Non-Clinical Pharmacokinetic/Pharmacodynamic and Early Clinical Studies Supporting Development of a Novel Subcutaneous Formulation for the Monoclonal Antibody Rituximab

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- clinical trials
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Abstract

This overview article describes the non-clinical pharmacology, pharmacokinetic and clinical dose-finding programs supporting the development of a novel subcutaneous formulation for rituximab, a monoclonal antibody that selectively targets CD20-positive B-lymphocytes. The subcutaneous route of administration is expected to improve convenience for patients and to reduce healthcare professional resource use compared with conventional intravenous infusion. Various non-clinical and clinical studies were conducted to support the bridge from the approved intravenous formulation to the novel subcutaneous treatment. The underlying hypothesis for these studies was that achieving subcutaneous rituximab serum trough concentrations that are at least as high as those reached with the intravenous formulation would result in at least the same degree of receptor saturation. Preclinical mouse xenograft and cynomolgus monkey B-cell depletion studies were performed at intravenous and subcutaneous doses that were previously found to result in comparable serum concentrations in pharmacokinetic studies in the same species. Results from these non-clinical assessments guided dose selection for the subsequent phase 1b dose finding trials in patients with follicular lymphoma as part of maintenance treatment. A fixed dose of 1 400 mg was found to result in noninferior serum trough concentrations to the intravenous formulation. Clinical trials in the induction setting in patients with follicular lymphoma and chronic lymphocytic leukemia are currently ongoing.

Abbreviations

AUC	area under the serum concentration-time curve
BSA	body surface area
CD20+	CD20-positive
CHOP	cyclophosphamide, doxorubicin, vincristine and prednisone
CI	confidence interval
CLL	chronic lymphocytic leukemia
CR	complete response
CRu	unconfirmed complete response
C_{max}	maximum concentration
C_{trough}	trough concentration
CVP	cyclophosphamide, vincristine and prednisone
DLBCL	diffuse large B-cell lymphoma
F	bioavailability
FL	follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
FU	follow up
IV	intravenous
mAb	monoclonal antibody
ORR	overall response rate
PK	pharmacokinetic
PR	partial response
R-CHOP	rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone
rHuPH20	recombinant human hyaluronidase
SC	subcutaneous
SD	standard deviation
T_{max}	time to maximum serum concentration
U	units

Introduction

Rituximab is a chimeric murine/human monoclonal antibody (mAb) that specifically binds to CD20, a hydrophobic trans-membrane protein present on the surface of B-lymphocytes [1]. Over the past decade, rituximab has become the standard of care for management of patients

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suffering from various B-cell malignancies, including follicular lymphomas (FL), diffuse large B-cell lymphoma (DLBCL) and chronic lymphocytic leukemia (CLL) [2].

Rituximab is administered as an intravenous (IV) infusion over several hours and frequently, infusion-related reactions may require further prolongation of the infusion time [3]. The procedure required to establish IV access is considered invasive and can be painful, particularly in patients with malignant diseases who are treated repeatedly [4]. To overcome these issues, a subcutaneous (SC) formulation of rituximab is currently in development. Subcutaneous administration of rituximab takes less than 10 min and is a simple alternative to the current practice of IV administration. This new route of administration could thus reduce the time a patient spends in the hospital and eliminate hospital burden associated with IV administration (e.g., preparation of the infusion bag, nursing time for IV dosing, rental of day beds) as has been reported for the SC vs. IV administration of heparin or for the mAb trastuzumab [5, 6].

Data from a multicenter, prospective, time-and-motion study of trastuzumab (PrefHer) showed that, compared with IV infusion, active healthcare professional time for the SC injection using a single-use injection device was reduced by 28 % in Denmark and 34 % in France [6]. In addition, patient chair time was reduced by 68–69 % across both countries. These improvements could ultimately result in an increase in the number of patients receiving treatment with trastuzumab, especially in countries that have limited infusion capacity. Furthermore, both patients and healthcare professionals prefer the SC route of administration; in the PrefHer study, 91.5 % of 236 patients and 73.8 % of 103 healthcare professionals preferred the SC formulation to IV administration [6].

