01 April 2016
EMA/276108/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

MabThera

International non-proprietary name: rituximab

Procedure No. EMEA/H/C/000165/X/0101/G

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	adverse event
ARR	administration-related reaction
AUC	area under the serum concentration - time curve
BSA	body surface area
CD20	cluster of differentiation 20
CI	confidence interval
CLL	chronic lymphocytic leukemia
CR	complete response
CRR	complete response rate
Cru	unconfirmed complete response
CSR	clinical study report
Ctrough	trough or minimum serum concentration
ECLIA	electrochemiluminescence immunoassay
ELISA	enzyme-linked immunosorbent assay
GMR	geometric mean ratio
HACA	human anti-chimeric antibody
HAHA	human anti-human antibody
ITT	intent to treat
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Minimal Residual Disease
NCA	non-compartmental analysis
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin's lymphoma
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
q2m/q3m	once every 2/3 months

q3w	once every 3 weeks
rHuPH20	recombinant human hyaluronidase
RMP	risk management plan
SAE	serious adverse event
SAP	safety analysis population
SC	subcutaneous
SD	stable disease
SMQ	Standardized MedDRA Query
SOC	system organ class

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Roche Registration Limited submitted to the European Medicines Agency (EMA) on 05 November 2014 an extension application grouped with two type II variations to the Marketing Authorisation of MabThera. The application concerned a new strength of 1600 mg solution for subcutaneous injection, an update of the product information of 1400 mg solution for subcutaneous injection strength as a consequence to the line extension application, and an update of the RMP to include new information relevant to chronic lymphocytic leukaemia and update of the educational materials.

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008, Annex I point 2(c) – Change or addition of a new strength/potency and Article 7.2 of Commission Regulation (EC) No 1234/2008 – Grouping of variations.

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Not applicable

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Sinan B. Sarac Co-Rapporteur: Pieter de Graeff

- The application was received by the EMA on 5 November 2014.
- The procedure started on 26 November 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 18 February 2015.
- The CHMP adopted a report on similarity of MabThera on 26 February 2016.
- PRAC RMP Assessment Report adopted by PRAC on 12 March 2015.
- During the meeting on 26 March 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant..
- The applicant submitted the responses to the CHMP consolidated List of Questions on 1 February 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 2 March 2016.

- During the meeting on 17 March 2016 the Pharmacovigilance Risk Assessment Committee (PRAC) endorsed the relevant sections of the joint CHMP/PRAC Assessment Report.
- During the meeting on 1 April 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation for a new strength MabThera 1600 mg solution for subcutaneous injection, and a positive recommendation for the approval to the variations to Product Information and Risk Management Plan.

2. Scientific discussion

2.1. Introduction

Rituximab is a chimeric murine/human monoclonal antibody that binds to cluster of differentiation 20 (CD20) protein, a hydrophobic transmembrane protein present on the cell surface of pre-B- and mature B-lymphocytes but not on hematopoietic stem cells, pro-B-cells, normal plasma cells, or other normal tissue. In particular, CD20 is present on the malignant B-lymphocytes in the majority of patients with mature B-cell lymphomas and leukemias. The binding of rituximab to CD20 on B-lymphocytes eliminates these cells via a number of different possible mechanisms, including antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and induction of apoptosis.

MabThera (rituximab) received MA in EU in June 1998 as concentrate for solution for infusion (strengths 100 mg and 500 mg) for intravenous use initially for the treatment of CD20-positive non-Hodgkin's lymphoma (NHL), and subsequently for the following indications: treatment of chronic lymphocytic leukaemia (CLL), rheumatoid arthritis (RA), granulomatosis with polyangiitis (GPA), and microscopic polyangiitis (MPA).

A subcutaneous formulation in which rituximab has been concentrated 12-fold to 120 mg/mL with the addition of recombinant human hyaluronidase (rHuPH20) was approved in February 2014 for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy; as a maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy; as monotherapy for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy; for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy. The recommended dose of MabThera subcutaneous formulation used for adult patients with NHL is a subcutaneous injection at a fixed dose of 1400 mg irrespective of the patient's body surface area.

The present application for a line extension provides data to support the registration of an additional strength of the subcutaneous formulation: 1600 mg, which is intended for the treatment of CLL only.

Currently, immunochemotherapy with rituximab, fludarabine and cyclophosphamide (R-FC) is the standard of care in previously untreated patients with CLL requiring treatment and clinically established treatment option for patients with previously treated CLL. The recommended dose of rituximab IV for patients with CLL (previously untreated and relapsed/refractory) is 375 mg/m^2 body surface area (BSA) at the first treatment cycle followed by 500 mg/m^2 BSA at each subsequent cycle at intervals of 4 weeks, for a total of six cycles.

With the current rituximab IV formulations provided as concentrate, solutions have to be prepared and administered as infusions, over typically 2 – 4 hours. For many patients the relatively long infusion times

and need for repeated invasive IV access are undesirable aspects of the current therapeutic approach. Increased usage of rituximab has also placed a strain on medical resources at many centers with respect to time and resources required to prepare and administer the infusion. As for MabThera 1400 mg solution for subcutaneous injection in NHL, the new 1600 mg subcutaneous strength, for use in CLL, will offer significant benefits for both patients and healthcare providers such as: a shorter administration time (approximately 7 minutes), an alternative route of administration for patients with poor venous access, improved patient convenience and comfort, alleviation of resource constraints associated with the IV route of administration.

The same technology as for MabThera 1400 mg solution for subcutaneous injection is used in the new 1600 mg strength i.e. adding recombinant human hyaluronidase (rHuPH20), a permeation enhancer, in the SC formulation. Hyaluronidase transiently hydrolyses hyaluronan (a component of the SC matrix) resulting in decreased viscosity of the SC matrix and, thus, to an improved delivery of SC administered drugs into the systemic circulation. The decreased viscosity of the SC matrix allows administration of larger volumes of fluid.

The currently applied for indication for the subcutaneous formulation of rituximab has the same target population as rituximab IV, i.e. "*MabThera 1600 mg solution for subcutaneous formulation injection is indicated in adults in combination with chemotherapy for the treatment of patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia. Only limited data are available on efficacy and safety for patients previously treated with monoclonal antibodies including MabThera or patients refractory to previous MabThera plus chemotherapy.*"

The applicant has received CHMP Scientific advice on quality aspects – specifically on use of rHUPH20 as an excipient, in line with advice received in the context of the 1400 mg SC strength; the advice has been followed.

2.2. Quality aspects

2.2.1. Introduction

F. Hoffmann - La Roche Ltd. (Roche) is the Marketing Authorization Holder (MAH) for MabThera. This medicinal product was initially approved for marketing in Europe in 1998 as concentrate for solution for infusion (strengths 100 mg and 500 mg (10 mg/ml)).

A new formulation (solution for subcutaneous injection) was developed as an alternative to the currently above-mentioned licensed pharmaceutical forms: MabThera 1400 mg solution for subcutaneous injection (120 mg/ml), which was granted a Market Authorization on 21 March 2014 (EMEA/H/C/156/X/83).

The present application provides data to support the registration of an additional strength of the subcutaneous formulation: 1600 mg solution for subcutaneous injection. The active substance is formulated with the same excipients as the 1400 mg presentation. The finished product in MabThera 1600 mg is presented in a Type I glass vial with butyl rubber stopper, aluminium over seal and a blue plastic flip-off disk.

2.2.2. Active Substance

The manufacture and control of 1400 mg and the 1600 mg MabThera SC solutions are identical. To achieve a higher strength corresponding to the fixed dose posology regimen of 1600 mg, the volume of finished product solution in the vial had to be increased accordingly and is therefore filled into a larger vial (20mL).

Although the filling of additional product into a slightly bigger vial only covers few sections of the dossier, all previously submitted sections in Notice to Applicants format has been provided again but now as electronic CTD format. Some few issues have been introduced into these new CTD dossier sections. However, these changes are all based on requirements/issues raised in procedure EMEA/H/C/156/X/83 (introduction of MabThera SC, 1400 mg) and are therefore acceptable.

The manufacture and control of rituximab active substance 120 mg/ml remains unchanged compared to the approved process (EMEA/H/C/156/X/83).

A shelf life of 24 months at -20°C is approved for rituximab SC active substance (120 mg/ml).

2.2.3. Finished Medicinal Product

Description and composition of MabThera SC, 1600 mg is identical to the currently approved MabThera SC 1400 mg (EMEA/H/C/156/X/0083).

The only difference in the finished product manufacturing process of the 1600 mg strength, compared to the currently approved process, is the higher fill volume needed to achieve the target 1600 mg strength.Validation of the manufacturing for MabThera SC 1600 mg was preceded by both process development and extensive manufacturing experience with MabThera SC 1400 mg manufactured in the same facility.

The program for the validation of the MabThera SC 1600 mg finished product manufacturing process consisted of the manufacture of three consecutive finished product batches at commercial batch size. All three validation batches were processed at the commercial manufacturing facility, using the process and type of equipment to be used for commercial manufacturing. All the relevant qualification procedures for the equipment (compounding, fill and finish) and areas were performed prior to the process validation batches.

Beside the in-process controls applicable to the routine manufacturing process additional testing was performed during the validation.

All in-process and release data presented for the three validation batches are within the specifications and support that the manufacture of MabThera SC 1600 mg is consistent and robust.

The finished product specification for MabThera SC 1600 mg is identical to the already approved specification for MabThera SC 1400 mg, with one exception, which is the extractable volume. For MabThera SC 1600 mg the specification for extractable volume is: minimum 13.4 ml.

The vial, stopper and seal used for MabThera SC 1600 mg are of the same quality as already used for the 1400 mg presentation and do therefore not call for comments. For the 1600 mg presentation, a 20 ml vial is used. For the currently approved 1400 mg presentation, a 15 ml vial is used.

Based on all the stability data generated with the commercial product (SC 1600 mg), together with the supportive stability data, a shelf life of MabThera SC 1600 mg (20 ml vial) of 30 months at 2-8°C is acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The issue identified during the review was addressed by the Applicant. This issue resulted in a Recommendation for future quality development.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

In conclusion, based on the review of the Quality data provided, this line extension application is considered approvable.

2.2.6. Recommendation for future quality development

In the context of the obligation of marketing authorisation holders to take due account of technical and scientific progress, the CHMP recommended a point for investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

In support of the current extension application for a 1600 mg rituximab SC formulation for use in CLL, the Applicant has submitted updated nonclinical overviews, and referenced the studies already submitted in support of the 1400 mg rituximab SC formulation (approved for NHL).

In the overview, safety margins have been re-calculated to reflect the higher dose level of the current application. This higher dose (1600 mg rituximab), is achieved by administering a slightly higher volume, of the already approved formulation used for the 1400 mg rituximab SC.

2.3.2. Pharmacology

No new studies were submitted as part of this application.

2.3.3. Pharmacokinetics

No new studies were submitted as part of this application.

2.3.4. Toxicology

No new studies were submitted as part of this application.

2.3.5. Ecotoxicity / environmental risk assessment

N/A

2.3.6. Discussion on non-clinical aspects

In support of the current extension application for a 1600 mg rituximab SC formulation for use in CLL, the Applicant has made reference to the studies already submitted in support of the 1400 mg rituximab SC formulation (approved for NHL).

Overall the nonclinical pharmacology, pharmacokinetics and toxicology of rituximab SC have been well characterized. Overall, the available data are considered appropriate to support the proposed Extension Application of rituximab SC.

Lack of any new nonclinical studies supporting the new strength of rituximab for subcutaneous injection is accepted. Furthermore, the slightly decreased margins of safety are considered to be of no concern, as rituximab is well known from use in the clinical setting, following IV administration.

2.3.7. Conclusion on the non-clinical aspects

The lack of any new nonclinical studies supporting the new strength of rituximab for subcutaneous injection is accepted. Current knowledge of non-clinical aspects is adequate to cover this new strength for sc use. No revisions of the PI were made as a result of the assessment of this line extension.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1: Overview of the rituximab SC development programme in support of this application.

CLL indication (current line extension application)			
BO25341/ SAWYER	previously untreated CLL patients Part 1: N=64 Part 2: N=176 Primary analysis completed. FU ongoing	phase Ib two-part, randomized, open-label, parallel group, multicenter pilot dose-finding/confirmation and C_{trough} non-inferiority study of rituximab in combination with FC	to select and confirm a rituximab SC dose that achieves non-inferior serum C_{trough} to rituximab IV 500 mg/m^2

2.4.2. Pharmacokinetics

Data from study BO25341 are provided in this application to support the registration of MabThera 1600 mg solution for subcutaneous injection as an alternative to the licensed IV formulation in the CLL indications.

Study design SAWYER

Study BO25341 was a two-part, randomized, open-label, parallel-group, multicenter, Phase Ib study. Part 1 was designed to investigate several test doses of rituximab SC in order to determine a dose of rituximab SC that would yield non-inferior C_{trough} compared with the approved 500 mg/m^2 IV dose in CLL.

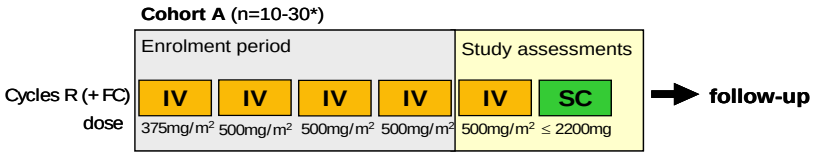
Part 2 was designed to demonstrate C_{trough} non-inferiority of the 1600-mg dose of rituximab SC selected in Part 1 versus 500 mg/m^2 rituximab IV given in combination with fludarabine and Cyclophosphamide (FC) every q4w.

For Part 1 only, treatment with up to 4 cycles of rituximab IV (375 mg/m2 in Cycle 1 followed by 500 mg/m^2 in Cycles 2-4) in combination with fludarabine + cyclophosphamide (FC) chemotherapy as

first-line therapy for CLL was allowed. For Part 2, eligible patients must not have received any previous treatment for CLL.

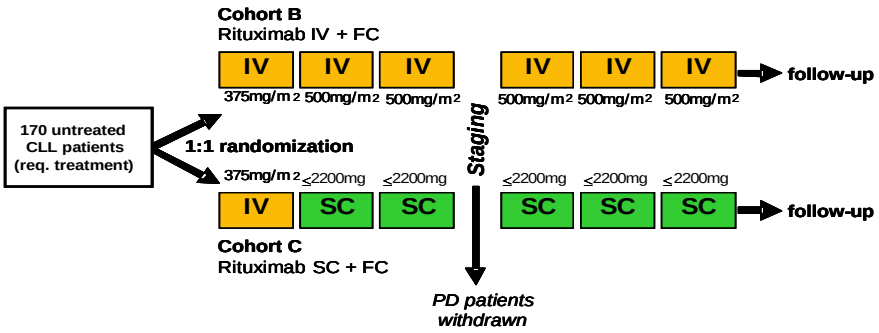
Rituximab IV doses were calculated on a body surface area (BSA)-adjusted basis at study entry and the calculated dose was not subsequently adapted for changes in body weight during the course of the treatment period. Rituximab SC was administered using a fixed dose principle (i.e., the dose was not adjusted to BSA, but could be amended based on PK results up to a maximum of 2200 mg). This trial was designed as a non-inferiority study to show that serum trough concentrations (Ctrough) of SC rituximab are comparable to IV rituximab. There was no expectation of major differences in efficacy between the two routes of administration.

Figure 1 Part 1: Overview of Study Design



*Depending on the variability of PK data obtained from the first 10–30 patients, additional patients may be enrolled into cohort A, up to a total of approximately 60.

Figure 2 Part 2: Overview of Study Design



Results

Part 2 of study BO25341/SAWYER: Dose Confirmation

Primary Pharmacokinetic Endpoint: C_{trough} at Cycle 5

Observed PK data from 134 evaluable patients (69 patients given rituximab IV and 65 patients given rituximab SC in Cycles 5 and 6) were analysed using NCA.

The PK results for the primary endpoint, a rituximab SC dose that yields comparable serum C_{trough} to rituximab IV, demonstrate that 1600 mg of rituximab SC is non-inferior when compared to rituximab IV 500 mg/m^2 at Cycle 5. A summary of the observed C_{trough} data at Cycle 5 is shown in table 2. The geometric mean C_{trough} values for the IV and SC formulations are 61.5 μg/mL (CV% 63.9) and 97.5 μg/mL (CV% 42.6), respectively. These values yield a mean $C_{trough(SC)}/C_{trough(IV)}$ ratio (adjusted by tumour load at baseline) of 1.53 with a 90% CI: 1.27 to 1.85. The primary objective of Part 2 of the trial, non-inferiority of C_{trough} for the SC formulation compared with the IV formulation in CLL, has been demonstrated, as the lower bounds of the 90% CIs are above the pre-specified non-inferiority boundary of 0.8. The variability in the C_{trough} data at Cycle 5, as shown by the CV%, were lower for the rituximab SC arm at 42.6% compared with 63.9% in the rituximab IV arm.

Table 2 C_{trough} at Cycle 5 and AUC_{τ} at Cycle 6 and IV/SC Ratios

	Rituximab IV 500 mg/m^2	Rituximab SC 1600 mg	
PK parameter	Geometric Mean (CV%)	Geometric Mean (CV%)	Geometric Mean Ratio [90% CI]
C_{trough} (μg/mL) at Cycle 5 [N]	61.50 (63.9) [69]	97.5 (42.6) [65]	1.53 [1.27–1.85)
AUC_{τ} (μg • day/mL) at Cycle 6 [N]	3630 (32.8) [58]	4088 (34.6) [51]	1.10 [0.98–1.24)

Source: BO25341 CSR Table 15.

