatment arms. No new clinically relevant safety signals were noted.

The incidence of all-grade AEs in monotherapy was similar in the two treatment arms (82% IV vs. 81% SC). Adverse events were reported with similar incidence in the two treatment arms in all system organ classes (SOCs) with the exception of General disorders and administration site conditions (23% IV vs. 34% SC), specifically due to a difference of injection site erythema (none for IV vs. 8% SC). The most frequent AEs across both arms were cough, upper respiratory tract infection, and neutropenia.

Grade ≥ 3 AEs were reported with similar incidence between the two treatment arms (29% IV vs. 27% SC). The most frequent Grade ≥ 3 AEs were neutropenia and pneumonia.

The incidence of SAEs was also consistent between the rituximab IV and SC arms (22% vs. 19%). SAEs were reported with similar incidence between the two treatment arms in all SOCs. The most frequent SAE was pneumonia.

The incidence of deaths in this analysis population was low (5%) and balanced across the SC and IV arms (5% IV vs. 4% SC). Deaths due to AEs (the most frequent cause of death) occurred with similar incidence in both treatment arms (4% IV vs. 1% SC).

The incidence of AEs leading to treatment discontinuation was consistent between the rituximab IV and SC arms (4% vs. 6%). With the exception of neutropenia which was reported in 2 patients (1%) in the rituximab SC arm (vs none in the rituximab IV arm), all other AEs that led to treatment discontinuation were each reported in a single patient.

7.4 OVERVIEW OF SAFETY IN CLL PATIENTS

The overall safety profile observed in SAWYER Stage 2 in CLL patients was similar for the rituximab SC and IV treatment arms and was as expected for this patient population based on clinical trial and post-marketing experience with rituximab IV.

The incidence of AEs was slightly higher in the rituximab SC arm (96%) compared with the rituximab IV arm (91%). The most frequent AEs were neutropenia, nausea, thrombocytopenia, pyrexia, anemia, and vomiting.

The incidence of Grade ≥ 3 AEs was balanced between the rituximab IV and rituximab SC arms (71% vs 69%). The most common Grade ≥ 3 AEs were blood and lymphatic system disorders (neutropenia, leukopenia, febrile neutropenia, thrombocytopenia, and anemia).

SAEs were reported at comparable incidence between the two treatment arms (33% IV vs. 29% SC). The most common SAEs were febrile neutropenia and neutropenia.

The overall incidence of death in SAWYER Stage 2 was low (5%). The incidence of deaths due to disease progression (the most frequent cause of death) was similar in both treatment arms (2 patients IV vs. 3 patients SC). The individual AE terms that led to patient death occurred in 1 patient each.

The incidence of AEs leading to discontinuation of study drug was similar across the treatment arms (8% IV vs. 11% SC). Neutropenia and thrombocytopenia were the only adverse events which led to withdrawal of more than 1 patient in either treatment arm.

7.5 SELECTED ADVERSE EVENTS

7.5.1 Administration-Related Reactions

Across the studies, ARRs were defined as any AE occurring within 24 hours of treatment administration (rituximab IV or SC) and considered by the investigator as causally related to treatment.

In the integrated combination therapy analysis, the incidence of ARRs was balanced between the rituximab IV and rituximab SC populations (32% vs. 34%) (Table 12). However, the incidence of local cutaneous reactions represented by injection-site related events was higher in the rituximab SC arm compared with the rituximab IV arm, which was mainly driven by events of injection site erythema (5% vs. none) and injection site pain (2% vs. none).

The median duration of ARRs was 1 day for the rituximab IV arm (range: 1-448 days) and the rituximab SC arm (range: 1-733 days). In the rituximab IV arm, most events (70% [171/246 events]) resolved in 1 day, and 12% (29/246 events) resolved in longer than 28 days. In the rituximab SC arm, over half of the events (55% [238/431 events]) resolved in 1 day, and 12% (50/431 events) resolved in longer than 28 days.

Table 12 Administration-Related Reactions by Preferred Term Occurring in ≥ 2% of Patient in Either Arm in Combination Therapy in NHL (Safety Analysis Population)

Body System/ Adverse Event	Rituximab IV N=413 No. (%)	Rituximab SC N=566 No. (%)	Total N=979 No. (%)
All Body Systems			
Total Pts with at least one AE	**131 (32)**	**192 (34)**	**323 (33)**
General Disorders and Administration Site Conditions			
Total Pts with at least one AE	40 (10)	85 (15)	125 (13)
Chills	17 (4)	15 (3)	32 (3)
Injection Site Erythema	0	26 (5)	26 (3)
Pyrexia	9 (2)	11 (2)	18 (2)
Injection Site Pain	0	9 (2)	9 (1)
Skin and Subcutaneous Tissue Disorders			
Total Pts with at least one AE	38 (9)	47 (8)	85 (9)
Pruritus	15 (4)	14 (2)	29 (3)
Rash	7 (2)	12 (2)	19 (2)
Erythema	9 (2)	9 (2)	18 (2)
Gastrointestinal Disorders			
Total Pts with at least one AE	33 (8)	35 (6)	68 (7)
Nausea	13 (3)	12 (2)	25 (3)
Vomiting	9 (2)	5 (1)	14 (1)
Respiratory, Thoracic and Mediastinal Disorders			
Total Pts with at least one AE	25 (6)	30 (5)	55 (6)
Throat irritation	10 (2)	9 (2)	19 (2)
Dyspnea	7 (2)	11 (2)	18 (2)
Blood and Lymphatic System Disorders			
Total Pts with at least one AE	18 (4)	15 (3)	33 (3)
Neutropenia	8 (2)	6 (1)	14 (1)
Vascular Disorders			
Total Pts with at least one AE	10 (2)	14 (2)	24 (2)
Flushing	3 (1)	9 (2)	12 (1)

In the integrated rituximab monotherapy analysis, the incidence of ARRs was higher in the rituximab SC arm (20%) compared with the rituximab IV arm (3%) (Table 13). Similarly, the incidence of local cutaneous reactions represented by injection-site related events was also higher in the rituximab SC arm compared with the rituximab IV arm, which was mainly driven by events of injection site erythema (7% vs. none), injection site pain (2% vs. none), and injection site edema (2% vs. none).

The median duration of ARRs was 1 day (range: 1-408 days) for the rituximab IV arm and 2 days (range: 1-261 days) for the rituximab SC arm. In the rituximab IV arm, most events (73% [8/11 events]) resolved in 1 day, and 18% (2/11 events) resolved in longer than 28 days. In the rituximab SC arm, 46% (71/154 events) of the events resolved in 1 day, and only 3% (4/154 events) resolved in longer than 28 days.

Table 13 Administration-Related Reactions by Preferred Term Occurring in ≥ 2% of Patient in Either Arm in Rituximab Monotherapy in NHL (Safety Analysis Population)

Body System/ Adverse Event	Rituximab IV N=255 No. (%)	Rituximab SC N=249 No. (%)	Total N=504 No. (%)
All Body Systems			
Total Pts with at least one AE	**8 (3)**	**50 (20)**	**58 (12)**
General Disorders and Administration Site Conditions			
Total Pts with at least one AE	3 (1)	34 (14)	37 (7)
Injection Site Erythema	0	17 (7)	17 (3)
Injection Site Pain	0	6 (2)	6 (1)
Injection Site Oedema	0	5 (2)	5 (1)
Skin and Subcutaneous Tissue Disorders			
Total Pts with at least one AE	1 (<1)	16 (6)	17 (3)
Erythema	0	11 (4)	11 (2)
Rash	0	4 (2)	4 (1)
Musculoskeletal and Connective Tissue Disorders			
Total Pts with at least one AE	1 (<1)	6 (2)	7 (1)
Myalgia	0	5 (2)	5 (1)

In Stage 2 of the SAWYER (CLL) study, the incidence of ARRs was balanced between the rituximab IV and SC arms (45% vs. 44%) (Table 14). Overall, 2% (2/89) of patients in the rituximab IV arm and 42% (36/85) of patients in the rituximab SC arm were reported to have AEs under HLGT administration site reactions (for the evaluation of local cutaneous reactions). In the rituximab SC arm, the most common events of local cutaneous reactions were injection site erythema (26%), injection site pain (16%), and injection site swelling (5%); other local cutaneous reactions were reported in less than 2% of patients. The majority of events of local cutaneous reactions were Grade 1 or 2, and Grade 3 events were only reported in two patients in the rituximab SC arm (one patient experienced injection site erythema, injection site pain, and injection site swelling at Cycle 2; while the other patient experienced injection site erythema during Cycles 2 and 3). The median duration of ARRs in this study was 1 day for both the rituximab IV arm (range: 1-118 days) and the rituximab SC arm (range: 1-126 days).

Table 14 Administration-Related Reactions by Preferred Term Occurring in ≥ 2% of Patient in Either Arm in CLL (Safety Analysis Population)

Body System/ Adverse Event	Rituximab IV N=89 No. (%)	Rituximab SC N=85 No. (%)	Total N=174 No. (%)
General Disorders and Administration Site Conditions			
Chills	6 (7)	9 (11)	15 (9)
Pyrexia	8 (9)	7 (8)	15 (9)
Injection Site Erythema	0	10 (12)	10 (6)
Injection Site Dermatitis	0	2 (2)	2 (1)
Gastrointestinal Disorders			
Nausea	11 (12)	2 (2)	13 (7)
Vomiting	6 (7)	3 (4)	9 (5)
Abdominal Pain	3 (3)	1 (1)	4 (2)
Vascular Disorders			
Hypotension	6 (7)	1 (1)	7 (4)
Flushing	3 (3)	2 (2)	5 (3)
Hot Flush	2 (2)	0	2 (1)
Hypertension	2 (2)	0	2 (1)
Nervous System Disorders			
Headache	5 (6)	2 (2)	7 (4)
Tremor	1 (1)	2 (2)	3 (2)
Dizziness	0	2 (2)	2 (1)
Dysgeusia	2 (2)	0	2 (1)
Skin and Subcutaneous Tissue Disorders			
Hyperhidrosis	2 (2)	2 (2)	4 (2)
Erythema	1 (1)	2 (2)	3 (2)
Pruritus	1 (1)	2 (2)	3 (2)
Rash	1 (1)	2 (2)	3 (2)
Musculoskeletal and Connective Tissue Disorders			
Back Pain	3 (3)	1 (1)	4 (2)
Respiratory, Thoracic and Mediastinal Disorders			
Dyspnea	3 (3)	1 (1)	4 (2)
Injury, Poisoning and Procedural Complications			
Infusion Related Reaction	0	2 (2)	2 (1)

Investigator text for Adverse Events encoded using MedDRA version 17.0.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
Includes Adverse Events commenced on or after Cycle 1 Day 1.

7.5.2 Neutropenia and Febrile Neutropenia

In the integrated combination therapy analysis, the incidence of neutropenia was balanced between the rituximab IV and SC arms (27% vs. 30%; Table 15). The incidence of Grade ≥ 3 neutropenia was slightly higher in the rituximab SC arm (25%) compared with the rituximab IV arm (19%). Among patients with neutropenia, only a small proportion of the events were considered as serious (12% [13/112 patients] IV vs. 13% [23/171 patients] SC). The imbalance of Grade ≥ 3 neutropenia between rituximab IV and SC arms does not appear to affect rituximab treatment or patient outcome since the incidence of treatment discontinuations due to neutropenia was similar in the SC and

IV arms (1/413 patient in IV vs 3/566 patients in SC), and none of these events led to death.

The overall incidence of febrile neutropenia was balanced between the rituximab IV and SC arms (9% vs. 12%), however some imbalances were observed for this event in patients with low BSA (5% vs 14%). The majority of the events in the overall combination chemotherapy analysis population were Grade ≥ 3 (100% [37/37 patients] IV vs. 99% [66/67 patients] SC) and also considered as serious (86% [32/37 patients] IV vs. 88% [59/67 patients] SC).

The higher incidence of febrile neutropenia in the low BSA subgroup of patients in the combination chemotherapy analysis population appears to be driven by one of the two studies included in the analysis, namely the MabEase study in DLBCL, where 7% of patients (5/72) in the IV arm compared with 18% of patients (24/136) in the SC arm in the low BSA subgroup reported febrile neutropenia. Of note, none of the patients in the rituximab SC arm (all BSA groups) discontinued rituximab or died due to febrile neutropenia in this study, compared with 2 discontinuations and 1 death for the rituximab IV group, indicating that febrile neutropenia was manageable among patients treated with rituximab SC arm in this study.

Febrile neutropenia is a well-known risk associated with rituximab and has been well managed in patients in the SC arm (including low BSA patients), and the numerical differences are therefore not considered to impact the overall benefit/risk profile of rituximab SC.

Table 15 Adverse Events of Neutropenia and Febrile Neutropenia in Combination Therapy in NHL (Safety Analysis Population)

Body System/ Adverse Event	Rituximab IV N=413 No. (%)	Rituximab SC N=566 No. (%)	Total N=979 No. (%)
Total Pts with Neutropenia and Febrile Neutropenia	**136 (33)**	**209 (37)**	**345 (35)**
Total Number of AEs	149	238	387
Neutropenia	112 (27)	171 (30)	283 (29)
Febrile Neutropenia	37 (9)	67 (12)	104 (11)

In the integrated rituximab monotherapy analysis, the incidences of neutropenia were balanced between the rituximab IV and SC arms (8% vs. 10%) (Table 16). The incidence of Grade ≥ 3 neutropenia was also balanced between the two treatment arms (6% IV vs. 7% SC). Among the 47 patients with neutropenia, only 2 patients in the rituximab IV arm and 1 patient in the rituximab SC arm experienced the event as serious.

A total of 4 patients (2 patients [1%] IV vs. 2 patients [1%] SC) experienced febrile neutropenia, and all the events were Grade ≥ 3 and serious except for 1 patient in the rituximab SC arm who experienced Grade 4 febrile neutropenia, but non-serious.

Table 16 Adverse Events of Neutropenia and Febrile Neutropenia in Rituximab Monotherapy in NHL (Safety Analysis Population)

Body System/ Adverse Event	Rituximab IV N=255 No. (%)	Rituximab SC N=249 No. (%)	Total N=504 No. (%)
Total Pts with Neutropenia and Febrile Neutropenia	**21(8)**	**26(10)**	**47(9)**
Total Number of AEs	22	27	49
Neutropenia	20(8)	25 (10)	45(9)
Febrile Neutropenia	2(1)	2(1)	4(1)

In SAWYER Stage 2, the incidence of neutropenia was slightly higher in the rituximab SC arm (65%) compared with the rituximab IV am (58%), and the incidence of febrile neutropenia was balanced between the two treatment arms (8% IV vs 11% SC); see Table 11.

7.5.3 Infections and Infestations

In the integrated combination therapy analysis, the overall incidence of any grade events of infections and infestations was slightly higher in the rituximab SC arms (46%) compared with the rituximab IV arm (41%) (Table 17).

The incidence of individual infections and infestations events was balanced between the two treatment arms, and common events (occurring in ≥ 5% of patients in either arm) were urinary tract infection (7% IV vs. 4% SC), pneumonia (3% IV vs. 6% SC), and upper respiratory tract infection (3% IV vs. 6% SC). The majority of the events were Grade 1 or 2 in severity.

The incidences of Grade ≥ 3 events (13% SC vs. 8% IV) and SAEs (13% SC vs. 8% IV) were both slightly higher in the rituximab SC arm compared with the rituximab IV arm, and pneumonia was the most common severe (Grade ≥ 3) and serious event. Most severe and serious events were each reported in a single patient.

Post-hoc logistic regression analysis was conducted in order to investigate whether there were differences in the incidence of infections in the rituximab SC versus rituximab IV treatment groups. Results demonstrated that was no significant increase of risk of infections in the overall SC arm or in low BSA patients.

Infections are related to rituximab biologic nature and its B-cell-depleting mechanism of action. This risk is known and is generally manageable in the clinical setting in which rituximab is given. The slightly higher incidence of Grade ≥ 3 events and SAEs of infections observed in the rituximab SC arm in combination therapy only does not have any impact on the overall benefit risk of rituximab SC.

Table 17 Adverse Events of Infection and Infestations by Preferred Term Occurring in ≥ 5% of Patients in Either Arm in Rituximab Combination Therapy in NHL (Safety Analysis Population)

Body System/ Adverse Event	Rituximab IV N=413 No. (%)	Rituximab SC N=566 No. (%)	Total N=979 No. (%)
All Body Systems			
Total Pts with at least one AE	**380 (92)**	**533 (94)**	**913 (93)**
Infections and Infestations			
Total Pts with at least one AE	170 (41)	262 (46)	432 (44)
Pneumonia	14 (3)	36 (6)	50 (5)
Urinary Tract Infection	28 (7)	22 (4)	50 (5)
Upper Respiratory Tract Infection	14 (3)	33 (6)	47 (5)

In the integrated rituximab monotherapy analysis, the overall incidences of any grade events of infections and infestations were consistent between the rituximab IV and SC arms (53% vs. 49%) (Table 18).

The incidences of individual infections and infestations events were also consistent between the two treatment arms and the most common event was upper respiratory tract infection (10% IV vs. 13% SC). The majority of the events were Grade 1 or 2 in severity.

The incidences of Grade ≥ 3 events (6% IV vs. 9% SC) and SAEs (5% IV vs. 9% SC) were balanced between the two treatment arms, and pneumonia was the most common severe (Grade ≥ 3) and serious event. Most other severe and serious events were each reported in a single patient.

Table 18 Adverse Events of Infection and Infestations by Preferred Term Occurring in ≥ 5% of Patients in Either Arm in Rituximab Monotherapy in NHL (Safety Analysis Population)

Body System/ Adverse Event	Rituximab IV N=255 No. (%)	Rituximab SC N=249 No. (%)	Total N=504 No. (%)
All Body Systems			
Total Pts with at least one AE	**208 (82)**	**202 (81)**	**410 (81)**
Infections and Infestations			
Total Pts with at least one AE	136 (53)	123 (49)	259 (51)
Upper Respiratory Tract Infection	25 (10)	32 (13)	57 (11)
Nasopharyngitis	23 (9)	15 (6)	38 (8)
Bronchitis	18 (7)	15 (6)	33 (7)
Urinary Tract Infection	24 (9)	9 (4)	33 (7)
Sinusitis	15 (6)	14 (6)	29 (6)
Pneumonia	6 (2)	15 (6)	21 (4)
Rhinitis	12 (5)	6 (2)	18 (4)

In SAWYER (NHL) Stage 2, the overall incidence of any grade events of infections and infestations was slightly higher in the rituximab SC arm (56%) than in the rituximab IV arm (49%). The most common event (occurring in ≥ 10% of patients in either arm) was

upper respiratory tract infection (12% IV vs 13% SC), and the incidence of individual events between the rituximab IV and rituximab SC arms was similar (Table 19).

Table 19 Adverse Events of Infection and Infestations Occurring in ≥ 5% of Patients in Either Arm in CLL (Safety Analysis Population)

Body System/ Adverse Event	Rituximab IV N=89 No. (%)	Rituximab SC N=85 No. (%)	Total N=174 No. (%)
All Body Systems			
Total Pts with at least one AE	**81 (91)**	**82 (96)**	**163 (94)**
Infections and Infestations			
Total Pts with at least one AE	44 (49)	48 (56)	92 (53)
Upper Respiratory Tract Infection	11 (12)	11 (13)	22 (13)
Bronchitis	5 (6)	6 (7)	11 (6)
Respiratory Tract Infection	4 (4)	7 (8)	11 (6)
Urinary Tract Infection	7 (8)	2 (2)	9 (5)
Pneumonia	5 (6)	2 (2)	7 (4)

7.6 ANALYSIS OF SAFETY RESULTS IN SUBPOPULATIONS: EFFECT OF BSA

Patients treated with rituximab SC arms received a higher median cumulative dose of rituximab compared with patients in the IV arms in line with BSA-based dosing with the IV product versus a fixed dosing regimen with the SC product.

Key safety findings (i.e., AEs of any grade, Grade ≥ 3 AEs, and SAEs) were summarized by treatment arms and BSA to explore the potential relationship between exposure and safety, in particular in patients with low BSA.

Overall, in monotherapy and combination therapy settings, the incidence of all-grade AEs was similar among patients in low, medium, and high BSA groups for patients treated with rituximab SC, and the incidence across BSA subgroups was balanced between IV and SC groups (Table 20).

In the combination therapy population, some imbalances in Grade ≥ 3 AEs and SAEs were observed between BSA subgroups, but did not result in imbalances in treatment discontinuation or AEs leading to deaths by treatment arm.

There was a higher incidence of Grade ≥ 3 AEs and SAEs in patients with low BSA in the SC arm, as noted also for the overall population (Section 7.3.1). In the IV arm, where patients received BSA-adjusted doses of rituximab, the incidence of Grade ≥ 3 AEs and SAEs was also numerically higher in low BSA subgroups as compared to high BSA subgroups indicating that patients with low BSA in general may experience more Grade ≥ 3 AEs or SAEs than patients with higher BSA.

Differences observed between the IV and SC arm in low BSA patients was mainly driven by neutropenia (29% SC vs 21% IV) and febrile neutropenia (14% vs 5%) for Grade ≥ 3

AEs, and febrile neutropenia only (13% vs 5%) for SAEs. There was no apparent increase in incidence of infections in the SC arm in low BSA patients. The increased incidence of febrile neutropenia observed in low BSA patients in the overall combination chemotherapy population was driven by numerical differences in one study (MabEase), as described in Section 7.5.2. Febrile neutropenia is a well-known risk for rituximab in combination chemotherapy and appears to have been well managed in patients treated with rituximab SC (including low BSA patients), and the numerical differences observed between the IV and SC groups are therefore considered acceptable and do not change the overall benefit/risk profile of rituximab SC.

To further investigate these imbalances, a post-hoc logistic regression analysis was conducted. Univariate and multivariate models were used to quantify the impact of treatment, age, gender, and BSA on the risk of SAEs and Grade ≥ 3 AEs, with interaction terms included to investigate the assumption of homogeneity of the treatment effect within these covariate categories. In the multivariate model, BSA was fitted as a continuous covariate (rather than the three categories) to more fully reflect the full range of BSA values observed in the trials. Results demonstrated that the risk of SAEs and Grade ≥ 3 AEs is increased with increased age and decreased BSA (there was no gender effect), however, no significant differential effect between these factors and treatment (rituximab SC vs. rituximab IV) was observed in the multivariate model. Therefore, the association between age and BSA and the risk of SAEs or Grade ≥ 3 AEs is assessed to be consistent between rituximab SC and rituximab IV in the combination chemotherapy setting.

For monotherapy, the incidences of AEs, Grade ≥ 3 AEs and SAEs were generally balanced among patients in low, medium, and high BSA subgroups within each treatment group. Imbalances between treatment groups were noted for all-grade AEs in patients with low BSA (89% IV vs. 80% SC) or high BSA (77% IV vs. 84% SC), as well as SAEs for patients with medium BSA (25% IV vs. 19% SC).

In SAWYER Stage 2 in CLL, BSA did not appear to affect the incidence of all-grade AEs or SAEs, however, there was a trend towards a higher incidence of Grade ≥ 3 AEs with lower BSA in both IV and SC arms. This apparent trend must be considered in light of the low patient numbers per BSA category (24-35 patients per subgroup). Patients with low BSA and hence the highest exposure following administration of rituximab SC at the fixed dose of 1600 mg did not appear to report Grade ≥ 3 AEs more frequently than those receiving the BSA-adjusted dose of rituximab IV (77% IV vs 83% SC).

In summary, although patients with low BSA experienced a relatively higher exposure to rituximab with fixed dosing of the SC product compared with BSA-adjusted dosing of rituximab IV and some numerical differences were observed for SAEs and Grade ≥ 3 AEs in patients with low BSA between the SC and IV arms, the safety profile of rituximab SC is considered to be acceptable, manageable, and consistent with rituximab IV. This is further supported by exploratory logistic regression analyses where no significant

differential effect between BSA and treatment (rituximab SC vs. rituximab IV) was observed.

Table 20 Adverse Events, Grade ≥3 Adverse Events, and Serious Adverse Events in Subgroups (BSA) for NHL and CLL Populations (Safety Analysis Population)

	NHL (Rituximab SC 1400 mg)				CLL (Rituximab SC 1600 mg)	
	Combination Chemotherapy (SABRINA induction, MabEase)		**Rituximab Monotherapy** (SABRINA maintenance, SparkThera Stage 2)		**Rituximab + FC Chemotherapy** (SAWYER Stage 2)	
	IV	**SC**	**IV**	**SC**	**IV**	**SC**
BSA subgroup	**n/N (%) of Patients**				**n/N (%) of Patients**	
Patients with at least one AE	122/131 (93)	206/217 (95)	71/80 (89)	82/102 (80)	31/35 (89)	24/24 (100)
low	131/147 (89)	157/169 (93)	72/91 (79)	57/72 (79)	28/29 (97)	30/31 (97)
medium	127/135 (94)	170/180 (94)	65/84 (77)	63/75 (84)	22/25 (88)	28/30 (93)
high						
Patients with at least one Grade≥3 AE						
low	67/131 (51)	145/217 (67)	23/80 (29)	25/102 (25)	27/35 (77)	20/24 (83)
medium	79/147 (54)	93/169 (55)	27/91 (30)	22/72 (31)	18/29 (62)	20/31 (65)
high	62/135 (46)	84/180 (47)	23/84 (27)	20/75 (27)	18/25 (72)	19/30 (63)
Patients with at least one serious AE (SAE)						
low	39/131 (30)	90/217 (41)	16/80 (20)	19/102 (19)	14/35 (40)	7/24 (29)
medium	52/147 (35)	63/169 (37)	23/91 (25)	14/72 (19)	7/29 (24)	10/31 (32)
high	29/135 (21)	51/180 (28)	16/84 (19)	15/75 (20)	8/25 (32)	8/30 (27)

Subgroups for **NHL** analysis populations were based on 33rd and 66th percentiles of BSA at baseline for SABRINA and applied to both integrated analysis populations: Low BSA $\leq$ 1.73 m^2, medium BSA between 1.73 m^2 and 1.92 m^2, and high BSA $\geq$ 1.92 m^2.

Subgroups for **CLL** were based on 33rd and 66th percentiles of BSA at baseline for SAWYER Stage 2 (BSA range 1.41-2.42 m^2): Low BSA $\leq$ 1.81 m^2, medium BSA between 1.81 m^2 and 2.00 m^2, and high BSA $\geq$ 2.00 m^2.