This review article describes the non-clinical pharmacology/pharmacokinetics (PKs) and early clinical approach supporting the development of a novel SC formulation of rituximab. Early development activities for a novel SC formulation for the mAb trastuzumab have been described previously [7], and will be referred to as appropriate.

Scientific Basis for Dose Selection Approach

In line with the dose selection approach for the SC formulation of trastuzumab [7], the aim of the dose-finding studies reviewed here was to select a dose of rituximab SC that achieves serum trough concentrations (C_{trough}) at least as high as those reached with the approved IV formulation, while maintaining the clinical dosing frequency for a given indication. The selected SC dose was then to be confirmed by a formal PK noninferiority test to compare it against the approved IV regimen. The key assumption supporting this dose selection approach was that clinical response is driven by the concentration of a given mAb, and that optimal efficacy is obtained when all accessible target sites are saturated.

The validity of this PK-based bridging concept is supported by the clinical data generated for the SC formulation of trastuzumab. As part of the trastuzumab clinical program, a phase I study was conducted in healthy male volunteers and female patients with HER2-positive early breast cancer. This study was designed to select a fixed SC dose of trastuzumab that resulted in C_{trough} and area under the serum concentration-time curve (AUC) values at least as high as those achieved with the approved IV regimen [8]. The selected fixed dose of 600 mg was subsequently confirmed in a phase III study, which showed that noninferior trastuzumab serum trough concentrations achieved using SC dosing result in comparable efficacy (measured as pathologic complete response) to the IV regimen [9].

Approved Rituximab Doses and Dosing Regimens

The recommended dose of rituximab for adult patients in the approved non-Hodgkin's lymphoma indications is 375 mg/m^2 body surface area (BSA) per IV infusion [10]. 4 different dosing schedules are currently approved (○ **Table 1**). The recommended dose of rituximab for previously untreated and relapsed/refractory patients with CLL is 375 mg/m^2 BSA administered on day 0 of the first treatment cycle, followed by 500 mg/m^2 BSA administered on day 1 of each subsequent cycle for 6 cycles in total [10].

Rituximab SC Formulation

Intravenous MabThera® (rituximab) is approved as a liquid formulation containing 10 mg/mL rituximab (excipients: sodium citrate, polysorbate 80, sodium chloride, sodium hydroxide, hydrochloric acid and water for injections) that is available in 2 vial sizes containing 10 mL and 50 mL of MabThera™, respectively.

The development of a ready-to-use SC formulation of rituximab became feasible with the recent advances in the preparation of highly concentrated mAb formulations [11, 12] and the availability of recombinant human hyaluronidase (rHuPH20), an enzyme that enables rapid SC administration of volumes exceeding 2 mL [13]. A liquid formulation of MabThera containing

Table 1 European Medicines Agency approved rituximab dosing regimens [10].

Regimen	Indication	Frequency	Treatment duration
Monotherapy [a]	Relapsed/refractory FL (stage 3–4)	Induction or retreatment: q1w	4 weeks
Combination therapy [b]			
R-chemotherapy	Previously untreated or relapsed/refractory (stage 3–4) FL	Induction: day 1 of each chemotherapy cycle	8 cycles
		Maintenance: q2m for untreated FL; q3m for relapsed/refractory FL	Until PD or up to 2 years
	Previously untreated or relapsed/refractory CLL	Day 0 of first treatment cycle then day 1 of each subsequent cycle [c]	6 cycles
R-CHOP	DLBCL	Day 1 of each chemotherapy cycle	8 cycles

[a] Patients who respond to rituximab induction treatment can be treated again with rituximab. [b] Rituximab should be administered on day 1 of each chemotherapy cycle after IV administration of the glucocorticoid component of the chemotherapy, if applicable. [c] First dose 375 mg/m^2, followed by 500 mg/m^2 for cycles 2–6. PD: disease progression; q1w: weekly; q2m: every 2 months; q3m: every 3 months; R-CHOP: rituximab plus CHOP

Study type	Species and strain	Route of administration
PK assessment/formulation testing	Minipig/Göttingen	IV and SC
PK assessment	Cynomolgus monkey	SC
PK assessment/xenograft model	Mouse/SCID beige mice	IV and SC
B-cell depletion [14]	Cynomolgus monkey	IV and SC

Table 2 Overview of non-clinical PK and pharmacodynamic studies for rituximab SC.