Secondary Pharmacokinetic Endpoints

AUC at Cycle 6

The secondary endpoint in Part 2 was the estimated ratio of observed rituximab serum AUC_{sc}/AUC_{iv} during Cycle 6.

The geometric mean AUC_{τ} values for the IV and SC formulations, respectively, are 3630 μg • day/mL (CV% 32.8) and 4088 μg • day/mL (CV% 34.6). These values yield a mean $AUC_{\tau(SC)}/AUC_{\tau(IV)}$ ratio (adjusted by tumour load at baseline) of 1.10 with 90% CI 0.98 to 1.24). Variability in the AUC values was low, as expressed by the CV% (32.8% in the rituximab IV arm and 34.6% in the rituximab SC arm), and the data are comparable in both treatment arms.

C_{max}, t_{max} and $t_{1/2}$ at Cycle 6

Table 3 shows a summary of the other observed secondary PK parameters, C_{max}, t_{max} and $t_{1/2}$ data. The t_{max} for rituximab IV occurs soon after the end of infusion and for rituximab SC at around 3 days as expected. The C_{max} is lower for rituximab SC of 202 μg/mL, compared with rituximab IV of 280 μg/mL, as the intravenous dose is injected directly into the systemic circulation while the SC dose has to be absorbed and distributed to the circulation from the site of injection via the lymphatic system, resulting in slower delivery to systemic circulation and an overlap of the absorption and distribution/elimination phases after SC administration. As expected, the half-life is the same for both routes of administration, showing that the terminal elimination is independent of the route of administration and as a consequence of comparable exposures in the central compartment.

Table 3 Summary of C_{max}, t_{max} and Half-life Pharmacokinetic Parameters at Cycle 6

PK Parameter	Rituximab IV			Rituximab SC			Geometric Mean Ratio[a] [90% CI]
	n	Geometric Mean	CV%	n	Geometric Mean	CV%	
C_{max} (μgmL)	58	280	24.6	51	202	36.1	0.719 [0.653,0.792]
t_{max} (day)	58	0.22	131	51	3.14	71.4	14.9 [11.2,19.7]
$t_{1/2}$ (day)	58	30.1	34.4	50	30.7	30.0	1.01 [0.895,1.14]

PK = pharmacokinetic; IV = intravenous; SC = subcutaneous; CI = confidence interval; CV = coefficient of variation.
[a] Geometric mean ratio adjusted for tumour load at baseline.
[b] CV calculated on the original scale. Source: BO25341 CSR Table 16.

Subgroup Analyses on Observed PK Data

In moving from a BSA-adjusted dosing approach to a fixed-dose approach, it is important to ensure that patients with high BSA would be adequately exposed and those with low BSA would not be over-exposed to rituximab. For the C_{trough} at Cycle 5, the geometric mean ratio showed no monotonic change as the BSA increased. Similarly for the AUC at Cycle 6, the geometric mean ratio showed no monotonic change with respect to BSA in the subgroup analysis. This confirms that patients with a high BSA are not being underexposed. There was no effect of gender on exposure determined by Ctrough at Cycle 5 and AUC at Cycle 6. There appears to be a trend of increasing GMR with tumour load at baseline for both C_{trough} and AUC. Results from these analyses are summarized in table 4.

Table 4 Additional Pharmacokinetic Data – Subgroup Analyses

Subgroup	C_{trough} at Cycle 5			AUCτ at Cycle 6		
	Geometric Mean		Geometric[1] Mean Ratio (SC/IV) [90% CI]	Geometric Mean		Geometric[1] Mean Ratio (SC/IV) [90% CI]
	Rituximab IV	Rituximab SC		Rituximab IV	Rituximab SC	
Body Surface Area (BSA)*						
Low (n)	66.14 (24)	131.54 (16)	1.538 [1.127; 2.098]	3825.93 (17)	5281.12 (10)	1.258 [0.960; 1.649]
Medium (n)	67.06 (22)	80.46 (24)	1.164 [0.804; 1.687]	3738.56 (20)	3824.50 (19)	1.010 [0.832; 1.226]
High (n)	52.48 (23)	96.89 (25)	1.943 [1.472; 2.564]	3383.59 (21)	3856.03 (22)	1.168 [0.975; 1.400]
Gender						
Male (n)	56.08 (44)	88.56 (48)	1.594 [1.276; 1.990]	3364.85 (38)	3889.08 (41)	1.158 [1.010; 1.328]
Female (n)	72.34 (25)	127.74 (17)	1.483 [1.082; 2.033]	4194.12 (20)	5020.60 (10)	1.124 [0.911; 1.386]
Tumour Load at Baseline*						
Low (n)	78.08 (14)	100.74 (24)	1.290 [0.856; 1.994]	4186.12 (12)	3981.22 (17)	0.951 [0.727; 1.243]
Medium (n)	64.20 (25)	98.14 (21)	1.529 [1.163; 2.009]	3758.08 (20)	4231.21 (16)	1.126 [0.932; 1.360]
High (n)	52.48 (27)	93.21 (20)	1.776 [1.255; 2.514]	3269.37 (23)	4067.34 (18)	1.244 [1.027; 1.507]

[1] Adjusted GMR value
*Patients were grouped, based on BSA or tumour load, into one of three subpopulations; low (BSA ≤ 33rd percentile), medium (BSA between 33rd and 66th percentiles) and high (BSA ≥ 66th percentile; tumour load: low (≤ 3608), medium (3608 < Tumour Load ≤ 7305) and high (> 7305).
Source: BO25341 CSR Table 17

2.4.3. Pharmacodynamics

Pharmacodynamic Analysis

Peripheral blood $CD19^+$ lymphocyte counts (B cells) were summarized for the safety analysis population (SAP)

B-cell Depletion and Repletion

Pharmacodynamic markers from blood samples included peripheral blood $CD19^+$ B cell counts measured pre-dose before each administration of study drug and during follow-up. In this study, B-cell depletion was defined as < 80 cells/mm^3.

Part 1

In Part 1, baseline B-cell counts before treatment were not available as patients had already begun treatment with rituximab IV.

At pre-dose Cycle 5, a high proportion (94%) of patients were already B-cell depleted and > 90% of patients remained so until the 6-month follow-up visit. Patients' B cells began to replete by the 9-month follow-up visit. At this time point, the proportion of patients who were B-cell depleted had dropped to 66% and continued to decrease during subsequent visits. At the 12-, 15-, 18-, 21- and 24-month follow-up visits, the proportion of B-cell depleted patients was 52% (25/48 patients), 43% (17/40), 36% (15/42), 32% (13/41) and 21% (9/42), respectively.

Consistent results were observed for the normal B-cell ($CD5^-/CD19^+$ B cells) depletion and repletion, with median B-cell counts of 0 cell/mm^3 observed after the first cycle of treatment through the 6-month follow-up visit and a increase observed from the 9-month follow-up visit onwards.

Part 2

At baseline, as expected for this patient population, median B-cell counts were high; 69930 cells/mm^3 in the rituximab IV arm versus 50565 cells/mm^3 in the rituximab SC arm (Table 5). Following the first cycle of treatment, patients began to deplete, with 28% of patients being B-cell depleted at pre-dose Cycle 2. A continuous increase in the proportion of B-cell depleted patients was observed with subsequent cycles of treatment and by Cycle 6, 96% of patients were B-cell depleted in the two treatment arms. Patients remained B-cell depleted until the 9-month follow-up visit, when signs of repletion were seen. At this time point, the proportion of patients who were B-cell depleted had dropped to 66% as for Part 1. At the 12-month follow-up visit, the proportion of B-cell depleted patients was 41% (16/39 patients). However, at later time points the number of patients was too low to provide meaningful data. The pattern of B-cell depletion was similar in the two treatment arms.

Table 5 Part 2: Summary of Total B-cell (CD19+ B-cells) Depletion and Repletion (SAP)

Visit		Rituximab IV 500 mg/m2 N=89	Rituximab SC 1600 mg N=85	Total N=174
Cycle 6 Day 1	n	71	63	134
	Median	3	3	3
	75%-ile	4	6	5
	Range	0-3612	0-4234	0-4234
	Depletion*	68 (95.8%)	60 (95.2%)	128 (95.5%)
FU 28 Day Visit	n	66	63	129
	Median	2	2	2
	75%-ile	4	4	4
	Range	0-1299	0-2749	0-2749
	Depletion*	63 (95.5%)	61 (96.8%)	124 (96.1%)
FU 56 Day Visit	n	63	67	130
	Median	2	2	2
	75%-ile	4	4	4
	Range	0-14331	0-3539	0-14331
	Depletion*	58 (92.1%)	65 (97.0%)	123 (94.6%)
FU 3 Month Visit	n	65	67	132
	Median	2	2	2
	75%-ile	4	5	5
	Range	0-39037	0-16413	0-39037
	Depletion*	62 (95.4%)	62 (92.5%)	124 (93.9%)
FU 6 Month Visit	n	60	68	128
	Median	3	3	3
	75%-ile	12	9	9
	Range	0-1356	0-22630	0-22630
	Depletion*	53 (88.3%)	62 (91.2%)	115 (89.8%)
FU 9 Month Visit	n	50	45	95
	Median	30	16	23
	75%-ile	125	98	118
	Range	1-2721	0-890	0-2721
	Depletion*	33 (66.0%)	30 (66.7%)	63 (66.3%)
FU 12 Month Visit	n	21	18	39
	Median	119	66	100
	75%-ile	229	268	268
	Range	9-2951	4-1770	4-2951
	Depletion*	7 (33.3%)	9 (50.0%)	16 (41.0%)
FU 15 Month Visit	n	3	0	3
	Median	140		140
	75%-ile	370		370
	Range	59-370		59-370
	Depletion*	1 (33.3%)		1 (33.3%)
FU 18 Month Visit	n	1	1	2
	Median	497	165	331
	75%-ile			497
	Range			165-497
	Depletion*	0 (0.0%)	0 (0.0%)	0 (0.0%)
Withdr./Termination	n	13	12	25
	Median	61	5	25
	75%-ile	164	56	150
	Range	2-16952	0-35325	0-35325
	Depletion*	7 (53.8%)	10 (83.3%)	17 (68.0%)
Overall (worst value)**	n	88	85	173
	Median	1	1	1
	75%-ile	3	2	3
	Range	0-17747	0-2749	0-17747
	Depletion*	79 (89.8%)	82 (96.5%)	161 (93.1%)

In case of multiple assessments only the worst value (i.e. lowest) is considered.
Normal plus Malignant B-cell depletion (CD19+ B-cells) is estimated by the sum of CD5+/CD19 and CD5-/CD19+ cells.
* Depletion is defined as <80 cells/mm^3.
Percentages are based upon the number of patients with non-missing values.
** Based upon all non-baseline visits, including unscheduled visits.

Program : $PROD/cdt3490c/c25341a/lb029a.sas
Output : $PROD/cdt3490c/c25341o/reports/lb029a_S_002.out
22MAY2014 9:21 Page 1,2 and 3 of 3

2.4.4. Discussion on clinical pharmacology

Rituximab SC 1400 mg was approved on March 21, 2014 as an alternative to rituximab IV for induction and maintenance treatment of patients with NHL. The dose and dosing interval of rituximab IV is different for NHL (375 mg/m2) and CLL indications (375 mg/m2 at Cycle 1 followed by 500 mg/m2 at Cycles 2 – 6), therefore, a specific PK study investigating the CLL doses was conducted.

Rituximab exerts its anti-B-cell activity upon binding to its target (CD20), after systemic distribution via the blood. In view of the identical active ingredient in both formulations, the clinical development program for rituximab SC is based on the assumption that serum rituximab levels after SC administration at least as high as after IV infusion would result in at least the same degree of target-site saturation and would hence result in at least the same degree of efficacy, regardless of the route of administration or first-line or relapsed/refractory settings. Therefore, the clinical development program for the rituximab SC formulation was based on pharmacokinetic (PK)-bridging to the corresponding established rituximab IV doses and dosing intervals for NHL and CLL indications, demonstrating PK non-inferiority of the rituximab SC formulation. The dose and dosing interval of rituximab IV is different for NHL and CLL indications, therefore, separate PK-bridging studies for rituximab SC were conducted for NHL and CLL.

This has been established in the development of rituximab SC 1400 mg, developed as an alternative to rituximab IV for induction and maintenance treatment of patients with NHL based on the results from studies BP22333/SparkThera and BO22334/SABRINA. In addition, data on safety, immunogenicity, and pharmacodynamics (B-cell depletion) collected from these studies showed comparability of the safety profile for both rituximab formulations.

In CLL, the PK-bridging study BO25341 was designed as a non-inferiority study in order to ensure that all patients would have a non-inferior Ctrough rituximab exposure when treated with a fixed dose of rituximab SC as compared with the established rituximab IV regimen (375 mg/m2 at Cycle 1 followed by 500 mg/m2 at Cycles 2 – 6).

The clinical development program for rituximab 1600 mg SC is based on the assumption that serum rituximab levels after SC administration at least as high as after IV infusion will result in at least the same degree of target-site saturation and will result in at least the same degree of efficacy, regardless of the route of administration. Therefore, the clinical development program supporting the current line extension is based on a PK-based bridging study to the corresponding established rituximab IV doses and dosing intervals and intended to demonstrate non-inferiority of the rituximab SC formulation. This is considered acceptable.

To limit the risk of underexposing patients to rituximab when administered SC, a non-inferior margin (of 0.8) was applied only to the lower limit of the two sided 90% CI of the GMR of Ctrough(SC)/Ctrough(IV). As was agreed for the SC application for NHL, the use of non-inferiority margins rather than bioequivalence margins is considered acceptable given the wide therapeutic window of rituximab. The risk of adverse effects possibly caused by overexposure to rituximab and was further substantiated by subgroup analysis for BSA and gender and based on experience regarding safety of rituximab gained previously in the development program.

A two-step approach was followed to select and confirm a rituximab SC dose that achieves non-inferior serum Ctrough to rituximab IV 500 mg/m2: first, the fixed dose (1870mg) predicted from the phase Ib study BP22333 in follicular lymphoma was tested in Part 1 of study BO25341. Then, it was adjusted as necessary (by adding patient sub cohorts) to allow for the selection of a fixed SC dose that would yield comparable drug exposure to that achieved with the established rituximab IV dose for CLL (500 mg/m2). Subsequently, non-inferiority in terms of Ctrough with the selected dose of rituximab SC compared with rituximab IV was evaluated in Part 2 of study BO25341.

The initial fixed dose used in Part 1 of the SAWYER study was predicted based on dose-finding studies performed in the SparkThera study, submitted as part of the approval of the sc formulation in the NHL indication. This extrapolation is considered reasonable as SC absorption is not expected to differ significantly between NHL and CLL patients.

However, based on preliminary population PK analyses of the first 10 patients dosed at 1870 mg, two further sub-cohorts were enrolled sequentially and dosed at 1400 mg and 1600 mg, respectively. Model based simulations predicting serum Ctrough and AUC showed that 1600 mg was to be used in Part 2 of the SAWYER study.

In Part 2 of the SAWYER study the established fixed dose of 1600 mg rituximab SC was compared to 500 mg/m2 rituximab IV. This was assessed by a non-inferiority test with a lower boundary of at least 0.8 for the 90% CI with Ctrough pre-dose Cycle 6 as the primary PK endpoint and AUC at Cycle 6 as the secondary PK endpoint. This is considered appropriate.

The fixed dose of 1600 mg rituximab was chosen as this was predicted to yield a non-inferior Ctrough for rituximab SC over rituximab IV 500 mg/m2 given as a q4w regimen. In Part 2 of the SAWYER study, non-inferiority of the rituximab SC administration compared to the rituximab IV administration for the primary PK endpoint Ctrough was demonstrated and the variability in the Ctrough data at Cycle 5 were lower for the rituximab SC treatment group.

For the secondary PK endpoint of AUC, the AUC(sc)/AUC(iv) was 1.10 with 90% CI 0.98-1.24 and a low variability in both the SC and the IV arms. This is endorsed.

The tmax differed as expected between the SC and the IV dosing regimens and the tmax(sc)/tmax(iv) ratio was found to be 14.9. The Cmax(sc)/Cmax(iv) ratio was found to be 0.719. However, based on the rituximab MoA this difference is considered of less importance. Subgroup analyses of Ctrough at Cycle 5, the GMR showed no monotonic change as the BSA increased. Similarly for the AUC at Cycle 6, the GMR showed no monotonic change with respect to BSA in the subgroup analysis. This confirms that patients with a high BSA are not being underexposed. There was no effect of gender on exposure determined by Ctrough at Cycle 5 or AUC at Cycle 6. There appears to be a trend of increasing GMR with tumour load at baseline for both Ctrough and AUC.

The main objective of the SAWYER study was to demonstrate non-inferiority of Ctrough of rituximab administered SC as compared to IV.

To support rituximab 1600 mg SC as alternative for rituximab 500 mg/m2 in CLL, non-inferiority for the primary PK endpoint Ctrough of rituximab after cycle 5 was demonstrated comparing the rituximab 1600 mg SC administration to the rituximab IV 500 mg/m2 administration.

The main concern when changing from dosing based on BSA to a fixed dose is that this would result in higher exposure in patients with lower BSA (and thereby possibly a systematic overexposure of fx. Females) and a lower exposure in patients with higher BSA. However, fixed dosing proved possible as the higher exposure in females was not related to an increased frequency of AEs and efficacy of rituximab remained unchanged in patients with higher BSA indicating sufficient rituximab exposure.

The total number of quantifiable plasma samples from the REACH and the SAWYER studies are considered sufficient to provide robust PK data.