7.7 EXPOSURE-SAFETY RELATIONSHIPS

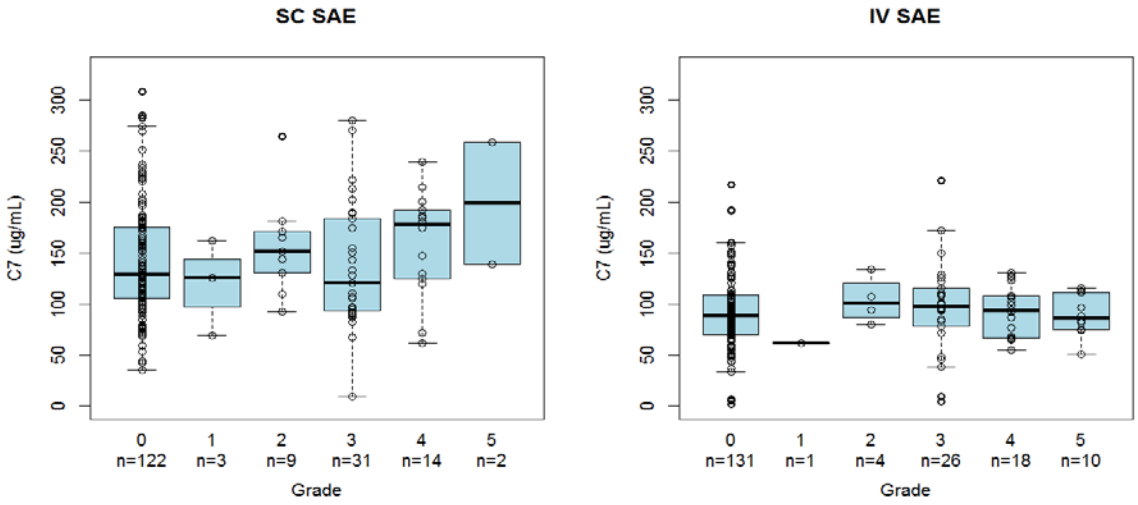
Exposure-response analyses were conducted based on data from SABRINA (FL) and SAWYER (CLL) Stage 2 to investigate the relationship between rituximab exposure and safety. The analyses utilized exposure measures derived from the developed and qualified population PK models (see Section 5.1.2).

7.7.1 SABRINA (FL)

For FL patients in SABRINA, graphical exposure-safety analyses investigated relationships of occurrence and grades of SAEs, serious infections, Grade ≥ 3 AEs, ARRs, and neutropenia in Cycle 1 (where all patients received IV rituximab) with exposure by comparing the distributions of C_{max} in Cycle 1. Relationships of occurrence and grades of SAEs, serious infections, Grade ≥ 3 AEs, ARRs, and neutropenia with exposure in all cycles beyond Cycle 1 were assessed by comparing the predicted distributions of C_{trough} values in Cycle 7 (C7) for patients with no events, and patients with all observed grades of the events, separately for SC and IV arms. Comparisons were performed overall, and for induction and maintenance separately. Patients that received less than 7 cycles of rituximab were not included in this analysis and further comparisons based on C7 exposure. Results from the analyses indicated:

- No evidence of a relationship between exposure and occurrence and grades of SAEs (Figure 26), serious infections, Grade ≥ 3 AEs, ARRs, or neutropenia, either at the first cycle or later, for either treatment arm.

Figure 26 Relationship between Rituximab Exposure (C7) and SAEs in SABRINA (FL)



Cumulatively, the graphical exposure-safety analysis of rituximab following IV and SC dosing in patients with FL indicated no correlation between rituximab exposure and

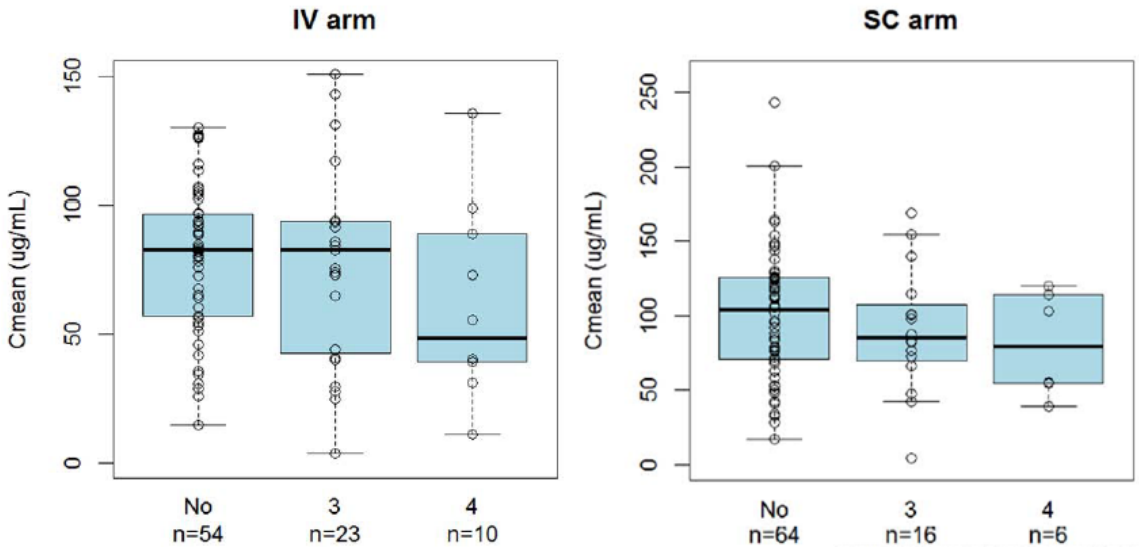
neutrophil counts, occurrence and grades of SAE, serious infections, Grade ≥ 3 AEs, neutropenia, or ARRs in either treatment arm.

7.7.2 SAWYER (CLL)

In SAWYER, graphical exposure-safety analyses were undertaken to assess the relationship between rituximab exposure and occurrence of SAEs, Grade ≥ 3 AEs, and occurrence and grades of neutropenia. Rituximab exposure was defined as the predicted average concentration (C_{mean}) for the individual patient. Results from those analyses indicated:

- No relationship between rituximab exposure and occurrence of SAEs (Figure 27), Grade ≥ 3 AEs, or neutropenia in either treatment arms.

Figure 27 Relationship between Rituximab Exposure (C_{mean}) and SAEs in SAWYER (CLL)



The predicted exposure is plotted versus the occurrence of SAEs using a box and whisker plot in patients who contributed to the PK analysis. For each subject, the exposure measures were computed using the individual subject's dosing history and the individual PK parameters from the population PK model developed on SAWYER data. Cmean is computed as the ratio of the cumulative AUC up to the time of the last dose+28 days and duration of time from zero till the last dose +28 days. No = Grade ≥ 3 AE did not occur, 3 and 4= AEs occurred with the maximum Grade of 3 and 4, respectively. Median values are designated by black lines in the center of the boxes. Boxes indicate the inter-quartile range (IQR). Whiskers represent 1.5*IQR. Circles represent the individual Cmean values

Thus, the graphical exposure-safety analysis indicated that there was no relationship with exposure for all considered endpoints for both treatment arms, and there were no differences between treatment arms.

Finally, an integrated analysis was conducted using IV and SC data across NHL and CLL patients in the PK/safety studies SABRINA and SAWYER Stage 2, respectively.

Investigated safety endpoints included SAEs, Grade ≥ 3 AEs, and the selected adverse events: ARRs, neutropenia, and SAEs from the SOC Infections and Infestations.

Logistic regression analyses of the pooled data showed no evidence of a significant relationship between rituximab exposure (C_{trough} or average concentration [C_{mean}]) and occurrence of SAE or Grade ≥ 3 AEs, ARRs, neutropenia, and risk of infections and infestations, either with rituximab SC or IV. None of the investigated endpoints showed any statistically significant relationships for either the entire induction period (Cycles 1-8) and from Cycles 2 to 8 (cycles after the initial IV dosing).

Cumulatively, the integrated exposure-safety analyses using pooled data across IV and SC treatment arms in NHL and CLL populations demonstrate no significant exposure-safety relationships for investigated safety endpoints and support the overall consistency of the safety profiles for the IV and SC treatments.

7.8 LABORATORY ABNORMALITIES AND IMMUNOGENICITY

Laboratory assessments in each study included routine hematology and chemistry assessments (including liver function tests). Laboratory abnormalities that were reported as AEs are addressed in the AE reporting sections. Laboratory data were generally consistent with patterns revealed by AE reporting, and did not otherwise reveal new safety signals.

Immunogenicity assessments for anti-rituximab antibodies and anti-rHuPH20 antibodies were systematically conducted in studies SABRINA (FL), SparkThera Stage 2 (FL), and SAWYER Stage 2 (CLL) for all patients at baseline, prior to each rituximab treatment as well as up to 2 years post rituximab treatment. Overall, evaluation of the clinical relevance of anti-rituximab antibodies and anti-rHuPH20 antibodies indicates that there was no apparent impact of the presence of anti-rituximab or anti-rHuPH20 antibodies on rituximab PK, safety (AEs, ARRs, and anaphylactic reactions) or efficacy (ORR). Immunogenicity data for the three studies are presented in accordance with the proposed harmonization of reporting clinical immunogenicity data (i.e., baseline prevalence and post-baseline incidence [induced, enhanced, or unaffected by treatment]) (Shankar 2014).

7.8.1 Anti-Rituximab Antibodies

The data from SparkThera Stage 2 (FL), SABRINA (FL), and SAWYER Stage 2 (CLL) indicate that the incidence of anti-rituximab antibodies among patients after SC administration of rituximab is consistent with that observed after IV administration (Table 21).

The post-baseline incidence of anti-rituximab antibodies (treatment-induced and treatment-enhanced HACA responses) in SparkThera, Stage 2, was 4% in the IV group

versus 1% in the SC group based on the final data including 9 months of follow-up post last dose of rituximab.

In SABRINA (FL), the post-baseline incidence of anti-rituximab antibodies (treatment-induced and treatment-enhanced responses) was 1% in the IV group and 2% in the SC group based on a conservative assessment (pre- vs post-Cycle 1 IV) of the available data. Three patients in the SC arm with a treatment-induced response each developed anti-rituximab antibodies following the first cycle of rituximab IV and prior to receiving rituximab SC.

The incidence of anti-rituximab antibodies in SAWYER Stage 2 (CLL) was 7% in the IV group compared with 2% in the SC group. Both patients in the rituximab SC arm developed a response following Cycle 1 (i.e., following the first cycle of rituximab IV) and prior to SC administration.

Table 21 Baseline Prevalence and Post-Baseline Incidence of Anti-Rituximab Antibodies across Studies

	Rituximab IV n/N (%)	Rituximab SC n/N (%)	Median follow-up time (median treatment duration)
SparkThera Stage 2 (FL)			
Baseline	0/76 (0%)	1/77 (1%)	26 months follow-up (17 months treatment)
Post-baseline[a]	3/77 (4%)	1/77 (1%)	
SABRINA Stage 1 + 2 (FL)			
Baseline	12/208 (6%)	5/191 (3%)	37 months follow-up (27 months treatment)
Post-baseline[a]	3/206 (1%)	4/197 (2%)[b]	
SAWYER Stage 2 (CLL)			
Baseline	0/87 (0%)	2/85 (2%)	14 months follow-up (5 months treatment)
Post-baseline[a]	6/89 (7%)	2/85 (2%)[c]	

a Treatment-induced/-enhanced response.
b Three patients had a treatment-induced response following the first cycle of rituximab IV. Only one of these three patients had a positive response following rituximab SC.
c Both patients in the rituximab SC arm tested positive for anti-rituximab antibodies at predose Cycle 2 following the first cycle of rituximab IV. One of these two patients had a positive response following rituximab SC.

In summary, the results indicate no increased risk of immunogenicity associated with rituximab SC compared with rituximab IV. Additionally, there was no suggestion of clinical consequences in patients with a positive HACA response based on exploratory analyses comparing key findings, such as ORR and incidence of AEs, ARRs, and anaphylactic reactions, between patients who were negative for anti-rituximab antibodies

at all timepoints versus the small number of patients with a positive response at any timepoint during the studies.

7.8.2 Anti-rHuPH20 Antibodies

Baseline prevalence rates of anti-rHuPH20 antibodies in the rituximab SC studies were in the range of 6% to 11% across the three studies and were consistent with the presence of rHuPH20 reactive antibodies in rHuPH20 treatment naïve patients and healthy volunteers of 3% to 11% as reported in the literature (Rosengren 2015). For the majority of patients who were antibody-positive at baseline in the three rituximab SC studies, the baseline assay signal was not enhanced after the start of treatment.

The post-baseline incidence of anti-rHuPH20 antibodies (treatment-induced and treatment-enhanced responses) ranged between 5% and 13% across the three studies (Table 22).

In SABRINA (FL), in which anti-rHuPH20 antibody sampling was initially done for both SC and IV arms but later performed only in patients receiving rituximab SC as only this formulation includes rHuPH20, 8% of patients in the rituximab IV control arm tested positive for anti-rHuPH20 antibodies post-baseline (Table 22). Among patients treated with the SC formulation, the post-baseline incidence of anti-rHuPH20 antibodies was 5% higher relative to the IV (control) arm (13%).

Table 22 Baseline Prevalence and Post-Baseline Incidence of Anti-rHuPH20 Antibodies across Studies

	Rituximab IV n/N (%)	Rituximab SC n/N (%)	Median follow-up time (median treatment duration)
SparkThera Stage 2 (FL)			
Baseline	–	5/77 (6%)	26 months follow-up (17 months treatment)
Post-baseline[a]	–	4/77 (5%)	
SABRINA Stage 1 + 2 (FL)			
Baseline	7/68 (10%)[b]	21/188 (11%)	37 months follow-up (27 months treatment)
Post-baseline[a]	5/66 (8%)[b]	26/197 (13%)	
SAWYER Stage 2(CLL)			
Baseline	–	9/84 (11%)	14 months follow-up (5 months treatment)
Post-baseline[a]	–	9/85 (11%)	

a Treatment-induced/-enhanced anti-rHuPH20 antibody response.
b Anti-rHuPH20 antibody testing conducted in rituximab IV patients (negative control) in Stage 1 only.

Importantly, none of the patients who tested positive for anti-rHuPH20 antibodies at any point during any of the rituximab SC studies tested positive for neutralizing antibodies.

Furthermore, there was no evidence to suggest a worsening of safety profile or loss of efficacy in patients with a positive antibody response compared with those who were negative throughout.

7.9 SAFETY CONCLUSIONS

Overall, the safety profile of rituximab SC is considered acceptable, manageable, and consistent with that of rituximab IV.

Although patients received rituximab IV at Cycle 1 of treatment, safety was reviewed over all cycles, both including and excluding Cycle 1 data, to allow a robust comparison of the safety profiles related to rituximab SC and rituximab IV.

The most common adverse events with rituximab SC and rituximab IV across the clinical studies were in line with the established safety profile for RITUXAN. Events that occurred with a higher incidence in the SC arm compared with the IV arm were reflective of the change in the route of administration and included ARRs, and specifically local cutaneous reactions, which were mostly mild or moderate in intensity.

Patients treated with rituximab SC received a higher median cumulative dose of rituximab compared to those treated with rituximab IV. A higher dose is needed to compensate for reduced bioavailability of the antibody when administered via the SC route and ensure non-inferior exposures for patients across the entire BSA range with a fixed dosing approach. Desipite a higher median cumulative dose there were no unexpected toxicities with the SC product and the overall safety of rituximab SC was similar to rituximab IV.

Some numerical differences between SC and IV treatment groups in regard to incidence of Grade ≥ 3 AEs and SAEs were apparent in the NHL combination chemotherapy analysis population, with higher incidences in the rituximab SC arm, while the overall safety profile in the rituximab monotherapy clinical setting and in the CLL setting was well balanced between the treatment groups.

The numerical differences in the combination chemotherapy setting were driven by a higher incidence of Grade ≥ 3 neutropenia, Grade ≥ 3 infections, and serious infections in the rituximab SC arm in the overall population. Neutropenia and infections are known and manageable risks in patients treated with rituximab in combination with chemotherapy. The higher incidence of these events in the rituximab SC arm did not result in imbalances in treatment discontinuation or AEs leading to deaths, and the safety profile of the SC formulation in the combination chemotherapy setting is therefore considered acceptable and manageable.

The numerical differences in certain events in the overall combination chemotherapy setting appeared to be driven by patients with low BSA, with higher incidence of Grade ≥ 3 neutropenia and febrile neutropenia, and SAEs of febrile neutropenia among patients treated with rituximab SC. However, there was no apparent clinical impact of the higher

incidence of these events in the SC arm, and the safety profile of rituximab SC in low BSA patients in the combination chemotherapy setting is also considered to be acceptable and manageable. Neutropenia and infections are well-known risks and were well managed in the combination therapy clinical setting with no overall impact on the benefit/risk profile of rituximab SC.

In addition, exposure-safety analyses using pooled data across IV and SC treatment arms in NHL and CLL populations support the overall comparability of safety profiles for the IV and SC treatments.

The immunogenic potential of rituximab in the SC product administered via the SC route of administration appears to be low and consistent with that observed in patients receiving rituximab IV. There was no suggestion of clinical consequences (worsening of efficacy or safety profile) in patients with a positive anti-rituximab antibody response. The incidence of anti-rHuPH20 antibodies was in the range seen prior to and following rHuPH20 exposure in other trials including patients and healthy volunteers (Rosengren 2015), and no neutralizing antibodies were observed.

Overall, the comprehensive safety database of over 1500 patients with different disease states (FL, DLBCL, CLL) treated with rituximab SC across the five randomized, controlled clinical studies provides evidence that rituximab SC has a safety profile consistent with RITUXAN in the treatment of B-cell malignancies. The SC route of administration, fixed dose regimen, and co-formulation with rHuPH20 do not influence the overall benefit/risk profile of rituximab, and the benefit/risk assessment of rituximab SC is therefore considered favorable.

7.10 POST-MARKETING EXPERIENCE (EX-US)

Since initial marketing approval in the United States (November 1997), rituximab IV (RITUXAN/MabThera) has been approved in approximately 135 countries worldwide to date and used in 4.4 million patients with hematologic malignancies.

Rituximab (MabThera) 1400 mg solution for SC injection was first approved in the EU on March 21, 2014, for the treatment of patients with NHL and has since been approved in approximately 50 other countries. In May 2016, MabThera 1600 mg for SC injection gained its first approval in the EU for the treatment of patients with CLL.

The estimated cumulative market exposure to rituximab (both IV and SC) up to September 30, 2016, was 5,378,160 patients, of which hematologic malignancies account for 4,431,334 patients (autoimmune indications account for 946,826 patients). Within hematologic malignancies, the majority of patient exposures were in NHL (3,415,439). By formulation, 34,179 patients had been exposed to rituximab SC 1400 mg compared with approximately 4.4 million exposed to rituximab IV. Post-marketing information with rituximab SC 1600 mg in CLL is currently not available as it was recently approved in the EU and is under review elsewhere globally.

Overall, the observations from the post-marketing setting with rituximab SC 1400 mg in NHL (Appendix 5) were consistent with the safety profile established in the clinical trials. No new safety signals have emerged from the post-marketing experience with rituximab SC, and the overall safety profile of rituximab SC remains consistent with that of RITUXAN.

8. EVALUATION OF PATIENT-REPORTED OUTCOMES AND HEALTHCARE PROFESSIONAL OPINIONS

The key study to evaluate the additional benefit anticipated with rituximab SC therapy, namely reduced treatment burden and increased patient satisfaction, was the large phase IIIb PrefMab study (FL/DLBCL), which featured a two-arm crossover study design to investigate patient preference for the SC or IV route of administration via the Patient Preference Questionnaire (PPQ).

The PPQ consisted of two questions about the patient's experiences and preferences. In the first question, patients were asked to report, based on their overall experience, on their preference for the route of rituximab administrations (IV, SC or no preference). In the second question, patients are asked to rate their preference on a 3-point scale (very strong, fairly strong, not very strong). Patients were also asked to provide two main reasons for their treatment preference. The PPQ was administered after 6 and 8 cycles of treatment to allow patients to have experience with both routes of administration and to determine if additional treatment by one route or another modified their preference.

Supportive evidence of patient preference was provided through SAWYER Stage 1 (CLL) in which, after the single SC injection at Cycle 6, patients and their treating nurses were asked which dosing route they preferred (IV or SC).

In addition, patient satisfaction was evaluated using the Cancer Treatment Satisfaction Questionnaire (CTSQ) and the specifically developed Rituximab Administration Satisfaction Questionnaire (RASQ) in the PrefMab and MabEase studies. The CTSQ is a 16-item validated questionnaire measuring 3 domains related to patients' satisfaction with cancer therapy: expectations of therapy, feelings about side effects, and satisfaction with therapy (Trask 2008). The RASQ is a 20-item validated questionnaire measuring the impact of the mode of treatment administration on 5 domains: physical impact, psychological impact, impact on activities of daily living, convenience, and satisfaction. In addition, there are 4 descriptive questions that are not part of the 5 domains and are scored separately (Theodore-Oklota 2016). In both PrefMab (FL/DLBCL) and MabEase (DLBCL), the CTSQ was completed prior to rituximab administration, whereas the RASQ was completed immediately after rituximab administration and before administration of chemotherapy. For both the CTSQ and RASQ, a higher score on a scale of 0 to 100 was a more positive indicator.

To gather data on how the SC formulation is perceived by staff administering rituximab at the clinical sites, physicians and nurses in the SABRINA (FL) and SAWYER Stage 2 (CLL) studies were asked to answer two questions on their opinion of the convenience and potential time-savings of rituximab SC compared with rituximab IV.

Type I error control was not applied to patient- or HCP-reported outcomes. The PPQ and HCP questions were simple and required straightforward decisions to state preference or opinion. The more complex CTSQ and RASQ were quantitatively validated. Overall, the methods employed were robust and informative.

8.1 PATIENT PREFERENCE

Patient preference for the SC or IV route of administration of rituximab was the primary endpoint in the dedicated, crossover design PrefMab trial, conducted in 1L FL and DLBCL, in which rituximab is given in combination with standard of care therapy for 6-8 cycles. Patients were randomized to receive either rituximab SC at Cycles 2-4 (after the first cycle rituximab IV; Arm A) or rituximab IV at Cycles 1-4 (Arm B). After interim staging, patients were crossed over to the alternative route of administration for the remaining four cycles. While recognizing the open-label design of the study, patients in both treatment arms and at both assessment timepoints (Cycle 6 and Cycle 8) indicated a preference for rituximab SC via the PPQ. The treatment sequence of rituximab IV and SC did not appear to have an effect on patient preference for SC treatment.

At Cycle 6, 495/620 patients (79.8%, 95% CI [76.5%;82.9%]) preferred SC administration, with 36.1% expressing a very strong preference and another 34.4% expressing a fairly strong preference for SC administration.

After Cycle 8, overall 477/591 patients (80.7%, 95% CI [77.3%;83.8%]) expressed a preference for SC administration (Table 23). A very strong preference for SC administration was expressed by 39.3% of patients, while a fairly strong preference was recorded for 34.3% of patients. A total of 471 patients (83.2%) retained their preference between Cycle 6 and Cycle 8. The most common reasons provided after Cycle 8 for patients preferring SC administration were: requires less time in the clinic (69.4%), feels more comfortable during administration (36.9%), and feels less emotionally distressing (29.3%).

Table 23 PrefMab (FL/DLBCL) Number (%) of Patients Indicating a Preference for Rituximab SC over Rituximab IV After Cycle 8 (ITT Population)

Variable	Arm A n = 372	Arm B n = 371	Total n = 743
Patients completing PPQ-Cycle 8 (n)	**293**	**298**	**591**
Patients who prefer SC (n [%])	**226 (77.1%)**	**251 (84.2%)**	**477 (80.7%)**
95% CI (%)	[71.9; 81.8]	[79.6; 88.2]	[77.3; 83.8]
Strength of preference			
Very strong	117 (39.9%)	115 (38.6%)	232 (39.3%)
Fairly strong	92 (31.4%)	111 (37.2%)	203 (34.3%)
Not very strong	16 (5.5%)	25 (8.4%)	41 (6.9%)
Patient didn't answer the question	1 (0.3%)	0	1 (0.2%)
Reason for preference[a]			
Feels less emotionally distressing	82 (28.0%)	91 (30.5%)	173 (29.3%)
Requires less time in the clinic	205 (70.0%)	205 (68.8%)	410 (69.4%)
Lower level of injection site pain	40 (13.7%)	52 (17.4%)	92 (15.6%)
Feels more comfortable during admin	98 (33.4%)	120 (40.3%)	218 (36.9%)
Other reason	5 (1.7%)	5 (1.7%)	10 (1.7%)
Patient didn't answer the question	17 (5.8%)	19 (6.4%)	36 (6.1%)
Patients who prefer IV (n [%])	**37 (12.6%)**	**29 (9.7%)**	**66 (11.2%)**
Strength of preference			
Very strong	7 (2.4%)	15 (5.0%)	22 (3.7%)
Fairly strong	15 (5.1%)	7 (2.3%)	22 (3.7%)
Not very strong	15 (5.1%)	6 (2.0%)	21 (3.6%)
Patient didn't answer the question	0	1 (0.3%)	1 (0.2%)
Reason for preference[a]			
Feels less emotionally distressing	16 (5.5%)	15 (5.0%)	31 (5.2%)
Requires less time in the clinic	3 (1.0%)	4 (1.3%)	7 (1.2%)
Lower level of injection site pain	18 (6.1%)	14 (4.7%)	32 (5.4%)
Feels more comfortable during admin	25 (8.5%)	19 (6.4%)	44 (7.4%)
Other reason	1 (0.3%)	0	1 (0.2%)
Patient didn't answer the question	5 (1.7%)	7 (2.3%)	12 (2.0%)
Patients with no preference [n (%)]	**30 (10.2%)**	**18 (6.0%)**	**48 (8.1%)**

Patients were randomized to receive either rituximab SC at Cycles 2-4 (after the first cycle rituximab IV; Arm A) or rituximab IV at Cycles 1-4 (Arm B). After the fourth cycle, patients were crossed over to the alternative route of administration for the remaining four cycles.

Percentages are based on total number of patients completing the questionnaire (n=591).

a On the PPQ, patients were asked, “If you have a preference for one of the administration routes, what are the TWO main reasons for your preference?” therefore percentages add up to greater than 100%.

These data are supported by data in Stage 1 of SAWYER, in which CLL patients and their treating nurses were asked about their preference of dosing route (IV or SC) after the rituximab SC injection at Cycle 6, and 91% of patients (and a similar percentage of their treating nurses) indicated a preference for rituximab SC over rituximab IV.

8.2 PATIENT SATISFACTION

The RASQ, included in the PrefMab and MabEase trials, assesses the impact of the mode of treatment administration across 5 domains. In PrefMab (1L FL/DLBCL), mean scores (scale of 0 to 100, a higher score being a more positive indicator) were higher for the SC arm in four of the five domains, with the largest difference observed in the domains of convenience (81.02 SC vs 59.03 IV) and impact on activities of daily living (83.95 SC vs 57.66 IV). In MabEase (1L DLBCL), mean scores were higher for the SC arm in all five domains (Table 24).

Table 24 Summary of RASQ Mean Scores in PrefMab and MabEase Studies (ITT Population)

		PrefMab (Cycle 4 and 8)		MabEase (Cycle 7)	
Domain		**After IV treatment N=740**	**After SC treatment N=687**	**Rituximab IV N = 144**	**Rituximab SC N = 284**
Physical impact	Mean	82.26	82.07	81.49	86.24
	(SD)	(15.584)	(15.850)	(16.848)	(14.012)
	n	622	619	140	278
Psychological impact	Mean	77.70	84.01	78.65	85.65
	(SD)	(16.377)	(14.356)	(18.233)	(13.920)
	n	614	612	141	277
Impact on activities of daily living	Mean	57.66	83.95	57.38	83.77
	(SD)	(25.148)	(16.537)	(19.230)	(16.117)
	n	433	461	140	266
Convenience	Mean	59.03	81.02	60.14	82.32
	(SD)	(20.750)	(13.119)	(17.473)	(13.428)
	n	619	599	143	279
Satisfaction	Mean	74.86	87.28	77.39	89.58
	(SD)	(19.368)	(14.964)	(18.232)	(12.051)
	n	617	624	141	282

RASQ: Rituximab Administration Satisfaction Questionnaire; SD: standard deviation.
On a scale of 0 to 100, a higher score is a more positive indicator.