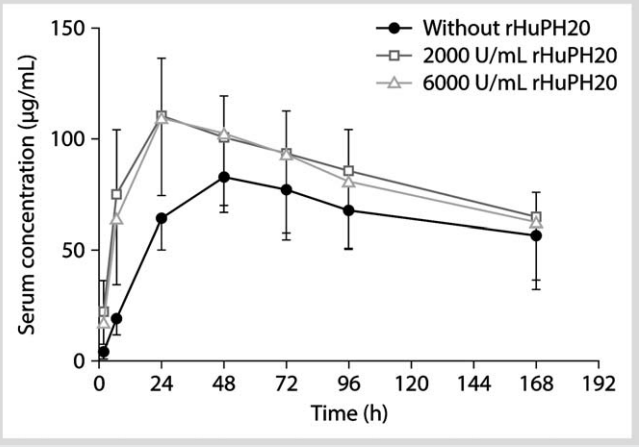

Fig. 1 Time course of rituximab serum concentrations in minipigs following single subcutaneous administration of rituximab at 120 mg/animal containing either 0, 2000 or 6000 U/mL rHuPH20 (n = 5 per dose group).

120 mg/mL rituximab and 2000 units (U)/mL rHuPH20, has been developed for SC administration [14]. This formulation is administered using a syringe with a hypodermic needle.

Non-Clinical Pharmacology and PK Studies Supporting Development of the SC Formulation for Rituximab

Non-clinical pharmacology and PK studies were conducted to support the design of the clinical dose-finding study by assessing (i) the absorption and elimination of rituximab, and (ii) its preclinical efficacy at similar serum concentrations for the SC and IV administration routes (**Table 2**).

Non-Clinical PK Studies

To explore the effect of different rHuPH20 concentrations on the SC absorption of rituximab, a PK study was conducted in minipigs. This study was similar in design to one carried out during the development of the SC formulation of trastuzumab [7]. 4 groups of female minipigs (5 per dose group) received a single IV dose of rituximab at 9.6 mg/kg or a single SC dose of rituximab at 120 mg/animal (about 14 mg/kg) containing 0, 2000 or 6000 U/mL rHuPH20, respectively (for IV and SC dosing of the formulation without rHuPH20 see [15], for other dose groups; data on file, F. Hoffmann-La Roche Ltd.). A fifth group received a dose of rituximab SC at 240 mg/animal (≈ 27.6 mg/kg) containing 2000 U/mL rHUPH20 to explore dose linearity of SC absorption. The SC injection volumes were 1 and 2 mL for the 120 mg and 240 mg dose groups, respectively.

The lower trastuzumab SC dose (120 mg) was selected to limit the dose volume to 1 mL, the typical dose volume for conventional SC formulations. The IV dose of 9.6 mg/kg was selected to obtain a similar systemic exposure to that achieved with the 120 mg/animal SC dose (about 14 mg/kg), assuming a SC bioavailability of approximately 70 %.

The rHuPH20 concentrations selected for testing in the minipig model took into consideration results from a clinical study using rHuPH20 co-formulated with an undisclosed large protein molecule therapeutic (LPMT) in rheumatoid arthritis patients [16]. Data suggested a concentration-dependent effect of rHuPH20 on LPMT absorption, with the highest effect on LPMT absorption observed at rHuPH20 concentrations of 1800 and 3500 U/mL. Based on these data, 2 rHuPH20 concentrations ranging from the lower end of maximum effect concentration range (2000 U/mL) to the highest concentration tested in the LPMT study (6000 U/mL) were selected for the minipig study in order to further assess whether a lower or higher rHuPH20 concentration would result in different absorption kinetics of rituximab. This dose selection was also consistent with results from a mouse dye dispersion study, which demonstrated that administration of a co-formulation containing 500–5000 U/mL rHuPH20 achieved a dispersion profile similar to sequential administration of a solution containing 100 U/mL rHuPH20 followed by dye injection [7].