The PK parameter estimates were in good agreement with the results of the earlier population PK analyses. In addition, the MAH argues that time-dependent clearance, inter-compartment clearance, central compartment volume, peripheral compartment volume, absorption rate constant and bioavailability were in the range typical for monoclonal antibodies. The PK results included in this submission are considered sufficient.

Study BO25341 was also designed to provide additional data on safety, immunogenicity and pharmacodynamics to enable a comparison of the safety profile of both rituximab formulations and assess whether a change in the route of administration is associated with new and clinically relevant safety findings. Further, exploratory efficacy endpoints (response rates and minimal residual disease [MRD]) were assessed as additional evidence to support the conclusion based on study BO22334 that the subcutaneous route of administration does not impair the anti-B-cell activity of rituximab.

There was no difference in B-cell depletion apparent between rituximab SC and rituximab IV. Eight patients had transient antibody (HACA) expression against rituximab (data presented under Clinical safety). Presence of anti-rituximab HACAs seemed to result in lower rituximab exposure, however, no diminished effect on B-cell depletion was observed when positive HACAs were present.

As expected, B-cell depletion was observed. The pattern of B-cell depletion was similar in the SC and the IV treatment arms.

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetic data submitted are considered sufficient to support the 1600 mg strength as administration in the treatment of adult patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia - in combination with chemotherapy. B-cell repletion was observed as anticipated.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

See Pharmacology section 2.4.

2.5.2. Main study

Study SAWYER – BO25341

Methods

Part 1 (Pilot Dose Selection)

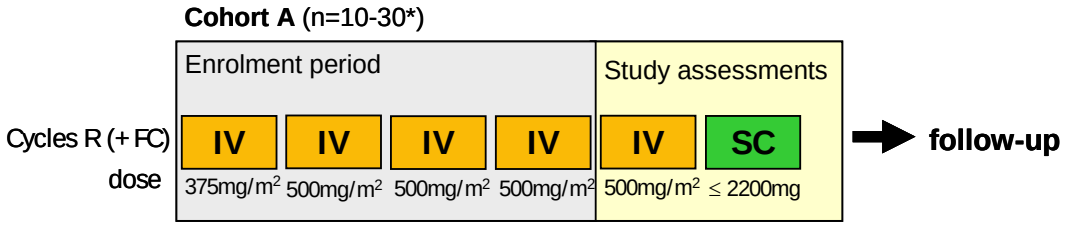
An overview of Part 1 of the BO25341 study design is shown in Figure 1. It was planned to enroll 10 previously untreated CLL patients into Cohort A. Following preliminary analysis of rituximab PK data from these first 10 patients, approximately 20 additional patients could be enrolled. Dependent on further analysis, and considering the theoretical possibility of observing increased variability in rituximab PK parameters due to patients receiving either oral or IV FC, a further 30 patients could be enrolled i.e., Cohort A could include up to approximately 60 patients. Patients were all enrolled to Cohort A; initially to the 1870 mg sub-cohort and then sequentially additional sub-cohorts depending on the PK results.

Data from all patients enrolled after the initial 10 patients were analyzed on an ongoing basis. Patients were all enrolled to Cohort A; initially to the 1870 mg sub-cohort and then sequentially additional sub-cohorts depending on the PK results.

Patients could be enrolled at any point during their treatment with rituximab IV in combination with FC, prior to the commencement of treatment Cycle 5 and should have completed previous treatment without experiencing Grade 3 or 4 infusion-related reactions to rituximab (Figure 1). In Cycle 5 (and previous cycles), patients received rituximab IV and subsequently in Cycle 6, rituximab IV was replaced by a single

rituximab SC dose. Pharmacokinetic parameters for rituximab were assessed during Cycles 5 (rituximab IV) and 6 (rituximab SC).

Figure 1 Part 1 - Overview of Study Design



*Depending on the variability of PK data obtained from the first 10-30 patients, additional patients may be enrolled into cohort A, up to a total of approximately 60.

Part 2 (C_{trough} Non-Inferiority)

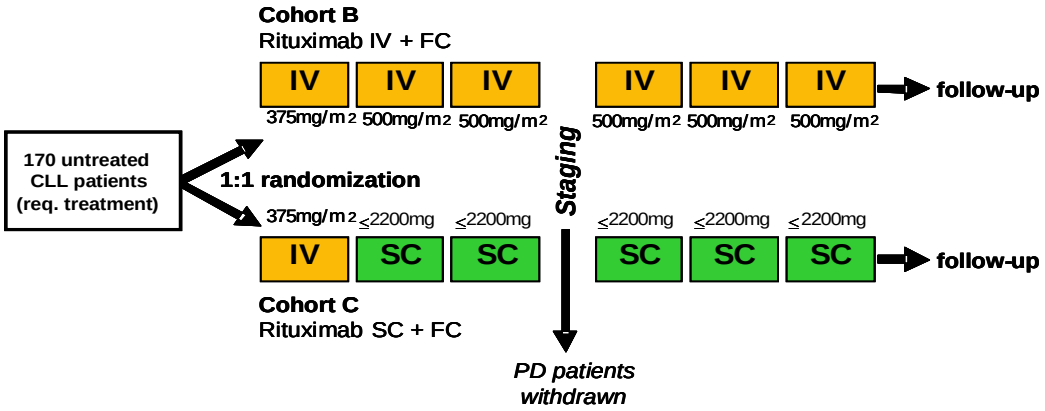
An overview of Part 2 of the BO25341 study design is shown in Figure 2. Approximately 170 patients with previously untreated CLL were planned to be randomized 1:1 either to Cohort B (rituximab IV) or to Cohort C (rituximab SC). Patients received rituximab IV in the first treatment cycle.

Cohort B: Patients received chemotherapy (FC) in combination with rituximab IV at a dose of 375 mg/m^2 in Cycle 1, and then FC in combination with rituximab IV 500 mg/m^2 on Day 1 of each subsequent cycle (Cycles 2-6).

Cohort C: Patients received chemotherapy (FC) in combination with rituximab IV at a dose of 375 mg/m^2 in Cycle 1, and then FC in combination with rituximab SC at the dose selected in Part 1 in all subsequent cycles (Cycles 2-6).

Rituximab pharmacokinetics was assessed throughout the study.

Figure 2 Part 2 - Overview of Study Design



Post-Treatment Follow-Up

The follow-up period comprised both regular follow-up and survival follow-up.

Regular follow-up period

All patients who completed study treatment without disease progression were followed up monthly for the first 3 months after their last dose of trial treatment and then every 3 months until 3 years, and every 6 months until 4 years after their last dose of trial treatment. In Part 2, responding patients who withdrew from treatment due to an AE after interim staging (to be performed before treatment Cycle 4) and did not receive further anti-leukemia treatment entered regular follow up.

Survival follow-up period

Patients who entered survival follow up directly after premature treatment withdrawal and patients withdrawn from regular follow up due to reasons other than death, withdrew consent or lost to follow up were followed for disease progression, new anti-leukemia treatment and survival for a maximum 4 years from the last dose of the study medication.

Study Participants

Inclusion Criteria

Patients who met all of the following criteria were eligible for enrolment:

1. Documented CD20+ B-CLL confirmed according to iwCLL criteria.
2. CLL requiring treatment according to iwCLL criteria.
3. An ECOG performance status of 0-1.
4. Negative serum pregnancy test one week prior to *study* treatment, *or* 14 days prior to treatment with a confirmatory urine pregnancy test within 1 week prior to study treatment. This was needed both for pre-menopausal women and for women who were < 2 years after the onset of menopause.
5. Age ≥ 18 years.
6. Life expectancy > 6 months.
7. Able and willing to provide written informed consent and to comply with the study protocol procedures.

Exclusion Criteria

Patients were excluded from the study if any of the following criteria applied:

1. Transformation to aggressive B-cell malignancy (*e.g.* diffuse large cell lymphoma/ Richter's syndrome, or prolymphocytic leukemia).
2. History of other malignancy unless the patient was treated with curative intent and had been in remission for ≥ 5 years* prior to study enrolment. Patients with a history of curatively treated basal or squamous cell carcinoma of the skin, or in situ carcinoma of the cervix or breast were generally eligible.

(*Any patients with a history of malignancy with less than 5 years in remission had to be approved by the Roche Clinical Scientist prior to enrolment.)

3. Cumulative illness rating scale (CIRS) score > 6.
4. Women who are pregnant or lactating.
5. Fertile men or women of childbearing potential unless:
   - Surgically sterile or > 2 years after the onset of menopause;
   - Willing to use an effective contraceptive method throughout the study period and up to 12 months after last dose of study treatment.
6. Hepatitis B seropositivity, unless clearly due to vaccination.
7. Known HIV infection.
8. Clinically significant auto-immune cytopenia, Coombs-positive hemolytic anemia as judged by the treating physician.

9. Inadequate liver function:

   - Alkaline phosphatase and transaminases > 2 × ULN[#];
   - Total bilirubin > 2 × ULN[#].

   ([#]patients with values out of range in the presence of CLL involvement of the liver could be eligible when mutually agreed between the Investigator and Roche Clinical Scientist)

10. Inadequate renal function: creatinine clearance < 70 mL/min calculated according to the Cockcroft and Gault formula.
11. Concomitant disease requiring prolonged use of glucocorticoids (> 1 month), unless the dose was below 20 mg/day prednisone equivalent.
12. Known hypersensitivity with anaphylactic reaction to humanized monoclonal antibodies or any of the study drugs.
13. Cerebral dysfunction which would have made it impossible to perform immuno-chemotherapy.
14. Active bacterial, viral or fungal infection requiring systemic therapy.
15. Any coexisting medical or psychological condition that would preclude participation in the required study procedures.
16. History of treatment with another investigational agent or participation in another clinical trial within 30 days prior to study enrolment.
17. Uncontrolled concomitant diseases, including significant cardiovascular disease (such as New York Heart Association class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina) or pulmonary disease (including obstructive pulmonary disease and history of symptomatic bronchospasm).

Additional Exclusion Criteria for Patients Enrolled in Part 1 Only

– Any previous treatment for CLL except up to 4 cycles of rituximab IV (375 mg/m^2 in Cycle 1 followed by 500 mg/m^2 in Cycles 2–4) in combination with FC chemotherapy as first-line therapy for CLL.

– Previous rituximab infusion-related reaction of CTC Grade 3 or 4.

Additional Exclusion Criterion for Patients Enrolled in Part 2 Only

– Any previous treatment for CLL.

Treatments

Rituximab IV

Rituximab IV was administered at 500 mg/m^2 (375 mg/m^2 in Cycle 1). This dose was calculated based on baseline body surface area (BSA) values and not subsequently adapted for changes in body weight during the course of the treatment period.

Part 1 (Cohort A, Cycle 5)

Cohort A patients received rituximab IV at 500 mg/m^2 on Day 1 of Cycle 5. If enrolled at an earlier cycle, patients received rituximab IV at 375 mg/m^2 in Cycle 1 (on Day 0 or Day 1 according to local practice) and 500 mg/m^2 on Day 1 of Cycles 2-5.

Part 2 (Cohort B and C)

Cohort B and C patients received rituximab IV at 375 mg/m^2 on Day 0 of Cycle 1. Cohort B patients further received rituximab IV at 500 mg/m^2 on Day 1 of Cycles 2-6.

Rituximab SC

Rituximab SC was administered at a fixed dose of ≤ 2200 mg with no dose adaptations made for BSA.

Part 1 (Cohort A, Cycle 6)

Cohort A patients received rituximab SC at a fixed dose of 1870 mg (the initial starting dose predicted from the NHL study BP22333) on Day 1 of Cycle 6. This dose could be amended depending on PK results obtained during the conduct of Part 1 but was not to exceed 2200 mg.

Part 2 (Cohort C)

After receiving rituximab IV 375 mg/m^2 in Cycle 1, Cohort C patients received on Day 1 of Cycles 2–6 rituximab SC at a fixed dose, selected based on data from Part 1.

The SC injection should be manually pushed at a flow rate of approximately 2 mL/min, therefore an administration volume of 15.6 mL (corresponding to the 1870 mg dose) should take approximately 7 to 8 minutes.

Fludarabine and Cyclosphosphamide

Fludarabine and cyclophosphamide could be administered immediately one after the other. Prior to the start of Part 2, the decision to administer FC chemotherapy IV or orally was made on a per center basis and each center was to use a single route of FC administration for all patients throughout Part 2 of the study.

Fludarabine was administered either as an IV infusion at 25 mg/m^2 on Days 1–3 of all cycles or given orally (p.o.) as part of an approved dosing regimen as follows:

24 mg/m^2 p.o. on Days 1–5 of all cycles

30–40 mg/m^2 p.o. on Days 1–3 of all cycles.

Cyclophosphamide was administered as an IV infusion at 250 mg/m^2 on Days 1–3 of all cycles or given p.o. as part of an approved dosing regimen as follows:

150 mg/m^2 p.o. on Days 1–5 of all cycles

200–250 mg/m^2 p.o. on Days 1–3 of all cycles.

A center could only administer oral fludarabine or cyclophosphamide at a different dosage from those outlined above following discussion and agreement with the Roche Clinical Scientist. This did not include dose reductions or dose delays due to toxicity.

Rituximab (both IV and SC) was administered prior to FC with full emergency resuscitation facilities immediately available and patients were closely supervised by the investigator at all times.

Objectives

Part 1 (Pilot dose Selection)

Primary objective:

- To select a rituximab SC dose that would result in C_{trough} levels comparable to rituximab IV.

Secondary objectives:

- The rate of incidence of injection-related reactions (IRR, also referred to as administration-related reactions [ARR]) during the rituximab SC cycle
- Patient and nurse preference regarding SC or IV administration

Part 2 (C_{trough} non-inferiority)

Primary objective:

- To demonstrate non-inferiority in observed C_{trough} levels between the confirmed rituximab SC dose and the reference rituximab IV dose.

Secondary objectives, in addition to those listed below in Section 0:

- To evaluate safety parameters with rituximab SC vs rituximab IV
- To assess site experience, specifically:
    - physician / nurse opinions on time savings with rituximab SC vs rituximab IV
    - physician / nurse opinions on the convenience of rituximab SC vs rituximab IV

Exploratory objectives, in addition to those listed below in Section 0:

- Assessment of minimal residual disease (MRD) with rituximab SC vs rituximab IV

Parts 1 and 2

Secondary objectives for both Parts 1 and 2:

- To assess additional PK parameters (including AUC) of both rituximab SC and IV
- To compare the immunogenicity of rituximab SC with that of rituximab IV
- To examine peripheral blood B-cell levels and B-cell depletion and repletion with rituximab SC vs rituximab IV

Exploratory objectives for both Parts 1 and 2:

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

Outcomes/endpoints

The primary endpoint in Part 1 and Part 2 was the Ctrough level of rituximab after either rituximab IV or rituximab SC administration. Secondary endpoints included AUC, Cmax, and tmax of rituximab. (See Clinical Pharmacology section).

Exploratory efficacy endpoints were response rates, Time-to-event endpoints (PFS, EFS and OS) and minimal residual disease (MRD).

Sample size

A maximum of approximately 60 patients were planned for Part 1 and approximately 170 patients for Part 2. In Part 2, the sample size was based primarily on C_{trough} levels of rituximab. A standard non-inferiority margin of 0.8 for the geometric mean ratio (GMR) of C_{trough}SC/C_{trough}IV was used based on a coefficient of variation of 63%. With these assumptions, a sample size of 68 patients in each treatment group was required to achieve 80% power with a one-sided α value of 0.05, assuming that the true PK of rituximab SC was 5% above that for rituximab IV. Allowing for a 20% dropout rate for not achieving valid PK data, a total of 170 patients were needed (85 per treatment arm).

Randomisation

In Part 1, all patients were enrolled into Cohort A and sequentially assigned to the 3 doses (1870 mg, 1400 mg and 1600 mg) of rituximab SC depending on the variability of the PK data in the course of the conduct of Part 1 of this study.

In Part 2, patients were randomized via an Interactive Voice Response System (IVRS) between the rituximab IV (Cohort B) or rituximab SC (Cohort C) formulation in a 1:1 fashion using permuted block randomization method. Randomization was stratified by route of chemotherapy (oral versus IV) and Binet Stage (A, B or C).

Patients who withdrew prior to treatment start could be replaced. However, patients who prematurely discontinued from the study, for any reason, after receiving at least a single dose of treatment could not be replaced.

Blinding (masking)

Part 1 of the study was evaluated on an ongoing basis in an open-label fashion.

For Part 2, the statistician, clinical scientist and clinical pharmacologist were fully blinded to treatment allocation. However, the study was open-label to the physician and patient.

Statistical methods

Since efficacy data are considered exploratory, no formal statistical testing was performed.

All efficacy endpoints were analyzed based on the "All Patients" population for Part 1 and the ITT population for Part 2. The tumor response analysis for Part 2 was also performed on the PPP. Patients were analyzed according to the treatment to which they were assigned (Part 1) or randomized (Part 2).

Tumor response was assessed by the investigator based on peripheral blood counts, physical examination, B-symptoms, CT-scan and bone marrow biopsy results, if applicable.

In Part 1, the response rates (CR, CRi and PR) at the 3 month follow-up visit are presented descriptively.

In Part 2, response rates at the 3-month follow-up visit were analyzed in frequency tables including 95% Pearson-Clopper confidence intervals (CI) by treatment group. For the difference in response rates, 95% CI (Hauck-Andersen) were calculated.