Data from the CTSQ in the PrefMab and MabEase studies indicate that patients' expectations of therapy, feelings about side effects, and satisfaction with treatment are equivalent regardless of whether patients received IV or SC treatment (Table 25).

Table 25 Summary of CTSQ Mean Scores in PrefMab and MabEase Studies (ITT Population)

		PrefMab (Cycle 4 and 8)		MabEase (Cycle 7)	
Domain		**After IV treatment N=740**	**After SC treatment N=687**	**Rituximab IV N = 141**	**Rituximab SC N = 280**
Expectations of therapy	Mean	80.84	81.96	82.94	79.35
	(SD)	(18.365)	(17.856)	(16.536)	(17.422)
	n	631	627	141	280
Feelings about side effects	Mean	60.69	61.62	57.62	60.69
	(SD)	(22.266)	(22.323)	(23.339)	(21.594)
	n	630	624	141	276
Satisfaction with therapy	Mean	84.58	85.38	83.60	85.92
	(SD)	(12.207)	(11.284)	(13.451)	(11.428)
	n	619	623	141	278

CTSQ: Cancer Treatment Satisfaction Questionnaire; SD: standard deviation.
On a scale of 0 to 100, a higher score is a more positive indicator.

8.3 HEALTHCARE PROFESSIONAL OPINIONS

Data gathered from nurses and physicians in SABRINA (FL) and SAWYER Stage 2 (CLL) indicate a prevailing opinion from healthcare professionals that rituximab SC saves time and is more convenient than rituximab IV. The majority (> 85%) of staff in the SABRINA study responded that at least 1 hour could be saved by using the SC formulation in routine clinical practice. Similarly, in SAWYER Stage 2, the majority (> 90%) of staff responded at least 1 hour could be saved by using the SC formulation in routine clinical practice. The majority of staff in both studies responded at the end of treatment that the SC formulation is more convenient than the IV formulation: 97% in SABRINA (FL) and 91% in SAWYER (CLL).

8.4 PATIENT-REPORTED OUTCOME AND HEALTHCARE PROFESSIONAL OPINION CONCLUSIONS

In summary, PrefMab showed that patients with different types of B-cell malignancies showed a strong preference for rituximab SC over rituximab IV, with ‘requires less time in the clinic’ given as the most common reason. PrefMab data were supported by consistent results of patient preference from SAWYER Stage 1, as well as satisfaction questionnaires from PrefMab and MabEase studies. Patient-reported outcomes were aligned with opinions from HCPs gathered from SABRINA and SAWYER studies indicating rituximab SC is more convenient than rituximab IV and could be associated with time-savings of 1 h when used in routine clinical practice. As rituximab SC has comparable efficacy and safety to rituximab IV, the results of patient preference, patient satisfaction, and healthcare professional opinions demonstrate the additional benefit and clinical value of rituximab SC.

9. RESULTS: PHARMACOECONOMIC MEASURES

Pharmacoeconomic data were evaluated across the clinical development program as improved resource utilization at treatment facilities was another anticipated benefit related to the shorter administration time of rituximab SC.

The PrefMab and MabEase lymphoma studies evaluated the time required for rituximab administration at all cycles by measuring the time from the start of the rituximab SC injection or the rituximab IV infusion to the end of the injection or infusion, respectively. The MabEase study further evaluated chair/bed and hospital time associated with a single treatment cycle of R-CHOP immunochemotherapy.

9.1 PHARMACOECONOMIC MEASURES

Based on data from studies PrefMab and MabEase in NHL, rituximab administration time per treatment cycle from Cycle 2 onwards (following Cycle 1 IV) is reduced from hours with rituximab IV to approximately 5 minutes with rituximab SC.

In Cycle 1 of the PrefMab study (IV treatment for both treatment arms), the median administration time was 4 hours (240.0 minutes). The median administration time of rituximab SC at Cycles 2-4 in Arm A and Cycles 5-8 in Arm B was 6.0 minutes. For IV administration, the median administration time was 2.9-3.1 hours (172.8-183.3 minutes) at later cycles (Cycles 5-8 for Arm A and Cycles 2-4 for Arm B).

Administration times in the MabEase study for both treatment groups were consistent with data from the PrefMab study. At Cycle 1 (rituximab IV for both groups), the median administration time was 4.0 hours, whereas from Cycle 2 onwards the median administration time ranged from 2.6 to 3.0 hours for the IV group and 0.1 hours (i.e., 6 minutes) for the SC group.

The MabEase study also evaluated chair/bed and hospital time associated with a single treatment cycle of R-CHOP immunochemotherapy. At Cycle 2, when patients in the SC arm received their first injection of rituximab SC in combination with CHOP chemotherapy, a greater proportion of patients in the SC group compared with the IV group received treatment with a chair/bed time of less than 4 hours (82.9% SC vs 37.3% IV) or even less than 2 hours (26.8% SC vs 1.1% IV). This trend continued over subsequent cycles. A similar pattern was seen in hospital time associated with a cycle of R-CHOP treatment: a greater proportion of patients in the SC group than the IV group had a stay of less than 4 hours in hospital at Cycle 2 (36.9% SC vs 10.1% IV) and at subsequent cycles.

In summary, the data support that rituximab SC offers substantial time savings compared with rituximab IV administration (6-7 minutes with SC injection versus 2.5 hours or longer with IV infusion), which translates into tangible and meaningful

benefits for the patient and potentially relieve strain on infusion centers and ultimately allow more patients access to this life-saving drug.

10. BENEFIT/RISK CONCLUSIONS

Rituximab (RITUXAN) has a well-established safety and efficacy profile and is standard of care for various B-cell malignancies (NCCN Guidelines) based on more than two decades of clinical research (including 8 randomized, phase III studies across multiple indications) and experience with 4.4 million patients treated in clinical practice. Its mechanism of action is well characterized, specifically binding to CD20 antigen on the surface of normal and malignant B-cells.

Rituximab SC was developed using a PK-based clinical bridging approach with the underlying scientific consideration that achieving serum rituximab exposures (C_{trough}) at least as high as those achieved with approved RITUXAN doses would result in at least the same degree of target saturation and therefore expected efficacy outcomes, regardless of the route of administration. The program was primarily designed to evaluate the effects of a change in the route of administration on the overall benefit/risk profile of rituximab in the treatment of B-cell malignancies.

PK-bridging demonstrated C_{trough} non-inferiority with rituximab SC 1400 mg and 1600 mg doses compared with RITUXAN 375 mg/m^2 and 500 mg/m^2 doses at the schedules established in the treatment of NHL and CLL, respectively. Pharmacodynamic data confirm the findings from the PK-studies and demonstrated that rituximab SC achieves a similar PD effect (B-cell depletion and recovery after completing rituximab treatment) in NHL and CLL patients as RITUXAN.

Consistent efficacy for rituximab IV and rituximab SC was demonstrated across all prespecified primary and secondary endpoints across three randomized, controlled efficacy studies in FL, DLBCL and CLL. There were no clinically meaningful differences in efficacy between the SC and IV routes of administration based on demonstration of consistent efficacy between SC and IV treatment groups across all studies, as measured by response rates and time-to-event endpoints. Additionally, both the IV and SC arms in the rituximab SC efficacy studies performed consistent with the rituximab IV experimental arm from earlier studies in similar patient populations that established the benefit of rituximab treatment in NHL and CLL indications.

Overall, the development included a comprehensive safety database of over 1500 patients from five randomized, controlled clinical studies across different disease states (FL, DLBCL, CLL) treated with rituximab SC in combination with chemotherapy and/or as a single agent. Aside from administration-related reactions, there were no new clinically relevant safety signals observed with rituximab SC for NHL or CLL, and the safety profile of rituximab SC is considered acceptable, manageable, and consistent to that of rituximab IV. Post-marketing experience based on over 34,000 patients exposed since rituximab SC

was approved in the EU in 2014 was consistent with the safety profile from the clinical program and no new safety signals were detected.

Rituximab SC was developed as an option to simplify and shorten administration relative to RITUXAN, aimed at reducing the treatment burden for patients. Patients treated in the clinical program expressed preference for rituximab SC over IV because of less time in the clinic, comfort during administration, less emotional distress while receiving treatment, and lower levels of injection site pain. Furthermore, doctors and nurses consistently responded that rituximab SC was more convenient than the IV formulation and could lead to time-savings when used in routine clinical practice, which may allow more patients access to this life-saving drug.

Overall, the entirety of the data from five clinical studies including over 1500 patients treated with rituximab SC across the disease states that have been approved for RITUXAN (FL, DLBCL, CLL) demonstrates positive benefit/risk and supports full approval of rituximab SC for the full range of oncology indications that are currently approved for RITUXAN.

11. REFERENCES

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Appendix 1 Rituximab Pharmacokinetics

RITUXIMAB IV: EVIDENCE FOR ASSOCIATION BETWEEN EXPOSURE AND OUTCOMES FROM LITERATURE SEARCH

A prospective clinical investigation of a dose/exposure-efficacy relationship for rituximab was never formally conducted. Rituximab IV dose selection for NHL and CLL was based on the current thinking of chemotherapeutic agents during the time of its development. In view of rituximab's benefit risk profile, it is no longer considered ethical to undergo efforts to establish such relationship as it would require patients to receive rituximab doses below the clinically established rituximab doses. However, rituximab's PK is well investigated and, while no formal prospective exposure response analysis has been conducted for intravenous rituximab, exploratory analyses of published nonclinical and clinical data provides evidence for relationships between rituximab exposure and response, as summarized below.

Nonclinical investigations have characterized the dose-concentration-effect relationship of rituximab in murine syngeneic models of lymphoma expressing human CD20 (Dayde 2009). Results from these experiments showed that the lowest tested dose, 6 mg/kg of rituximab, did not modify survival, with median survival time being 22 days (range, 16-27 days), whereas mice treated with 12, 20, or 40 mg/kg of rituximab had a significantly longer survival than those of the control group with median survival times of 28 days (range, 19-34 days), 32 days (range, 19-60 days), and 43 days (range, 37-60 days), respectively. The 20 mg/kg (intermediate) dose was considered high enough to enable the study of inter-individual variability in response because 23% achieved a CR and 59% achieved a PR. The nonclinical experiment supports that at low rituximab doses no clinical benefit is observed over control, while increasing rituximab doses (and, presumably, exposure) were associated with prolonged survival in mice.

Similarly, multiple clinical investigations, including sponsor's historical data, have identified or suggested relationships between rituximab exposure and clinical outcome and are summarized below. Additionally, a literature search was conducted using the PubMed database, searching for the term "rituximab concentration clinical response". The search resulted in 78 publications, from which those with original exposure-response relationship data are summarized according to relevance below.

- Berinstein et al. (1998) reported on the outcome of the first phase III trial IDEC-102-05 with rituximab evaluating the safety and efficacy of once weekly times four dosing of rituximab (IDEC-C2B8) in patients with relapsed low-grade or follicular B-cell lymphoma. The authors observed a statistically significant correlation between the median mAb concentration and responding versus non-responding patients at multiple time-points during the treatment and follow-up, with lower exposures being observed in non-responders.
- Yin et al. (2010) later analyzed data from study IDEC 102-05 study using a population PK approach to characterize sources of between patient variability in

rituximab PK and to investigate the association between PK and clinical outcomes of rituximab in patients with NHL. The association of rituximab PK with response and time to progression (TTP) in the follicular lymphoma subgroup was evaluated by logistic and Cox regression, respectively. In the FL subgroup (N = 111), a positive association of rituximab serum concentrations pre-second infusion with overall response rate and TTP was observed among patients with low concentrations (< 35 μg/mL): odds ratio 1.72 (95% CI [1.14;2.60], p = 0.009) for response and HR 0.75 (95% CI [0.64;0.91], p = 0.0032) for TTP (per 5 μg/mL). In contrast, no association with response or TTP was seen for FL patients with higher serum concentrations (i.e., above ≥ 35 μg/mL). Similar results were observed for timepoints at 1 and 3 months post-treatment. The association was not qualitatively affected by baseline characteristics or disease factors. The authors concluded that higher rituximab concentrations are associated with better clinical outcomes only in those with serum concentrations in a low range.

- Maloney (1997) evaluated rituximab in patients with relapsed low-grade NHL using 4 weekly doses of 375 mg/m^2. The Wilcoxon rank sum test was used to examine the relationship between the pre-infusion and post-infusion rituximab concentrations and the clinical response. A correlation was observed between clinical response and the median values of rituximab serum levels before the second infusion (p = 0.029), with responders having a median of 82.7 μg/mL (range, 1.2 to 125.3 μg/mL) versus non-responders with a median of 21.9 μg/mL (range, 1.1 to 99.0 μg/mL).
- Lazzarino et al. (2005) investigated combinations of rituximab, vincristine, and 5-day cyclophosphamide for heavily pretreated follicular lymphoma. They considered that the regimen designed on the basis of the PK of rituximab was important for the clinical efficacy of the combination and considered trough concentrations of rituximab above 25-50 μg/mL the cutoff level for rituximab efficacy.
- Gordan et al. (2005) investigated patients with CD20-positive lymphoproliferative disorders receiving four weekly doses of rituximab IV at the standard dose of 375 mg/m^2 followed by a PK-based maintenance dosing where a single infusion of 375mg/m^2 rituximab was given whenever the serum rituximab level decreased below 25 μg/mL. Monthly serum analysis demonstrated significant differences in mean rituximab serum levels at 1 month (181 μg/mL vs 93 μg/mL) and at 4 months (49 μg/mL vs 9 μg/mL) for responders and non-responders, respectively.
- Igarashi et al. (2002) investigated association between rituximab C_{trough} and both response and PFS in a phase II Japanese study in relapsed patients with indolent B-cell lymphoma and mantle cell lymphoma. The analysis showed that there was a significant difference in PFS between the patients showing higher serum rituximab levels (≥ 70 μg/mL; i.e., value near to either the mean,

68.0 μg/mL, or the median, 71.5 μg/mL) and those showing lower serum rituximab levels (log-rank test, $p < 0.05$).

- Tobinai et al. (2004) conducted a Japanese multicenter phase II and PK study of rituximab in relapsed or refractory patients with aggressive B-cell lymphoma. There was a significant difference in mean C_{trough} (before week 8 dosing) and AUC (week 8 dosing) for responders compared with non-responders (59.7 ± 11.4 and 43.0 ± 6.4 μg/mL, respectively, $p = 0.015$, and 609,000 ± 147,000 and 383,000 ± 177,000 μg • h/mL, respectively; $p = 0.037$). There were no significant differences in C_{max} and serum half-life of rituximab between the two groups.
- Jäger et al. (2012) demonstrated an association between rituximab C_{trough} levels and response to treatment in FL patients. Serum concentrations during induction cycles 2 and 4 showed significant correlation with complete response (CR) rates at the end of induction ($p = 0.005$). Meanwhile, a correlation between AUC and C_{trough} indicated that C_{trough} could be used as surrogate for AUC in further analysis ($R = 0.454$; $p = 0.007$).

In summary, multiple publications provide consistent evidence for associations between rituximab exposure and outcomes. Multiple studies, both nonclinical and clinical, have demonstrated or suggested an association between rituximab C_{trough} and AUC and efficacy in B-cell malignancies. Low rituximab C_{trough} and AUC have been associated with poorer outcomes for evaluated efficacy endpoints, with reports postulating the need to consider or target PK exposures to ensure clinical efficacy.

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Appendix 2 Additional Information on rHuPH20

DATA FROM NONCLINICAL STUDIES

Nonclinical studies with rHuPH20 have demonstrated that rHuPH20 is a locally and transiently acting, permeation enhancer. rHuPH20 has a half-life of less than 30 minutes in skin. Additionally, rHuPH20 was undetectable in plasma after subcutaneous administration at doses used clinically (Wynne 2013). The effects of rHuPH20 on the SC injection site are also reversible because the half-life of hyaluronan in skin is less than 2 days (Fraser 1997). rHuPH20 was well tolerated in animal models after acute and chronic administration (data on file; Kang 2012; Kang 2013).

Studies in the minipig, a translational model of human skin, have demonstrated that rHuPH20 improves dispersion of therapeutic proteins infused in the SC tissue, reduces tissue pressure and induration, including loss of elasticity/pliability of tissue, maintains blood flow at the injection site, and improves absorption of the therapeutic protein (Kang 2012; Kang 2013).

Increased absorption of rituximab by rHuPH20 was demonstrated in a minipig model. Compartmental PK modeling demonstrated approximately a three-fold increase in absorption rate of rituximab with rHuPH20-containing formulations as compared to formulations without rHuPH20 (Bittner 2014). Rapid absorption of rituximab with SC formulations containing rHuPH20 was also confirmed in mice and Cynomolgus monkeys (Bittner 2014).

The nonclinical development program for rituximab SC demonstrates similar safety and PD with the SC and IV formulations. An 8-week general toxicity study in Cynomolgus monkeys confirmed that the change in route of administration and use of rHuPH20 did not change the overall established safety characteristics of rituximab. A rabbit local tolerance study demonstrated that rituximab SC was well tolerated. Additionally, results from development and reproductive toxicity studies in mice indicated suitable safety margins (HYLENEX USPI). A pharmacology study in Cynomolgus monkeys demonstrated similar depletion of CD20+ B-cells in blood following IV or SC administration of rituximab, despite differences in peak concentrations, when similar serum trough levels were achieved.

The nonclinical safety data support the proposed rHuPH20 doses in human. No toxicity was noted in the general toxicity studies with rHuPH20 in the Cynomolgus monkey. Repeated-dose toxicity was assessed in Cynomolgus monkeys in a 7-day study with daily IV and SC doses of 5 mg/kg (580,000 U/kg) as well as in a 39-week study with weekly SC doses up to 2 mg/kg (201,900-232,000 U/kg) with no adverse toxicological findings. Local tolerance at the administration sites was examined in Cynomolgus monkey as part of the repeat-dose toxicity studies, and was well tolerated for both SC as well as IV routes of administration.

The nonclinical package for rituximab SC supports a well-tolerated formulation containing rituximab and rHuPH20. No specific safety concerns were observed. These nonclinical data are in alignment with the extensive clinical experience with rituximab IV and the rituximab SC clinical experience containing rHuPH20 (as outlined in Section 2.2.2).

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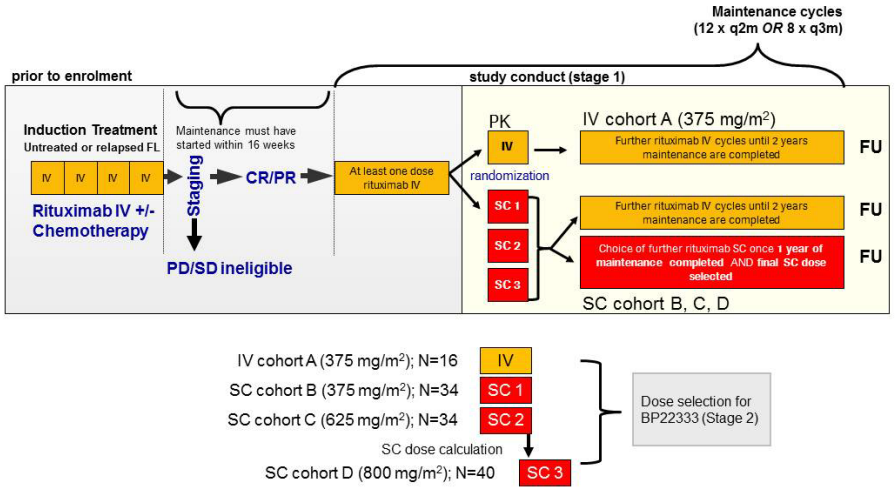
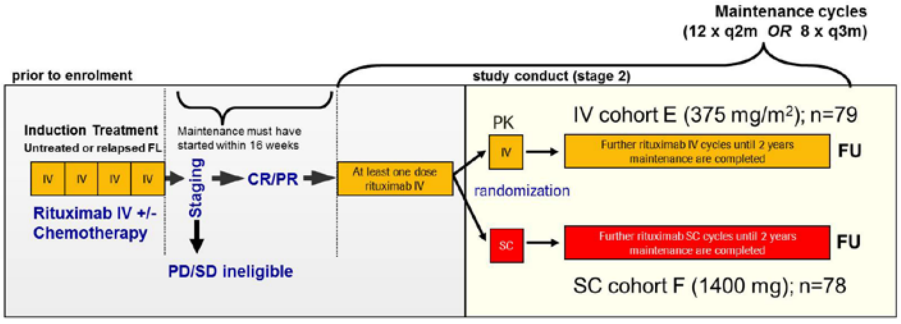
Appendix 3 Synopses of Individual Studies in Clinical Development Program

SYNOPSIS OF CLINICAL STUDY – SPARKTHERA

TITLE OF THE STUDY	BP22333/SparkThera – A Two-Stage Phase Ib Study to Investigate the Pharmacokinetics, Safety, and Tolerability of Rituximab Subcutaneous (SC) Formulation in Patients with Follicular Lymphoma (FL) as Part of Maintenance Treatment
PERIOD OF TRIAL	First patient entered: September 08, 2009 Data cut-off / LPLV: July 15, 2013
CLINICAL PHASE	Ib
OBJECTIVES	**Primary Objectives** **Stage 1 (Dose Finding)** • To determine a rituximab SC dose that yielded comparable serum trough concentrations (Ctrough) to rituximab IV. **Stage 2 (Dose Confirmation)** • To demonstrate comparable Ctrough of rituximab SC and rituximab IV with the SC dose determined from Stage 1, as assessed by a non-inferiority test with a lower boundary above 0.8 for the two-sided 90% confidence interval. **Secondary Objectives** **Stage 1 (Dose Finding)** • To compare the safety profile of different doses of rituximab SC with the safety profile of rituximab IV (in particular, the incidence and severity of infusion-/ injection-related reactions). • To evaluate area under the serum concentration – time curve (AUC) levels of rituximab SC compared with that of rituximab IV. • To examine peripheral blood B-cell depletion and repletion with rituximab SC and rituximab IV. **Stage 2 (Dose Confirmation)** • To examine peripheral blood B-cell depletion and repletion with rituximab SC and IV. • To compare the safety profile of rituximab SC with the safety profile of rituximab IV (in particular, the incidence and severity of infusion-/injection-related reactions). • To evaluate AUC levels with rituximab SC compared with those of rituximab IV.

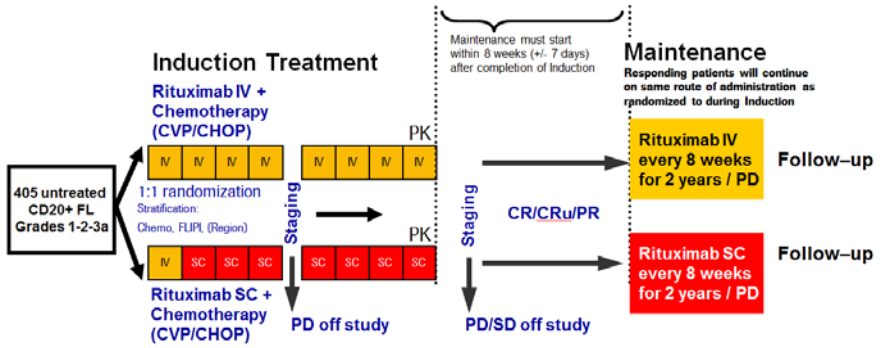
STUDY DESIGN	**Stage 1 (Dose Finding)**  **Stage 2 (Dose Confirmation)**  This was a two-stage randomized, open-label, multicenter adaptive Phase Ib study in patients aged 18 years or older with follicular lymphoma. **In Stage 1**, one single cycle of rituximab SC was administered to select a dose of rituximab SC that would result in rituximab Ctrough values comparable to those achieved with the IV regimen. Patients who had received at least one dose (infusion) of rituximab IV in the maintenance setting were randomized initially in 1:2:2 fashion to receive a single cycle of either rituximab IV 375 mg/m2 (Cohort A) or rituximab SC (375 or 625 mg/m2; Cohorts B and C, respectively) and thereafter resume rituximab IV treatment. Following a preliminary assessment of PK data from the first 25 patients enrolled, an additional cohort was opened at a higher dose of rituximab SC (800 mg/m2; Cohort D) and the allocation was adjusted to 1:2:2:2. **In Stage 2**, patients were randomized 1:1 to receive rituximab IV 375 mg/m2 (Cohort E) or rituximab SC at the dose selected in Stage 1 [1400 mg (Cohort F)] to demonstrate noninferiority of the rituximab Ctrough levels with the SC dose compared with the IV dose. Patients randomized to an SC cohort in Stage 1 who had received at least 1 year of rituximab IV maintenance were given the option to switch to the final selected rituximab SC dose for the remaining cycles of their maintenance treatment (SC extension phase).

STUDY DESIGN (continued)	After completing maintenance treatment, patients in both Stage 1 and Stage 2 had three scheduled follow-up visits at 3, 6, and 9 months after their last cycle of rituximab.
NUMBER OF SUBJECTS	Stage 1: 124 patients randomized 1:2:2:2 to Cohorts A - D: - 16 patients in Cohort A (rituximab IV 375 mg/m2) - 34 patients in Cohort B (rituximab SC 375 mg/m2) - 34 patients in Cohort C (rituximab SC 625 mg/m2) - 40 patients in Cohort D (rituximab SC 800 mg/m2) Stage 2: 157 patients randomized to Cohorts E and F: - 79 patients in Cohort E (rituximab IV 375 mg/m2) - 78 patients in Cohort F (rituximab SC 1400 mg)
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Adult patients with follicular lymphoma who had achieved at least a partial response after induction treatment with rituximab IV (as monotherapy or in combination with chemotherapy) and received at least one cycle of rituximab IV 375 mg/m2 in the maintenance phase.
TRIAL DRUG	Rituximab SC was supplied as a ready-to-use liquid formulation with a nominal content of 120 mg/mL rituximab and 2000 U/mL recombinant human hyaluronidase (rHuPH20) in 10-mL vials.
DOSE / ROUTE / REGIMEN / DURATION	Patients in the dose-finding part of Stage 1 received a single cycle of rituximab SC at one of three different BSA adjusted test doses: 375, 625, and 800 mg/m2. Patients participating in the SC extension phase in Stage 1 received between 1 and 5 cycles of rituximab SC (1400 mg) at the dose selected in the dose-finding part of Stage 1. Patients in Stage 2 received between 1 and 11 cycles of rituximab SC 1400 mg. Rituximab SC was administered using a 27-gauge needle inserted in the subcutaneous space in the abdomen, with a flow rate of approximately 2 mL/min. Rituximab was given on Day 1 of each cycle. The dosing regimen was once every three months (q3m) or once every two months (q2m) for a total of 8 or 12 cycles, respectively, of rituximab maintenance (24 months).
REFERENCE DRUG	Rituximab IV (MabThera®/Rituxan®) was supplied as 100 mg/10 mL vials and 500 mg/50 mL vials.
DOSE / ROUTE / REGIMEN / DURATION	Rituximab IV was administered at the standard dose of 375 mg/m2 by IV infusion throughout the study. Rituximab was given on Day 1 of each cycle. The dosing regimen was once every three months (q3m) or once every two months (q2m) for a total of 8 or 12 cycles, respectively, of rituximab maintenance (24 months).