PK profiles and parameters are shown in **Fig. 1** and **Table 3**. Following SC administration, rituximab absorption was more rapid with rHuPH20-containing formulations. At the SC dose level of 120 mg/animal the median time to maximum serum levels (T_{max}) was shortened from 48 h without rHuPH20 to 24 h for both of the rHuPH20-containing formulations. Average maximum serum levels of rituximab (C_{max}) for the rHuPH20-containing formulations were increased relative to the levels obtained for the formulation without rHuPH20. The extent of bioavailability (mean ± standard deviation [SD]) of rituximab SC at 120 mg/animal from non-compartmental PK analysis ranged between 52 and 71 % (data on file, F. Hoffmann-La Roche Ltd.).

Doubling the rituximab SC dose had no obvious impact on absorption and disposition, as shown in **Table 3**. At the 240 mg dose of rituximab SC, exposure ($AUC_{0-672\,h}$ and C_{max}) was roughly twice as high as that for the 120 mg SC dose.

Compartmental PK modeling revealed approximately 3-fold higher estimates for the absorption rate constants associated with the rHuPH20-containing formulations relative to the rate constant associated with the control formulation (without rHuPH20). This modeling approach indicated that the average absorption rate constants were 0.0221, 0.0803, and 0.0557 h^{-1} at 0, 2000 and 6000 U/mL of rHUPH20, respectively. Thus, there was no further increase in the absorption rate constants when increasing the rHuPH20 concentration from 2000 to 6000 U/mL. There was no relevant difference in the absorbed fraction of rituximab from the various formulations. The estimate for the absorbed fraction of rituximab was 68.9 % when utilizing data from all 4 SC dose groups.

A further study was conducted to support planning and SC dose selection for a pharmacology study on B-cell depletion in cynomolgus monkeys (see non-clinical pharmacology studies section). In this study, male cynomolgus monkeys were administered a single dose of rituximab SC at 20 mg/kg [17]. The

Table 3 Non-compartmental PK parameters for rituximab in female minipigs following single SC administration of rituximab with varying recombinant human hyaluronidase concentrations (mean ± SD).

Parameter	Dosing regimen (n = 5/dose group)			
	120 mg/0 U/mL rHuPH20	120 mg/2 000 U/mL rHuPH20	120 mg/6 000 U/mL rHuPH20	240 mg/2 000 U/mL rHuPH20
C_{max} (µg/mL)	82.6 ± 15.8	110 ± 26.2	110 ± 33.3	230 ± 37.3
T_{max}[a] (h)	48	24	24	36
$AUC_{0-672\,h}$ (h*µg/mL)	24 100 ± 10 600	32 700 ± 8 060	26 300 ± 12 300	52 800 ± 16 200
F (%)	52.4 ± 29.2	70.7 ± 28.1	57.4 ± 33.2	57.8 ± 25.7

[a] Median value. F: bioavailability; T_{max}: time to maximum serum concentration

Table 4 Treatment groups in non-clinical xenograft study in employing the Z138 human mantle cell lymphoma cell line in female SCID beige mice and rituximab serum trough concentrations after first and last rituximab administration.