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

Subgroup analyses were performed on response rate at the 3-month follow-up visit based on:

- BSA category:
    - upper and lower 33rd percentiles: low (≤ 1.81 m^2), medium (1.81 m^2 $<$ BSA $\leq$ 2.00 m^2) and high (> 2.00 m^2)
    - upper and lower 20th percentiles (extreme low/high BSA): low (≤ 1.72 m^2), medium (1.72 m^2 $<$ BSA $\leq$ 2.07 m^2) and high (> 2.07 m^2)
- gender
- C_{trough} at cycle 5 (low: $C_{trough} \leq 88.75$ µg/mL & high: $C_{trough} > 88.75$ µg/mL)

Time to Event Endpoints

Time-to-event endpoints (PFS, EFS and OS) are included in the study but were not analyzed by this cut-off.

Minimal Residual Disease (MRD)

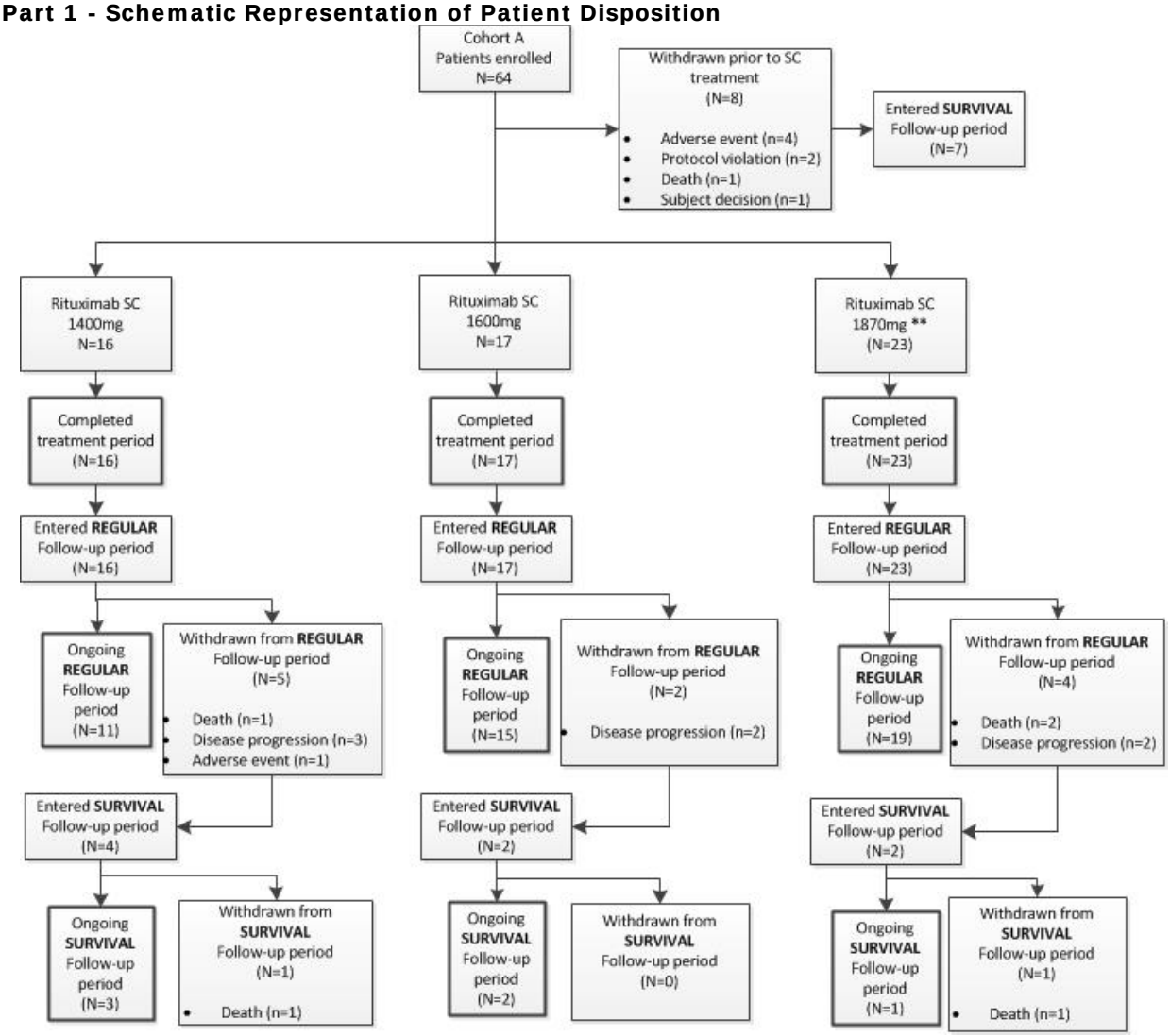
Analysis on MRD, which was assessed by quantitative PCR or flow cytometry, was performed in Part 2 only. The results of flow cytometry were only used where PCR results were unavailable.

The MRD status was assigned as positive or negative based on a pre-defined cut-off. MRD negativity was defined as a level of $< 10^{-4}$ (i.e., 1 CLL cell in a background of 10,000 leukocytes). MRD status is summarized in frequency tables including 95% Pearson-Clopper CI by treatment group. For the difference in MRD negative status between treatment arms, 95% CI (Hauck-Andersen) were calculated.

Results

Participant flow

Part 1 - Schematic Representation of Patient Disposition



**One patient in this sub-cohort received 1000 mg of rituximab SC in error
Source: pd002_E_001 and pd004_s001

A total of 8 patients withdrew from part 1 of the study treatment period prior to receipt of their rituximab SC dose (Cycle 6). The most common reason for withdrawal was due to AEs (4 patients). Two patients were withdrawn due to a protocol violation. One patient was withdrawn due to death (respiratory failure) and one patient withdrew consent.

None of the 56 patients treated with rituximab SC withdrew from any dose sub-cohorts during Cycle 6 (SC dose).

During the regular follow-up period, 5 patients were withdrawn from the 1400 mg SC sub-cohort (1 due to death, 3 due to disease progression and 1 due to an AE), 2 from the 1600 mg sub-cohort (both due to disease progression) and 4 from the 1870 mg SC sub-cohort (2 due to disease progression and 2 due to death). During the survival follow-up period, 2 patients withdrew due to death, 1 in the 1400 mg sub-cohort and 1 in the 1870 mg sub-cohort.

Recruitment

A total of 64 patients were enrolled in Part 1 from 33 sites in 12 countries (Italy 5 (14 patients -22% of study population), Germany 4 (highest recruiting country, enrolling 8 patients -11.9% of the study population), Poland 3, France 3, Spain 4, Czech Republic 3, Australia 3, Slovakia 2, Canada 2, Croatia 2, Mexico 1, Greece 1). A total of 176 patients were enrolled in Part 2 from 68 sites in 19 countries (Germany 10, Italy 6, Poland 4, Russia 5, Spain 6, Czech Republic 3, Canada 4, Australia 5, Brazil 4, France 5, Mexico 2, Argentina 3, Turkey 3, Slovakia 1, Chile 2, Croatia 1, Portugal 1, New Zealand 2, Greece 1).

Baseline data

In Part 1 population comprised predominantly White (95%) male (73%) with a median age of 60 years (range 38 - 77 years) and median BSA of 1.94 m^2. When considering the small patient numbers in each dose sub-cohort, the treatment sub-cohorts are considered comparable with respect to baseline demographic characteristics.

At baseline, 55% of the patients had Binet Stage B disease, with the median time from diagnosis of CLL to enrolment being 16.4 months (range 0.3 - 153.6 months). The majority of patients did not have B-symptoms at screening (83%) or prior to the first line of rituximab-FC treatment (78%).

The patient population in Part 2 was similar to that in Part 1 and comprised predominantly White (96%) male (65%) with a median age of 60 years (range 25−78 years) and median BSA of 1.9 m^2). The study arms were well balanced for baseline demographic characteristics except that there were more male in the rituximab SC arm (60% IV vs 71% SC).

At baseline, the majority of patients had Binet Stage B disease (62%, a baseline stratification factor) and typical CLL characterization (93%), with the median time from diagnosis of CLL to randomization being 18.5 months (range 0 − 388.5 months). Approximately one-third of patients had B-symptoms at screening and prior to receiving rituximab IV (375 mg/m^2) in Cycle 1. The study arms were comparable with respect to baseline disease characteristics.

Numbers analysed

Outcomes and estimation

<u>Part 1</u>

Overall Response rate (ORR)

In Part 1, the investigator assessed ORR at the 3 month follow-up visit was 95% for the overall population. The ORR was similar across the three SC dose sub-cohorts (94%, 94% and 96% for the SC 1400 mg, 1600 mg and 1870 mg sub-cohorts, respectively). In the “ITT-like” patient population (53/64 including patients who did not get an SC administration), the ORR was 83%.

In this part of the study, patients could be enrolled at any treatment cycle prior to Cycle 5; therefore, for some patients the in-study baseline tumor assessment was not a pretreatment baseline tumor assessment. In addition, no CT scan was required at study entry. These may affect the response assessment at the 3-month follow-up visit. Efficacy in Part 1 was assessed as an explorative endpoint and should be interpreted with caution.

Table 5

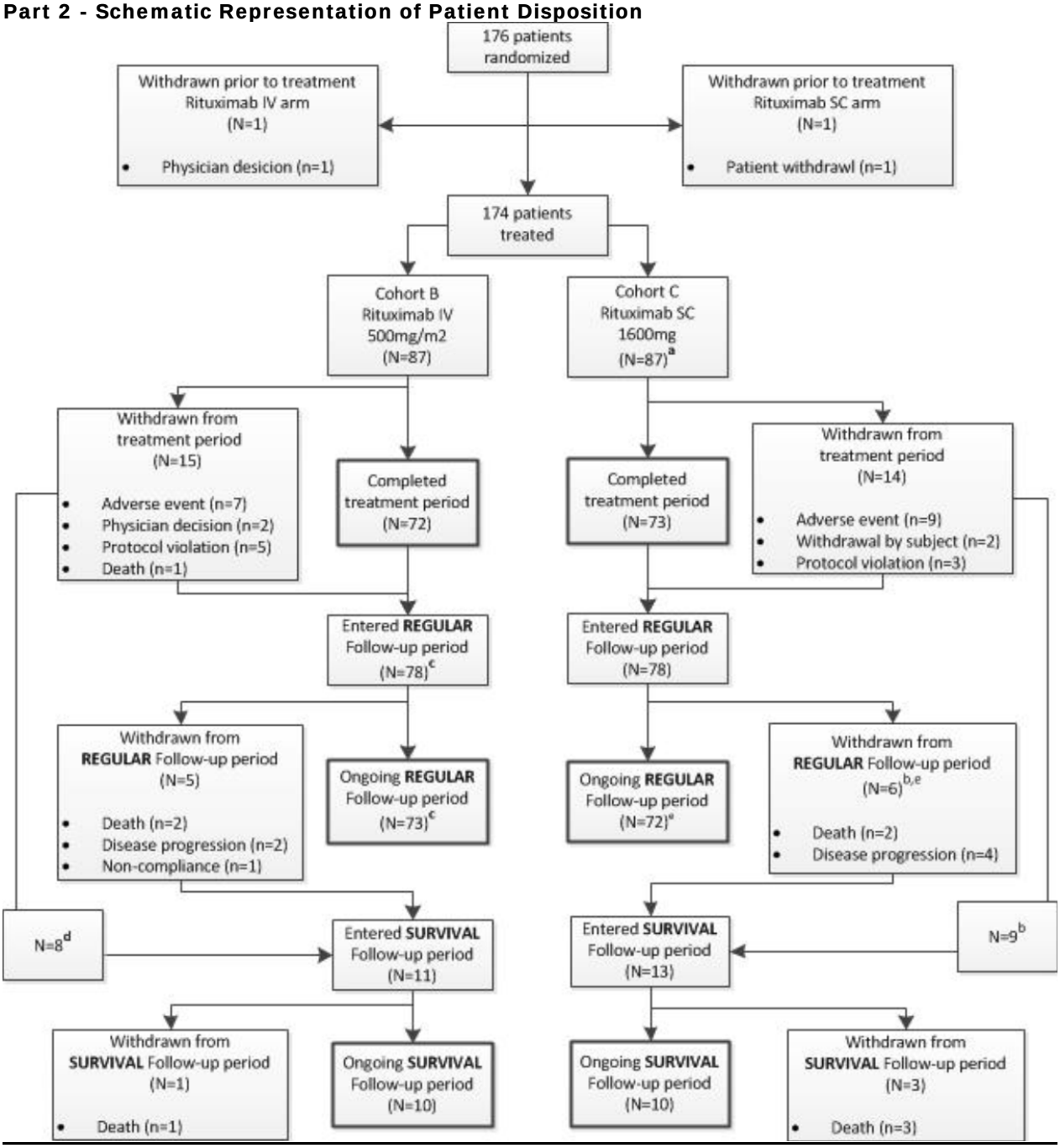
rr_visit_A_001 Overall Tumor Responses As Reported By The Investigator By Visit - Stage 1 (All Patients)

Protocol(s): BO25341 (C25341O)
Analysis Population: All Patients - Stage 1 (N=64)
Snapshot Date: 07MAY2014 Clinical Cutoff Date: 12FEB2014

	Rituximab SC 1400 mg N=16 No. (%)	Rituximab SC 1600 mg N=17 No. (%)	Rituximab SC 1870 mg N=23 No. (%)	No SC Dose Received N=8 No. (%)	Total N=64 No. (%)
FU 3 Month Visit					
Complete Response (CR)	1 (6%)	6 (35%)	3 (13%)	0	10 (18%)
Complete Response Incom. BM Rec. (CRi)	4 (25%)	3 (18%)	6 (26%)	0	13 (23%)
Partial Response (PR)	10 (63%)	7 (41%)	13 (57%)	0	30 (54%)
Stable Disease (SD)	1 (6%)	1 (6%)	1 (4%)	0	3 (5%)
Progressive Disease (PD)	0	0	0	0	0
n	16	17	23	0	56
Withdr./Termination					
Complete Response (CR)	1 (33%)	0	0	0	1 (10%)
Complete Response Incom. BM Rec. (CRi)	0	0	0	0	0
Partial Response (PR)	0	0	0	4 (100%)	4 (40%)
Stable Disease (SD)	0	0	0	0	0
Progressive Disease (PD)	2 (67%)	2 (100%)	1 (100%)	0	5 (50%)
n	3	2	1	4	10
Unscheduled (1)					
Complete Response (CR)	0	0	0	0	0
Complete Response Incom. BM Rec. (CRi)	0	0	0	0	0
Partial Response (PR)	0	0	0	0	0
Stable Disease (SD)	1 (50%)	0	0	0	1 (33%)
Progressive Disease (PD)	1 (50%)	0	1 (100%)	0	2 (67%)
n	2	0	1	0	3

Percentages are based on n (the sum over all categories).

Part 2 - Schematic Representation of Patient Disposition



Overall Response Rate (ORR)

In Part 2, the ORR at the 3 month follow-up visit was similar in patients treated with rituximab IV and SC (80.7% for IV arm vs 85.2% for SC arm). The proportion of patients with a complete response (CR/CRi) was similar in the rituximab IV (33.0%) and rituximab SC (26.1%) treatment arms (table 6).

Table 6: Part 2 - Summary of Tumor Response at the 3-Month Follow-Up Visit (ITT Population)

rr001_I_002 Tumor Response At 3 Months Of Follow-up - Stage 2 (Intent-To-Treat Population)

Protocol(s): BO25341 (C25341O)
Analysis Population: Intent-To-Treat Population - Stage 2 (N=176)
Snapshot Date: 07MAY2014 Clinical Cutoff Date: 12FEB2014

	Rituximab IV 500 mg/m2 (N=88)		Rituximab SC 1600 mg (N=88)
Responders$	71 (80.7 %)		75 (85.2 %)
Non-Responders	17 (19.3 %)		13 (14.8 %)
95% CI for Response Rates*	[70.9; 88.3]		[76.1; 91.9]
Difference in Response Rates		4.55	
95% CI for Difference in Response Rates#		[-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*	[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#		[-20.9; 7.3]	
p-Value (Chi-squared Test)		0.3216	
Odds Ratio		0.72	
95% CI for Odds Ratio		[0.38;1.38]	
Partial Response (PR)	42 (47.7 %)		52 (59.1 %)
95% CI for PR Rates*	[37.0; 58.6]		[48.1; 69.5]
Difference in PR Rates		11.36	
95% CI for Difference in PR Rates#		[-3.9; 26.7]	
p-Value (Chi-squared Test)		0.1308	
Odds Ratio		1.58	
95% CI for Odds Ratio		[0.87;2.87]	
Stable Disease (SD)	1 (1.1 %)		0 (0.0 %)
95% CI for SD Rates*	[0.0; 6.2]		[0.0; 4.1]
Progressive Disease (PD)	2 (2.3 %)		2 (2.3 %)
95% CI for PD Rates*	[0.3; 8.0]		[0.3; 8.0]
Not Evaluated/Missing (NE) &	14 (15.9 %)		11 (12.5 %)

Overall Tumor Response: 3 Months FU (RESP3MFU)
$ Patients with end of treatment response of CR, CRi or PR
* 95% CI for one sample binomial using Pearson-Clopper
# Approximate 95% CI for difference of two rates using Hauck-Anderson method
& Patients with Non Evaluated/Missing response assessments are classified as Non-Responders.

Program : $PROD/cdt3490c/c25341a/rr001.sas
Output : $PROD/cdt3490c/c25341o/reports/rr001_I_002.out
07MAY2014 16:07 Page 1 of 1

The results for ORR based on the PPP were consistent with those for the ITT population, with rates of 95.5% and 96.7% for the rituximab IV and SC arms, respectively. The proportion of patients with a complete response (CR/CRi) was also consistent with the results obtained from the ITT population (34.7% for the IV arm vs 31.6% for the SC arm).

Ancillary analyses

A number of subgroup analyses were performed.