CRITERIA FOR EVALUATION	
EFFICACY	Tumor response data were not collected, hence there were no planned analyses of efficacy for this study.
PHARMACOKINETICS	The primary endpoint for Stage 1 and Stage 2 was to demonstrate non-inferiority in rituximab Ctrough levels after rituximab IV or after rituximab SC. Secondary PK endpoints for Stage 1 and Stage 2 were AUC0-τ, Cmax, tmax, and t1/2 of rituximab. All PK analyses were based on patients for whom PK assessments were available. Patients were analyzed according to treatment received.
PHARMACODYNAMICS	Pharmacodynamics endpoints included B-cell levels, as measured by peripheral blood CD19+ lymphocyte counts, and B-cell depletion and repletion.
SAFETY	Safety endpoints included adverse events (AEs), serious AEs (SAEs), and administration-related reactions (ARRs); human anti-chimeric/anti-human antibody levels; as well as hematology and clinical chemistry parameters. All patients who received at least one dose of study treatment, whether prematurely withdrawn from the study or not, were included in the safety analysis population (SAP).
STUDY POPULATION	
PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS	The patient populations were comparable across the cohorts within each stage and across the two stages. Median age at baseline was 59 and 58 years for Stage 1 and Stage 2, respectively. There were more female patients randomized overall, with 52% in Stage 1 and 58% in Stage 2. Median BSA was 1.84 m2 in Stage 1 and 1.82 m2 (1.81 and 1.84 m2 for the rituximab IV and SC arms, respectively) in Stage 2. The majority of patients had Grade 1 or 2 FL. In Stage 2, the median number of cycles of rituximab maintenance therapy received immediately prior to entering the study was one cycle. More than half of the patients (56%) had achieved a complete response (CR) to the preceding induction treatment with rituximab.

SYNOPSIS OF CLINICAL STUDY – SABRINA

TITLE OF THE STUDY	BO22334/SABRINA – 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 follicular lymphoma followed by maintenance treatment with either rituximab SC or rituximab IV
PERIOD OF TRIAL	First Patient Screened: February 04, 2011 Data cut-off (updated analysis): January 11, 2016
CLINICAL PHASE	III
OBJECTIVES	**Primary Objectives** **Stage 1** • To estimate the ratio of trough serum concentrations of rituximab obtained at Cycle 7, 21 days after subcutaneous (SC) administration to that obtained after intravenous (IV) administration (Ctrough, SC/Ctrough, IV during Cycle 7 of induction treatment). **Stage 2** • To estimate the overall response rate (ORR, comprising complete response [CR], complete response unconfirmed [CRu], and partial response [PR]) in each treatment arm at the end/completion of induction treatment. **Secondary Objectives** **Stage 1** • To compare observed rituximab serum concentrations area under the serum concentration-time curve (AUC) (rituximab IV vs SC) during induction treatment given every 3 weeks. • To explore additional rituximab PK parameters during induction treatment, including, but not limited to, predicted PK parameter for induction regimens given every 4 weeks. • To compare ORR of rituximab SC and rituximab IV given in combination with chemotherapy (CHOP or CVP) as induction treatment at the end/completion of induction treatment. **Stage 1 and Stage 2** • To compare peripheral blood B-cell depletion and repletion after rituximab SC and rituximab IV treatment.

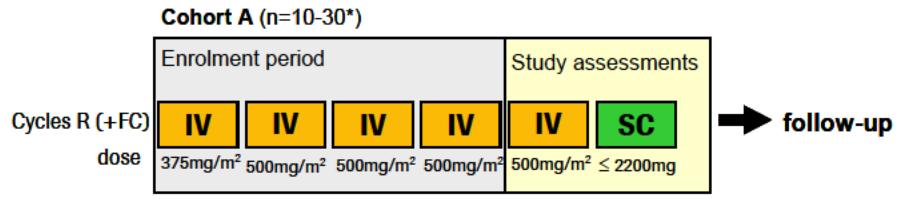
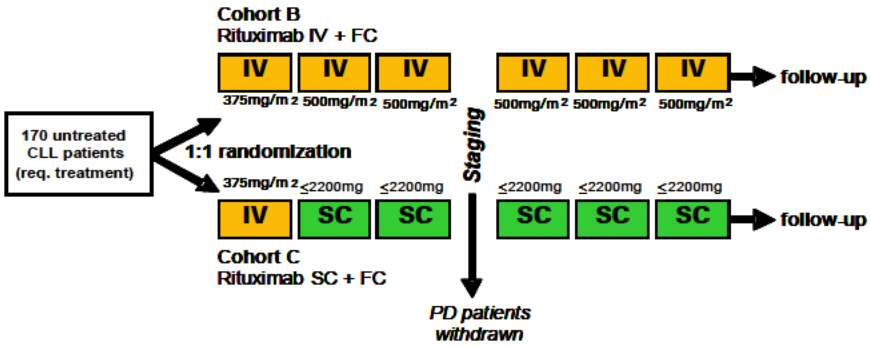
OBJECTIVES (continued)	• To compare complete response rates (CRR, comprising CR and CRu) of rituximab SC and rituximab IV given in combination with chemotherapy (CHOP or CVP) at the end/completion of the induction treatment. • To compare ORR and CRR of rituximab SC and rituximab IV at the end/completion of the maintenance treatment. • To compare progression-free survival (PFS), event-free survival (EFS), and overall survival (OS) of rituximab SC and rituximab IV when given in combination with chemotherapy during induction followed by maintenance as monotherapy. • To compare observed rituximab serum Ctrough levels (rituximab IV vs SC) during induction. • To compare observed rituximab serum Ctrough levels (rituximab IV vs SC) during maintenance treatment. • To compare the safety profile of rituximab SC with the safety profile of rituximab IV according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. – Adverse events (AEs) including laboratory values – Incidence and severity of administration-related reactions (ARRs) – Physical examination including weight, performance status, and vital signs (pulse rate and blood pressure) – Prior and interval medical history, prior treatments for cancer, concomitant medications – Immunogenicity. • To gather physician/nurse opinions on resource savings with rituximab SC compared with rituximab IV. • To assess physician/nurse opinions on the convenience with rituximab SC compared with rituximab IV.
STUDY DESIGN	 The overall study design is identical for the two stages of the study, except for more intensive PK sampling schedule during Stage 1 relative to Stage 2. Stage 1 of the study was designed to confirm that rituximab SC resulted in non-inferior C_{trough} levels compared with rituximab IV, when given as part of induction treatment every 3 weeks. Stage 2 was designed to further investigate the efficacy and safety of rituximab SC compared with rituximab IV.

STUDY DESIGN (continued)	Enrollment for Stage 2 started after the rituximab SC dose was established in Stage 1 (completion of induction). The study design and treatment arms were identical in both stages and it was prespecified that data from Stage 1 and Stage 2 would be combined for efficacy and safety analyses. Patients were randomized 1:1 to rituximab IV 375 mg/m^2 or rituximab SC 1400 mg, the dose predicted from model-based simulations based on PK data from the phase Ib study BP22333/SparkThera to achieve non-inferior rituximab C_{trough} values compared with the IV regimen (375 mg/m^2) in induction.
NUMBER OF SUBJECTS	A total of 410 patients were randomized (127 patients in Stage 1 and 283 patients in Stage 2): 205 patients to rituximab IV and 205 patients to rituximab SC. Three patients discontinued prior to study treatment. A total of 407 patients received at least one dose of rituximab (204 IV and 203 SC).
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Adult patients with previously untreated, CD20-positive follicular lymphoma (FL) of Grade 1, 2, or 3a requiring therapy
TRIAL DRUG	Rituximab SC 120 mg/mL
DOSE / ROUTE / REGIMEN / DURATION	*Induction Phase:* Cycle 1 given as rituximab IV 375 mg/m2 followed by 7 cycles (Cycles 2 − 8) of rituximab SC 1400 mg in combination with up to 8 cycles of CHOP or CVP chemotherapy administered every 3 weeks. *Maintenance Phase:* Patients achieving at least PR entered rituximab SC 1400 mg maintenance therapy once every 8 weeks for 24 months (Cycles 9 − 20). Rituximab SC was administered using a 27-gauge needle inserted in the SC space in the abdomen, with a flow rate of approximately 2 mL/min.
REFERENCE DRUG	Rituximab IV 500 mg/50 mL Rituximab IV 100 mg/10 mL
DOSE / ROUTE / REGIMEN / DURATION	*Induction Phase:* Cycle 1 − 8 given as rituximab IV 375 mg/m2 in combination with up to 8 cycles of CHOP or CVP chemotherapy administered every 3 weeks. *Maintenance Phase:* Patients achieving at least PR entered rituximab IV 375 mg/m2 maintenance therapy once every 8 weeks for 24 months (Cycles 9 − 20). Rituximab IV was administered by IV infusion through a dedicated line.
CRITERIA FOR EVALUATION	
EFFICACY	*Primary Endpoint:* investigator-assessed ORR (comprising CR, CRu, and PR) at the end/completion of induction treatment; independent review committee-assessed ORR was analyzed to support the primary analysis. *Secondary Endpoints:* CRR (CR and CRu) at the end/completion of induction treatment; ORR and CRR at the end/completion of maintenance treatment; Time-to event endpoints (PFS, EFS, OS).

PHARMACOKINETICS	*Primary Endpoint:* the estimated ratio of observed rituximab serum Ctrough, SC/Ctrough, IV at Cycle 7 of induction treatment (given every 3 weeks). *Secondary Endpoints:* rituximab serum AUC during induction treatment (assessed in Stage 1 only); rituximab serum Ctrough levels at each induction treatment cycle; and rituximab serum Ctrough levels at each maintenance treatment cycle..
PHARMACODYNAMICS	Pharmacodynamics endpoints included B-cell levels, as measured by peripheral blood CD19+ lymphocyte counts, and B-cell depletion and repletion.
SAFETY	*Secondary Endpoints:* comparison of the safety profiles of rituximab SC and rituximab IV, including incidence and severity of ARRs and immunogenicity. Safety assessments included AEs, standard laboratory assessments, 12-lead ECG, vital signs, Eastern Cooperative Oncology Group performance status, left ventricular ejection fraction values, and B symptoms. Immunogenicity assessments included anti-rituximab antibodies and anti-rHuPH20 antibodies.
PHARMACOECONOMICS AND OUTCOMES RESEARCH	*Secondary Endpoints:* Physician / nurse opinions on resource savings and convenience with rituximab SC compared with rituximab IV
STUDY POPULATION	
PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS	Across the two stages, the overall demographics and baseline characteristics were balanced between the treatment arms with the exception of gender and FL grade. Slightly more female patients (53%) were randomized in the study than male patients (47%). However, a higher proportion of females were randomized to the rituximab SC arm (59% female). The treatment arms in the combined Stage 1+2 population were otherwise balanced in regard to baseline demographics, characterized by a median age of 57 years and median BSA of 1.83 m2 (1.84 and 1.80 m2 for the rituximab IV and SC arms, respectively). Despite the imbalances between the treatment arms in regard to Grade 1 FL (22% IV vs. 33% SC) and Grade 2 FL (53% IV vs. 46% SC), the Grade 1 and Grade 2 FL are similar in terms of prognostic outcomes. These observed imbalances were not expected to impact the overall study results. Median time to first diagnosis was comparable between the two arms (1.6 months IV vs. 1.5 months SC). Overall, 64% of patients were assigned to CHOP chemotherapy during induction.

SYNOPSIS OF CLINICAL STUDY – SAWYER

TITLE OF THE STUDY	BO25341/SAWYER – 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
PERIOD OF TRIAL	First patient enrolled: April 13, 2011 Data cut-off (primary analysis): May 07, 2014 Data cut-off (updated analysis for time to event analyses only): March 10, 2016
CLINICAL PHASE	Ib
OBJECTIVES	**Primary** (Pilot dose confirmation, Part 1) • To confirm a selected SC rituximab dose results in Ctrough levels that are comparable to IV rituximab Primary (Ctrough non-inferiority, Part 2) • To establish non-inferiority in observed Ctrough levels between the confirmed SC rituximab dose and the reference IV rituximab dose Secondary (Part 1) • To describe the rate of incidence of injection-related reactions during the SC rituximab cycle • To describe patient and nurse preference regarding SC or IV administration **Secondary** (Part 2) • To evaluate safety parameters among patients who received SC rituximab, compared to patients who received IV rituximab only • To assess site experience, specifically: – physician / nurse opinions on time savings with rituximab SC compared with rituximab IV – physician / nurse opinions on the convenience of rituximab SC compared with rituximab IV Secondary (both Part 1 and Part 2) • To assess additional PK parameters (including AUC) of both SC and IV rituximab • To compare the immunogenicity of SC rituximab with that of IV rituximab • To examine peripheral blood B-cell levels and B-cell depletion and repletion with SC rituximab compared to IV rituximab • Exploratory assessment of the efficacy of SC rituximab compared to IV rituximab, including – Response rate [Complete Response (CR), Complete Response with incomplete bone marrow recovery (CRi), Partial Response (PR) – Progression-free survival – Event free survival – Overall survival

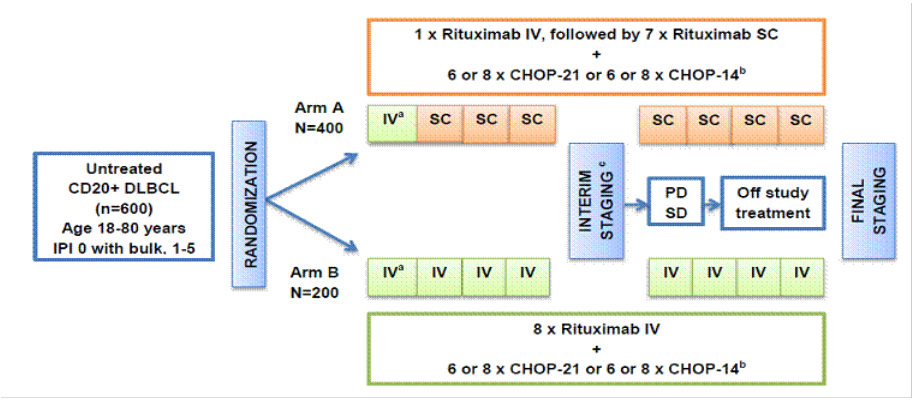
STUDY DESIGN	**Part 1 (Pilot Dose Confirmation)**  **Part 2 (C_{trough} Non-Inferiority)**  A two-part, randomized, open-label, parallel-group, multicenter, Phase Ib study. All patients received treatment with rituximab (IV or SC) in combination with chemotherapy (fludarabine and cyclophosphamide). Rituximab IV doses were calculated on a BSA-adjusted basis, as per standard clinical practice. Rituximab SC was administered using a fixed dose principle (i.e. all patients received the same dose to a maximum of 2200 mg). Part 1 - Pilot dose selection In Part 1, a single cycle of rituximab SC was administered to select a dose of rituximab SC that would result in rituximab Ctrough values comparable to those achieved with the IV regimen. Patients could be enrolled at any point during their first-line treatment with rituximab IV (Cycle 1 375 mg/m2, Cycle 2 onwards: 500 mg/m2) in combination with FC, prior to the commencement of treatment on study at Cycle 5. At Cycle 5, patients received rituximab IV 500 mg/m2. At Cycle 6, rituximab IV was replaced by rituximab SC at one of three different doses (1400, 1600, 1870 mg). PK data were integrated into a population PK model, and model-based simulations predicted that a fixed dose of 1600 mg rituximab SC would achieve non-inferior rituximab Ctrough values and comparable AUC levels compared with rituximab IV 500 mg/m2 q4w. The selected dose was then evaluated in Part 2. Part 2 - Ctrough non-inferiority In Part 2, patients were randomized 1:1 to receive rituximab IV 500 mg/m2 or rituximab SC at the dose selected in Part 1 (1600 mg) to demonstrate non-inferiority of the rituximab Ctrough levels with the SC dose compared with the IV dose. All patients in Part 2 received rituximab IV 375 mg/m2 at Cycle 1, followed by 5 cycles of rituximab SC 1600 mg or 5 cycles of rituximab IV 500 mg/m2 at Cycles 2-6, in combination with up to 6 cycles of FC chemotherapy administered every 4 weeks. The median follow-up for SAWYER (part 2) was 14.1 months.

STUDY DESIGN (continued)	After completing treatment, patients in both Part 1 and Part 2 are followed monthly until 3 months after their last dose of rituximab, then every 3 months until 3 years, and then every 6 months until 4 years after their last dose of rituximab.
NUMBER OF SUBJECTS	Part 1: 64 patients enrolled sequentially to Cohort A; 56 patients treated: - 16 patients in rituximab 1400 mg SC sub-cohort - 17 patients in rituximab 1600 mg SC sub-cohort - 23 patients in rituximab 1870 mg SC sub-cohort Part 2: 176 patients randomized to Cohort B and C: 174 patients treated - 87 patients in Cohort B (rituximab IV 500 mg/m2) - 87 patients in Cohort C (rituximab SC 1600 mg)
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Adult patients with previously untreated chronic lymphocytic leukemia (CLL; documented CD20+ B-CLL confirmed according to iwCLL criteria).
TRIAL DRUG	Rituximab SC was supplied as a ready-to-use liquid formulation with a nominal content of 120 mg/mL rituximab and 2000 U/mL recombinant human hyaluronidase (rHuPH20) in 10 mL vials and 11.7 mL vials.
DOSE / ROUTE / REGIMEN / DURATION	Patients in Part 1 received a single cycle of rituximab SC at one of three different test doses: 1400 mg, 1600 mg, and 1870 mg on Day 1 of Cycle 6. After receiving rituximab as an IV infusion in Cycle 1 (375 mg/m2), patients received rituximab SC at a fixed dose of 1600 mg on Day 1 of Cycles 2-6.
REFERENCE DRUG	Rituximab IV (MabThera®/Rituxan®) was supplied as 100 mg/10 mL vials and 500 mg/50 mL vials.
DOSE / ROUTE / REGIMEN / DURATION	Patients in Part 1 received rituximab IV at 500 mg/m2 on Day 1 of Cycle 5. If enrolled at an earlier cycle, patients received rituximab IV at 375 mg/m2 in Cycle 1 (on Day 0 or Day 1 according to local practice) and 500 mg/m2 on Day 1 of Cycles 2-5. In Part 2, patients received rituximab IV at 375 mg/m2 on Day 0 of Cycle 1 and an IV infusion at 500 mg/m2 on Day 1 of Cycles 2–6.
CRITERIA FOR EVALUATION	
EFFICACY	Exploratory assessments of tumor response rate and minimal residual disease.
PHARMACODYNAMICS:	Pharmacodynamics endpoints included B-cell levels, as measured by peripheral blood CD19+ lymphocyte counts, and B-cell depletion and repletion.
PHARMACOKINETICS:	The primary endpoint for Part 1 and Part 2 was to demonstrate non-inferiority in rituximab Ctrough levels after rituximab IV or after rituximab SC. Secondary PK endpoints for Part 1 and Part 2 were AUC0-τ, Cmax, tmax, and t1/2 of rituximab. All PK analyses were based on patients for whom PK assessments were available. Patients were analyzed according to treatment received.

SAFETY	Safety endpoints included adverse events (AEs), serious AEs (SAEs), and administration-related reactions (ARRs); human anti-chimeric/anti-human antibody levels; as well as hematology and clinical chemistry parameters. All patients who received at least one dose of study treatment, whether prematurely withdrawn from the study or not, were included in the safety analysis population (SAP).
PHARMACOECONOMICS AND OUTCOMES RESEARCH	Physician / nurse opinions on resource savings and convenience with rituximab SC compared with rituximab IV.
STUDY POPULATION	
PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS	The patient population in Part 1 was predominantly white (95%), male (73%), with a median age of 60 years and median BSA of 1.94 m2. Over half of the patients (55%) had Binet Stage B disease. The median time from first CLL diagnosis to study enrolment was 16.4 months. The majority of patients did not have B symptoms at screening (83%) or prior to treatment (78%). The patient population in Part 2 was similar to Part 1, predominantly white (96%), male (65%), with a median age of 60 years and median BSA of 1.9 m2 (1.86 and 1.97 m2 for the rituximab IV and SC arms, respectively). Overall, the treatment arms were balanced with respect to demographic characteristics, with the exception of more males in the rituximab SC arm (60% IV vs. 71% SC). Baseline disease characteristics were similar between the two arms. Over half of the patients (62%) had Binet Stage B disease and the majority had typical CLL characterizations (93%), with median time from first CLL diagnosis to randomization being 18.5 months.

SYNOPSIS OF CLINICAL STUDY – MABEASE

TITLE OF THE STUDY	MO28107/MabEase - A comparative, randomized, parallel group, multi-center, Phase IIIb study to investigate the efficacy of subcutaneous (SC) rituximab versus intravenous (IV) rituximab both in combination with CHOP (R-CHOP) in previously untreated patients with CD20-positive diffuse large B-cell lymphoma (DLBCL).
PERIOD OF TRIAL	22 Aug 2012 to 31 Dec 2015 (data cut-off for updated analysis)
CLINICAL PHASE	IIIb
OBJECTIVES	**Primary:** • To estimate the efficacy of rituximab administered SC or IV in combination with cyclophosphamide, vincristine, doxorubicin and prednisone (CHOP), as measured by complete response rate (including complete response unconfirmed; CR/CRu) approximately one month after the end of rituximab-based treatment. **Secondary:** • To compare patient satisfaction with rituximab SC versus rituximab IV in patients with DLBCL, as measured by the validated Cancer Treatment Satisfaction Questionnaire (CTSQ) and the Rituximab Administration Satisfaction Questionnaire (RASQ). • To evaluate the effects of method of administration (rituximab SC or rituximab IV) in terms of: – Rituximab administration time, defined as the time from start to end of the rituximab SC injection or from start to end of the rituximab IV infusion – Chair time, defined as the time the patient occupies an infusion chair/bed for a single treatment cycle of R-CHOP immunochemotherapy – Hospital time, defined as the time the patient is in hospital for the course of one cycle of R-CHOP immunochemotherapy. • To evaluate event-free survival (EFS), progression-free survival (PFS) and overall survival (OS) from randomization, and disease-free survival (DFS) from CR/CRu. • To evaluate the safety of rituximab SC compared with rituximab IV in patients with DLBCL, focusing on serious adverse events (SAEs), grade ≥ 3 adverse events (AEs), grade ≥ 3 application-associated reactions (AAR), and infusion-related reactions (IRR) according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.0).

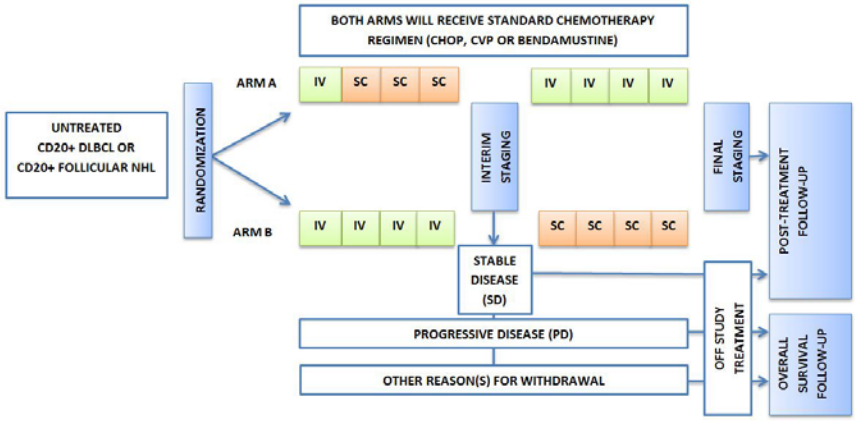
STUDY DESIGN	 Patients were randomly allocated to rituximab SC or rituximab IV in 2:1 ratio, with stratification according to age (< 60 vs ≥ 60 years), International Prognostic Index (IPI) risk category (low, low-intermediate, high-intermediate, high), and chemotherapy regimen (CHOP-21 vs CHOP-14). Patients randomized to Arm A received rituximab SC at the 1400 mg dose confirmed to achieve non-inferior rituximab Ctrough values compared with the IV regimen (375 mg/m2) in the NHL induction setting in study BO22334/SABRINA. Study treatment in both treatment groups consisted of 8 cycles of rituximab administered in combination with either 6 or 8 cycles of commercially available standard CHOP chemotherapy administered every 14 days (CHOP-14) or every 21 days (CHOP-21). Patients randomized to rituximab SC received the first rituximab dose by IV infusion (375 mg/m2) followed by 7 cycles of rituximab SC 1400 mg in combination with 6-8 cycles of CHOP-14 or CHOP-21 chemotherapy, to a total of 8 rituximab doses. Patients randomized to rituximab IV received 8 cycles of rituximab IV 375 mg/m2 in combination with 6-8 cycles of CHOP-14 or CHOP-21 chemotherapy. For patients who were originally scheduled to receive 8 cycles of rituximab in combination with CHOP-14 or CHOP-21 but who achieved CR/CRu after 4 cycles (interim staging), further chemotherapy could be reduced to two additional cycles of CHOP chemotherapy in combination with rituximab followed by two cycles consisting of rituximab only. After completion of induction treatment, patients were followed every 3 months for the first 2 years and then every 6 months until the end of the study defined as when the last patient has completed at least 24 months of follow-up after their last dose of induction treatment, or earlier if one of the following is documented for all treated patients: disease recurrence, withdrawal from the study, loss to follow-up, or death.
NUMBER OF SUBJECTS	Patients in All randomized population (RND) = 576; patients randomized to Arm A (rituximab SC) = 381; Patients randomized to Arm B (rituximab IV) = 195. Patients in Intent-To-Treat (ITT) population = 519; ITTCTSQ population = 421; ITTRASQ population = 428;

NUMBER OF SUBJECTS (continued)	Per Protocol (PP) population = 445; Safety population (SAF) = 572.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Adult patients aged ≥ 18 and ≤ 80 years with histologically confirmed, previously untreated CD20-positive DLBCL according to the World Health Organization (WHO) classification system; an IPI score of 1-5 or IPI score of 0 with bulky disease, defined as one lesion ≥ 7.5 cm; at least one bi-dimensionally measurable lesion defined as ≥1.5 cm in its largest dimension on computed tomography (CT) scan, combined positron emission tomography (PET)-CT scan or magnetic resonance imaging (MRI); adequate hematologic function; and Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.
TRIAL DRUG	The test product was rituximab SC, containing rituximab at a concentration of 120 mg/mL, and human recombinant hyaluronidase (rHuPH20) at a concentration of 2000 U/mL.
REFERENCE DRUG	The comparator was rituximab IV, containing rituximab at a concentration of 10 mg/mL.
DOSE / ROUTE / REGIMEN / DURATION	Rituximab SC was administered as single injections at a fixed dose of 1400 mg for all patients. Rituximab IV was administered as single infusions of 375 mg/m2 body surface area (BSA). Rituximab (SC and IV) was administered in combination with commercially available standard CHOP chemotherapy (cyclophosphamide, hydroxydaunorubicin, vincristine and prednisone). Centers chose the planned CHOP treatment for each patient prior to randomization. Study treatment in both treatment groups consisted of 8 cycles of rituximab administered in combination with either 6 or 8 cycles CHOP-14, or 6 or 8 cycles of CHOP-21. The chemotherapy regimen selected for each patient was then maintained for that patient throughout the entire treatment period. For patients in both arms who were originally planned to receive 8 cycles of CHOP-14 or CHOP-21 but who achieved CR/CRu at interim staging (after 4 cycles), further chemotherapy could be reduced to 2 additional cycles of R-CHOP followed by 2 cycles of rituximab only (administered according to the previous chemotherapy schedule), to ensure all patients received 8 cycles of rituximab treatment.
CRITERIA FOR EVALUATION	
EFFICACY	**Primary endpoint:** - Complete response rate (CR/CRu) based primarily on the Investigator's assessment according to the International Working Group response criteria (Cheson et al. 1999), at the end of induction treatment (Visit 10). **Secondary endpoints:** - Progression-free survival, defined as the time from randomization to the first occurrence of progression of disease/relapse, or death from any cause. - Event-free survival, defined as the time from randomization to first occurrence of progression of disease or relapse, or initiation of a non–protocol-specified anti-lymphoma therapy or death, whichever occurs first.