Group	Dose (mg/kg)	Administration route	Rituximab serum trough concentration (µg/mL; [mean ± SD])	
			After first administration	After third administration
1 (vehicle group)	NA			
2	3	IV	16.9 ± 4.8	30.0 ± 14.2
3	10	IV	46.8 ± 6.5	70.3 ± 18.6
4	30	IV	152.6 ± 33.9	224.3 ± 43.3
5	5	SC	22.0 ± 1.9	33.6 ± 8.6
6	16	SC	74.9 ± 24.3	115.9 ± 37.1
7	50	SC	181.8 ± 35.8	246.7 ± 82.7
8 (mice without tumor)	10	IV	43.5 ± 6.2	124 ± 18.1

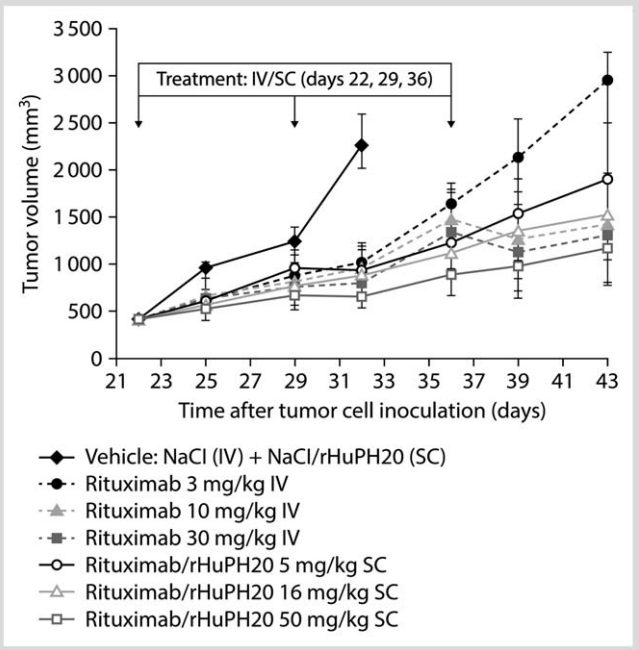

Fig. 2 Treatment effects in a non-clinical xenograft study employing the Z138 human mantle cell lymphoma cell line in female SCID beige mice.

rituximab SC formulation contained rHuPH20 at a nominal concentration of 6 000 U/mL. Maximum serum concentrations of 300 ± 10.8 µg/mL rituximab (mean ± SD) were reached by 24 h post dose. The average apparent clearance (clearance divided by bioavailability [CL/F]) after SC administration was 7.23 mL/day/kg. The SC bioavailability of rituximab was estimated to be close to complete, based on a comparison with available data after IV administration of rituximab to cynomolgus monkeys (data on file, F. Hoffmann-La Roche Ltd.).

Non-Clinical Pharmacology Studies

Non-clinical pharmacology studies have been conducted to support the hypothesis that comparable rituximab serum trough concentrations following SC and IV administration result in the same efficacy, regardless of the route of administration.

The pharmacodynamic effects of rituximab SC were compared with those of rituximab IV in a xenograft model employing the Z138 human mantle cell lymphoma cell line [18] in female SCID beige mice (data on file, F. Hoffmann-La Roche). Corresponding IV and SC dosages yielding a similar range of rituximab trough concentration levels were selected based on a PK study conducted in the same species, in which the rituximab SC bioavailability was estimated at 62 % (data on file, F. Hoffmann-La Roche Ltd.). In the xenograft model study, mice received 3 treatments weekly on days 22, 29 and 36 following tumor cell inoculation at 3, 10 or 30 mg/kg IV or at 5, 16 or 50 mg/kg SC (**Table 4**). An additional group without tumors was dosed at 10 mg/kg IV.

As illustrated in **Fig. 2**, treatment with corresponding doses of 10 mg/kg IV and 16 mg/kg SC, or 30 mg/kg IV and 50 mg/kg SC, showed comparable anti-tumor activity. SC treatment at 5 mg/kg was slightly more efficacious than IV treatment at 3 mg/kg; however, this difference was not statistically significant. Serum levels of rituximab given at corresponding IV and SC doses were in the same range, with a maximum 2-fold deviation (**Table 4**). It is of note that in the mid- and high-dose groups, the therapeutic effect may have reached saturation. Therefore, the comparison of IV and SC dosing regimens is best based on the results from the low-dose groups (i.e., the 3 mg/kg IV and 5 mg/kg SC groups). The results of the xenograft tumor model study, particularly those from the low dose groups, suggest that when similar trough concentrations of rituximab are reached by SC and IV administration, similar efficacy is achieved in this xenograft model.