Subgroup Analyses of Overall Response Rate (ORR) by BSA, Gender and C_{trough}

The ORR at 3 months was analyzed on the ITT population by BSA category, gender and C_{trough}.

Overall, subgroup analyses supported the analysis on the total ITT population and ORR was comparable between rituximab IV and rituximab SC in the subgroups explored. The greatest difference in ORR between treatment arms was observed in the medium BSA subgroup, with a 11.0% difference in ORR (95% CI: -9.1%;31.1%) in favor of rituximab SC).

Note; some caution should be applied in interpreting the results given the possibility of bias introduced by other baseline prognostic variables (eg, comorbidities, patient's history, environment), the risk of

false-positive findings resulting from multiple comparisons, and small sample sizes within subgroups (and therefore low statistical "power").

- **BSA**

Numerical differences were observed in the low, medium and high BSA sub-groups between the IV and the SC arms (upper and lower 33rd percentiles). A 5.7% difference in ORR was observed in the low BSA subgroup in favor of rituximab IV; this is in contrast to ORR for the medium and high BSA subgroups, where it was higher (11.0% and 5.7%) in favor of the rituximab SC arm. However, the ORR CIs overlapped for all subgroups, and there were no apparent differences despite the variable point estimates.

A further exploratory analysis of response rates at the extremes of BSA based on the upper and lower 20th percentiles of BSA demonstrated that response rates were, in general, consistent with the above analyses. However, these analyses are again limited by the small sample size in the upper and lower 20th percentiles.

- **Gender**

Although numerical differences between both arms in each gender and between gender in each arm were observed, there were no apparent differences when taking into consideration the small patient numbers and slight imbalance between the arms with respect to gender.

- **C_{trough}**

With respect to C_{trough} at Cycle 5, the ORR was numerically higher in the low C_{trough} subgroup (5.1% difference [95% CI: -8.9%;19.2%]), in favor of the SC arm. Despite the numerical differences, in view of the small sample sizes, the ORR was considered to be comparable between low and high C_{trough} at Cycle 5 in both arms.

Table 7 Part 2 - Subgroup Analyses of Response Rate at the 3-Month Follow-up Visit

	Response Rate (CR, CRi, PR) at the 3-Month Follow-up Visit [95% CI]		
Subgroup	Rituximab IV N = 88	Rituximab SC N = 88	Difference [95% CI]
BSA (low: BSA ≤ 1.81 m^2; medium: 1.81 m^2 < BSA ≤ 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 vs female)			
Male	n = 53 81.1% [68.0%;90.6%]	n = 62 90.3% [80.1%;96.4%]	9.19% [-4.7%;23.1%]
Female	n = 35 80.0% [63.1%;91.6%]	n = 26 73.1% [52.2%;88.4%]	-6.92% [-30.8%; 17.0%]
*C_{trough} at cycle 5 (low: C_{trough} ≤ 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%;99.99%]	n = 41 95.1% [83.5%;99.4%]	-1.03% [-13.0%;11.0%]

* Excludes patients with a missing Ctrough assessment at Cycle 5 (n=19 IV arm, n=23 SC arm).

Minimal Residual Disease (MRD)

At the 3-month follow-up visit, the proportion of evaluable patients that were MRD negative was comparable between the IV and SC arms (66.1% IV vs 53.1% SC). It should be noted that the MRD results at 3 months are all based on PCR except for one patient in the rituximab IV arm for whom no PCR

result was available and the analysis was performed by flow cytometry (table 8). In addition, MRD status was also analyzed at baseline, 28 days, 6 months and 1 year after the end of treatment.

Table 8: Minimal Residual Disease Status at 3-Months (ITT Population)

rr_mrd2_I_002 MRD Response Rate - At 3 Months Of Follow-up - Excluding Patients With A Missing MRD Assessment - Stage 2 (Intent-To-Treat Population)

Protocol(s): BO25341 (C25341O)
Analysis Population: Intent-To-Treat Population - Stage 2 (N=176)
Snapshot Date: 07MAY2014 Clinical Cutoff Date: 12FEB2014

	Rituximab IV 500 mg/m2 (N=88)		Rituximab SC 1600 mg (N=88)
Patients with a non-missing Response	62 (100.0 %)		64 (100.0 %)
Responders (Negative MRD result)	41 (66.1 %)		34 (53.1 %)
Non-responders (Positive/Inconcl. MRD result)	21 (33.9 %)		30 (46.9 %)
95% CI for Responders Response Rates*	[53.0; 77.7]		[40.2; 65.7]
Difference in Responder Rates		-13.00	
95% CI for Difference in Responder Rates#		[-30.9; 4.9]	
p-Value (Chi-squared Test)		0.1371	
Odds Ratio		0.58	
95% CI for Odds Ratio		[0.28;1.19]	
Negative result: PCR $	40 (64.5 %)		34 (53.1 %)
95% CI for Neg.-PRC Rates*	[51.3; 76.3]		[40.2; 65.7]
Difference in Neg.-PRC Rates		-11.39	
95% CI for Difference in Neg.-PRC Rates#		[-29.4; 6.6]	
p-Value (Chi-squared Test)		0.1941	
Odds Ratio		0.62	
95% CI for Odds Ratio		[0.30;1.27]	
Negative result: Flow cytometry $	1 (1.6 %)		0 (0.0 %)
95% CI for Neg.-Flow Rates*	[0.0; 8.7]		[0.0; 5.6]
Difference in Neg.-Flow Rates		-1.61	
95% CI for Difference in Neg.-Flow Rates#		[-5.6; 2.4]	
p-Value (Chi-squared Test)		0.3077	
Odds Ratio		0.00	
95% CI for Odds Ratio		[0.00;>1000]	
Positive result: PCR or Flow cytometry	16 (25.8 %)		22 (34.4 %)
95% CI for Positive Rates*	[15.5; 38.5]		[22.9; 47.3]
Inconclusive MRD result &	5 (8.1 %)		8 (12.5 %)
95% CI for Inconclusive MRD result*	[2.7; 17.8]		[5.6; 23.2]
Missing	0 (0.0 %)		0 (0.0 %)

MRD Response at 3 Months Follow-up (MRDRESP)
* 95% CI for one sample binomial using Pearson-Clopper
# Approximate 95% CI for difference of two rates using Hauck-Anderson method
$ Results from flow cytometry were only considered in case no PRC results were available or were inconclusive. The MRD status was considered to be 'Positive', if a previous tumor assessment had reported disease progression.
& Patients where neither a 'Negative' nor a 'Positive' status could not be confirmed, were classified as Non-Responders.

Program : $PROD/cdt3490c/c25341a/rr_mrd2.sas
Output : $PROD/cdt3490c/c25341o/reports/rr_mrd2_I_002.out
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Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Supportive study(ies)

N/A

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

BO25341 is a two-part randomized, open-label, parallel-group, multicenter, Phase Ib study in patients with previously untreated CLL. In Part 1 patients were eligible at any time prior to Cycle 5 of their first-line therapy with rituximab IV (375 mg/m^2 in Cycle 1 followed by 500 mg/m^2 in Cycles 2 – 4) in combination with FC chemotherapy.

The efficacy data presented is based on a clinical cut-off date of 12 February 2014 and a snapshot date of 7 May 2014. Efficacy parameters presented includes response rates and MRD assessment at 3 months of follow up. Time-to-event endpoints (PFS, EFS and OS) were not included yet as these data are not mature.

The SAWYER study was designed as a PK-based bridging study with Ctrough being the primary endpoint. Efficacy endpoints were explorative as the SABRINA study had already previously evaluated the potential impact of the SC route of administration of rituximab and found it comparable to the IV route of administration. The design of the SAWYER study including inclusion and exclusion criteria, primary/secondary/exploratory endpoints, power calculations, randomisation, blinding and statistical methods are considered overall appropriate.

Efficacy data and additional analyses

The dose of 1600 mg was selected for the part 2 of the study.

Response rates were similar in each arm, with an overall response rate of 80.7% (95% CI: 70.9; 88.3) and 85.2% (95% CI: 76.1; 91.9) in the MabThera intravenous and subcutaneous arms, respectively. Complete response rate point estimates were 33.0% (95% CI: 23.3; 43.8) and 26.1% (95% CI: 17.3; 36.6) in the MabThera intravenous and subcutaneous arms, respectively. Overall the results confirm that MabThera subcutaneous formulation 1600 mg has a comparable benefit/risk profile to that of MabThera intravenous formulation 500 mg/m^2. The results on efficacy exploratory endpoints -albeit that the study was not powered to compare the efficacy of IV and SC rituximab- do not give rise to concern regarding the efficacy of SC rituximab. Time-to-event endpoints (PFS, EFS and OS) included in the study but were not analyzed by this cut-off.

Pharmacoeconomic parameters (resource savings and convenience) were also included as secondary parameters in study BO25341 to assess site experience on time savings and convenience of rituximab SC compared with rituximab IV. Such data are not part of the scope of the present assessment.

The recommended dose of MabThera subcutaneous formulation used for adult patients with CLL is a subcutaneous injection at a fixed dose of 1600mg irrespective of the patient's body surface area.

As it will be discussed under Clinical safety, in patients who had transient antibody (HACA) expression against rituximab and although presence of anti-rituximab HACAs seemed to result in lower rituximab exposure, no diminished effect on B-cell depletion was observed when positive HACAs were present. B-cell depletion is considered a measure of rituximab activity and thus may provide an indicator of the

potential neutralizing effect of anti-rituximab antibodies, therefore, there was no apparent impact of the presence of anti-rituximab antibodies on B-cell depletion.

The requirement for the final CSR of study SAWYER was already included in Annex II. Data from other ongoing studies as per the PhV will contribute to the long term efficacy and safety information with the sc rituximab.

2.5.4. Conclusions on the clinical efficacy

As it has been previously established that the subcutaneous route of administration has no impact on efficacy, the PK-based bridging study supported by exploratory response rate endpoints was considered sufficient to support the new strength of *1600 mg* of rituximab SC *for the treatment of patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia in combination with chemotherapy.* Time-to-event endpoints (PFS, EFS and OS) were not analysed as not yet mature.

The CHMP considers the following measures necessary to address issues related to efficacy:

- Final CSR of study SAWYER will be submitted by Q4 2018.

2.6. Clinical safety

Patient exposure

All patients who received at least one dose of study medication, whether prematurely withdrawn from the study or not, were included in the safety analysis population. Patients were analysed according to the actual treatment received.

Patient exposure

Part 1

The safety analysis population included all 64 patients enrolled into Part 1. Of these, 8 patients did not receive any rituximab SC dose and are therefore summarized separately. One further patient assigned to the rituximab 1870 mg SC sub-cohort received rituximab SC 1000 mg during Cycle 6 in error; safety information is presented separately for this patient. The treatment sub-cohorts included the following number of patients:

16 patients rituximab SC 1400 mg

17 patients rituximab SC 1600 mg

22 patients rituximab SC 1870 mg

1 patient rituximab SC 1000 mg

8 patients no rituximab SC dose administered

Part 2

Of the 176 patients (88 in each arm) enrolled into Part 2 of the study, two patients (one in each arm) were excluded from the safety analysis population because they withdrew from the study prior to receiving any treatment. Two additional patients in the SC arm, who only received the first dose of study treatment (rituximab IV), were included in the rituximab IV arm for the safety analyses. Hence, the safety analysis population comprised 89 patients in the IV arm and 85 patients in the SC arm.

Exposure to rituximab - Part I of the study

All patients in the three rituximab SC treatment sub-cohorts received treatment with rituximab IV 500 mg/m^2 during cycle 5 During Cycle 6, 16 patients received rituximab 1400 mg SC, 17 patients received rituximab 1600 mg SC and 22 patients received rituximab 1870 mg SC. One patient received rituximab 1000 mg SC in error during Cycle 6. The median treatment duration in Cycles 5 and 6 was 29 days in all three sub-cohorts.

Exposure to chemotherapy was comparable across the sub-cohorts. In the overall safety population, the median cumulative dose of cyclophosphamide (oral and IV) administered in Cycles 5 and 6 was 2445 mg and the median duration of treatment was 31 days (range: 3-58 days). For fludarabine (oral and IV), the figures were 264 mg and 31 days (range: 3-58 days), respectively.

Exposure to rituximab - Part 2 of the study

Apart from the 2 patients who withdrew prior to study drug treatment, all 174 patients received the first dose of rituximab IV (375 mg/m^2) in Cycle 1. A comparable proportion of patients in both arms (81% IV vs 86% SC) received all six scheduled cycles of study treatment. Overall, the median treatment duration was 4.7 months. The higher median cumulative dose of rituximab in the SC arm (8720 mg) compared to the IV arm (5232 mg) is due to the fixed dosing regimen for SC administration.

The median duration of rituximab SC administration was 7.0 minutes, with the majority of SC injections (89%; 330/369 injections) being given in less than 9 minutes. Very few injections (2%; 9/369) took longer than 11 minutes to administer.

Of note, one patient is reported to have had an administration time of 66 minutes; for this patient, administration was stopped and re-started.

Exposure to chemotherapy

Exposure to chemotherapy was comparable between the rituximab IV and SC arms. In the overall Part 2 safety population, the median number of cycles for both fludarabine and cyclophosphamide was six and the median cumulative doses (oral and IV) were 840 mg and 7508 mg, respectively

The justification for which patients to include and exclude from the population on which patient exposure data were derived in both parts of the SAWYER study is endorsed. The MAH argues that the FC exposure was comparable between cohorts. This is endorsed.

Adverse events

Part 1

In Part 1, patients could be enrolled at any point during their treatment with rituximab IV in combination with FC, prior to commencement of treatment in Cycle 5. In Cycle 5 (and previous cycles), patients received rituximab IV and subsequently in Cycle 6, rituximab IV was replaced by a single rituximab SC dose (the first sub-cohort received 1870 mg rituximab SC and thereafter two sub-cohorts, with 1400 mg and 1600 mg rituximab SC doses, were sequentially opened).

The presentation of safety information in this document is restricted to data collected in Cycle 6 since it is the only period during which rituximab SC was administered, and hence the only cycle which provides supportive safety information for rituximab SC. An overview of safety data collected in Cycle 5 (rituximab IV) has been provided for comparison.

The overall safety experience in the pooled rituximab SC sub-cohorts during Cycle 6 was generally consistent with that in Cycle 5 where rituximab IV was given. There were no new safety signals identified for rituximab SC in Part 1 of Study BO25341. When considering the limited number of patients in Part 1, the incidence of safety events are considered comparable during Cycles 5 and 6. The most commonly reported AEs in Cycle 5 were neutropenia (1400 mg sub-cohort: 38%; 1600 mg sub-cohort: 18%; 1870 mg sub-cohort: 23%) and leukopenia (1400 mg sub-cohort: 6%; 1600 mg sub-cohort: 24%; 1870 mg

sub-cohort: 0%) and in Cycle 6 were neutropenia (1400 mg sub-cohort: 19%; 1600 mg sub-cohort: 12%; 1870 mg sub-cohort: 27%) and injection site erythema (1400 mg sub-cohort: 0%; 1600 mg sub-cohort: 12%; 1870 mg sub-cohort: 18%) and injection site pain (1400 mg sub-cohort: 0%; 1600 mg sub-cohort: 18%; 1870 mg sub-cohort: 14%). Between the SC dose sub-cohorts (Cycle 6), a numerically higher incidence of all grade AEs was seen with increasing dose; the imbalance was already observed during Cycle 5. However, the incidence of Grade ≥ 3 AEs and SAEs was low and similar in all three rituximab SC sub-cohorts. Given the small sample size, the numerical differences observed between the SC dose sub-cohorts should be interpreted with caution.

Part 2

The overall safety profile of rituximab SC was comparable to that of rituximab IV and consistent with the expected safety profile of rituximab IV in a similar CLL population. There were no new safety signals identified for rituximab SC.

The incidence of safety events was similar between the treatment arms with the exception of a higher frequency of related AEs in the SC arm (58% IV vs 79% SC) mainly due to local cutaneous reactions. The most commonly reported AEs were neutropenia (58% IV vs 65% SC), thrombocytopenia (26% IV vs 24% SC), pyrexia (25% IV vs 32% SC), nausea (35% IV vs 38% SC) and vomiting (22% IV vs 21% SC).

Common adverse events

Part 1, Cycle 6

The majority of patients (66% [37/56]) experienced at least one AE during Cycle 6. The most commonly reported AEs by preferred term were neutropenia (21%), injection site erythema (11%), injection site pain (11%), vomiting (7%) and diarrhea (7%). All other AEs were reported in <= 5% of the study population.

Across the three SC dose sub-cohorts, numerical differences were seen in the incidence of all-grade AEs; 44% (7/16), 59% (10/17) and 86% (19/22) for the 1400 mg, 1600 mg and 1870 mg arms, respectively, however this should be considered in light of the small number of patients in each sub-cohort. Of note, a similar imbalance between the SC dose sub-cohorts was already observed in Cycle 5. The higher incidence of all-grade AEs in the 1600 mg and 1870 mg dose sub-cohorts was mainly driven by local cutaneous reactions (injection site erythema/pain) as well as *gastrointestinal disorders* (eg, diarrhea and vomiting).

Part 2

In Part 2, the proportion of patients reporting at least one AE of any grade was comparable between the study arms (91% IV vs 96% SC). It should be noted that data from Cycle 1 (when all patients, including those in the rituximab SC arm received rituximab IV [375 mg/m^2]) are included in the analysis.

The most common (>50% in at least one study arm) SOCs in which AEs were reported were:

Blood and lymphatic disorders: 70% IV vs 75% SC, most commonly neutropenia, thrombocytopenia, anemia and leukopenia.

General disorders and administration site conditions: 48% IV vs 71% SC, most commonly pyrexia, asthenia, chills, fatigue and injection site erythema/pain.