EFFICACY (continued)	- Disease-free survival in patients achieving CR/CRu, defined as the time from the date of the initial CR/CRu until the date of progression or death from any cause. - Overall survival, defined as the time from randomization until death from any cause. Since finalization of the protocol, additional endpoints that warrant consideration in clinical trials of DLBCL have been published in the literature. - Event-free survival at 24 months (EFS24), defined for each patient on the basis of his/her EFS status at 24 months after the date of randomization i.e., on Study Day 730. EFS24 was set to "Yes" for patients with EFS duration 730 days. All other patients had EFS24 set to "No". - Progression-free survival at 24 months (PFS24), defined for each patient on the basis of his/her PFS status at 24 months after the date of randomization; a similar indicator was defined for PFS24, as for EFS24.
SAFETY	Safety analyses were performed using the SAF population, which included all patients who received at least one dose of study drug, according to the treatment they received. Adverse events, SAEs, administration-related reactions (ARRs), AARs, IRRs, AEs of Special Interest, laboratory evaluations, vital signs measurements, electrocardiogram (ECG) evaluations, physical examination, ECOG performance status, and concomitant medications were summarized.
PATIENT-REPORTED OUTCOMES	The ITTCTSQ and ITTRASQ populations were used for analyses of patient-reported outcomes, and included all patients in the ITT population who completed the CTSQ and RASQ questionnaires, respectively, at Visit 3/Cycle 3 and Visit 8/Cycle 7.
PHARMACOECONOMICS	Rituximab administration time was summarized for each treatment group, each cycle and for all cycles combined (across all patients). Chair time, and hospital time were summarized for each cycle and for all cycles combined (across all patients).
STUDY POPULATION	
PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS	The demographic characteristics were balanced between the two treatment arms. Most patients were white (79%), and more than half of patients (54%) were male. The study population had a median age of 64 years (61% of patients aged >= 60 years) with median BSA of 1.83 m2 (1.84 and 1.83 m2 for the rituximab IV and SC arms, respectively). The baseline characteristics between the two treatment arms were similar. Approximately, 61% of patients were classified as International Prognostic Index (IPI) low or low-intermediate risk. The majority of patients (90%) were scheduled to receive CHOP-21.

SYNOPSIS OF CLINICAL STUDY – PREFMAB

TITLE OF THE STUDY	MO28457/PrefMab - A Randomized, Open-Label, Multi-Centre Study to Evaluate Patient Preference with Subcutaneous Administration of Rituximab versus Intravenous Rituximab in Previously Untreated Patients with CD20+ Diffuse Large B-Cell Lymphoma or CD20+ Follicular Non-Hodgkin's Lymphoma Grades 1, 2, or 3a
PERIOD OF TRIAL	20 December 2012 to 19 January 2015 (data cut-off for primary analysis)
CLINICAL PHASE	IIIb
OBJECTIVES	**Primary:** • To evaluate the proportion of patients indicating an overall preference via a Patient Preference Questionnaire (PPQ) for either the subcutaneous (SC) or the intravenous (IV) route of rituximab administration **Secondary:** • To evaluate and compare the methods of rituximab administration (SC versus IV) in terms of : – Rituximab administration time, defined as the time from start to end of the rituximab SC injection or from start to end of the rituximab IV infusion – Patient-assessed satisfaction and convenience using the Cancer Therapy Satisfaction Questionnaire (CTSQ) and Rituximab Administration Satisfaction Questionnaire (RASQ) – Immunogenicity (anti-rituximab and anti-human recombinant hyaluronidase [rHuPH20] antibodies) and the associated rituximab concentration level at each anti-rituximab sampling time point • To evaluate efficacy of rituximab SC in terms of: – Complete response (CR) rate, including complete response unconfirmed (CRu), 28 (± 3) days after Day 1 of the last dose of induction treatment – Event-free survival (EFS) – Disease-free survival (DFS) – Progression-free survival (PFS) – Overall survival (OS) **Safety** The safety objectives for this study were to evaluate the safety of rituximab SC and rituximab IV in patients with diffuse large B-cell (DLBCL) or follicular non-Hodgkin's lymphoma (NHL), focusing on serious adverse events (SAEs), Grade ≥ 3 adverse events (AEs), and Grade ≥3 infusion/injection-related reactions (IIRRs) according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.

STUDY DESIGN	 Patients were randomized at a 1:1 ratio to Arm A or Arm B with different treatment sequences to receive either rituximab SC at Cycles 2-4 (after the first cycle rituximab IV; Arm A) or rituximab IV at Cycles 1-4 (Arm B). After the fourth cycle, patients were crossed over to the alternative route of administration for the remaining 4 cycles. Eligible patients were randomized in 1:1 ratio to Arm A or Arm B, with stratification according to age (< 60 vs ≥ 60 years), IPI or FLIPI risk category (low, low-intermediate, high-intermediate, and high), and chemotherapy regimen (CHOP, CVP, or bendamustine), which was selected by the investigator before randomization and maintained throughout the duration of the study. Treatment cycles were repeated every 14, 21, or 28 days, depending on the chemotherapy regimen selected. Study treatment in both treatment groups comprised 8 cycles of rituximab administered in combination with approved, commercially available CHOP, CVP, or bendamustine chemotherapy: - Patients randomized to Arm A received one cycle of rituximab IV 375 mg/m2, then three cycles of rituximab SC 1400 mg, followed by four cycles of rituximab IV 375 mg/m2 after interim staging. - Patients randomized to Arm B received four cycles of rituximab IV 375 mg/m2 followed by four cycles of rituximab SC 1400 mg after interim staging. Patients whose treatment plan included 6 cycles of chemotherapy received rituximab monotherapy at Cycles 7 and 8. After induction treatment was completed, patients were followed every 3 months for the first 2 years and then every 6 months until the end of the study defined as when the last patient has completed at least 24 months of follow-up, has disease recurrence, is withdrawn from the study, is lost to follow-up, or dies, whichever occurs first.

NUMBER OF SUBJECTS	A total of 743 patients (372 in Arm A and 371 in Arm B) were randomized, and 740 patients received at least one dose of study drug (three patients died prior to treatment administration). A total of 619 patients (311 in Arm A and 308 in Arm B) completed the study.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Adults (≥18 and ≤80 years) with histologically confirmed, previously untreated CD20+ DLBCL or CD20+ follicular NHL Grades 1, 2, or 3a, according to the World Health Organization (WHO) classification system. In this trial, patients with follicular NHL Grade 3b were excluded because these patients usually require more aggressive treatment than permitted in the trial.
TRIAL DRUG	The test product was rituximab SC, containing rituximab at a concentration of 120 mg/mL, and human recombinant hyaluronidase (rHuPH20) at a concentration of 2000 U/mL.
DOSE / ROUTE / REGIMEN / DURATION	The rituximab SC dose was 1400 mg for all patients, independent of patient body surface area (BSA). This translated into an injection volume of 11.7 mL. Investigators were instructed to administer rituximab SC into the abdominal area prior to chemotherapy (with the exception of the corticosteroid component). Treatment cycles were repeated every 14, 21, or 28 days, depending on the chemotherapy regimen selected.
REFERENCE DRUG	The comparator was rituximab IV, containing rituximab at a concentration of 10 mg/mL.
DOSE / ROUTE / REGIMEN / DURATION	Rituximab IV was also considered an investigational medicinal product in this trial. Rituximab 10 mg/mL was administered at a dose of 375 mg/m2 BSA as a single IV infusion, followed by administration of chemotherapy. At Cycle 1, Day 1, the first dose rituximab IV (for both Arms A and B) was always administered as a slow IV infusion, according to local practice. Patients were to be weighed prior to each treatment, and the patient's BSA was recalculated if necessary. Investigators were instructed to administer rituximab IV prior to chemotherapy (with the exception of the corticosteroid component). Treatment cycles were repeated every 14, 21, or 28 days, depending on the chemotherapy regimen selected.
CRITERIA FOR EVALUATION	
PATIENT-REPORTED OUTCOMES	All patients were required to complete the PPQ for the route of administration following rituximab therapy in Cycles 6 and 8. Patients who prematurely discontinued treatment during the study completed the questionnaire at the time of discontinuation, as long as they had been administered at least one dose via each treatment route post randomization. Patient satisfaction with administration of cancer therapy was evaluated using the CTSQ and RASQ in Cycles 4 and 8. The CTSQ was completed prior to rituximab administration, whereas the RASQ was completed immediately after rituximab administration and before chemotherapy administration.
SAFETY	Safety assessments included AEs, SAEs, IIRRs, routine safety laboratory tests, vital sign measurements, and recording of concomitant medications. All clinical AEs and SAEs, as well as laboratory abnormalities, were recorded regardless of their intensity/grading. Grading was according to the NCI CTCAE, v4.0.

SAFETY (continued)	Immunogenicity (measured with anti-rituximab and anti-human recombinant rHuPH20 antibodies) and the associated rituximab concentration level at each anti-rituximab sampling time point were also evaluated. All patients were evaluated for anti-rituximab antibodies, antirHuPH20 antibodies, and rituximab concentration predose during Cycles 1 to 8, at the interim and final staging, at 6 and 12 months follow-up, and at end of study.
PHARMACOECONOMICS	Time required for application of rituximab was evaluated by measuring the time from the start of the rituximab SC injection to the end of the injection, and the start of the rituximab IV infusion to the end of the infusion. These times were estimated on a per-patient and per-cycle basis.
EFFICACY	Efficacy of rituximab is being evaluated during induction and follow-up in terms of CR/CRu rate, PFS, EFS, DFS, and OS and will be reported at the final analysis
STUDY POPULATION	
PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS	Overall, demographics and baseline characteristics were balanced between the two treatment arms. Most patients were white (70%), and the median age was 60 years (51% of patients aged >= 60 years) with median BSA of 1.79 m2 (1.77 and 1.80 m2 for Arms A and B, respectively). Over half of patients (63%) were diagnosed with DLBCL, 44% had a history of lymphoma-related surgery, and 36% had a history of general surgery. Approximately, 64% of patients were classified as IPI low or low-intermediate risk. During induction, 69% of patients were assigned to CHOP-21 chemotherapy.

Appendix 4 Clinical Pharmacology Results, Supplementary Information

RITUXIMAB SC AND IV: POPULATION PK ANALYSES FROM SABRINA AND SAWYER IN NHL AND CLL POPULATIONS

A dedicated population PK analysis was conducted based on data from SABRINA in NHL patients based on the established population PK model for rituximab IV (Levi 2008). A separate dedicated population PK analysis was conducted including data from SAWYER Part 2 to describe the PK properties of rituximab IV and SC in the CLL population based on the established model in CLL patients (Li 2012). The objectives of these dedicated population PK analyses were to describe the PK of rituximab IV and rituximab SC in NHL and CLL population, to identify or confirm covariates which influence rituximab PK, and generate rituximab PK parameters for investigation of exposure-response (efficacy/safety) relationships.

Using prior historical PK models of rituximab (Levi 2008, Li 2012), a population PK modeling approach using nonlinear mixed-effects modeling with NONMEM v7.3.0 software was applied to the NHL and CLL population treated with rituximab. A population PK analysis was conducted specifically on patients with NHL from SparkThera and SABRINA studies. A model dedicated to patients with CLL was developed using data from BO17072/REACH and SAWYER studies.

In both patient populations, rituximab serum concentrations following IV and SC administration were best described by a two-compartment population PK model with combined time-dependent elimination clearance (CL_T) characterizing the known target-mediated elimination of rituximab associated with removal of target B cells (i.e. non-renewable target) and a time-independent elimination clearance (CL_{inf}), typical for IgG antibody elimination, and first order SC absorption (see also Section 3.1.1).

In the NHL population the PK parameters were: time-independent clearance (CL_{inf}, 200 mL/day), inter-compartment clearance (Q, 573 mL/day), central volume (V_C, 4540 mL), peripheral volume (V_P, 4270 mL), terminal half-life (33.2 days), absorption rate constant (k_a, 0.344 day^{-1}), and SC bioavailability (F_{SC}, 64.6%). In the CLL population the PK parameters were: time-independent clearance (CL_{inf}, 207 mL/day), inter-compartment clearance (Q, 420 mL/day), central volume (V_C, 4990 mL), peripheral volume (V_P, 3700 mL), terminal half-life (32.0 days), absorption rate constant (k_a, 0.372 day^{-1}), and SC bioavailability (F_{SC}, 63.3%). PK characteristics were consistent with those of typical monoclonal antibodies and population PK parameters estimates of rituximab IV and SC are comparable between CLL and FL population. Conditional simulations of the IV and SC regimens showed that the majority of patients in both cohorts were close to steady state by the end of Cycle 8 for NHL and Cycle 6 for CLL.

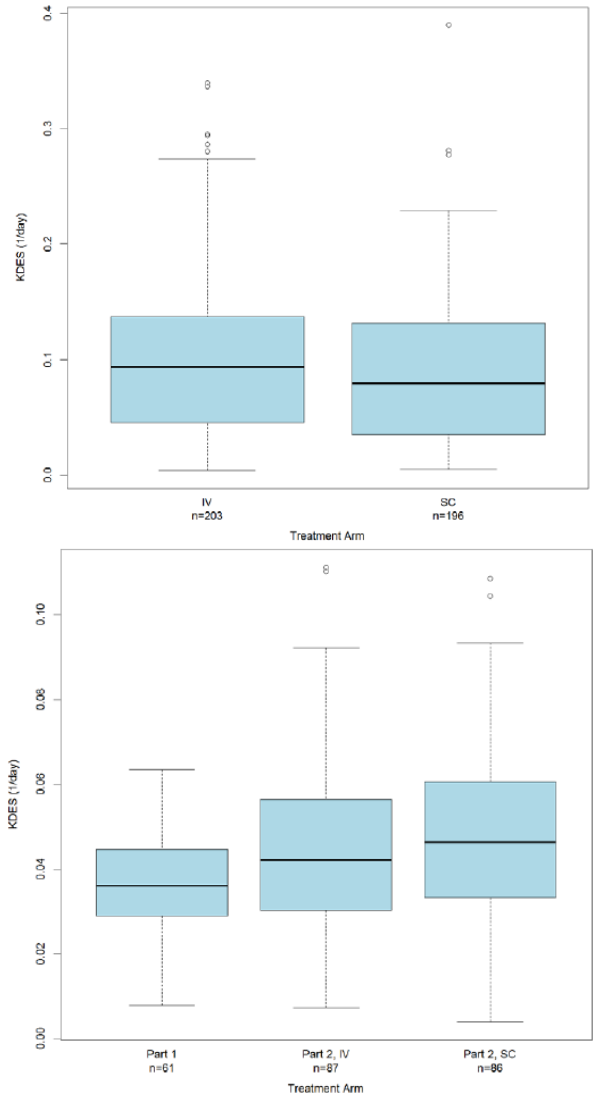
As typical for mAbs, rituximab PK parameters depended on body size measures. Clearance (both, CL_{inf} and CL_T terms), volume of the central and peripheral

compartments (V_C and V_P), and intercompartmental clearance (Q) increased with BSA. Regardless, in patients with extreme values of BSA (defined as 2.5th and 97.5th percentiles of the covariate distributions), clearance and central volume were within 35% and 29% respectively of the corresponding values for patients with mean BSA for NHL patients in SABRINA and within 25% and 16% of the corresponding values for patients with mean BSA for CLL patients in SAWYER. Simulations from the analyses demonstrate that NHL patients receiving 1400 mg rituximab SC or CLL patients receiving 1600 mg ritixumab SC achieve non-inferior exposures (C_{trough} and AUC) relative to BSA-based dosing of rituximab IV across the entire BSA range.

In addition to dependence on body size, higher B-cell/white blood cell count and higher tumor size at baseline increased time-dependent clearance in NHL and CLL patients, consistent with target-mediated elimination. In the NHL population, the rate constant of decay of CL_T with time (k_{des}) was lower in patients with higher baseline tumor size. In the CLL population, the initial time-dependent clearance was 7.5 times higher than time-independent clearance and also higher than that observed in NHL, potentially due to the higher number of malignant cells in circulation for CLL. Higher B-cell count and higher tumor size at baseline lead to lower initial exposure and longer time needed to achieve the same exposure as that seen in patients with lower disease burden.

Results from the dedicated population PK analyses in NHL and CLL populations importantly demonstrated that all rituximab PK parameters are comparable between rituximab IV and rituximab SC cohorts confirming the performance of the rituximab SC dosage form in demonstrating comparable PK to established rituximab IV. K_{des} values which are associated with reduction of time-varying clearance of rituximab and reflective of the rate of elimination of target B cells were similar in both NHL and CLL patients for the IV and SC formulations (Figure 1). These analyses confirm that rituximab elimination of target B cells is comparable and target saturation is achieved and maintained similarly with the IV and SC dosing regimens. Therefore, mechanistically, the comparability of K_{des} supports the comparability of anticipated anti-B-cell activity between routes of administration in both NHL and CLL populations.

Figure 1: Distributions of Individual Predictions of K_{des} Parameters for IV and SC Treatment Arms in NHL Population from SABRINA (left) or CLL Population from SAWYER (right)



Cumulatively, population PK analyses confirm the results achieved from the PK-based clinical bridging and the analyses demonstrated that the rituximab SC dosing regimens (1400 mg in NHL patients, 1600 mg in CLL patients) provide comparable model based PK parameters and achieve non-inferior exposures compared to the reference rituximab IV regimens across all BSA subgroups, including patients with high BSA.

References

[Levi 2008] Levi M, Li J, Frey N et al. Characterization of the time-varying clearance of rituximab in non-Hodgkin's lymphoma patients using a population pharmacokinetic analysis. American Conference on Pharmacometrics (ACoP). 2008.

[Li 2012] Li J, Zhi J, Wenger M et al. Population pharmacokinetics of rituximab in patients with chronic lymphocytic leukemia. J Clin Pharmacol. 2012;52:1918-1926.

Appendix 5 Efficacy Results, Supplementary Information

SABRINA SUBGROUP ANALYSES

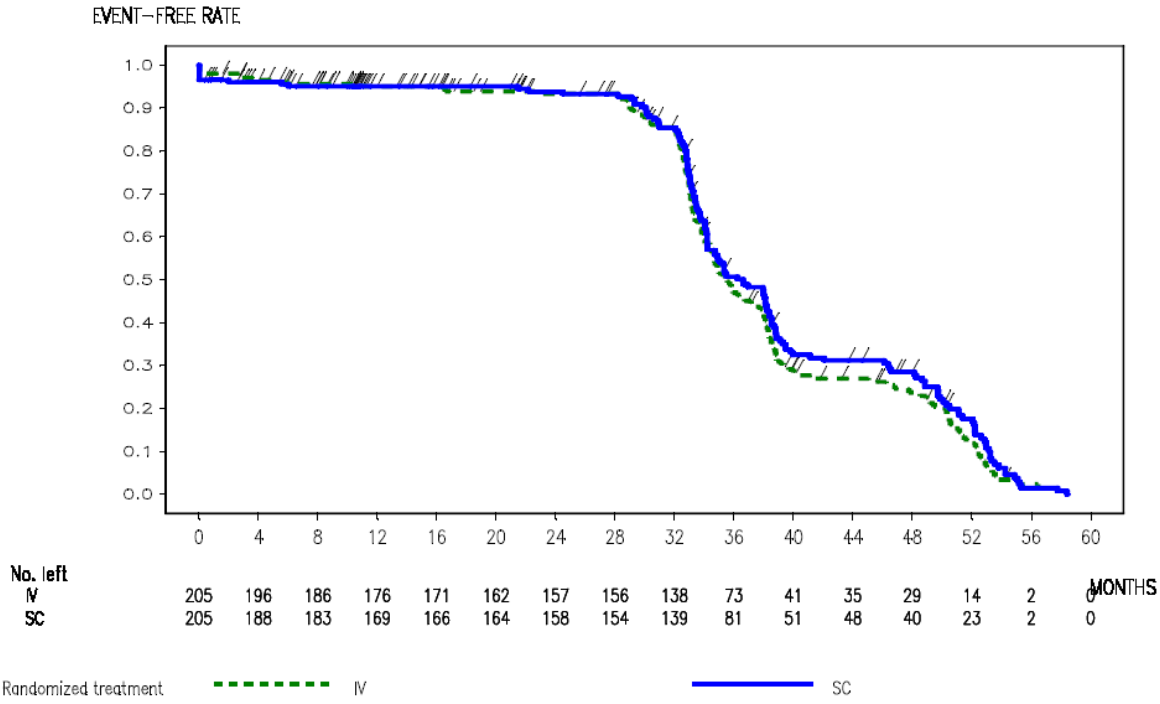
Table 1 SABRINA Subgroup Analyses of ORR at the End of Induction (ITT Population)

	Overall Response Rate (CR, CRu, PR) at End of Induction [95% CI]		
Subgroup	**Rituximab IV + chemo N = 205**	**Rituximab SC + chemo N = 205**	**Difference [95% CI]**
C_{trough} at Cycle 7 *(low: ≤ 88 μg/mL; medium: 88 μg/mL $< C_{trough} \leq 138$ μg/mL; high: $C_{trough} > 138$ μg/mL)*			
Low	n = 87 88.5% [79.9;94.3]	n = 32 96.9% [83.8;99.9]	8.37% [–2.3;19.0]
Medium	n = 69 92.8% [83.9;97.6]	n = 50 94.0% [83.5;98.7]	1.25% [–8.8;11.3]
High	n = 29 93.1% [77.2;99.2]	n = 91 94.5% [87.6;98.2]	1.40% [–10.8;13.6]
Body Surface Area *(low: BSA ≤ 1.73 m^2; medium: 1.74 m^2 $<$ BSA ≤ 1.92 m^2; high: BSA > 1.93 m^2)*			
Low	n = 56 89.3% [78.1;96.0]	n = 85 78.8% [68.6;86.9]	–10.46% [–23.3;2.4]
Medium	n = 77 80.5% [69.9;88.7]	n = 58 87.9% [76.7;95.0]	7.41% [–5.7;20.6]
High	n = 72 86.1% [75.9;93.1]	n = 62 88.7% [78.1;95.3]	2.60% [–9.5;14.7]
Gender			
Male	n = 106 83.0% [74.5;89.6]	n = 85 89.4% [80.8;95.0]	6.39% [–3.9;16.7]
Female	n = 99 86.9% [78.6;92.8]	n = 120 80.8% [72.6;87.4]	–6.04% [–16.3;4.2]
Chemotherapy Regimen			
CHOP	n = 130 86.2% [79.0;91.6]	n = 132 87.9% [81.1;92.9]	1.72% [–6.8;10.3]
CVP	n = 75 82.7% [72.2;90.4]	n = 73 78.1% [66.9;86.9]	–4.58% [–18.1;9.0]
FLIPI *(low risk: FLIPI ≤ 1 ; intermediate risk: FLIPI $= 2$; high risk: FLIPI ≥ 3)*			
Low	n = 44 81.8% [67.3;91.8]	n = 42 81.0% [65.9;91.4]	–0.87% [–18.7;17.0]
Intermediate	n = 66 84.8% [73.9;92.5]	n = 73 93.2% [84.7;97.7]	8.30% [–2.9;19.5]
High	n = 95 86.3% [77.7;92.5]	n = 90 78.9% [69.0;86.8]	–7.43% [–18.9;4.1]

SABRINA PFS SENSITIVITY ANALYSES

The rate of censoring is low and consistent between treatment groups until shortly before 30 months, after which point the number of censored patients increases greatly. The PFS Kaplan-Meier curves are thus robust up to 30 months, which is consistent with median follow-up of 37 months.

Figure 1 Reverse Kaplan-Meier Plot of Progression-Free Survival (ITT Population)



Reverse Kaplan-Meier is calculated in the same way as the Kaplan-Meier estimate of the time-to-event function, but with the meaning of the status indicator reversed. Hence, event is here the last assessment without a PFS event whilst censoring occurring at the time of the 1st documented disease progression. One year duration is defined as 364 days.

Three sensitivity analyses were conducted for PFS, considering different approaches for missing data:

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

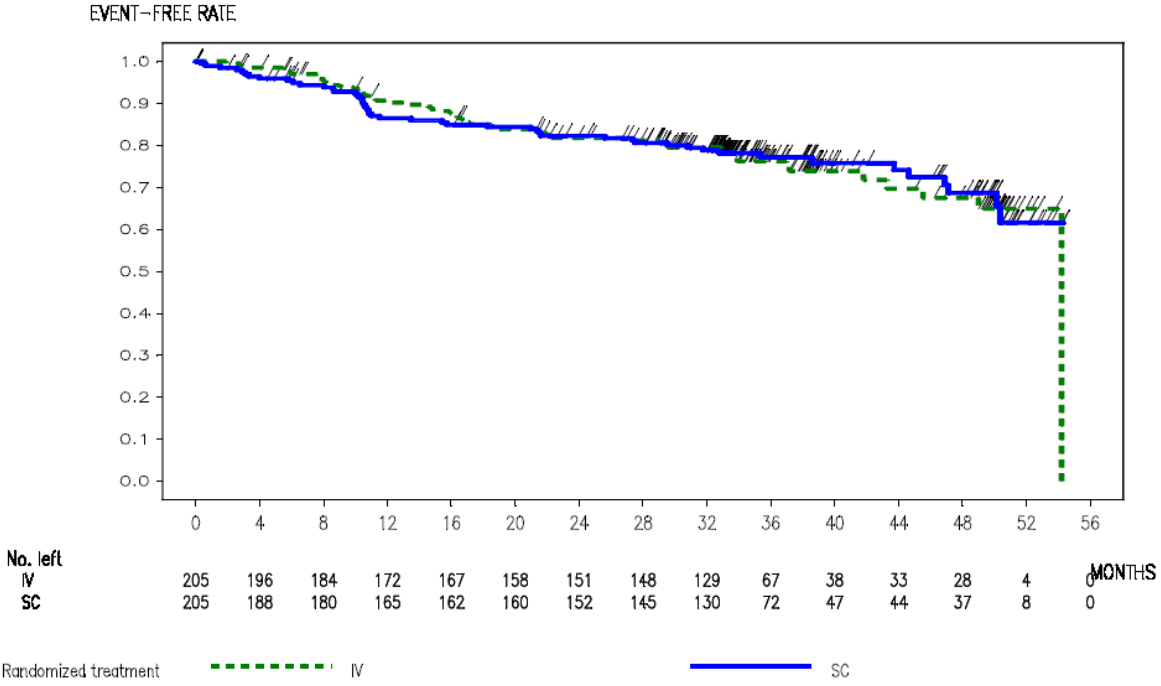
These sensitivity analyses were consistent with each other and less separation was observed between these three Kaplan-Meier curves than in the primary PFS analysis. The hazard ratios were 0.96 (95% CI [0.65, 1.42]), 0.95 (95% CI [0.64, 1.41]), and 0.95

(95% CI [0.64, 1.41]) for PFS sensitivity analyses PFS-A, PFS-B and PFS-C , respectively.