Mao et al. [17] studied the impact of the route of administration on B-cell depletion in cynomolgus monkeys. Animals were treated twice, one week apart, with either rituximab IV or ritux-

imab SC (2×10 mg/kg). The same dose level was used for both routes, as the preparatory PK study described earlier had indicated a close-to-complete SC bioavailability of rituximab in cynomolgus monkeys. Peripheral CD20-positive (CD20+) B-cell depletion was studied over a 2-month period. CD20 target coverage and the level of B-cell depletion in secondary lymphoid organs were measured at distal lymph nodes 9 days following the second dosing. While initial peak serum concentrations of rituximab were higher following IV administration, serum trough levels were comparable between dosing routes on days 2, 7, 9 and 14, i.e., 2 and 7 days after dosing on days 0 and 7, respectively. CD20+ B-cell depletion in blood was greater than 99% compared with baseline for both rituximab SC and rituximab IV by day 9 (i.e., 2 days post-second dose). The duration of B-cell depletion was equally sustained 2 months after rituximab SC and IV dosing. Rituximab SC and IV both fully covered distal lymph node B-cell surface CD20, reducing the staining of free surface CD20 by 95% compared with baseline measurements. Administration via both modes also depleted lymph node B-cells to a similar extent 9 days after the second dose (SC: 57% vs. IV: 42%). These results demonstrate that despite initial peak serum drug level differences, rituximab SC has a similar pharmacodynamic effect and durability compared with rituximab IV.

Clinical Development Program

The early clinical development program to support the SC formulation in the FL indication was designed to identify a rituximab SC dose that would result in rituximab C_{trough} serum levels at least as high as those achieved with standard doses of rituximab IV. Further clinical studies were designed to compare efficacy and safety with the 2 routes of administration.

Rituximab Dose Selection for Clinical Dose-Finding Trial

To account for the comparatively high variability observed for the SC bioavailability of rituximab in animal models (see previous section on non-clinical PK studies), the initial clinical doses of rituximab SC were chosen to cover a bioavailability range between 60% and 100%. Therefore, the selected rituximab starting dose for the SC formulation in the dose-finding trial was 375 mg/m^2, assuming a SC bioavailability of 100%. The second predefined dose was 625 mg/m^2, assuming a SC bioavailability of 60%. An additional SC dose of 800 mg/m^2 was administered following interim PK analysis to account for a lower bioavailability of only 40%. Generating PK data over a broad range of exposures was necessary for selecting a fixed SC dose for formal PK comparison with the approved IV regimen.

Readers are referred to previous publications for the supporting rationale and examples of fixed dosing of monoclonal antibodies [7, 19, 20].

Clinical Trials

A phase Ib study (SparkThera; NCT00930514/BP22333) was conducted in the maintenance setting in patients with previously treated or untreated FL (grade 1, 2 or 3a) who had responded to rituximab-based induction treatment. The maintenance setting was selected for dose finding because in this patient population, tumor load is lower and the risk of underdosing patients during dose finding was considered less critical than that associated with treating patients during induction treatment. Stage 1 of this study was designed to identify a fixed rituximab SC dose yielding rituximab C_{trough} levels comparable to those achieved after administration of rituximab IV (375 mg/m^2 given every 2 or 3 months). As described previously [21], eligible patients who had received at least 1 dose of rituximab IV (375 mg/m^2) in the maintenance setting were randomized to one of 4 rituximab maintenance treatment groups. Patients received a single dose of either rituximab IV [375 mg/m^2 (n=16)] or rituximab SC [375 mg/m^2 (n=34), 625 mg/m^2 (n=34), or 800 mg/m^2 (n=40)]. Following this single dose, all patients continued receiving maintenance doses of rituximab IV (375 mg/m^2) every 2 or 3 months for a further year. At the end of this year, patients who had already received a single dose of rituximab SC had the option to receive rituximab SC at the final fixed dose (1 400 mg) for the remaining year of the 2-year maintenance period, or continue with rituximab IV (**Fig. 3a**). The PK data generated in stage 1 were used to select the dose of rituximab SC for stage 2 of the study [22].