Gastrointestinal disorders: 56% in each arm, most commonly nausea, vomiting and diarrhea.

Infections and infestations: 49% IV vs 56% SC most commonly upper respiratory tract infections.

AEs with a difference of >10% between treatment arms included injection site erythema (0% IV vs 26% SC) and injection site pain (0% IV vs 16% SC).

In addition, there was an overall higher incidence of AEs with SC compared to IV rituximab in the SOC of *skin and subcutaneous tissue disorders* (30% IV vs 44% SC; mainly due to erythema and pruritus) and *musculoskeletal and connective tissue disorders* (22% IV vs 32% SC; mainly due to arthralgia and pain in the extremity). Conversely, a higher incidence of *vascular disorders* (21% IV vs 11% SC; mainly hypotension and hypertension) and the AE preferred term anemia (24% IV vs 13% SC) was reported in the rituximab IV arm.

There were no other noteworthy differences between the study arms with respect to the type and frequency of other all-grade AEs.

The MAH argues that the overall safety experience in the pooled rituximab SC sub-cohorts during Cycle 6 of Part 1 of the SAWYER study was generally consistent with that in Cycle 5 where rituximab IV was administered. This is endorsed.

Differences in frequency of AEs during Part 2 in the SOC of *skin and subcutaneous tissue disorders* and *musculoskeletal and connective tissue disorders* were more prominent in the SC cohort as were injection site erythema and injection site pain. On the contrary, a higher incidence of *vascular disorders* and anaemia was reported in the rituximab IV arm. The AEs on which differences were observed between groups were generally of low Grade severity.

The MAH argues that the overall safety profile of rituximab SC was comparable to that of rituximab IV and consistent with the expected safety profile of rituximab IV in a similar CLL population. This is endorsed.

Serious adverse events and deaths

SAEs

Part 1, Cycle 6

During Cycle 6 of Part 1, two patients in the rituximab SC 1600 mg sub-cohort experienced a SAE. The cases were Grade 3 diarrhea and Grade 3 cholecystitis both of which were considered by the investigator as unrelated to rituximab. There were no SAEs reported in the other sub-cohorts during Cycle 6.

Part 2

The overall frequency of SAEs was comparable between the study arms (33% IV vs 29% SC). The most common SAEs were reported in the SOC of *blood and lymphatic system disorders* (mainly febrile neutropenia and neutropenia) and *infections and infestations* (various events). There was no noteworthy difference between the arms with respect to the frequency and type of SAEs, with the exception of febrile neutropenia which was more common in the rituximab SC arm (4% IV vs 11% SC) and neutropenia which was more common in the IV arm (9% IV vs 1% SC).

The incidence of SAEs during Cycle 1 (when all patients received rituximab IV) was comparable in both treatment arms (8% IV vs 6% SC). The incidence of SAEs during Cycles 2-6 was similar (17% IV vs 18% SC) and the incidence did not change notably over the course of treatment.

The MAH argues that the incidence of SAEs was comparable between treatment arms and that the incidence did not change notably over the course of the treatment. This is endorsed.

Deaths

Part 1

At the study snapshot date of May 7, 2014, six patients enrolled in Part 1 of the study had died, however, no deaths occurred during treatment Cycle 6. Two patients died due to disease progression and four died due to an AE.

All but one death occurred during the follow-up period. One patient died during the treatment phase (Cycle 4), before receiving rituximab SC, due to acute respiratory failure. The cause of death was reported after the data snapshot date. All deaths were considered by the investigator as unrelated to rituximab. One death occurred after data snapshot date. One patient in the SC 1400 mg sub-cohort died from a brain neoplasm, more than 2 years after the last dose of study treatment. This death was considered by the investigator as unrelated to rituximab**.**

Part 2

In Part 2, nine deaths had been reported by the snapshot date; 4/89 patients (5%) in the rituximab IV arm and 5/85 patients (6%) in the rituximab SC arm. The majority of deaths were due to disease progression (2 IV vs 3 SC). The most common cause of death unrelated to disease progression was infections; listeriosis in the IV arm and herpes zoster and PML in the SC arm. The two deaths (herpes zoster, PML) in the SC arm were considered by the investigator as related to rituximab.

The deaths were, however, balanced between groups. This is endorsed.

Laboratory findings

Haematology

Part 1

In Part 1 of the study, no meaningful changes from baseline were observed in haematology parameters.

Part 2

The observed changes in haematology laboratory parameters are consistent with those expected from rituximab in combination with chemotherapy. They included on-treatment decreases in white blood cell, neutrophil, lymphocyte counts and platelets which were recovering towards the normal range by the time of the data snapshot. No noteworthy difference was observed between the arms with respect to median values for these parameters over time. There were no meaningful changes observed for other hematologic parameters.

There was no notable difference between the study arms in the proportion of patients with clinically relevant shifts from baseline (from Grade 0, 1 or 2 at baseline to Grade 3 or 4 post-baseline) in haematology laboratory parameters

Serum Chemistry

In both parts of Study BO25341, no consistent trends or patterns were observed with respect to changes from baseline in median values in serum chemistry parameters. Median values generally showed little change over time and remained within the normal range. No noteworthy differences were observed between the arms.

There were no noteworthy clinically relevant shifts from baseline in serum chemistry parameters with the exception of high uric acid levels. The proportion of patients with clinically relevant shifts of uric acid levels (from Grade 0 at baseline to Grade 3 or 4 post-baseline) was 20% in the IV arm and 14% in the SC arm. Four patients in the rituximab IV arm and two patients in the rituximab SC arm experienced a shift from Grade 0 baseline to Grade 4 post-baseline.

It should be noted that NCI-CTCAE Grade 1 is defined as values above the upper limit of normal (ULN) but $\leq$ 0.59 mmol/L without physiological consequences while Grade 3 is defined as $>$ ULN but $\leq$ 0.59 mmol/L with physiological consequences. NCI-CTC grading does not allow for Grade 2. In Study BO25341, NCI-CTCAE grades for uric acid were assigned only on the basis of laboratory values and a worst-case analysis was applied in all cases. Conservatively all values above the ULN but $\leq$ 0.59 mmol/L were set to Grade 3 regardless of clinical consequences. In this study, none of the patients with this shift

in uric acid levels experienced AEs of Grade ≥ 3 severity that plausibly could have been a result of elevated uric acid levels. Therefore, it appears that uric acid levels up to 0.59 mmol/L would have been assigned to NCI-CTCAE Grade 1 rather than to Grade 3 if the grading had been assigned by the investigator.

There was no consistent change in other biochemical markers that would suggest tumour lysis syndrome or uric acid nephropathy (eg, calcium, potassium, creatinine, and albumin).

Observed changes in haematology laboratory parameters were consistent with those expected from rituximab in combination with chemotherapy. No notable differences were observed between groups for neither haematology laboratory parameters nor serum chemistry with the exception of high uric acid levels which were more prevalent in the IV group.

No other indications of tumour lysis syndrome or uric acid nephropathy were detected. This is endorsed.

Safety in special populations

Data on AEs in subgroups are presented for only Part 2 of Study BO25341.

- **Age**

The incidence of all-grade AEs in both treatment arms was comparable across the three age categories (< 65 years, 65 - 70 years and > 70 years). The proportion of patients (>90%) who experienced AEs in the three age categories was comparable in the two treatment arms, and there was no trend in the incidence of adverse events with age.

- **Gender**

In both treatment arms, the incidence of all-grade AEs was generally comparable between males and females (IV arm: 89% of females' vs 92% of males; SC arm: 100% of females' vs 95% of males). In both treatment arms, SAEs and Grade ≥ 3 AEs occurred at a higher incidence in females than males (IV arm: 42% of females vs 26% of males; SC arm: 36% of females vs 27% of males), with events in the SOC of blood and lymphatic system disorders being the main driver for the observed difference.

There were no other noteworthy differences observed with respect to the safety of rituximab administration (given IV or SC) and gender.

- **Race**

Since the study population comprised predominantly White patients (90%), no analysis on the type and frequency of AEs by race was performed.

- **Body Surface Area**

<u>All-Grade Adverse Events</u>

The overall proportion of patients who experienced at least one AE in the IV and SC arms was comparable across the three BSA subgroups. In both treatment arms, patients in the low BSA compared with the medium and high BSA categories had a higher incidence of events in the *blood and lymphatic system* SOC (85% low vs 73% medium vs 58% high); mainly more AEs of neutropenia and febrile neutropenia.

Within the low BSA subgroup, the incidence of AEs was generally comparable between the IV and SC arms except for injection site erythema which was reported exclusively in the SC arm (5/24 patients; 21%). There were no other noteworthy differences observed between the treatment arms within each BSA category.

<u>Serious Adverse Events</u>

The overall proportion of patients in the IV and SC arms who experienced at least one SAE was generally comparable across the three BSA subgroups. In both arms, patients in the low BSA compared with the medium and high BSA categories had a higher incidence of events in the *blood and lymphatic system* SOC (22% vs 10% vs 11%, respectively); the difference was mainly accounted for by an imbalance in febrile neutropenia.

There were no other noteworthy differences in the incidence of SAEs observed between treatment arms within each BSA category.

Grade ≥ 3 Adverse Events

The overall proportion of patients in the IV and SC arms who experienced at least one Grade ≥ 3 AE was higher in the low BSA subgroup compared with the medium and high BSA subgroups.

In both treatment arms, the difference was mainly accounted for by a higher incidence of events in the *blood and lymphatic system* SOC in the low BSA subgroup (75% vs 58% vs 51%, respectively); mainly neutropenia and febrile neutropenia.

There were no other noteworthy differences in the incidence of Grade ≥ 3 AEs observed between treatment arms within each BSA category.

Adverse Events by BSA Category and Treatment Cycle

In Cycle 1 and Cycles 2-6, a comparable proportion of patients experienced all-grade AEs and SAEs across the three BSA categories in both IV and SC arms. Both in Cycle 1 and Cycle 2-6, there was a trend for a higher incidence of Grade ≥ 3 AEs in the low BSA subgroup in both IV and SC arms. There were no other noteworthy differences observed.

Adverse Events by Extremes of BSA

Exploratory analyses of all-grade AEs, Grade ≥ 3 AEs and SAEs at the extremes of BSA based on the upper (> 2.07) and lower 20th (< 1.72) percentiles of BSA demonstrated that the AE profile was generally consistent with the analyses based on the 33rd and 66th percentiles although interpretation of the results was limited by the small sample size in the upper (16 IV vs 19 SC) and lower (18 IV vs 12 SC) 20th percentile BSA categories.

No different safety signals were detected based on age, gender or race. Patients in the low BSA group generally experienced a higher incidence of events in the *blood and lymphatic system* SOC compared with patients in the medium and high BSA categories. However, in general the differences between groups is considered sufficiently low to support a fixed dose SC rituximab regimen.

Table 9 Part: Adverse Events by BSA and Treatment Cycle (Safety Analysis Population)

Number of patients with at least one AE		All		Low BSA		Medium BSA		High BSA	
		IV N=89 (%)	SC N=87 (%)	IV N=35 (%)	SC N=24 (%)	IV N=29 (%)	SC N=31 (%)	IV N=25 (%)	SC N=30 (%)
All	AE	81 (91)	82 (96)	31 (89)	24 (100)	28 (97)	30 (97)	22 (88)	28 (93)
	SAE	29 (33)	25 (29)	14 (40)	7 (29)	7 (24)	10 (32)	8 (32)	8 (27)
	Grade≥3 AE	63 (71)	59 (69)	27 (77)	20 (83)	18 (62)	20 (65)	18 (72)	19 (63)
Cycle 1*	AE	67 (75)	57 (67)	25 (71)	15 (63)	25 (86)	23 (74)	17 (68)	19 (63)
	SAE	7 (8)	5 (6)	3 (9)	1 (4)	2 (7)	2 (6)	2 (8)	2 (7)
	Grade≥3 AE	23 (26)	18 (21)	11 (31)	5 (21)	8 (28)	7 (23)	4 (16)	6 (20)
Cycles 2-6	AE	76 (90)	80 (94)	31 (94)	23 (96)	26 (96)	30 (97)	19 (79)	27 (90)
	SAE	14 (17)	15 (18)	8 (24)	6 (25)	1 (4)	4 (13)	5 (21)	5 (17)
	Grade≥3 AE	44 (52)	55 (65)	20 (61)	19 (79)	13 (48)	20 (65)	11 (46)	16 (53)

* All patients received rituximab IV 375 mg/m^2 in Cycle 1

Data Sources: ae002_s002; ae002a_s002; ae002b_s002030; ae004_s002; ae016_s002; ae102_s002; ae038_s002.

Immunological events

Immunogenicity

Monoclonal antibodies provide highly effective therapies but may be associated with unwanted effects such as immunogenicity (i.e., they induce an immune response in patients). The assessment of immunogenicity and the factors contributing to it are topics of much ongoing research and discussion.

It is generally accepted that antibodies formed against therapeutic proteins may be transient with no clinical consequence or may have a range of implications on safety and/or efficacy of a drug (Shankar et al. 2014).

The change of route of administration may influence the immunogenic potential of drugs; therefore the clinical program for rituximab SC includes a comprehensive assessment of human anti-chimeric antibodies (HACAs; anti-rituximab antibodies) and human anti-human antibodies (HAHAs; anti-rHuPH20 antibodies) following administration of rituximab SC versus rituximab IV.

Part 1

Anti-Rituximab Antibodies

Samples for the anti-rituximab antibody (HACA) assay were collected starting pre-dose Cycle 5 (rituximab IV), and at each follow-up visit until 24 months after the last dose of rituximab.

The incidence of HACA was low; 3 of the 61 patients tested, one in each SC dose, who were negative for HACA at pre-dose Cycle 5 had a positive result for HACA post-Cycle 5 (treatment-induced HACA). All 3 patients were responders at the 3-month follow-up visit. Given the limited number of patients with positive HACA results, no definitive conclusion on the incidence of HACA positivity and their clinical consequences can be made.

Anti-rHuPH20 Antibodies

In Part 1 of the study, patients received one of three fixed doses of rituximab SC (1400 mg, 1600 mg and 1870 mg) at Cycle 6 only, although 1 patient received 1000 mg by mistake. Samples for the anti-rHuPH20 (HAHA) assay were collected prior to the administration of the rituximab SC dose, and at each follow-up visit until 9 months after the last dose of rituximab.

At baseline (pre-SC dose Cycle 6), 5/56 patients (9%) had positive results for HAHAs.

Post-SC dose Cycle 6, one of the 5 patients who had a HAHA-positive result at baseline became HAHA-negative and was considered to have a treatment-unaffected response. The other 4 patients (6.5%) tested positive for HAHAs at baseline and at subsequent time points; two were considered treatment unaffected and two were considered to have a treatment-enhanced response.

A further 2 patients who were baseline-negative for HAHA became positive and were considered to have a treatment-induced response. None of the patients with positive HAHA samples had neutralizing antibodies.

All patients with HAHAs were responders at the 3-month follow-up visit, with the exception of one patient who had stable disease. Due to the low number of HAHA-positive patients, full assessment of the impact of HAHA is limited.

Part 2

Anti-Rituximab Antibodies (HACAs)

In Part 2, samples for the HACA assay were collected at each treatment cycle prior to the administration of rituximab and at each follow-up visit until 24 months after the last dose of rituximab.

At baseline, prior to treatment with rituximab, the prevalence of HACA was 1% (2 patients from the rituximab SC arm) based on 172 evaluable patients. The two patients with a positive result at baseline became HACA negative after treatment with rituximab (i.e., these patients were considered to have a treatment unaffected response).

Additionally, 8 patients (6 patients in rituximab IV and 2 patients in rituximab SC) who were HACA negative at baseline developed a positive response at one or two time points following treatment (treatment-induced HACA response), giving a post-baseline incidence of HACA of 6.7% (6/89) and 2.3% (2/85), respectively. Among the patients with a positive HACA response at any time during the study there were no positive results for anti-rHuPH20 antibodies reported.

Anti-Rituximab Antibodies

To assess the potential impact of HACA on safety, the incidence of AEs, ARRs, and AEs potentially indicative of anaphylactic reactions was compared between patients who had a positive HACA response at any time point during the study and those who were negative for HACAs at all-time points.

Overall, the results in patients who were positive for HACAs were consistent with those of the overall rituximab-treated population with the most frequent AEs being neutropenia (2 patients in the rituximab IV arm, 4 patients in the rituximab SC arm), thrombocytopenia (2 patients in each arm), nausea (3 patients vs. 1 patient), pyrexia (2 patients vs 1 patient), and asthenia (2 patients vs. 1 patient).

ARRs were reported in 37/83 patients (45%) among HACA-negative patients and 3/6 patients among HACA-positive patients in the rituximab IV arm. In the rituximab SC arm, ARRs were reported in 35/81 patients (43%) among HACA-negative patients and 2/4 patients among HACA-positive patients.

AEs potentially indicative of anaphylactic reactions were reported in 36/83 patients (43%) among HACA-negative patients and 1/6 patients among HACA positive patients in the rituximab IV arm. In the rituximab SC arm, AEs potentially indicative of anaphylactic reactions were reported in 36/81 patients (44%) among HACA-negative patients compared with 1/4 patients among HACA-positive patients.

Given the small number of patients who developed HACA in this part of the study, as for Part 1, no definitive conclusion on the impact of HACA on efficacy and/or safety can be made.

Anti-rHuPH20 Antibodies

In Part 2, anti-rHuPH20 antibodies (HAHAs) were only measured in patients randomized to the rituximab SC arm. Samples for the HAHA assay were collected at each treatment cycle from Cycle 2 onwards prior to the administration of rituximab SC and at each follow-up visit until 9 months after the last dose of rituximab.