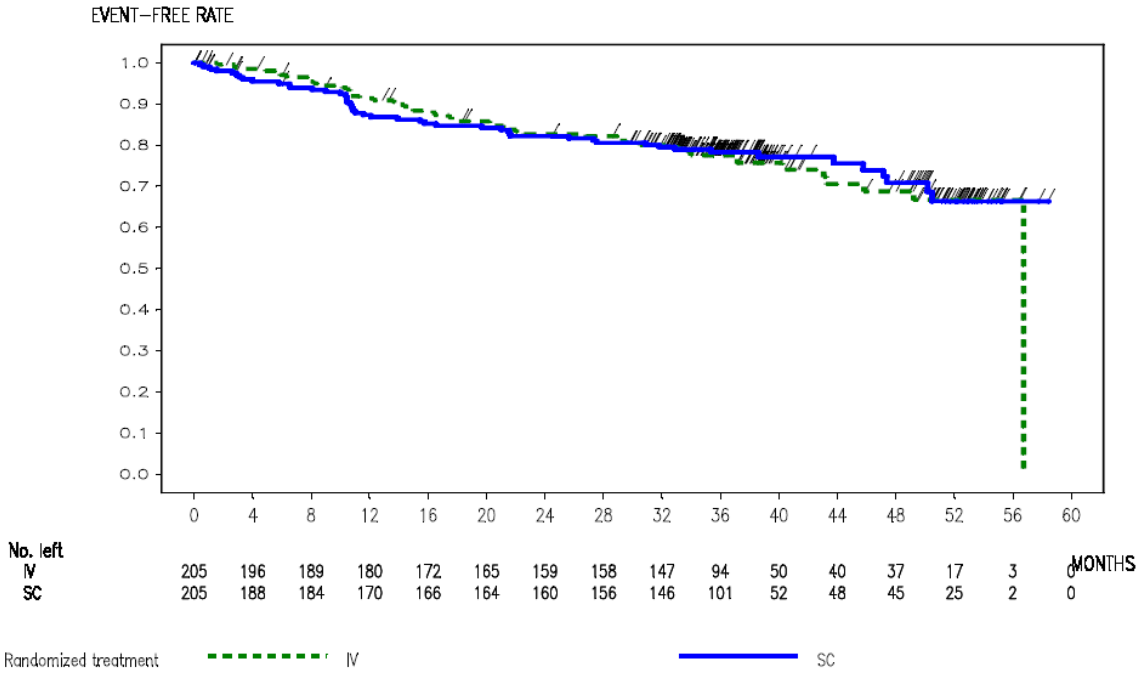
The most apparent difference between the Kaplan Meier curves for the primary analyses and the three sensitivity analyses (PFS-A, PFS-B, PFS-C) was the drop in PFS for the IV arm near month 40 in the primary analysis. Further investigation revealed that this appeared to be due to the outcomes for 4 patients who were considered as events in the primary analysis but censored in one or more of the sensitivity analyses, classified as follows: ‘lack of radiological confirmation’ (1 patient), and ‘two or more missed visits’ (3 patients).

Figure 2 SABRINA Kaplan-Meier Plot of PFS Sensitivity Analyses A-C (ITT Population)

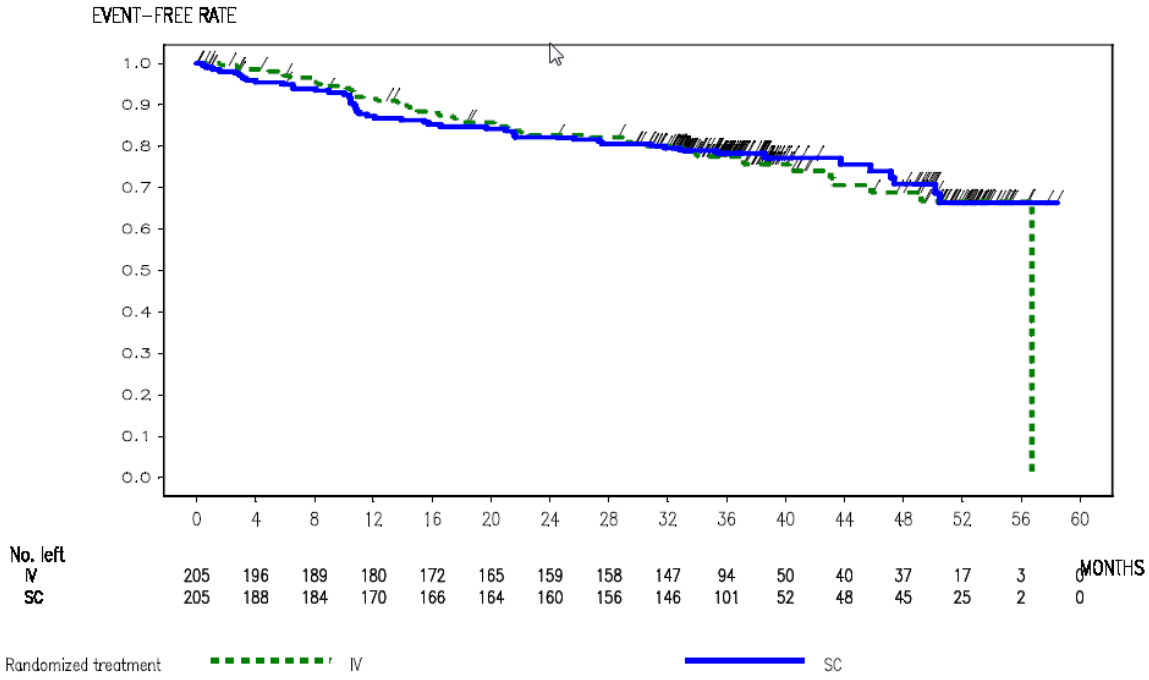
PFS-A: Using Radiological Assessments Only



PFS-B: Using Scheduled Visit Dates Only



PFS-C: Including All Signs of Clinical Progression



PFS-A – day of randomization until 1st radiologically confirmed disease progression, relapse after response or death from any cause – investigator assessment. Censoring occurs at last radiological response assessment. Patients with disease progression, relapse or death occurring after two or more missed response assessments are censored prior to the missed assessments.
PFS-B - day of randomization until the first scheduled visit after documentation of disease progression or relapse after response, or until the date of death from any cause – investigator assessment. Censoring occurs at last response assessment where disease status was evaluable and non-missing. Patients with disease progression, relapse or death occurring after two or more missed response assessments are censored prior to the missed assessments.
PFS-C - day of randomization until the first scheduled visit after documentation of disease progression or relapse after response, or until the date of death from any cause – investigator assessment. Unconfirmed claims of disease progression are included as events. Censoring occurs at last response assessment where disease status was evaluable and non-missing. Patients with disease progression, relapse or death occurring after two or more missed response assessments are censored prior to the missed assessments. One year duration is defined as 364 days.

Because of the apparent consistency of results from the three different approaches of handling progression data, the overall conclusions from the sensitivity analyses support the robustness of the primary PFS analysis.

SABRINA COMPARISON WITH HISTORICAL DATA

Overall response rates at the end of induction in the SABRINA study were very similar for the SC and IV treatment groups and similar to response rates observed in similar patient populations in earlier studies of R-CHOP and R-CVP with the IV formulation (Table 2).

Table 2 Comparison of End of Induction Response Rates in SABRINA Study with Historical Data for Rituximab IV

Reference (Study)	Treatment Group	N	Response Rate (% of Patients)		
			Complete (CR/CRu)	Partial (PR)	Overall (ORR)
SABRINA Stage 1+2 ITT	R(IV)+CHOP/CVP	205	32.2%	52.7%	84.9%
	R(SC)+CHOP/CVP	205	32.2%	52.2%	84.4%
CHOP subgroup	R(IV)+CHOP	130	34.6%	51.5%	86.2%
	R(SC)+CHOP	132	31.1%	56.8%	87.9%
CVP subgroup	R(IV)+CVP	75	28.0%	54.7%	82.7%
	R(SC)+CVP	73	34.2%	43.8%	78.1%
GLSG study (Hiddemann 2005)	R(IV)-CHOP	205	20%[a]	77%	96%
Study M39021 (Marcus 2008)	R(IV)-CVP	159	41%	40%	81%
Study MO18264/PRIMA (Salles 2011)	R(IV)-CHOP	881	67%	26%	93%
	R(IV)-CVP	268	53%	32%	85%

Rituximab IV was administered at the standard approved dose of 375 mg/m^2 in all studies. Response rates are based on investigator assessment of tumor response.

a CR only (CRu not reported).

Overall response rates at the end of maintenance were also very similar for the IV and SC treatment groups in the SABRINA study and similar to those observed for the rituximab IV maintenance arm in the large, phase III PRIMA study (Table 3). Complete response rates at the end of induction and at the end of maintenance were somewhat lower and partial responses were somewhat higher in the rituximab SC study for both arms compared with the legacy rituximab IV study.

Table 3 Comparison of End of Maintenance Response Rates in SABRINA Study with Historical Data for Rituximab IV

Reference (Study)	Treatment Group	N	Response Rate (% of Patients)		
			Complete (CR/CRu)	Partial (PR)	Overall (ORR)
SABRINA Stage 1+2 ITT[a]	R(IV)	178	56.2%	21.9%	78.1%
	R(SC)	172	50.6%	27.3%	77.9%
PRIMA (Maintenance ITT)	R(IV) maintenance	505	72.2%	6.8%	79.0%
	observation	513	52.7%	8.1%	60.7%

Rituximab IV was administered at the standard approved dose of 375 mg/m^2 in all studies. Response rates are based on investigator assessment of tumor response.

a Based on patients who received at least one cycle of maintenance treatment.

With regard to longer-term outcomes, a comparison of PFS data from the SABRINA study and the legacy rituximab IV study PRIMA is challenging owing to differences in study design. In SABRINA, patients were randomized into induction, with PFS a

secondary objective aimed at excluding any major differences in long-term efficacy with rituximab SC compared with rituximab IV. The PRIMA study was powered for PFS (primary endpoint) comparing 2 years of rituximab maintenance with observation alone. Patients were randomized to maintenance and observation arms at the end of induction with rituximab-containing immunochemotherapy; the choice of chemotherapy backbone was left to the investigator. With approximately 6 years median follow-up in the PRIMA study, median PFS in the rituximab maintenance group was still not reached and estimated to be around 8-10 years (Salles 2013).

The PRIMA study was the largest trial included in a recent meta-analysis of 3,837 patients with previously untreated FL that showed correlation of complete response rates at 30 months from randomization (CR30) with PFS in the first-line FL setting (Sargent 2015). The relationship between CR30 and PFS in the SABRINA study was explored and found to be highly consistent with that observed in the published meta-analysis. The observed odds ratio for CR30 of 1.05 (95% CI [0.68;1.60]) leads to a predicted PFS hazard ratio of 0.88, compared with the observed value of 0.84. The consistency of the correlation of CR30 and PFS in this study with earlier first-line FL trials, including study MO18264/PRIMA and several other rituximab IV trials in the induction and/or maintenance setting, further supports the robustness of the PFS results.

Overall, the data suggest that the rituximab IV (and rituximab SC) group in the SABRINA study performed as expected based on a comparison of short-term and longer-term efficacy measures with historical data from rituximab IV studies.

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MABEASE SUBGROUP ANALYSES

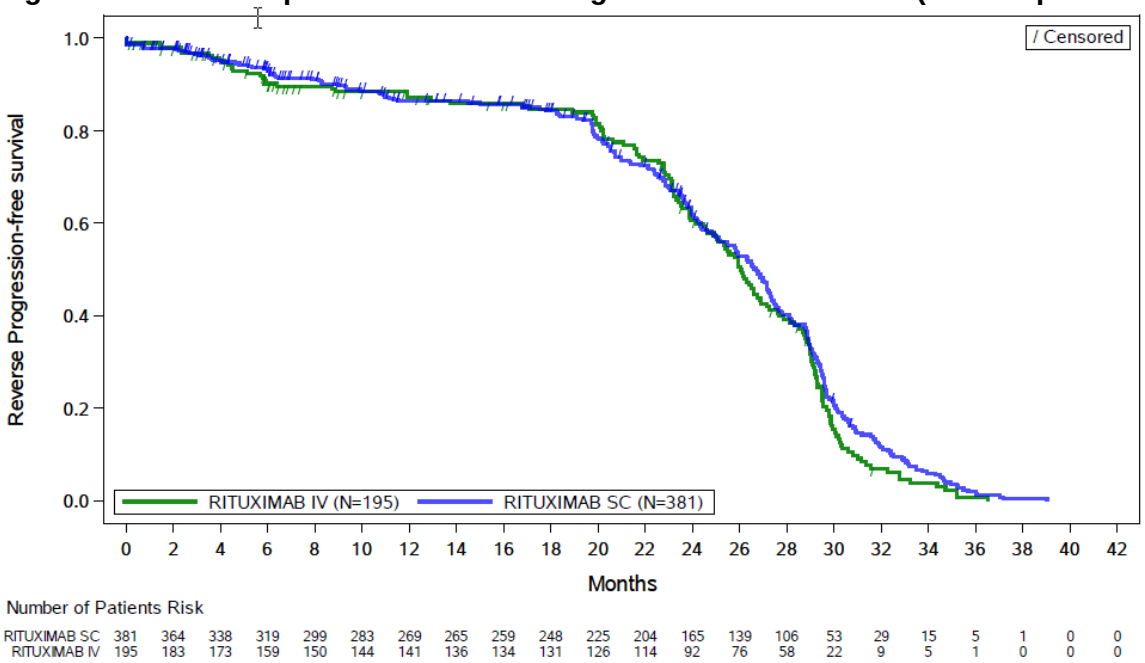
Table 4 MabEase Subgroup Analyses of CRR at the End of Treatment (RND Population)

	Complete Response Rate (CR, CRu) at End of Treatment [95% CI]		
Subgroup	**Rituximab IV n = 195**	**Rituximab SC n = 381**	**Difference [95% CI]**
Age			
< 60 years	n = 76 46.1% [34.8;57.3]	n = 147 43.5% [35.5;51.6]	–2.5% [–16.3;11.3]
≥ 60 years	n = 47 39.5% [30.7;48.3]	n = 115 49.1% [42.7;55.6]	9.6% [–1.2;20.5]
Chemotherapy Regimen			
CHOP-21	n = 173 43.9% [36.5;51.3]	n = 345 47.8% [42.6;53.1]	3.9% [–5.2;13.0]
CHOP-14	n = 22 27.3% [8.7;45.9]	n = 36 38.9% [23.0;54.8]	11.6% [–12.9;36.1]
Gender			
Male	n = 100 41.0% [31.4;50.6]	n = 209 49.3 [42.5;56.1]	8.3% [–3.5;20.1]
Female	n = 95 43.2% [33.2;53.1]	n = 172 44.2% [36.8;51.6]	1.0% [–11.4;13.4]
Body Surface Area			
Low *BSA ≤ 1.70 m^2*	n = 56 42.9% [29.9;55.8]	n = 115 45.2% [36.1;54.3]	2.4% [–13.5;18.2]
Medium *1.71 m^2-1.90 m^2*	n = 65 46.2% [34.0;58.3]	n = 123 48.8% [39.9;57.6]	2.6% [–12.4;17.6]
High *BSA > 1.90 m^2*	n = 74 37.8% [26.8;48.9]	n = 143 46.9% [38.7;55.0]	9.0% [–4.7;22.8]
IPI Risk Category			
Low	n = 61 57.4% [45.0;69.8]	n = 118 51.7% [42.7;60.7]	–5.7% [–21.0;9.7]
Low-intermediate	n = 57 40.4% [27.6;53.1]	n = 114 54.4% [45.2;63.5]	14.0% [–1.6;29.7]
High-intermediate	n = 47 34.0% [20.5;47.6]	n = 94 42.6% [32.6;52.5]	8.5% [–8.3;25.3]
High	n = 30 26.7% [10.8;42.5]	n = 55 29.1% [17.1;41.1]	2.4% [–17.4;22.3]
Race			
White	n = 156 42.9% [35.2;50.7]	n = 298 47.0% [41.3;52.6]	4.0% [–5.6;13.6]
Non-White	n = 39 38.5% [23.2;53.7]	n = 83 47.0% [36.3;57.7]	8.5% [–10.1;27.2]

MABEASE PFS SENSITIVITY ANALYSES

The reverse Kaplan-Meier plot (Figure 3) showed that the rate of censoring was low and consistent between treatment groups until shortly before 21 months, after which point the number of censored patients increased greatly. The PFS Kaplan-Meier curves are thus robust up to 21 months, which is consistent with median follow-up of 28 months.

Figure 3 Reverse Kaplan-Meier Plot of Progression-Free Survival (RND Population)



Time to event is calculated from randomization to last tumor or clinical assessment date. Patients will be censored at first occurrence of progression of disease or death from any cause.

Three sensitivity analyses were conducted for PFS, considering different approaches for missing data, similar to those conducted in the SABRINA study:

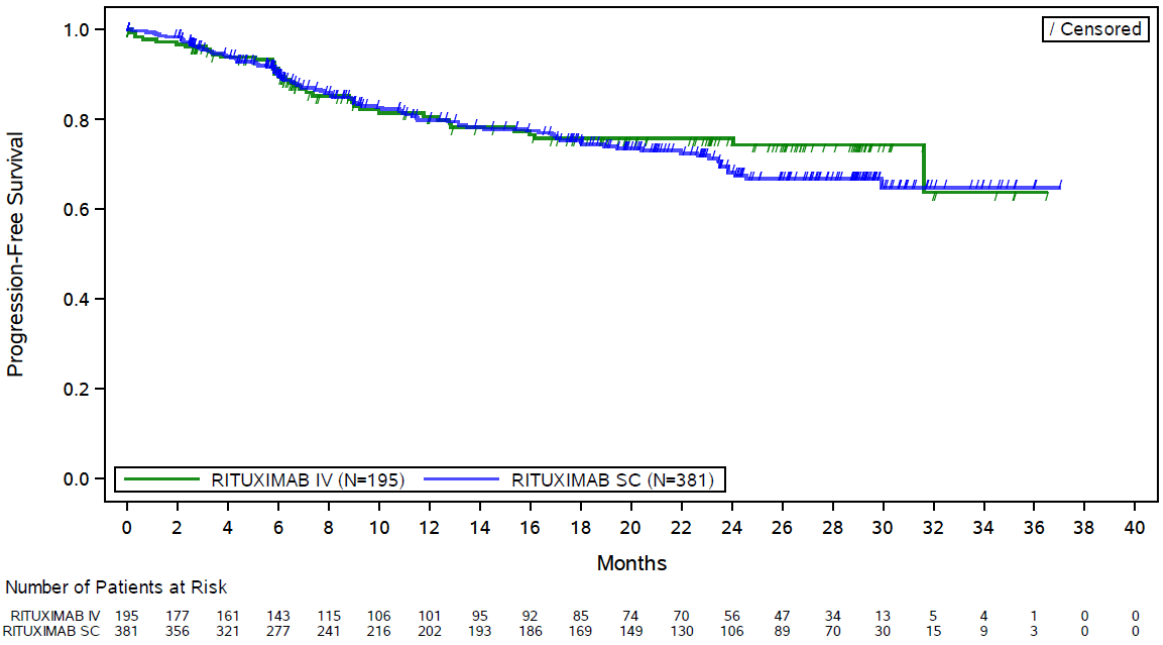
- In PFS-1, progression dates include only those based on radiological assessments; clinical progression was not considered a progression endpoint. Disease progression or deaths occurring after two or more missed visits were censored at the last visit.
- PFS-2 corrects for potential bias in follow-up schedules for tumor assessment by assigning the dates for censoring and events only at scheduled visit dates. Disease progression or deaths occurring after two or more missed visits were censored at the last visit.
- PFS-3 evaluates PFS including all signs of clinical progression as an event, such as when PD is recorded as a reason for treatment discontinuation. Disease progression or deaths occurring after two or more missed visits were censored at the last visit.

The HRs and 95% CIs for the three stratified analyses were 1.16 (95% CI [0.79;1.70]), 1.16 (95% CI [0.79;1.70]), and 1.15 (95% CI [0.79;1.66]) for PFS sensitivity analyses 1, 2, and 3 respectively.

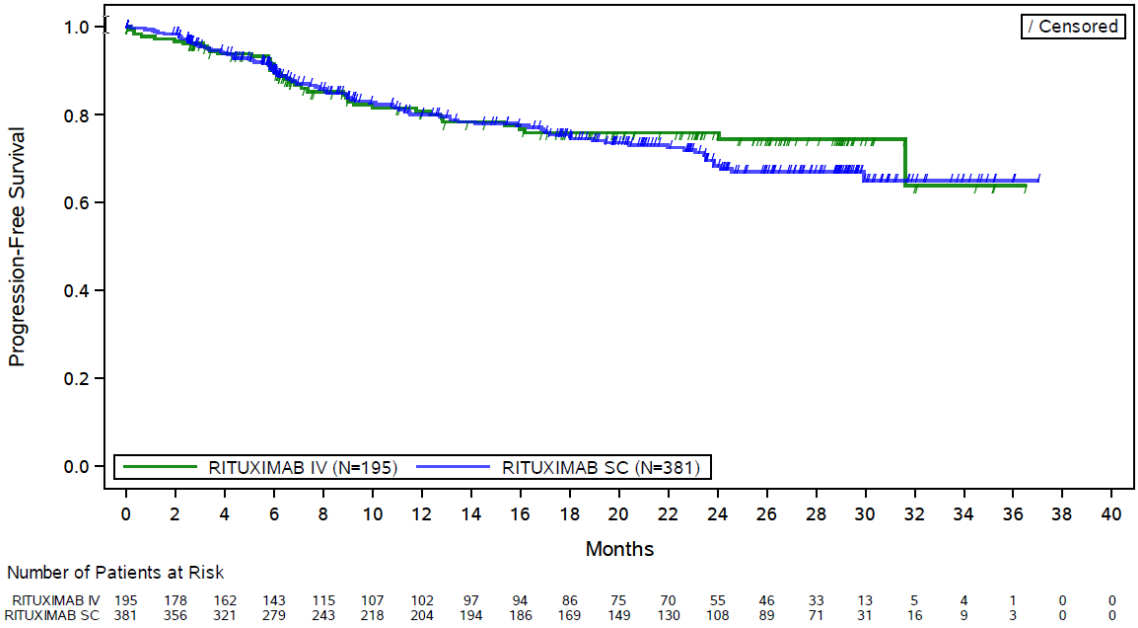
The first sensitivity analysis (PFS-1) considered progression and censoring based on available radiological evidence and was consistent with the primary analysis, though had less separation in the Kaplan-Meier curves until Month 23, after which point the separation appeared similar to the primary analysis. Sensitivity analyses 2 and 3 were consistent with each other and the primary PFS analysis.

Figure 4 MabEase Kaplan-Meier Plot of PFS Sensitivity Analyses 1-3 (RND Population)

PFS-A: Using Radiological Assessments Only



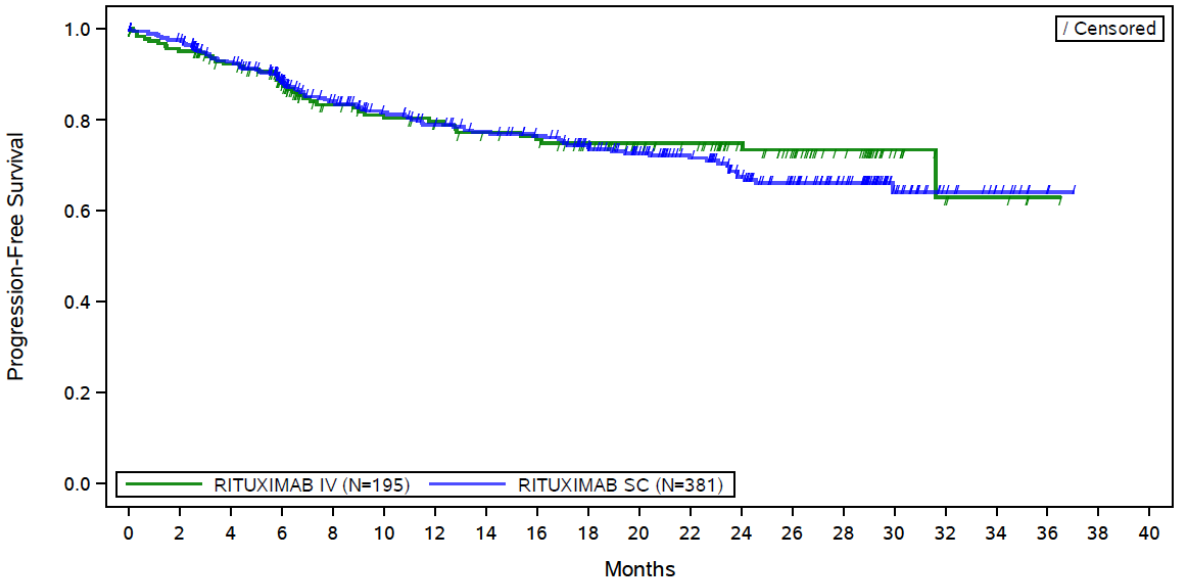
PFS-2: Using Scheduled Visit Dates Only



Number of Patients at Risk

RITUXIMAB IV	195	178	162	143	115	107	102	97	94	86	75	70	55	46	33	13	5	4	1	0	0
RITUXIMAB SC	381	356	321	279	243	218	204	194	186	169	149	130	108	89	71	31	16	9	3	0	0

PFS-3: Including All Signs of Clinical Progression



Number of Patients at Risk

RITUXIMAB IV	195	177	162	141	114	107	102	97	94	86	75	70	55	46	33	13	5	4	1	0	0
RITUXIMAB SC	381	354	321	278	241	218	204	194	186	169	149	130	108	89	71	31	16	9	3	0	0

Note: Time to event is calculated from randomization to first occurrence of progression of disease or death as defined in Table A of Appendix 3 in the Statistical Analysis Plan V2.0. Patients who have experienced none of these events at the time of analysis or who have been lost to follow-up will be censored according to the rules defined in Table A of Appendix 3 in the Statistical Analysis Plan V2.0.

MABEASE COMPARISON WITH HISTORICAL DATA

Complete response rates in the MabEase study were similar for the SC and IV treatment groups although somewhat lower than those observed in the three registration trials of rituximab IV in previously untreated DLBCL (GELA's BO16368/LNH.98-5, ECOG E4494,

and M39045/MInT), where rituximab IV-based treatments resulted in complete remission in 76% to 86% of patients.

Comparisons of the MabEase study with these earlier studies should be interpreted with caution owing to important differences in study design and patient populations. The GELA and ECOG studies evaluated R-CHOP therapy in older patients (>60 years) in all IPI risk categories, while the MInT study evaluated R-CHOP-like regimens in younger patients (<60 years) with low-risk disease (IPI score 0 or 1). The MabEase study included patients of all ages (median age 64 years), with 61% of patients aged 60 years or over, and all IPI risk groups.

The UK NCRI R-CHOP-14 versus R-CHOP-21 trial was a large phase III study of rituximab IV in a similar patient population to that in the MabEase study, including previously untreated patients of all ages (median age 61 years) and all IPI risk categories (Cunningham 2013). In that trial, complete response (CR/CRu) rates at the end of treatment based on IWG 1999 guidelines were 63% for the R-CHOP-21 group and 58% for the R-CHOP-14 group, which are more comparable to those observed in the MabEase study. With median follow-up of 46 months in the UK NCRI trial, 2-year PFS was 75% for both the R-CHOP-21 and R-CHOP-14 groups. In the MabEase study, with median follow-up of 28 months, 70% of patients in the rituximab SC arm and 78% in the rituximab IV arm were estimated to be progression-free at 2 years.

References

[Cunningham 2013] Cunningham D, Hawkes EA, Jack A et al. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. Lancet. 2013;381:1817-1826.