Stage 2 of SparkThera was designed to demonstrate serum C_{trough} noninferiority of the selected rituximab SC dose compared with that of the established rituximab IV dose (**Fig. 3b**). In total, 154 patients were randomized 1:1 to receive rituximab SC (1 400 mg) or rituximab IV (375 mg/m^2) for their remaining maintenance cycles. In line with the results from the minipig and mice studies, the SC bioavailability was estimated at 65% in stage 1 and 69% in stage 2 of the study. The study met its primary endpoint; specifically, the minimum rituximab concentration ratio for SC vs. IV was 1.24 when rituximab was given once every 2 months and 1.12 when rituximab was given once every 3 months [22] (**Table 5**). The 1 400 mg rituximab SC dose was therefore selected for study in the SABRINA phase 3 trial [23].

SABRINA (NCT01200758/BO22334) is a two-stage, international, phase III trial designed to investigate the PK, efficacy and safety of SC vs. IV administration of rituximab in patients with FL (grade 1, 2 or 3a) receiving induction and maintenance therapy (**Fig. 3c**). In stage 1 of the trial, previously untreated patients were randomized to receive rituximab IV 375 mg/m^2 or a fixed dose of 1 400 mg of rituximab SC, both given in combination with either CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or CVP (cyclophosphamide, vincristine and prednisone) chemotherapy. Patients who achieved a complete or partial response after 8 treatment cycles continued rituximab maintenance therapy as per their initial randomization with either SC or IV administration. The primary endpoint for stage 1 was to estimate the ratio of rituximab serum concentrations ($C_{trough,\ SC}$:$C_{trough,\ IV}$) at cycle 7 during induction treatment; the ratio was 1.62 (90% CI: 1.36 – 1.94), which met the limit for noninferiority of $C_{trough,\ SC}$ (ratio > 0.80) [23]. In addition, exploratory efficacy analyses demonstrated similar overall response rates (ORR; 84.4% IV and 90.5% SC) and complete response (CR) rates (29.7% IV and 46% SC). In the ongoing stage 2 portion of the study, efficacy is the primary endpoint and additional patients are being randomized to receive either SC or IV administration of rituximab. Data obtained from this trial were presented at the 54th American Society of Hematology Annual Meeting in Atlanta [23] and have been submitted in a marketing application to regulatory authorities in the European Union.