At baseline, prior to treatment with rituximab SC, the prevalence of HAHA was 10.7% (9/84 patients). After study drug administration, 9/85 patients were considered positive for anti-rHuPH20 antibodies, giving a post-baseline incidence of HAHAs of 10.5%.

Four of the patients with positive HAHA results at baseline became HAHA negative (or had no increase in endpoint titer) post-baseline and were considered to have a treatment-unaffected response. The other 5 patients with a positive HAHA result at baseline were considered to have a treatment-enhanced response.

Four patients who had a negative HAHA result at baseline developed a positive HAHA response at one or two time points following treatment and were considered to have a treatment-induced HAHA response.

Results in patients who were positive for HAHAs were consistent with those of the HAHA negative population with the most frequent AEs occurring in the SOCs blood and lymphatic system disorders, general and administration site conditions, and gastrointestinal disorders.

In the rituximab SC arm, a higher percentage of patients who were positive for HAHAs (7/13 patients; 54%) experienced ARRs compared with patients who were negative for HAHAs (30/72 patients; 42%). All ARRs in HAHA-positive patients were experienced by single patients, with the exception of injection site erythema, chills and vomiting which were each reported in 2 HAHA patients.

Nine of the 13 patients (69%) who were positive for HAHAs experienced an AE potentially indicative of an anaphylactic reaction (SMQ Anaphylactic reaction Wide) versus 28/72 patients (39%) who were negative for HAHAs. the most common events in both populations being erythema, cough and rash.

Due to the low number of patients who tested positive for HAHAs and the imbalance in sample size between the HAHA-positive patients (13 patients) and HAHA-negative patients (72 patients) in the SC arm, differences in incidence of ARRs and AEs potentially indicative of an anaphylactic reaction must be interpreted with extreme caution.

Three patients developed HACA antibodies during Pars 1 of the SAWYER study. All three patients were responders to rituximab treatment. Due to the limited number of patients with positive HACA results, no definitive conclusion on the incidence of HACA positivity and its possible clinical consequences can be drawn.

During Part 1 of the SAWYER study, five patients were reported to have positive results for HAHA at baseline (before exposure to SC rituximab). A further 2 patients became HAHA positive and were considered to have a treatment-induced response.

In Part 2 of the SAWYER study, 2 patients had positive HACA results at baseline and an additional 8 patients tested HACA positive during the study. This is endorsed.

Based on the limited data it does not appear that the presence of HACA has an effect on the PK of rituximab. In addition, all 10 patients with a positive HACA response were responders (indicative of rituximab efficacy despite the presence of HACA) but that given the small number of patients who developed HACA no definitive conclusion on the impact of HACA on efficacy and/or safety can be drawn.

During Part 2 of the SAWYER study, 9 patients tested positive for HAHA prior to SC rituximab administration. Four of these became HAHA negative during the study whereas five patients developed positive HAHA results during the study. This pattern of HAHA is similar to what was observed in the previously granted IV to SC MabThera line extension for NHL and thus gives no reason for concern. All 13 patients who had a positive HAHA result were responders and moreover, antibodies towards an excipient are not expected to influence efficacy.

There was an imbalance in the number of patients who were positive for HAHA and who experienced AEs potentially indicative of an anaphylactic reaction as compared with patients who were HAHA negative. However, the low number of patients who tested positive for HAHA and the imbalance in sample size between HAHA positive and negative patients should warrant caution when interpreting data.

Safety related to drug-drug interactions and other interactions

Not applicable

Discontinuation due to AES

Part 1, Cycle 6

No patient discontinued study treatment due to an AE during Cycle 6.

Part 2

A comparable proportion of patients in both arms discontinued study treatment due to an AE (8% IV vs. 11% SC). The most common AEs which led to treatment discontinuation were neutropenia (3 IV vs 1 SC)

and thrombocytopenia (1 IV vs 2 SC); all other AEs were reported in single patients. The majority of AEs leading to withdrawal were of Grade 3 or 4 severity.

Adverse Events Leading to Dose Interruption or Modifications

The protocol did not permit dose reductions for rituximab IV or rituximab SC. However, it was possible to delay a treatment cycle (due to AEs), stop and/or restart rituximab infusions/injections (due to AEs), or reduce the rate of the rituximab infusions.

Part 1, Cycle 6

During Cycle 6 Part 1, the proportion of patients who had a treatment modification (mainly dose delays) was similaracross the three SC dose sub-cohorts. The overall incidence of modifications across the sub-cohorts was 32% with the majority being due to AEs.

Part 2

The highest incidence of treatment modifications occurred in Cycle 1, where all patients received rituximab IV (28% IV arm vs 31% SC). During Cycles 2 and 3, more treatment modifications (mostly dose delays) occurred for patients in the IV arm than in the SC arm. However, during Cycles 4 to 6, treatment modifications (mainly dose delays) were more common in the SC arm. Overall, the majority of treatment modifications in each cycle were due to AEs.

A comparable and acceptably low number of patients discontinued in Part 2 of the SAWYER study. The most common AEs leading to discontinuation were neutropenia and thrombocytopenia. This is regarded acceptable. Treatment modifications were relatively common and fairly evenly distributed between the SC and IV treatment groups. The majority of treatment modifications were due to AEs.

Overdose

One patient in the present study BO25341 erroneously received an overdose of rituximab SC on one occasion. The patient randomized to the SC arm, received 660 mg of rituximab IV in the first treatment cycle, as planned. In Cycle 2, the patient received rituximab SC 2200 mg instead of 1600 mg in error.

2.6.1. Discussion on clinical safety

The incidence of SAEs was comparable between treatment arms and that the incidence did not change notably over the course of the treatment. Differences between treatment groups were observed and cutaneous/subcutaneous/connective tissue AEs were more prevalent with the SC formulation, which is acceptable. The occurrence of SAEs was balanced as were the low number of deaths of which the majority were due to disease progression. Laboratory findings were similar between the IV and SC treatment groups.

No different safety signals were detected based on special populations with the exceptions of BSA. Patients with low BSA generally experienced a higher incidence of AEs in the blood and lymphatic system SOC. However, in general the differences between groups were considered sufficiently low to raise any concern with the fixed dose SC rituximab regimen.

The incidence of treatment induced / enhanced anti- rituximab antibodies was similar in the 2 treatment arms; 6.7% (IV) vs 2.4.% (SC). The incidence of treatment induced / enhanced anti- rHuPH20 antibodies, only measured in patients in the SC arm was 10.6%. None of the patients who tested positive for anti-rHuPH20 antibodies, tested positive for neutralising antibodies. Presence of HACA and HAHA antibodies did not seem to impact safety nor efficacy. The SAWYER study in general did not reveal any new safety signals which were not already expected based on previous experience with rituximab SC.

A comparable and acceptably low number of patients discontinued in Part 2 of the SAWYER study.

Overdose occurred was moderate and no untoward events were observed.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The incidence of SAEs was comparable between treatment arms and the incidence did not change notably over the course of the treatment. No new safety concerns were noted.

The CHMP considers the following measures necessary to address issues related to safety:

- Submission of clinical study report from the clinical trials BO25341 including reports on long term safety in relation to BSA (as a measure for exposure variation) and to gender. (see RMP and Annex II)

2.7. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 13.0 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed this advice without changes.

The applicant implemented the changes in the RMP as requested by PRAC and/or CHMP.

The CHMP endorsed the Risk Management Plan version 14.0 with the following content (new text marked as underlined, deletions marked as strikethrough):

Safety concerns

Summary of safety concerns	
Important identified risks	~~Acute~~ Infusion-related reactions (All Indications) Infections <u>(including serious infections)</u> (All Indications) Impaired immunization response (All Indications) Progressive multifocal leukoencephalopathy (All Indications) Neutropenia (including prolonged) (All Indications) Hepatitis B reactivation (All Indications) Stevens-Johnson Syndrome/ toxic epidermal necrolysis (All Indications) Hypogammaglobulinemia (RA and GPA/MPA) Tumor lysis syndrome (NHL/CLL) Serious viral infections (NHL/CLL) Gastrointestinal perforation (NHL/CLL) ~~Posterior reversible encephalopathy syndrome (All Indications)~~ Local cutaneous reactions (NHL<u>/CLL</u> SC formulations)

Summary of safety concerns	
Important potential risks	Posterior reversible encephalopathy syndrome (All Indications) ~~De Novo hepatitis B (RA and GPA/MPA)~~ Opportunistic infections (All Indications) Prolonged B-cell depletion (All Indications) Off label use in pediatric patients (All Indications) Malignant events (RA and GPA/MPA) Impact on cardiovascular disease (RA and GPA/MPA) Gastrointestinal perforation (RA and GPA/MPA) Off label use in autoimmune disease (RA and GPA/MPA) Relapses (GPA/MPA) Acute myeloid leukemia and myelodysplastic syndrome (NHL/CLL) Second malignancies (NHL/CLL) Increased risk of Grade 3/4 and serious blood and lymphatic system adverse events in >70 year patients (~~NHL/~~CLL) Embryofetal toxicity resulting from systemic exposure to rHuPH20 (NHL/CLL SC formulations) Off-label use of the subcutaneous formulation (NHL/CLL SC formulations) Administration route error (NHL/CLL SC formulations)
Missing information	Use in pregnancy and lactation (All Indications) Immunogenicity and autoimmune disease (RA and GPA/MPA) Long term use in GPA/MPA patients (GPA/MPA) Immunogenicity associated with the subcutaneous formulation (NHL/CLL SC formulations) Effect of greater exposure in patients with low BSA after fixed-dose SC administration (NHL/CLL SC formulations)

Pharmacovigilance plan

Study / activity type, title and category (1-4)	**Objectives**	**Safety concerns addressed**	**Status**	**Date for submission of interim or final reports**
Study BO25341 (SAWYER): An adaptive, comparative, randomized, parallel-group, multi-center, Phase Ib study of subcutaneous rituximab versus	To compare the safety profiles of rituximab subcutaneous and rituximab intravenous formulations, including, comparing the immunogenicity of rituximab subcutaneous	Prolonged B-cell depletion; Immunogenicity associated with the subcutaneous formulation; effect of greater	Study ongoing	Primary Clinical Study Report (No. 1047897): September 2014 Immunogenicity report (both parts): Q42016

Study / activity type, title and category (1-4)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
intravenous rituximab both in combination with chemotherapy (fludarabine and cyclophosphamide), in patients with previously untreated CLL (interventional, ~~2~~ 1)	and rituximab intravenous	exposure in patients with low BSA after fixed-dose subcutaneous administration		Final report: ~~Q2~~ Q4 2018.
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 (interventional, ~~2~~ 1)	To compare the safety profiles of rituximab subcutaneous and rituximab intravenous formulations, including, comparing the immunogenicity of rituximab subcutaneous and rituximab intravenous	Prolonged B-cell depletion; immunogenicity associated with the subcutaneous formulation; effect of greater exposure in patients with low BSA after fixed-dose subcutaneous administration	Study ongoing	Primary Clinical Study Report (No. 1058994): June 2014. Immunogenicity report (both parts): Q42016 Final report: Q3 2018.
Study BA28478 (MabThera Autoimmune Drug Utilization Study) (retrospective non-interventional PASS, ~~2~~ 3)	Designed to address EMA follow-up measures (FUMs) 068 and 071.1 to evaluate off-label use and usage of the patient alert cards in the 5EU countries	Off-label use in autoimmune disease	Study planned Q4 ~~2014~~ 2015	Final report submission: Q3 2017
Study WA25615 Phase IIa, international, multicenter, open-label, single-arm study in pediatric	Evaluate the safety and tolerability of rituximab in pediatric patients with severe GPA/MPA	Off-label use in pediatric patients	Study ongoing	The common closeout date will occur 18 months after the enrollment of the last patient.

Study / activity type, title and category (1-4)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
GPA/MPA patients (interventional PASS, 3)				
Intergroup B-NHL-2010 Open-label, randomized, controlled, parallel-group, multicenter trial to evaluate the pharmacokinetics, pharmacodynamics, safety and efficacy or rituximab add-on to standard chemotherapy in children from 6 months to less than 18 years of age with advanced stage B-cell lymphoma (excluding primary mediastinal B-cell lymphoma), Burkitt and Burkitt-like lymphoma/leukemia conducted in accordance with the approved PIP (interventional, randomized, open-label, 3)	Evaluate the safety and tolerability of rituximab in pediatric patients with advanced stage B-cell lymphoma (excluding primary mediastinal B-cell lymphoma), Burkitt and Burkitt-like lymphoma/leukemia	Off-label use in pediatric patients	Study ongoing	June 2019
Plasma exchange and glucocorticoid dosing in the treatment of ANCA-associated vasculitis (PEXIVAS) (Phase III, interventional, randomized, open-label, comparative trial, 3)	Capture long-term safety data in order to further evaluate dose regimen of rituximab in relation to infection's frequency, seriousness and severity	Infections including serious infections	Study ongoing	2016
~~Maintenance of remission using rituximab in systemic~~	~~Assess number of major relapse (BVAS > 10) in each group at the end of~~	~~Relapses~~	~~Completed~~	~~Final data collection date for primary outcome~~

Study / activity type, title and category (1-4)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
~~Anti-Neutrophil Cytoplasm Antibody (ANCA) Associated Vasculitis (MAINRITSAN I) (Phase III, interventional, randomized, open-label, comparative trial, 3)~~	~~the maintenance treatment (18 months treatment + 10 months follow-up)~~			~~measure: June 2013.~~ ~~Estimated study completion date: December 2013.~~
Maintenance of remission using rituximab in systemic Anti-Neutrophil Cytoplasm Antibody (ANCA) Associated Vasculitis II (MAINRITSAN II) (Phase III, interventional, randomized, open-label, comparative trial, 3)	Number of relapses / Number of relapses (BVAS>0) majors and minors in each group at the end of the maintenance treatment (18 months treatment + 16 months follow-up)	Relapses	Study ongoing	Estimated study completion date: February 2018, Final data collection date for primary outcome measure: August 2017.
An international, open label, randomised controlled trial comparing rituximab with azathioprine as maintenance therapy in relapsing ANCA-associated vasculitis (RITAZAREM) (Phase III, interventional, randomized, open-label, comparative trial, 3)	Time to relapse / the primary endpoint is the time to disease relapse (either minor or major relapse) from randomization. Proportion of patients who maintain remission at 24 and 48 months	Relapses	Study ongoing	Estimated study completion date: December 2016. Final data collection date for primary outcome measure: December 2016.
Study ML19514 (local marketing study) First line treatment with rituximab combined with fludarabine, cyclophosphamide, and	Provision of data on B-cell depletion from maintenance part of this study, and to determine response rate (including negative minimal residual disease	Prolonged b-cell depletion	Study ongoing	The Primary Clinical Study Report was published in April 2014 with a data cutoff of 4 October 2012.

Study / activity type, title and category (1-4)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
mitoxantrone (R-FCM) and maintenance with rituximab of chronic lymphocytic leukemia (CLL) patients (Phase II, non-randomised study, 3)	response rate) obtained after R-FCM combination			Preparation final manuscript ongoing, and is expected by Q2 2015.
Study ML18434 (local marketing study) Early brief intensification by chemoimmunotherapy with FCR followed by FR and rituximab maintenance in chemonaive patients with B-CLL (Phase II, non-randomised study, 3)	Provision of data on B-cell depletion from maintenance part of the study	Prolonged b-cell depletion	Study ongoing	Final results on the induction treatment were reported at ASH (Bosch et al. [2008] abstract #2097. Data from maintenance part will become available by Q2 2015, due to the two year maintenance schedule.
British Society of Rheumatology Biologics Registry (BSRBR) (non-interventional observational PASS, 4)	Many patients receiving biological agents for the treatment of RA in the UK are followed in this observational registry. Its purpose is to evaluate the safety profile of these biological agents in prospective cohorts.	Infections including serious infections; opportunistic infections; malignant events; cardiac events (impact on cardiovascular disease); gastrointestinal perforation; use in pregnancy.	Study ongoing	6-montly reports included in the PSUR (PBRER) First interim analysis of safety data was safety performed when a total of 1,100 rituximab-treated patients have been followed for 3 years after their first rituximab infusion. After this, there will be follow-up through linkage to the National Cancer Registry in the U.K. Interim data included in PBRER

Study / activity type, title and category (1-4)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
				1053866 (Jan 2014 submission) and PBRER 1058003 (Jan 2015 submission) Five-year report expected Q4 2014
Anti Rheumatic Therapy in Sweden (ARTIS) (non-interventional PASS, 4)	Postmarketing surveillance on presently available biologics used in treating patients with rheumatic disease	Infections including serious infections; opportunistic infections; malignant events; cardiac events (impact on cardiovascular disease); gastrointestinal perforation; use in pregnancy.	Study ongoing	Final five-year report data included in PBRER 1053866 (January 2014 submission) Further extended for 3 years with an option to further extend: 6-monthly reports will be received.
A prospective cohort German Biologics Registry known as RABBIT [rheumatoid arthritis-observation of biologic therapy] (non-interventional observational PASS, 4)	Evaluate long term effectiveness of treatment with biological agents with regard to treatment continuation and clinical outcomes, and to study the long term safety of treatment with biologic therapy in RA	Infections including serious infections; opportunistic infections; malignant events; cardiac events (impact on cardiovascular disease); gastrointestinal perforation; use in pregnancy.	Study ongoing	Planned submission of final data: Q4 2015 6-monthly reports will be received. Interim data included in PBRER 1053866 (Jan 2014 submission) and PBRER 1058003 (Jan 2015 submission)
Study, WA27893 (RAVeR) A multi-centre (US-based), prospective, study	To characterize the long-term safety of rituximab in the treatment of GPA/MPA and to collect data on the	Infusion related reactions including acute; infections including	Study ongoing	April 2018

Study / activity type, title and category (1-4)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
designed to follow 100 rituximab-treated patients with GPA or MPA for a maximum of 4 years (non-interventional observational PASS, 4)	safety of re-treatment with rituximab in patients with GPA/ MPA.	serious; Hepatitis B reactivation; opportunistic infections; malignant events; impact on cardiovascular disease; gastrointestinal perforation; relapses; use in pregnancy and lactation; immunogenicity and autoimmune disease; long term use in GPA/MPA patients.		
Study GRAID II, cohort study, German Registry (non-interventional observational PASS, 4)	Collect data on the safety of treatment with rituximab in autoimmune patients	Hepatitis B reactivation; malignant events; impact on cardiovascular disease; gastrointestinal perforation; long term use in GPA/MPA patients.	Ongoing	Within 12 months of end of study, anticipated to be 2015 Interim data included in PBRER 1053866 (Jan 2014 submission) and PBRER 1058003 (Jan 2015 submission)
Addenbrooke's Vasculitis and Lupus Clinic, Cambridge University Hospital, U.K. (non-interventional, 4)	Determine the long-term safety of rituximab for the treatment of GPA/MPA.	Long term use in GPA/MPA patients	Study planned	Planned study start in Q1 2015. Protocol and submission timelines under discussion with Investigator Yearly reporting of new data. Extensive interim

Study / activity type, title and category (1-4)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
				report 3 years after study start.