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ECOG E4494: CSR E4494, Phase III trial of CHOP versus CHOP and chimeric anti-CD20 monoclonal antibody (IDEC-C2B8) in older patients with diffuse mixed, diffuse large cell, and immunoblastic large cell histology non-Hodgkin's lymphoma. August 2005.

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SAWYER SUBGROUP ANALYSES

Table 5 SAWYER Part 2 Subgroup Analyses of ORR at the End of Treatment (ITT Population)

	Response Rate (CR, CRi, PR) at the End of Treatment [95% CI]		
Subgroup	**Rituximab IV n = 88**	**Rituximab SC n = 88**	**Difference [95% CI]**
BSA *(low: BSA $\leq$ 1.81 m^2; medium: 1.81 m^2 < BSA $\leq$ 2.00 m^2; high: BSA > 2.00 m^2)*			
Low	n = 33 78.8% [61.1%;91.0%]	n = 26 73.1% [52.2%;88.4%]	–5.71% [–30.1%;18.6%]
Medium	n = 29 79.3% [60.3%;92.0%]	n = 31 90.3% [74.2%;98.0%]	11.01% [–9.1%;31.1%]
High	n = 26 84.6% [65.1%;95.6%]	n = 31 90.3% [74.2%;98.0%]	5.71% [–13.9%;25.3%]
Gender			
Male	n = 53 81.1% [68.0%;90.6%]	n = 62 90.3% [80.1%;96.4%]	9.19% [–4.7%;23.1%]
Female	n = 35 80.0% [63.1%;91.6%]	n = 26 73.1% [52.2%;88.4%]	–6.92% [–30.8%;17.0%]
C_{trough} *(low:* $C_{trough} \leq 88.75$ *µg/mL; high:* $C_{trough} > 88.75$ *µg/mL)*			
Low	n = 43 90.7% [77.9%;97.4%]	n = 24 95.8% [78.9%;99.9%]	5.14% [–8.9%;19.2%]
High	n = 26 96.2% [80.4%;99.9%]	n = 41 95.1% [83.5%;99.4%]	–1.03% [–13.0%;11.0%]

End of treatment response assessment conducted at the 3-month follow-up visit.

Appendix 6 Safety Results, Supplementary Information

Table 1 Summary of Studies Contributing to Safety Evaluation

Study	No. of Patients Safety-Evaluable[a]	Clinical Cutoff / Median Observation Time
SparkThera	**Stage 1:** 124 patients total 34 375 mg/m^2 34 625 mg/m^2 40 800 mg/m^2 16 rituximab IV 375 mg/m^2 SC extension: 43 rituximab SC 1400 mg[d] **Stage 2:** 154 patients total 77 rituximab SC 1400 mg 77 rituximab IV 375 mg/m^2	**Stage 1:** 15 July 2013 / 23 months **Stage 2:** 15 July 2013 / 26 months
SABRINA	407 patients total 197 rituximab SC 1400 mg 210 rituximab IV 375 mg/m^2	11 January 2016 / 37 months
SAWYER	**Stage 1:** 56 patients total 16 1400 mg 17 1600 mg 22 1870mg 1 1000mg **Stage 2:** 174 patients total 85 rituximab SC 1600 mg 89 rituximab IV 500 mg/m^2	**Stage 1:** 7 May 2014 / 30 months **Stage 2:** 7 May 2014 / 14 months[c]
MabEase	572 patients total 369 rituximab SC 1400 mg 203 rituximab IV 375 mg/m^2	31 December 2015 / 28 months
PrefMab[b]	740 patients total Cycle 1 – 371 rituximab IV 375 mg/m^2 in Arm A; 369 rituximab IV 375 mg/m^2 in Arm B Cycle 2 onwards – 687 patients received rituximab SC; 356 in Arm A and 331 in Arm B	19 January 2015 / 13 months

[a]Safety-evaluable patient population includes patients who received at least one dose of rituximab IV or SC.
[b]Patients were randomized to receive either rituximab SC at cycles 2-4 (after first IV cycle) or rituximab IV at cycles 1-4. After the fourth cycle, patients were crossed over to the alternate route of administration for the remaining four cycles.
[c]In SAWYER, the database extraction date for the primary analysis was used to calculate the mean observation time for safety.
[d]These patients received one cycle of rituximab SC in the dose-finding part, reverted to IV dosing, and later switched back to SC dosing with the final selected dose of rituximab SC.

Table 2 Extent of Exposure to Rituximab (Safety Analysis Population)

	1400 mg								1600 mg	
	BO22334/SABRINA (FL)		MO28107/MabEase (DLBCL)		MO28457/PrefMab (FL induction/ DLBCL)		BP22333/SparkThera Stage 2 (FL maintenance)		BO25341/SAWYER Part 2 (CLL)	
	IV (N = 210)	SC (N = 197)	IV (N = 203)	SC (N = 369)	IV-SC-IV (N = 371)	IV-SC (N = 369)	IV (N = 77)	SC (N = 77)	IV (N = 89)	SC (N = 85)
Number of cycles received [a]										
Mean (SD)	17 (6)	17 (5)	7 (2)	7 (1)	N/A	N/A	7 (3)	8 (3)	5 (2)	6 (1)
Median	20	20	8	8	N/A	N/A	7	9	6	6
Min–Max	1–20	2–20	1–8	2–8	N/A	N/A	1–11	1–11	1–6	2–6
Duration of exposure (months)										
Mean (SD)	22.0 (9.7)	22.4 (9.0)	4.2 (1.6)	4.5 (1.1)	4.8 (1.5)	4.8 (1.5)	13.8 (5.9)	14.8 (5.3)	4.4 (1.5)	4.8 (1.2)
Median	27.1	27.1	4.9	4.9	5.0	5.0	16.6	16.8	4.7	4.9
Min–Max	0–31.3	0.7–30.2	0–6.8	0.5–7.2	0–7.6	0–7.8	0–19.0	0–21.0	0–7.0	1.0–6.7
Cumulative dose (mg)										
Mean (SD)	11649 (4364)	23088 (7432)	4797 (1652)	9669 (2065)	7039 (1627)	7510 (2089)	4934 (2144)	11080 (4418)	4778 (1500)	8163 (1633)
Median	13199	27223	5230	10460	7400	8200	5012	9800	5232	8720
Min–Max	275–18750	1910–27516	275–8368	1906–12045	50–8984	40–9812	521–8900	1400–15400	596–6526	2144–9260

CLL: chronic lymphocytic leukemia; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; SD: standard deviation.
[a] All patients received IV rituximab at Cycle 1.

SAFETY IN NHL INDUCTION (COMBINATION THERAPY)

Table 3 Adverse Events by Preferred Term Occurring in ≥ 5% of Patients in Either Arm in Combination Therapy (Safety Analysis Population) (Part 1 of 2)

Body System/ Adverse Event	Rituximab IV N = 413 No. (%)	Rituximab SC N = 566 No. (%)	Total N = 979 No. (%)
All Body Systems			
Total Pts with at least one AE	380 (92)	533 (94)	913 (93)
Gastrointestinal Disorders			
Total Pts with at least one AE	222 (54)	318 (56)	540 (55)
Nausea	93 (23)	140 (25)	233 (24)
Constipation	90 (22)	104 (18)	194 (20)
Diarrhea	46 (11)	78 (14)	124 (13)
Vomiting	42 (10)	69 (12)	111 (11)
Abdominal Pain	33 (8)	48 (8)	81 (8)
Dyspepsia	24 (6)	34 (6)	58 (6)
Stomatitis	21 (5)	33 (6)	54 (6)
General Disorders and Administration Site Conditions			
Total Pts with at least one AE	194 (47)	277 (49)	471 (48)
Fatigue	59 (14)	104 (18)	163 (17)
Pyrexia	52 (13)	73 (13)	125 (13)
Asthenia	47 (11)	67 (12)	114 (12)
Mucosal Inflammation	28 (7)	38 (7)	66 (7)
Edema Peripheral	20 (5)	34 (6)	54 (6)
Chills	24 (6)	23 (4)	47 (5)
Injection Site Erythema	0	31 (5)	31 (3)
Blood and Lymphatic System Disorders			
Total Pts with at least one AE	186 (45)	281 (50)	467 (48)
Neutropenia	112 (27)	171 (30)	283 (29)
Anemia	66 (16)	114 (20)	180 (18)
Febrile Neutropenia	37 (9)	67 (12)	104 (11)
Leukopenia	34 (8)	38 (7)	72 (7)
Infections and Infestations			
Total Pts with at least one AE	170 (41)	262 (46)	432 (44)
Pneumonia	14 (3)	36 (6)	50 (5)
Urinary Tract Infection	28 (7)	22 (4)	50 (5)
Upper Respiratory Tract Infection	14 (3)	33 (6)	47 (5)
Nervous System Disorders			
Total Pts with at least one AE	165 (40)	227 (40)	392 (40)
Neuropathy Peripheral	54 (13)	66 (12)	120 (12)
Paresthesia	36 (9)	60 (11)	96 (10)
Headache	27 (7)	43 (8)	70 (7)
Dizziness	21 (5)	20 (4)	41 (4)
Dysgeusia	19 (5)	17 (3)	36 (4)
Skin and Subcutaneous Tissue Disorders			
Total Pts with at least one AE	131 (32)	204 (36)	335 (34)
Alopecia	70 (17)	113 (20)	183 (19)

Investigator text for Adverse Events encoded using MedDRA Version 18.1
Multiple occurrences of the same Adverse Event in one individual counted only once.
Table continues on next page

Table 3 Adverse Events by Preferred Term Occurring in ≥ 5% of Patients in Either Arm in Combination Therapy (Safety Analysis Population) (Part 2 of 2)

Body System/ Adverse Event	Rituximab IV N = 413 No. (%)	Rituximab SC N = 566 No. (%)	Total N = 979 No. (%)
All Body Systems			
Total Pts with at least one AE	380 (92)	533 (94)	913 (93)
Respiratory, Thoracic, and Mediastinal Disorders			
Total Pts with at least one AE	106 (26)	162 (29)	268 (27)
Cough	34 (8)	65 (11)	99 (10)
Dyspnea	20 (5)	41 (7)	61 (6)
Musculoskeletal and Connective Tissue Disorders			
Total Pts with at least one AE	89 (22)	151 (27)	240 (25)
Back Pain	23 (6)	31 (5)	54 (6)
Arthralgia	16 (4)	26 (5)	42 (4)
Myalgia	8 (2)	27 (5)	35 (4)
Investigations			
Total Pts with at least one AE	82 (20)	134 (24)	216 (22)
Neutrophil Count Decreased	32 (8)	52 (9)	84 (9)
Weight Decreased	12 (3)	35 (6)	47 (5)
Metabolism and Nutrition Disorders			
Total Pts with at least one AE	52 (13)	91 (16)	143 (15)
Decreased Appetite	27 (7)	33 (6)	60 (6)
Psychiatric Disorders			
Total Pts with at least one AE	47 (11)	72 (13)	119 (12)
Insomnia	28 (7)	40 (7)	68 (7)

Investigator text for Adverse Events encoded using MedDRA Version 18.1
Multiple occurrences of the same Adverse Event in one individual counted only once.

Table 4 Grade ≥ 3 Adverse Events by Preferred Term Occurring in ≥ 2 Patients in Either Arm in Combination Therapy (Safety Analysis Population) (Part 1 of 3)

Body System/ Adverse Event	Rituximab IV N = 413 No. (%)	Rituximab SC N = 566 No. (%)	Total N = 979 No. (%)
All Body Systems			
Total Pts with at least one AE	208 (50)	322 (57)	530 (54)
Blood and Lymphatic System Disorders			
Total Pts with at least one AE	116 (28)	190 (34)	306 (31)
Neutropenia	77 (19)	139 (25)	216 (22)
Febrile Neutropenia	37 (9)	66 (12)	103 (11)
Anemia	8 (2)	28 (5)	36 (4)
Leukopenia	10 (2)	17 (3)	27 (3)
Lymphopenia	6 (1)	5 (1)	11 (1)
Thrombocytopenia	4 (1)	6 (1)	10 (1)
Pancytopenia	0	2 (<1)	2 (<1)
Investigations			
Total Pts with at least one AE	38 (9)	65 (11)	103 (11)
Neutrophil Count Decreased	25 (6)	40 (7)	65 (7)
White Blood Cell Count Decreased	10 (2)	15 (3)	25 (3)
Lymphocyte Count Decreased	5 (1)	7 (1)	12 (1)
Platelet Count Decreased	2 (<1)	5 (1)	7 (1)
Alanine Aminotransferase Increased	0	6 (1)	6 (1)
Aspartate Aminotransferase Incrased	2 (<1)	2 (<1)	4 (<1)
Gamma-Glutamyltransferase Increased	2 (<1)	1 (<1)	3 (<1)
Weight Decreased	1 (<1)	2 (<1)	3 (<1)
Blood Alkaline Phosphatase Increased	0	2 (<1)	2 (<1)
Infections and Infestations			
Total Pts with at least one AE	35 (8)	71 (13)	106 (11)
Pneumonia	9 (2)	23 (4)	32 (3)
Sepsis	0	8 (1)	8 (1)
Lung Infection	1 (<1)	6 (1)	7 (1)
Septic Shock	3 (1)	3 (1)	6 (1)
Neutropenic Sepsis	4 (1)	1 (<1)	5 (1)
Urinary Tract Infection	2 (<1)	3 (1)	5 (1)
Herpes Zoster	1 (<1)	3 (1)	4 (<1)
Infection	2 (<1)	2 (<1)	4 (<1)
Lower Respiratory Tract Infection	2 (<1)	2 (<1)	4 (<1)
Cellulitis	0	3 (1)	3 (<1)
Respiratory Tract Infection	0	3 (1)	3 (<1)
Appendicitis	0	2 (<1)	2 (<1)
Oral Herpes	0	2 (<1)	2 (<1)
Gastrointestinal Disorders			
Total Pts with at least one AE	22 (5)	33 (6)	55 (6)
Diarrhea	4 (1)	8 (1)	12 (1)
Vomiting	3 (1)	3 (1)	6 (1)
Abdominal Pain	2 (<1)	3 (1)	5 (1)
Constipation	2 (<1)	2 (<1)	4 (<1)
Nausea	1 (<1)	2 (<1)	3 (<1)
Stomatitis	0	3 (1)	3 (<1)
Duodenal Ulcer	2 (<1)	0	2 (<1)
Upper Gastrointestinal Hemorrhage	0	2 (<1)	2 (<1)

Investigator text for Adverse Events encoded using MedDRA Version 18.1
Multiple occurrences of the same Adverse Event in one individual counted only once. *Table continues on next page*

Table 4 Grade ≥ 3 Adverse Events by Preferred Term Occurring in ≥ 2 Patients in Either Arm in Combination Therapy (Safety Analysis Population) (Part 2 of 3)

Body System/ Adverse Event	Rituximab IV N = 413 No. (%)	Rituximab SC N = 566 No. (%)	Total N = 979 No. (%)
All Body Systems			
Total Pts with at least one AE	208 (50)	322 (57)	530 (54)
General Disorders and Administration Site Conditions			
Total Pts with at least one AE	19 (5)	23 (4)	42 (4)
Mucosal Inflammation	5 (1)	4 (1)	9 (1)
Fatigue	5 (1)	2 (<1)	7 (1)
Asthenia	2 (<1)	4 (1)	6 (1)
Pyrexia	1 (<1)	2 (<1)	3 (<1)
Death	0	2 (<1)	2 (<1)
General Physical Health Deterioriation	0	2 (<1)	2 (<1)
Edema Peripheral	0	2 (<1)	2 (<1)
Respiratory, Thoracic, and Mediastinal Disorders			
Total Pts with at least one AE	20 (5)	16 (3)	36 (4)
Pulmonary Embolism	7 (2)	4 (1)	11 (1)
Dyspnea	4 (1)	1 (<1)	5 (1)
Hypoxia	1 (<1)	3 (1)	4 (<1)
Pneumonitis	0	2 (<1)	2 (<1)
Cardiac Disorders			
Total Pts with at least one AE	17 (4)	18 (3)	35 (4)
Atrial Fibrillation	2 (<1)	4 (1)	6 (1)
Cardiac Arrest	4 (1)	1 (<1)	5 (1)
Cardiac Failure Congestive	1 (<1)	3 (1)	4 (<1)
Myocardial Infarction	3 (1)	1 (<1)	4 (<1)
Acute Myocardial Infarction	0	2 (<1)	2 (<1)
Nervous System Disorders			
Total Pts with at least one AE	13 (3)	17 (3)	30 (3)
Neuropathy Peripheral	1 (<1)	6 (1)	7 (1)
Syncope	3 (1)	3 (1)	6 (1)
Presyncope	2 (<1)	1 (<1)	3 (<1)
Peripheral Motor Neuropathy	0	2 (<1)	2 (<1)
Metabolism and Nutrition Disorders			
Total Pts with at least one AE	6 (1)	15 (3)	21 (2)
Hyperglycemia	3 (1)	3 (1)	6 (1)
Hypokalemia	0	5 (1)	5 (1)
Hyponatremia	1 (<1)	4 (1)	5 (1)
Decreased Appetite	2 (<1)	1 (<1)	3 (<1)
Vascular Disorders			
Total Pts with at least one AE	7 (2)	11 (2)	18 (2)
Hypertension	1 (<1)	6 (1)	7 (1)
Musculoskeletal and Connective Tissue Disorders			
Total Pts with at least one AE	7 (2)	10 (2)	17 (2)
Back Pain	2 (<1)	1 (<1)	3 (<1)
Bone Pain	0	3 (1)	3 (<1)
Muscular Weakness	2 (<1)	0	2 (<1)
Osteoporosis	2 (<1)	0	2 (<1)

Investigator text for Adverse Events encoded using MedDRA Version 18.1
Multiple occurrences of the same Adverse Event in one individual counted only once.
Table continues on next page

Table 4 Grade ≥ 3 Adverse Events by Preferred Term Occurring in ≥ 2 Patients in Either Arm in Combination Therapy (Safety Analysis Population) (Part 3 of 3)

Body System/ Adverse Event	Rituximab IV N = 413 No. (%)	Rituximab SC N = 566 No. (%)	Total N = 979 No. (%)
All Body Systems			
Total Pts with at least one AE	208 (50)	322 (57)	530 (54)
Injury, Poisoning and Procedural Complications			
Total Pts with at least one AE	8 (2)	7 (1)	15 (2)
Femur Fracture	0	2 (<1)	2 (<1)
Infusion Related Reaction	2 (<1)	0	2 (<1)
Subdural Hematoma	2 (<1)	0	2 (<1)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)			
Total Pts with at least one AE	3 (1)	8 (1)	11 (1)
Non-Small Cell Lung Cancer	0	2 (<1)	2 (<1)
Psychiatric Disorders			
Total Pts with at least one AE	3 (1)	4 (1)	7 (1)
Anxiety	0	2 (<1)	2 (<1)
Ear and Labyrinth Disorders			
Total Pts with at least one AE	1 (<1)	2 (<1)	3 (<1)
Vertigo	0	2 (<1)	2 (<1)
Eye Disorders			
Total Pts with at least one AE	0	3 (1)	3 (<1)
Cataract	0	3 (1)	3 (<1)

Investigator text for Adverse Events encoded using MedDRA Version 18.1
Multiple occurrences of the same Adverse Event in one individual counted only once.

Table 5 Serious Adverse Events by Preferred Term Occurring in ≥ 2 Patients in Either Arm in Combination Therapy (Safety Analysis Population) (Part 1 of 2)

Body System/ Adverse Event	Rituximab IV N=413 No. (%)	Rituximab SC N=566 No. (%)	Total N=979 No. (%)
All Body Systems			
Total Pts With At Least One AE	120 (29)	204 (36)	324 (33)
Blood and Lymphatic System Disorders			
Total Pts With At Least One AE	47 (11)	76 (13)	123 (13)
Febrile Neutropenia	32 (8)	59 (10)	91 (9)
Neutropenia	13 (3)	23 (4)	36 (4)
Anaemia	3 (1)	4 (1)	7 (1)
Leukopenia	2 (<1)	0	2 (<1)
Infections and Infestations			
Total Pts With At Least One AE	35 (8)	73 (13)	108 (11)
Pneumonia	12 (3)	28 (5)	40 (4)
Sepsis	0	8 (1)	8 (1)
Septic Shock	3 (1)	3 (1)	6 (1)
Lung Infection	1 (<1)	4 (1)	5 (1)
Neutropenic Sepsis	4 (1)	1 (<1)	5 (1)
Infection	2 (<1)	2 (<1)	4 (<1)
Lower Respiratory Tract Infection	2 (<1)	2 (<1)	4 (<1)
Bronchitis	2 (<1)	1 (<1)	3 (<1)
Respiratory Tract Infection	0	3 (1)	3 (<1)
Appendicitis	0	2 (<1)	2 (<1)
Cellulitis	0	2 (<1)	2 (<1)
Herpes Zoster	0	2 (<1)	2 (<1)
Upper Respiratory Tract Infection	0	2 (<1)	2 (<1)
Gastrointestinal Disorders			
Total Pts With At Least One AE	14 (3)	27 (5)	41 (4)
Abdominal Pain	3 (1)	6 (1)	9 (1)
Constipation	3 (1)	0	3 (<1)
Diarrhoea	0	3 (1)	3 (<1)
Vomiting	0	3 (1)	3 (<1)
Upper Gastrointestinal Haemorrhage	0	2 (<1)	2 (<1)
General Disorders and Administration Site Conditions			
Total Pts With At Least One AE	15 (4)	22 (4)	37 (4)
Pyrexia	7 (2)	13 (2)	20 (2)
Chills	2 (<1)	2 (<1)	4 (<1)
Death	0	2 (<1)	2 (<1)
General Physical Health Deterioration	0	2 (<1)	2 (<1)
Respiratory, Thoracic and Mediastinal Disorders			
Total Pts With At Least One AE	19 (5)	16 (3)	35 (4)
Pulmonary Embolism	7 (2)	2 (<1)	9 (1)
Dyspnoea	5 (1)	1 (<1)	6 (1)
Interstitial Lung Disease	2 (<1)	1 (<1)	3 (<1)
Pleural Effusion	1 (<1)	2 (<1)	3 (<1)
Pneumonitis	0	3 (1)	3 (<1)
Pneumothorax	1 (<1)	2 (<1)	3 (<1)
Pulmonary Oedema	0	2 (<1)	2 (<1)

Investigator text for Adverse Events encoded using MedDRA Version 18.1
Multiple occurrences of the same Adverse Event in one individual counted only once. *Table continues on next page*

Table 5 Serious Adverse Events by Preferred Term Occurring in ≥ 2 Patients in Either Arm in Combination Therapy (Safety Analysis Population) (Part 2 of 2)

Body System/ Adverse Event	Rituximab IV N=413 No. (%)	Rituximab SC N=566 No. (%)	Total N=979 No. (%)
All Body Systems			
Total Pts With At Least One AE	120 (29)	204 (36)	324 (33)
Cardiac Disorders			
Total Pts With At Least One AE	15 (4)	17 (3)	32 (3)
Atrial Fibrillation	3 (1)	4 (1)	7 (1)
Cardiac Arrest	4 (1)	1 (<1)	5 (1)
Myocardial Infarction	3 (1)	1 (<1)	4 (<1)
Cardiac Failure Congestive	1 (<1)	2 (<1)	3 (<1)
Acute Myocardial Infarction	0	2 (<1)	2 (<1)
Investigations			
Total Pts With At Least One AE	4 (1)	16 (3)	20 (2)
Neutrophil Count Decreased	3 (1)	9 (2)	12 (1)
White Blood Cell Count Decreased	1 (<1)	4 (1)	5 (1)
Injury, Poisoning and Procedural Complications			
Total Pts With At Least One AE	7 (2)	10 (2)	17 (2)
Femur Fracture	0	2 (<1)	2 (<1)
Multiple Fractures	0	2 (<1)	2 (<1)
Nervous System Disorders			
Total Pts With At Least One AE	7 (2)	7 (1)	14 (1)
Syncope	1 (<1)	2 (<1)	3 (<1)
Cerebrovascular Accident	0	2 (<1)	2 (<1)
Presyncope	0	2 (<1)	2 (<1)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts And Polyps)			
Total Pts With At Least One AE	3 (1)	8 (1)	11 (1)
Non-Small Cell Lung Cancer	0	2 (<1)	2 (<1)
Metabolism and Nutrition Disorders			
Total Pts With At Least One AE	3 (1)	7 (1)	10 (1)
Hyponatremia	0	4 (1)	4 (<1)
Renal and Urinary Disorders			
Total Pts With At Least One AE	2 (<1)	2 (<1)	4 (<1)
Urinary Retention	2 (<1)	0	2 (<1)

Investigator text for Adverse Events encoded using MedDRA Version 18.1
Multiple occurrences of the same Adverse Event in one individual counted only once.

Table 6 Adverse Events Leading to Patient Deaths in Combination Therapy (Safety Analysis Population) (Part 1 of 2)

Body System/ Adverse Event	Rituximab IV N=413 No. (%)	Rituximab SC N=566 No. (%)	Total N=979 No. (%)
All Body Systems			
Total Pts With At Least One AE	19 (5)	34 (6)	53 (5)
Infections and Infestations			
Total Pts With At Least One AE	7 (2)	12 (2)	19 (2)
Pneumonia	2 (<1)	4 (1)	6 (1)
Septic Shock	3 (1)	2 (<1)	5 (1)
Lung Infection	0	2 (<1)	2 (<1)
Sepsis	0	2 (<1)	2 (<1)
Infection	1 (<1)	0	1 (<1)
Peritonitis	0	1 (<1)	1 (<1)
Pulmonary Tuberculosis	1 (<1)	0	1 (<1)
Respiratory Tract Infection	0	1 (<1)	1 (<1)
Cardiac Disorders			
Total Pts With At Least One AE	6 (1)	7 (1)	13 (1)
Cardiac Arrest	3 (1)	1 (<1)	4 (<1)
Myocardial Infarction	3 (1)	1 (<1)	4 (<1)
Cardiac Failure Congestive	0	2 (<1)	2 (<1)
Cardiac Failure	0	1 (<1)	1 (<1)
Cardiac Failure Acute	0	1 (<1)	1 (<1)
Left Ventricular Failure	0	1 (<1)	1 (<1)
General Disorders and Administration Site Conditions			
Total Pts With At Least One AE	1 (<1)	6 (1)	7 (1)
Death	0	2 (<1)	2 (<1)
General Physical Health Deterioration	0	2 (<1)	2 (<1)
Disease Progression	0	1 (<1)	1 (<1)
Multi-Organ Failure	0	1 (<1)	1 (<1)
Sudden Death	1 (<1)	0	1 (<1)
Respiratory, Thoracic and Mediastinal Disorders			
Total Pts With At Least One AE	4 (1)	1 (<1)	5 (1)
Respiratory Failure	1 (<1)	1 (<1)	2 (<1)
Acute Respiratory Failure	1 (<1)	0	1 (<1)
Epistaxis	1 (<1)	0	1 (<1)
Interstitial Lung Disease	1 (<1)	0	1 (<1)
Blood and Lymphatic System Disorders			
Total Pts With At Least One AE	1 (<1)	2 (<1)	3 (<1)
Febrile Neutropenia	1 (<1)	2 (<1)	3 (<1)
Gastrointestinal Disorders			
Total Pts With At Least One AE	0	3 (1)	3 (<1)
Abdominal Pain	0	1 (<1)	1 (<1)
Diarrhea	0	1 (<1)	1 (<1)
Gastrointestinal Hemorrhage	0	1 (<1)	1 (<1)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)			
Total Pts With At Least One AE	0	2 (<1)	2 (<1)
Lung Adenocarcinoma	0	1 (<1)	1 (<1)
Non-Small Cell Lung Cancer	0	1 (<1)	1 (<1)

Investigator text for Adverse Events encoded using MedDRA Version 18.1
Multiple occurrences of the same Adverse Event in one individual counted only once. *Table continues on next page*

Table 6 Adverse Events Leading to Patient Deaths in Combination Therapy (Safety Analysis Population) (Part 2 of 2)

Body System/ Adverse Event	Rituximab IV N=413 No. (%)	Rituximab SC N=566 No. (%)	Total N=979 No. (%)
All Body Systems			
Total Pts With At Least One AE	19 (5)	34 (6)	53 (5)
Nervous System Disorders			
Total Pts With At Least One AE	2 (<1)	0	2 (<1)
Cerebral Infarction	1 (<1)	0	1 (<1)
Coma Hepatic	1 (<1)	0	1 (<1)
Injury, Poisoning and Procedural Complications			
Total Pts With At Least One AE	0	1 (<1)	1 (<1)
Fall	0	1 (<1)	1 (<1)

Investigator text for Adverse Events encoded using MedDRA Version 18.1
Multiple occurrences of the same Adverse Event in one individual counted only once.