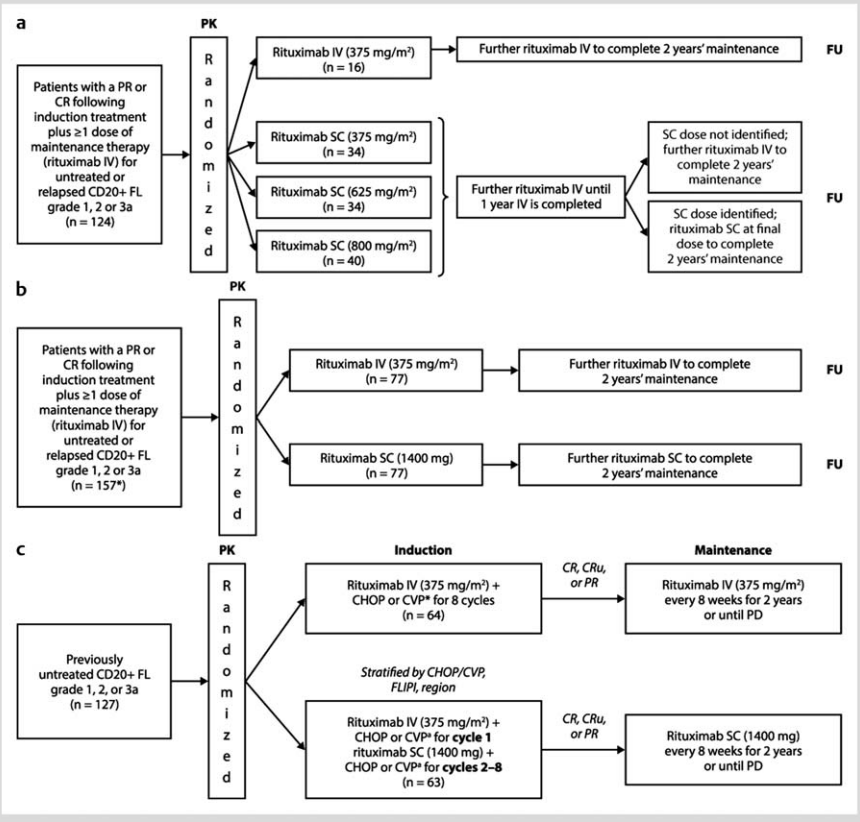

Fig. 3 Clinical trial schemas. **a** SparkThera phase Ib clinical trial: stage 1, dose finding. **b** SparkThera phase Ib clinical trial: stage 2, dose confirmation. **c** SABRINA phase III trial. [a] 3 patients were withdrawn prior to treatment. [b] CHOP: administered as cyclophosphamide (750 mg/m^2 IV on day 1), doxorubicin (50 mg/m^2 IV on day 1), vincristine [1.4 mg/m^2 IV on day 1 (2 mg maximum)], and prednisone (100 mg oral or IV on days 1–5) in every cycle. CVP: administered as cyclophosphamide (750 mg/m^2 IV on day 1), vincristine [1.4 mg/m^2 IV on day 1 (2 mg maximum)], and prednisone (40 mg/m^2 oral or IV on days 1–5) in every cycle. CRu: unconfirmed complete response; CVP: cyclophosphamide, vincristine and prednisone; FLIPI: Follicular Lymphoma International Prognostic Index; FU, follow-up.

Table 5 Expected C_{trough} levels stage 2 SparkThera trial.

Dosing regimen	Parameter	SC 1 400 mg (n = 77)	IV 375 mg/m^2 (n = 76)	Geometric mean ratio $C_{trough, SC}$:$C_{trough, IV}$ [90 % CI]
q2m	Geometric mean ± SD	32.2 ± 29.1	25.9 ± 16.3	1.24 [1.02–1.51]
q3m	Geometric mean ± SD	12.1 ± 16.5	10.9 ± 9.9	1.12 [0.86–1.45]

CI: confidence interval

Summary and Outlook

This review describes the early development of a novel SC formulation of rituximab. This formulation is expected to offer an attractive alternative to the more invasive and lengthier IV administration. Similar to the trastuzumab example [7], rituximab SC maintains the same administration frequency as the corresponding IV formulation, but is given as a fixed dose instead of the BSA-adjusted dose used for rituximab IV. ORR and CR data from stage 1 of the ongoing SABRINA trial support the validity of the basic bridging assumption used to calculate the SC dose, and demonstrate that rituximab SC serum trough concentrations that are at least as high as those achieved with IV dosing result in at least the same degree of clinical efficacy.

Using the SC formulation of rituximab may shorten treatment time significantly, by enabling administration in less than 10 min. Furthermore, the ready-to-use SC formulation has the potential to significantly reduce both medicine preparation time and hospital staff time per administration. Therefore, use of the rituximab SC formulation instead of the IV formulation is also expected to reduce both pharmacy time and the burden placed on hospital resources, as well as having the potential to provide improved patient convenience.

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Conflict of Interest

Drs. B. Bittner, W. Richter, F. Hourcade-Potelleret, F. Herting and J. Schmidt are former or current employees of F. Hoffmann-La Roche Ltd.

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