Table 7 Adverse Events Leading to Treatment Discontinuation (by Preferred Term Occurring in ≥ 2 Patients in Either Arm) in Combination Therapy (Safety Analysis Population)

Body System/ Adverse Event	Rituximab IV N=413 No. (%)	Rituximab SC N=566 No. (%)	Total N=979 No. (%)
All Body Systems			
Total Pts With At Least One AE	25 (6)	34 (6)	59 (6)
Infections and Infestations			
Total Pts With At Least One AE	6 (1)	9 (2)	15 (2)
Septic Shock	3 (1)	2 (<1)	5 (1)
Pneumonia	1 (<1)	3 (1)	4 (<1)
Lung Infection	0	3 (1)	3 (<1)
Blood and Lymphatic System Disorders			
Total Pts With At Least One AE	4 (1)	4 (1)	8 (1)
Neutropenia	1 (<1)	3 (1)	4 (<1)
Febrile Neutropenia	2 (<1)	1 (<1)	3 (<1)
Respiratory, Thoracic and Mediastinal Disorders			
Total Pts With At Least One AE	5 (1)	5 (1)	10 (1)
Pulmonary Embolism	2 (<1)	0	2 (<1)
Cardiac Disorders			
Total Pts With At Least One AE	5 (1)	3 (1)	8 (1)
Myocardial Infarction	2 (<1)	1 (<1)	3 (<1)
Cardiac Arrest	2 (<1)	0	2 (<1)

Investigator text for Adverse Events encoded using MedDRA Version 18.1
Multiple occurrences of the same Adverse Event in one individual counted only once.

SAFETY IN FL MAINTENANCE (RITUXIMAB MONOTHERAPY)

Table 8 Adverse Events by Preferred Term Occurring in ≥ 5% of Patients in Either Arm in Rituximab Monotherapy (Safety Analysis Population) (Part 1 of 2)

Body System/ Adverse Event	Rituximab IV N=255 No. (%)	Rituximab SC N=249 No. (%)	Total N=504 No. (%)
All Body Systems			
Total Pts With At Least One AE	208 (82)	202 (81)	410 (81)
Infections and Infestations			
Total Pts With At Least One AE	136 (53)	123 (49)	259 (51)
Upper Respiratory Tract Infection	25 (10)	32 (13)	57 (11)
Nasopharyngitis	23 (9)	15 (6)	38 (8)
Bronchitis	18 (7)	15 (6)	33 (7)
Urinary Tract Infection	24 (9)	9 (4)	33 (7)
Sinusitis	15 (6)	14 (6)	29 (6)
Pneumonia	6 (2)	15 (6)	21 (4)
Rhinitis	12 (5)	6 (2)	18 (4)
Gastrointestinal Disorders			
Total Pts With At Least One AE	61 (24)	75 (30)	136 (27)
Diarrhea	13 (5)	20 (8)	33 (7)
Abdominal Pain	9 (4)	14 (6)	23 (5)
Constipation	12 (5)	11 (4)	23 (5)
Nausea	5 (2)	12 (5)	17 (3)
General Disorders and Administration Site Conditions			
Total Pts With At Least One AE	58 (23)	84 (34)	142 (28)
Fatigue	17 (7)	15 (6)	32 (6)
Asthenia	11 (4)	20 (8)	31 (6)
Injection Site Erythema	0	19 (8)	19 (4)
Pyrexia	13 (5)	5 (2)	18 (4)
Musculoskeletal and Connective Tissue Disorders			
Total Pts With At Least One AE	67 (26)	73 (29)	140 (28)
Arthralgia	20 (8)	21 (8)	41 (8)
Back Pain	21 (8)	8 (3)	29 (6)
Myalgia	5 (2)	12 (5)	17 (3)
Respiratory, Thoracic and Mediastinal Disorders			
Total Pts With At Least One AE	58 (23)	60 (24)	118 (23)
Cough	33 (13)	30 (12)	63 (13)
Skin and Subcutaneous Tissue Disorders			
Total Pts With At Least One AE	49 (19)	60 (24)	109 (22)
Rash	7 (3)	17 (7)	24 (5)
Pruritus	14 (5)	5 (2)	19 (4)
Erythema	2 (1)	16 (6)	18 (4)
Nervous System Disorders			
Total Pts With At Least One AE	43 (17)	44 (18)	87 (17)
Headache	12 (5)	13 (5)	25 (5)

Investigator text for Adverse Events encoded using MedDRA Version 18.1
Multiple occurrences of the same Adverse Event in one individual counted only once.
Table continues on next page

Table 8 Adverse Events by Preferred Term Occurring in ≥ 5% of Patients in Either Arm in Rituximab Monotherapy (Safety Analysis Population) (Part 2 of 2)

Body System/ Adverse Event	Rituximab IV N=255 No. (%)	Rituximab SC N=249 No. (%)	Total N=504 No. (%)
All Body Systems			
Total Pts With At Least One AE	208 (82)	202 (81)	410 (81)
Blood and Lymphatic System Disorders			
Total Pts With At Least One AE	40 (16)	38 (15)	78 (15)
Neutropenia	20 (8)	25 (10)	45 (9)
Injury, Poisoning and Procedural Complications			
Total Pts With At Least One AE	27 (11)	44 (18)	71 (14)
Administration Related Reaction	4 (2)	26 (10)	30 (6)

Investigator text for Adverse Events encoded using MedDRA Version 18.1
Multiple occurrences of the same Adverse Event in one individual counted only once.

Table 9 Grade ≥ 3 Adverse Events by Preferred Term Occurring in ≥ 2 Patients in Either Arm in Rituximab Monotherapy (Safety Analysis Population)

Body System/ Adverse Event	Rituximab IV N=255 No. (%)	Rituximab SC N=249 No. (%)	Total N=504 No. (%)
All Body Systems			
Total Pts With At Least One AE	73 (29)	67 (27)	140 (28)
Blood and Lymphatic System Disorders			
Total Pts With At Least One AE	24 (9)	22 (9)	46 (9)
Neutropenia	16 (6)	18 (7)	34 (7)
Febrile Neutropenia	2 (1)	2 (1)	4 (1)
Leukopenia	2 (1)	2 (1)	4 (1)
Granulocytopenia	2 (1)	0	2 (<1)
Lymphopenia	2 (1)	0	2 (<1)
Infections and Infestations			
Total Pts With At Least One AE	16 (6)	22 (9)	38 (8)
Pneumonia	2 (1)	4 (2)	6 (1)
Sepsis	1 (<1)	2 (1)	3 (1)
Urinary Tract Infection	1 (<1)	2 (1)	3 (1)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts And Polyps)			
Total Pts With At Least One AE	8 (3)	9 (4)	17 (3)
Basal Cell Carcinoma	2 (1)	0	2 (<1)
Gastrointestinal Disorders			
Total Pts With At Least One AE	8 (3)	6 (2)	14 (3)
Colitis	0	2 (1)	2 (<1)
General Disorders and Administration Site Conditions			
Total Pts With At Least One AE	5 (2)	3 (1)	8 (2)
Death	2 (1)	0	2 (<1)
Respiratory, Thoracic and Mediastinal Disorders			
Total Pts With At Least One AE	4 (2)	3 (1)	7 (1)
Dyspnea	2 (1)	1 (<1)	3 (1)

Investigator text for Adverse Events encoded using MedDRA Version 18.1
Multiple occurrences of the same Adverse Event in one individual counted only once.

Table 10 Serious Adverse Events by Preferred Term Occurring in ≥ 2 Patients in Either Arm in Rituximab Monotherapy (Safety Analysis Population)

Body System/ Adverse Event	Rituximab IV N=255 No. (%)	Rituximab SC N=249 No. (%)	Total N=504 No. (%)
All Body Systems			
Total Pts With At Least One AE	55 (22)	48 (19)	103 (20)
Infections and Infestations			
Total Pts With At Least One AE	13 (5)	22 (9)	35 (7)
Pneumonia	2 (1)	5 (2)	7 (1)
Sepsis	1 (<1)	2 (1)	3 (1)
Urinary Tract Infection	1 (<1)	2 (1)	3 (1)
Lung Infection	2 (1)	0	2 (<1)
Urosepsis	0	2 (1)	2 (<1)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)			
Total Pts With At Least One AE	9 (4)	10 (4)	19 (4)
Basal Cell Carcinoma	2 (1)	0	2 (<1)
Blood and Lymphatic System Disorders			
Total Pts With At Least One AE	6 (2)	2 (1)	8 (2)
Febrile Neutropenia	2 (1)	1 (<1)	3 (1)
Neutropenia	2 (1)	1 (<1)	3 (1)
Nervous System Disorders			
Total Pts With At Least One AE	6 (2)	1 (<1)	7 (1)
Cognitive Disorder	2 (1)	0	2 (<1)
Musculoskeletal and Connective Tissue Disorders			
Total Pts With At Least One AE	3 (1)	3 (1)	6 (1)
Osteoarthritis	2 (1)	0	2 (<1)
General Disorders and Administration Site Conditions			
Total Pts With At Least One AE	4 (2)	1 (<1)	5 (1)
Death	2 (1)	0	2 (<1)
Renal and Urinary Disorders			
Total Pts With At Least One AE	1 (<1)	2 (1)	3 (1)
Hydronephrosis	0	2 (1)	2 (<1)

Investigator text for Adverse Events encoded using MedDRA Version 18.1
Multiple occurrences of the same Adverse Event in one individual counted only once.

Table 11 Adverse Events Leading to Patient Deaths in Rituximab Monotherapy (Safety Analysis Population)

Body System/ Adverse Event	Rituximab IV N=255 No. (%)	Rituximab SC N=249 No. (%)	Total N=504 No. (%)
All Body Systems			
Total Pts With At Least One AE	9 (4)	3 (1)	12 (2)
Infections and Infestations			
Total Pts With At Least One AE	4 (2)	1 (<1)	5 (1)
Creutzfeldt-Jakob Disease	0	1 (<1)	1 (<1)
Lung Infection	1 (<1)	0	1 (<1)
Pneumonia	1 (<1)	0	1 (<1)
Sepsis	1 (<1)	0	1 (<1)
Urinary Tract Infection	1 (<1)	0	1 (<1)
General Disorders and Administration Site Conditions			
Total Pts With At Least One AE	3 (1)	0	3 (1)
Death	2 (1)	0	2 (<1)
Multi-Organ Failure	1 (<1)	0	1 (<1)
Cardiac Disorders			
Total Pts With At Least One AE	0	1 (<1)	1 (<1)
Acute Myocardial Infarction	0	1 (<1)	1 (<1)
Injury, Poisoning and Procedural Complications			
Total Pts With At Least One AE	1 (<1)	0	1 (<1)
Traumatic Intracranial Haemorrhage	1 (<1)	0	1 (<1)
Nervous System Disorders			
Total Pts With At Least One AE	1 (<1)	0	1 (<1)
Hypoglycaemic Coma	1 (<1)	0	1 (<1)
Respiratory, Thoracic and Mediastinal Disorders			
Total Pts With At Least One AE	0	1 (<1)	1 (<1)
Acute Respiratory Failure	0	1 (<1)	1 (<1)

Investigator text for Adverse Events encoded using MedDRA Version 18.1
Multiple occurrences of the same Adverse Event in one individual counted only once.

Table 12 Adverse Events Leading to Treatment Discontinuation by Preferred Term in Rituximab Monotherapy (Safety Analysis Population)

Body System/ Adverse Event	Rituximab IV N=255 No. (%)	Rituximab SC N=249 No. (%)	Total N=504 No. (%)
All Body Systems			
Total Pts With At Least One AE	9 (4)	14 (6)	23 (5)
Blood and Lymphatic System Disorders			
Total Pts With At Least One AE	3 (1)	3 (1)	6 (1)
Neutropenia	0	2 (1)	2 (<1)
Agranulocytosis	1 (<1)	0	1 (<1)
Febrile Neutropenia	0	1 (<1)	1 (<1)
Leukopenia	1 (<1)	0	1 (<1)
Thrombocytopenia	1 (<1)	0	1 (<1)
Infections and Infestations			
Total Pts With At Least One AE	1 (<1)	3 (1)	4 (1)
Chronic Hepatitis B	0	1 (<1)	1 (<1)
Creutzfeldt-Jakob Disease	0	1 (<1)	1 (<1)
Infection	0	1 (<1)	1 (<1)
Reiter's Syndrome	1 (<1)	0	1 (<1)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)			
Total Pts With At Least One AE	1 (<1)	3 (1)	4 (1)
Invasive Ductal Breast Carcinoma	0	1 (<1)	1 (<1)
Kaposi's Sarcoma	0	1 (<1)	1 (<1)
Malignant Melanoma	0	1 (<1)	1 (<1)
Myelodysplastic Syndrome	1 (<1)	0	1 (<1)
Gastrointestinal Disorders			
Total Pts With At Least One AE	2 (1)	1 (<1)	3 (1)
Abdominal Pain	1 (<1)	0	1 (<1)
Colitis Ulcerative	0	1 (<1)	1 (<1)
Enterovesical Fistula	1 (<1)	0	1 (<1)
Respiratory, Thoracic and Mediastinal Disorders			
Total Pts With At Least One AE	1 (<1)	1 (<1	2 (<1)
Dyspnea	1 (<1)	1 (<1)	2 (<1)
Skin and Subcutaneous Tissue Disorders			
Total Pts With At Least One AE	1 (<1)	1 (<1)	2 (<1)
Rash Vesicular	0	1 (<1)	1 (<1)
Skin Ulcer	1 (<1)	0	1 (<1)
Hepatobiliary Disorders			
Total Pts With At Least One AE	0	1 (<1)	1 (<1)
Jaundice	0	1 (<1)	1 (<1)
Immune System Disorders			
Total Pts With At Least One AE	0	1 (<1)	1 (<1)
Hypersensitivity	0	1 (<1)	1 (<1)
Nervous System Disorders			
Total Pts With At Least One AE	1 (<1)	0	1 (<1)
Transient Ischemic Attack	1 (<1)	0	1 (<1)

Investigator text for Adverse Events encoded using MedDRA Version 18.1
Multiple occurrences of the same Adverse Event in one individual counted only once.

SAFETY IN CLL (RITUXIMAB + FC CHEMOTHERAPY)

Table 13 Adverse Events by Preferred Term Occurring in ≥5% of Patients in Either Arm in CLL (Safety Analysis Population) (Part 1 of 2)

Body System/ Adverse Event	Rituximab IV N = 89 No. (%)	Rituximab SC N = 85 No. (%)	Total N = 174 No. (%)
Blood and Lymphatic System Disorders			
Neutropenia	52 (58)	55 (65)	107 (61)
Thrombocytopenia	23 (26)	20 (24)	43 (25)
Anemia	21 (24)	11 (13)	32 (18)
Leukopenia	14 (16)	16 (19)	30 (17)
Febrile Neutropenia	7 (8)	9 (11)	16 (9)
Gastrointestinal Disorders			
Nausea	31 (35)	32 (38)	63 (36)
Vomiting	20 (22)	18 (21)	38 (22)
Diarrhea	10 (11)	10 (12)	20 (11)
Constipation	7 (8)	7 (8)	14 (8)
Abdominal Pain	5 (6)	8 (9)	13 (7)
General Disorders and Administration Site Conditions			
Pyrexia	22 (25)	27 (32)	49 (28)
Asthenia	15 (17)	7 (8)	22 (13)
Injection Site Erythema	-	22 (26)	22 (13)
Chills	9 (10)	11 (13)	20 (11)
Fatigue	9 (10)	9 (11)	18 (10)
Injection Site Pain	-	14 (16)	14 (8)
Infections and Infestations			
Upper Respiratory Tract Infection	11 (12)	11 (13)	22 (13)
Bronchitis	5 (6)	6 (7)	11 (6)
Respiratory Tract Infection	4 (4)	7 (8)	11 (6)
Urinary Tract Infection	7 (8)	2 (2)	9 (5)
Pneumonia	5 (6)	2 (2)	7 (4)
Skin and Subcutaneous Tissue Disorders			
Erythema	6 (7)	13 (15)	19 (11)
Rash	9 (10)	10 (12)	19 (11)
Pruritus	4 (4)	7 (8)	11 (6)
Respiratory, Thoracic and Mediastinal Disorders			
Cough	10 (11)	11 (13)	21 (12)
Dyspnea	7 (8)	3 (4)	10 (6)
Oropharyngeal Pain	3 (3)	5 (6)	8 (5)
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	1 (1)	8 (9)	9 (5)
Pain In Extremity	2 (2)	6 (7)	8 (5)
Bone Pain	2 (2)	5 (6)	7 (4)
Nervous System Disorders			
Headache	8 (9)	6 (7)	14 (8)

Investigator text for Adverse Events encoded using MedDRA version 17.0.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
Includes Adverse Events commenced on or after Cycle 1 Day 1.
Table continues on next page

Table 13 Adverse Events by Preferred Term Occurring in ≥5% of Patients in Either Arm in CLL (Safety Analysis Population) (Part 2 of 2)

Body System/ Adverse Event	Rituximab IV N = 89 No. (%)	Rituximab SC N = 85 No. (%)	Total N = 174 No. (%)
Vascular Disorders			
Hypotension	6 (7)	1 (1)	7 (4)
Hypertension	5 (6)	-	5 (3)
Psychiatric Disorders			
Insomnia	6 (7)	1 (1)	7 (4)

Investigator text for Adverse Events encoded using MedDRA version 17.0.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
Includes Adverse Events commenced on or after Cycle 1 Day 1.

Table 14 Grade≥3 Adverse Events by Preferred Term Occurring in ≥2% of Patients in Either Arm in CLL (Safety Analysis Population)

Body System/ Adverse Event	Rituximab IV N=89 No. (%)	Rituximab SC N=85 No. (%)	Total N=174 No. (%)
Blood and Lymphatic System Disorders			
Neutropenia	46 (52)	48 (56)	94 (54)
Leukopenia	11 (12)	12 (14)	23 (13)
Febrile Neutropenia	7 (8)	7 (8)	14 (8)
Thrombocytopenia	8 (9)	5 (6)	13 (7)
Anemia	8 (9)	4 (5)	12 (7)
Hemolytic Anemia	3 (3)	2 (2)	5 (3)
Hematotoxicity	-	2 (2)	2 (1)
Infections and Infestations			
Pneumonia	2 (2)	2 (2)	4 (2)
Pulpitis Dental	-	2 (2)	2 (1)
General Disorders and Administration Site Conditions			
Pyrexia	1 (1)	4 (5)	5 (3)
Asthenia	2 (2)	1 (1)	3 (2)
Injection Site Erythema	-	2 (2)	2 (1)
Gastrointestinal Disorders			
Diarrhea	3 (3)	-	3 (2)
Vomiting	1 (1)	2 (2)	3 (2)

Table 15 Serious Adverse Events by Preferred Term Occurring in ≥2% of Patients in Either Arm in CLL (Safety Analysis Population)

Body System/ Adverse Event	Rituximab IV N=89 No. (%)	Rituximab SC N=85 No. (%)	Total N=174 No. (%)
Blood and Lymphatic System Disorders			
Febrile Neutropenia	4 (4)	9 (11)	13 (7)
Neutropenia	8 (9)	1 (1)	9 (5)
Anemia	3 (3)	-	3 (2)
Infections and Infestations			
Upper Respiratory Tract Infection	2 (2)	1 (1)	3 (2)
Lower Respiratory Tract Infection	2 (2)	-	2 (1)
General Disorders and Administration Site Conditions			
Pyrexia	1 (1)	3 (4)	4 (2)

Table 16 Summary of Deaths in CLL (Safety Analysis Population)

Cause of Death	Rituximab IV N=89 No. (%)	Rituximab SC N=85 No. (%)	Total N=174 No. (%)
Total No. of Deaths	**4 (4)**	**5 (6)**	**9 (5)**
Disease Progression	2 (2)	3 (4)	5 (3)
Diarrhoea	1(1)	-	1 (<1)
Herpes Zoster	-	1 (1)	1 (<1)
Listeriosis	1 (1)	-	1 (<1)
Progressive Multifocal Leukoencephalopathy	-	1 (1)	1 (<1)

Table 17 Adverse Events Leading to Treatment Discontinuation in CLL (Safety Analysis Population)

Body System/ Adverse Event	Rituximab IV N = 89 No. (%)	Rituximab SC N = 85 No. (%)	Total N = 174 No. (%)
All Body Systems			
Total Pts With At Least One AE	7 (8)	9 (11)	16 (9)
Total Number of AEs	7	9	16
Blood and Lymphatic System Disorders			
Total Pts With At Least One AE	6 (7)	6 (7)	12 (7)
Neutropenia	3 (3)	1 (1)	4 (2)
Thrombocytopenia	1 (1)	2 (2)	3 (2)
Anemia	-	1 (1)	1 (<1)
Febrile Neutropenia	1 (1)	-	1 (<1)
Hematotoxicity	-	1 (1)	1 (<1)
Hemolytic Anemia	-	1 (1)	1 (<1)
Pancytopenia	1 (1)	-	1 (<1)
Total Number of AEs	6	6	12
Infections and Infestations			
Total Pts With At Least One AE	-	2 (2)	2 (1)
Cytomegalovirus Infection	-	1 (1)	1 (<1)
Meningitis	-	1 (1)	1 (<1)
Total Number of AEs	-	2	2
Renal and Urinary Disorders			
Total Pts With At Least One AE	1 (1)	-	1 (<1)
Renal Failure Acute	1 (1)	-	1 (<1)
Total Number of AEs	1	-	1
Skin and Subcutaneous Tissue Disorders			
Total Pts With At Least One AE	-	1 (1)	1 (<1)
Urticaria	-	1 (1)	1 (<1)
Total Number of AEs	-	1	1

Investigator text for Adverse Events encoded using MedDRA version 17.0.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
Includes Adverse Events commenced on or after Cycle 1 Day 1.

POST-MARKETING DATA: SUMMARY OF ADVERSE EVENTS

This section summarizes the adverse events reported in the company safety database for rituximab in NHL indications up to 31 December 2016 from any sources excluding those reported from the five company clinical studies (SparkThera, SABRINA, SAWYER, MabEase, and PrefMab). Caution should be exercised when interpreting the data below due to large differences in the number of patients exposed to rituximab IV and rituximab SC (3,415,439 vs 34,179) and the number of AEs reported (83121 vs. 2424 events) in the safety database.

The profile of the observed AEs for rituximab SC reported in the company safety database for NHL indications was consistent with the current knowledge about the drug observed during the course of the clinical development (see Table 18). Administration-related reactions (< 1% IV vs. 9% SC) and AEs related to local cutaneous reactions (High-Level Term [HLT] Injection site reactions) were more prevalent in patients receiving rituximab SC (8%) than those receiving rituximab IV (< 1%).

A slight difference in the proportion of reported AEs between rituximab IV and SC was further observed in Blood and lymphatic disorders (11% IV vs. 13% SC) and Infections and infections (12% IV vs. 17% SC), similar to the observations made during the course of clinical development. Differences were driven by events of neutropenia (6% IV vs. 8% SC), including febrile neutropenia (2% IV vs. 3% SC), and lower respiratory tract and lung infections (mainly represented by preferred term pneumonia [2% IV vs. 3% SC]).

Of note, in contrast, there was a higher proportion of AEs reported in patients receiving rituximab IV (3%) than in patients receiving rituximab SC (1%) in the hematology investigations (including blood groups), mainly due to HLT White blood cell analyses (2% IV vs. 1% SC) with preferred terms neutrophil count decreased (< 1% IV each) and white blood cell count decreased (1% IV vs. < 1% SC).

The proportion of serious AEs reported in patients receiving rituximab SC (70%) was higher than in those receiving rituximab IV (53%), which is largely due to the difference in the source of AEs reported, with more AEs reported from other clinical studies with rituximab SC (48% SC vs. 19% IV), non-serious AEs from clinical studies not being reported in the safety database.

The proportion of fatal AEs reported was similar between rituximab IV and SC (7% each).

Overall, the observations from the post-marketing setting with rituximab SC 1400 mg in NHL were consistent with evaluations in the clinical trials as described in Section 7.

Table 18 Summary of Adverse Events by System Organ Class Reported to the Global Rituximab Safety Database in NHL Indications with Rituximab IV and Rituximab SC 1400 mg

	Rituximab IV	Rituximab SC
	No. of Events Reported	No. of Events Reported
General disorders and administration site conditions	14619 (17.59%)	523 (21.58%)
Infections and infestations	10114 (12.17%)	411 (16.96%)
Blood and lymphatic system disorders	9299 (11.19%)	323 (13.33%)
Gastrointestinal disorders	7519 (9.05%)	163 (6.72%)
Respiratory, thoracic and mediastinal disorders	6389 (7.69%)	111 (4.58%)
Investigations	4783 (5.75%)	65 (2.68%)
Nervous system disorders	4752 (5.72%)	104 (4.29%)
Skin and subcutaneous tissue disorders	4410 (5.31%)	163 (6.72%)
Injury, poisoning and procedural complications	3349 (4.03%)	134 (5.53%)
Musculoskeletal and connective tissue disorders	2927 (3.52%)	56 (2.31%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2548 (3.07%)	83 (3.42%)
Cardiac disorders	2522 (3.03%)	78 (3.22%)
Vascular disorders	2324 (2.80%)	44 (1.82%)
Metabolism and nutrition disorders	1673 (2.01%)	36 (1.49%)
Immune system disorders	1636 (1.97%)	25 (1.03%)
Psychiatric disorders	1075 (1.29%)	15 (0.62%)
Hepatobiliary disorders	890 (1.07%)	17 (0.70%)
Renal and urinary disorders	863 (1.04%)	28 (1.16%)
Eye disorders	576 (0.69%)	16 (0.66%)
Ear and labyrinth disorders	270 (0.32%)	9 (0.37%)
Reproductive system and breast disorders	160 (0.19%)	4 (0.17%)
Pregnancy, puerperium and perinatal conditions	123 (0.15%)	0 (0.00%)
Surgical and medical procedures	119 (0.14%)	7 (0.29%)
Endocrine disorders	68 (0.08%)	2 (0.08%)
Product issues	51 (0.06%)	1 (0.04%)
Social circumstances	44 (0.05%)	2 (0.08%)
Congenital, familial and genetic disorders	18 (0.02%)	4 (0.17%)
Total	**83121 (100.00%)**	**2424 (100.00%)**

Data cut-off: 31 December 2016.