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

Risk minimisation measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
~~Acute~~ Infusion Related Reactions (All Indication)	MabThera is associated with infusion reactions, which may be related to release of cytokines and/or other chemical mediators. Premedication with intravenous glucocorticoid significantly reduced the incidence and severity of these events. **RA:** Section 4.4 of the EU SmPC states: In rheumatoid arthritis premedication with glucocorticoids should also be administered before each infusion of MabThera in order to reduce the frequency and severity of IRRs. **GPA / MPA:** Section 4.1 of the EU SmPC states: ~~For WC~~ In GPA and MPA patients, glucocorticoids are given in combination with rituximab as part of the specified indication.	For RA and GPA/MPA only: Education for healthcare professionals.
Infections (Including Serious Infections) (All Indications)	Section 4.4 of the EU SmPC states: Serious infections, including fatalities, can occur during therapy with MabThera. MabThera should not be administered to patients with an active, severe infection (e.g., tuberculosis, sepsis and opportunistic infections) or severely immunocompromised patients (e.g., in hypogammaglobulinemia or where levels of CD4 or CD8 are very low). Physicians should exercise caution when considering the use of MabThera in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection. Patients reporting signs and symptoms of infection following MabThera therapy should be promptly evaluated and treated appropriately.	Provision of a Patient Alert Card (PAC) was initially for rheumatoid arthritis patients, however following the extension of indication to GPA and MPA in April 2013, the PACs have been implemented for both RA, and GPA and MPA indications, by replacing the indication term with “non-oncology indications”. The PAC is supported by educational material developed for patients and healthcare professionals. The text of the PAC constitutes an appendix to the SmPC.

	Before giving a subsequent course of MabThera treatment, patients should be re-evaluated for any potential risk for infections.	~~Additional: Patient alert card was implemented and educational material is provided above.~~
Impaired Immune Response (All Indications)	Section 4.4 of the EU SmPC states: Physicians should review the patient's vaccination status and follow current immunization guidelines prior to MabThera therapy. Vaccination should be completed at least 4 weeks prior to first administration of MabThera. The safety of immunization with live viral vaccines following MabThera therapy has not been studied. Therefore vaccination with live virus vaccines is not recommended whilst on MabThera or whilst peripherally B cell depleted.	None.
Progressive Multifocal Leukoencephalopathy (All Indications)	Section 4.4 of the EU SmPC states: Use of MabThera maybe associated with an increased risk of Progressive Multifocal Leukoencephalopathy (PML). Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded.	Provision of a Patient Alert Card (PAC) was initially for rheumatoid arthritis patients, however following the extension of indication to GPA and MPA in April 2013, the PACs have been implemented for both RA, and GPA and MPA indications, by replacing the indication term with "non-oncology indications". The PAC is supported by educational material developed for patients and healthcare professionals. The text of the PAC constitutes an appendix to the SmPC. ~~Additional: Patient alert card was implemented and educational material is provided above.~~
Neutropenia (Including Prolonged) (All Indications)	Section 4.4 of the EU SmPC states: **RA and GPA/MPA** Physicians to measure blood neutrophils prior to each course of MabThera, and regularly up to 6-months after cessation of treatment, and upon signs or symptoms of infection **NHL and CLL** Regular full blood counts, including neutrophil and platelet counts, should be performed during MabThera therapy. ~~Section 4.8 of the EU SmPC states: In clinical trials with MabThera monotherapy given for 4 weeks, haematological abnormalities occurred in a minority of patients and were usually mild and~~	None.

	~~reversible. Severe (grade 3/4) neutropenia was reported in 4.2 %, anaemia in 1.1 % and thrombocytopenia in 1.7 % of the patients.~~	
Hepatitis B Reactivation (All Indications)	Section 4.4 of the EU SmPC states: Hepatitis B virus (HBV) screening, ~~including HBsAg-status, HBsAb-status and HBcAb-status~~, should be performed in all patients before initiation of treatment with MabThera ~~as per institutional guidelines~~. At minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guideline. Patients with active hepatitis B disease should not be treated with MabThera. Patients with positive hepatitis B serology (either HBsAg or HBcAb) should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.	None.
Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis (All Indications)	Section 4.4 of the EU SmPC states: Severe skin reactions such as Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome, some with fatal outcome, have been reported. In case of such an event, treatment should be permanently discontinued.	None.
Hypogammaglobulinemia (RA and GPA/MPA)	Section 4.4 of the EU SmPC states: Physicians should exercise caution when considering the use of MabThera in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection, e.g., hypogammaglobulinaemia. It is recommended that immunoglobulin levels are determined prior to initiating treatment with MabThera. **RA** Section 4.8 of the EU SmPC states: Hypogammaglobulinaemia (IgG or IgM below the lower limit of normal) has been observed in RA patients treated with MabThera. There was no increased rate in overall infections or serious infections after the development of low IgG or IgM. A small number of spontaneous and literature cases of hypogammaglobulinaemia have been observed in paediatric patients treated with MabThera, in some cases severe and requiring long-term immunoglobulin substitution therapy.	None.

	The consequences of long term B cell depletion in paediatric patients are unknown. ~~Hypogammaglobulinaemia has been observed in pediatric patients treated with MabThera/Rituxan, in some cases severe and requiring long-term immunoglobulin substitution therapy. The consequences of long-term B-cell depletion in pediatric patients are unknown.~~ **GPA/MPA** Section 4.8 of the EU SmPC states: Hypogammaglobulinaemia (IgA, IgG or IgM below the lower limit of normal) has been observed in GPA/MPA patients treated with MabThera. There was no increased rate in overall infections or serious infections in patients with low IgA, IgG or IgM.	
Tumor Lysis Syndrome (NHL/CLL)	Section 4.4 of the EU SmPC states: Patients with a high tumour burden or with a high number (≥25 x 109/l) of circulating malignant cells such as patients with CLL, who may be at higher risk of especially severe cytokine release syndrome, should only be treated with extreme caution. These patients should be very closely monitored throughout the first infusion. Consideration should be given to the use of a reduced infusion rate for the first infusion in these patients or a split dosing over two days during the first cycle and any subsequent cycles if the lymphocyte count is still >25 x 10^9/L. *Severe cytokine release syndrome* is characterised by severe dyspnea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. This syndrome may be associated with some features *of tumour lysis syndrome* such as hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphaetemia, acute renal failure, elevated Lactate dehydrogenase (LDH) and may be associated with acute respiratory failure and death. The acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest x-ray. The syndrome frequently manifests itself within one or two hours of initiating the first infusion. Patients with a history of pulmonary insufficiency	None.

	or those with pulmonary tumour infiltration may be at greater risk of poor outcome and should be treated with increased caution. Patients who develop severe cytokine release syndrome should have their infusion interrupted immediately (see section 4.2) and should receive aggressive symptomatic treatment. Since initial improvement of clinical symptoms may be followed by deterioration, these patients should be closely monitored until tumour lysis syndrome and pulmonary infiltration have been resolved or ruled out.	
Serious Viral Infections (NHL/CLL)	Section 4.4 of the EU SmPC states: Serious infections, including fatalities, can occur during therapy with MabThera. MabThera should not be administered to patients with an active, severe infection (e.g., tuberculosis, sepsis and opportunistic infections) or severely immunocompromised patients (e.g., in hypogammaglobulinemia or where levels of CD4 or CD8 are very low). Physicians should exercise caution when considering the use of MabThera in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection. Patients reporting signs and symptoms of infection following MabThera therapy should be promptly evaluated and treated appropriately. Before giving a subsequent course of MabThera treatment, patients should be re-evaluated for any potential risk for infections.	None.
Gastrointestinal Perforation (NHL/CLL)	Section 4.8 of the EU SmPC states: Gastrointestinal perforation in some cases leading to death has been observed in patients receiving MabThera for treatment of non Hodkgin lymphoma. In the majority of these cases, MabThera was administered with chemotherapy.	None.
Local cutaneous reactions (NHL/CLL SC formulations)	Section 4.4 of the EU SmPC states: Local cutaneous reactions were very common in patients receiving MabThera subcutaneous in clinical trials. Symptoms included pain, swelling, induration, haemorrhage, erythema, pruritus and rash. Some local cutaneous reactions occurred more than 24 hours after the MabThera subcutaneous administration. The majority of local cutaneous reactions seen following administration of MabThera subcutaneous formulation was mild or moderate and resolved without any specific treatment.	None.

Posterior Reversible Encephalopathy Syndrome (All Indications)	Section 4.4 of the SmPC states: Cases of posterior reversible encephalopathy syndrome (PRES) / reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms include visual disturbance, headache, seizures and altered mental status, with or without associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The reported cases had recognized risk factors for PRES/RPLS, including the patients underlying disease, hypertension, immunosuppressive therapy and/or chemotherapy.	None.
~~De Novo hepatitis B (RA and GPA/MPA)~~	~~Section 4.4 of the EU SmPC states: Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with MabThera. At minimum this should include HBsAgstatus and HBcAb status. These can be complemented with other appropriate markers as per local guidelines. Patients with active hepatitis B disease should not be treated with MabThera. Patients with positive hepatitis B serology (either HBsAg or HBcAb) should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.~~	~~None.~~
Opportunistic Infections (All Indications)	Section 4.4 of the EU SmPC states: Serious infections, including fatalities, can occur during therapy with MabThera. MabThera should not be administered to patients with an active, severe infection (e.g., tuberculosis, sepsis and opportunistic infections) or severely immunocompromised patients (e.g., in hypogammaglobulinemia or where levels of CD4 or CD8 are very low). Physicians should exercise caution when considering the use of MabThera in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection. Patients reporting signs and symptoms of infection following MabThera therapy should be promptly evaluated and treated appropriately. Before giving a subsequent course of MabThera treatment, patients should be re-evaluated for any potential risk for infections.	None.
Prolonged B-cell Depletion (All Indications)	Section ~~4.8~~ 5.1 of the EU SmPC states: ~~In the clinical trial evaluating MabThera maintenance treatment, median IgG levels~~	None.

	~~were below the lower limit of normal (LLN) (< 7 g/L) after induction treatment in both the observation and the MabThera groups. In the observation group, the median IgG level subsequently increased to above the LLN, but remained constant in the MabThera group. The proportion of patients with IgG levels below the LLN was about 60 % in the MabThera group throughout the 2 year treatment period, while it decreased in the observation group (36 % after 2 years).~~ In patients treated for haematological malignancies, B cell recovery began within 6 months of treatment and generally returned to normal levels within 12 months after completion of therapy, although in some patients this may take longer (up to a median recovery time of 23 months post-induction therapy). In rheumatoid arthritis patients, immediate depletion of B cells in the peripheral blood was observed following two infusions of 1000 mg MabThera separated by a 14 day interval. Peripheral blood B cell counts begin to increase from week 24 and evidence for repopulation is observed in the majority of patients by week 40, whether MabThera was administered as monotherapy or in combination with methotrexate. A small proportion of patients had prolonged peripheral B cell depletion lasting 2 years or more after their last dose of MabThera. In patients with granulomatosis with polyangiitis or microscopic polyangiitis, the number of peripheral blood B cells decreased to <10 cells/µL after two weekly infusions of rituximab 375 mg/m^2, and remained at that level in most patients up to the 6 month timepoint. The majority of patients (81%) showed signs of B cell return, with counts >10 cells/µL by month 12, increasing to 87% of patients by month 18.	
Off label Use in Pediatric Patients (All Indications)	Section 4.2 of the EU SmPC states: The safety and efficacy of MabThera in children below 18 years has not been established. No data are available.	The MAH does not consider that additional risk minimization measures are required for off label use in pediatric patients as the wording in the label was recently strengthened for this topic.
Malignant Events (RA and GPA/MPA)	Section 4.4 of the EU SmPC states: Immunomodulatory drugs may increase the risk of malignancy. On the basis of limited experience with MabThera in rheumatoid arthritis patients (a	None.

	possible risk for the development of solid tumours cannot be excluded at this time, although present data do not seem to suggest any increased risk.	
Impact on Cardiovascular Disease (RA and GPA/MPA)	Section 4.4 of the EU SmPC states: There are no data on the safety of MabThera in patients with moderate heart failure (NYHA class III) or severe, uncontrolled cardiovascular disease. In patients treated with MabThera, the occurrence of pre-existing ischemic cardiac conditions becoming symptomatic, such as angina pectoris, has been observed, as well as atrial fibrillation and flutter. Therefore, in patients with a known cardiac history, the risk of cardiovascular complications resulting from infusion reactions should be considered before treatment with MabThera and patients closely monitored during administration. Since hypotension may occur during MabThera infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to the MabThera infusion.	None.
Gastrointestinal Perforation (RA and GPA/MPA)	~~Section 4.8 of the EU SmPC states:~~ ~~Gastrointestinal perforation in some cases leading to death has been observed in patients receiving MabThera for treatment of non Hodkgin lymphoma. In the majority of these cases, MabThera was administered with chemotherapy.~~ The GI perforation has been included in the EU-RMP as a theoretical risk based on the Oncology identified risk, and the concomitant use of NSAIDs or corticosteroids by RA patients. The risk in Oncology has been described as related to TLS, and would therefore not apply to RA or GPA/MPA patients. Nonetheless, the data in RA and GPA/MPA are being collected from registries (for serious events) as well as via standard pharmacovigilance.	None.
Off label Use in Autoimmune Disease (RA and GPA/MPA)	*Note that the efficacy and safety of MabThera intravenous treatment of autoimmune diseases other than for rheumatoid arthritis and GPA/MPA has not been established.* The MAH believes that the best place to advice prescribers of the risks associated with the use of rituximab is in the label. Therefore, ~~it is proposed to ensure that label~~ wording in the label is maintained to reflect appropriate information related to off-label use.	None.

Relapses (GPA/MPA)	Section 5.1 of the EU SmPC states: *Retreatment with MabThera* Based upon investigator judgment, 15 patients received a second course of MabThera therapy for treatment of relapse of disease activity which occurred between 6 and 18 months after the first course of MabThera. The limited data from the present study preclude any conclusions regarding the efficacy of subsequent courses of MabThera in patients with GPA/MPA. Continued immunosuppressive therapy may be especially appropriate in patients at risk for relapses (i.e., with history of earlier relapses and Granulomatosis with polyangiitis, or patients with reconstitution of B-lymphocytes in addition to PR3-ANCA at monitoring). When remission with MabThera has been achieved, continued immunosuppressive therapy may be considered to prevent relapse. The efficacy and safety of MabThera in maintenance therapy has not been established.	None.
Acute Myeloid Leukaemia/ Myelodysplastic Syndrome (NHL/CLL)	None. ~~Section 4.4 of the EU SmPC states: immunomodulatory drugs may increase the risk of malignancy.~~	None.
Second Malignancies (NHL/CLL)	None. ~~Section 4.4 of the EU SmPC states: immunomodulatory drugs may increase the risk of malignancy.~~	None.
Increased risk of Grade 3/4 and serious blood and lymphatic system adverse events in >70 year patients (~~NHL/~~CLL)	Section 4.8 of the EU SmPC states: *Patient subpopulations - MabThera combination therapy* Elderly patients (≥65 years) The incidence of grade 3/4 blood and lymphatic adverse events was higher in elderly patients compared to younger patients (<65 years), with previously untreated or relapsed/ refractory CLL.	None.
Embryofetal toxicity resulting from systemic exposure to rHuPH20 (NHL/CLL SC formulations)	Section 4.6 of the EU SmPC states: Due to the long retention time of rituximab in B cell depleted patients, women of childbearing potential must employ effective contraceptive methods during and for 12 months after treatment with MabThera. Section 5.3 of the EU SmPC states: Specific studies to determine the effects of rituximab or rHuPH20 on fertility have not been performed. In general toxicity studies in cynomolgus monkeys	None.

	no deleterious effects on reproductive organs in males or females were observed. Additionally, no effects on semen quality were shown for rHuPH20. In embryofetal developmental studies in mice, rHuPH20 caused reduced fetal weight and loss of implantations at systemic exposures sufficiently in excess of human therapeutic exposure. There is no evidence of dysmorphogenesis (i.e. teratogenesis) resulting from systemic exposure to rHuPH20. ~~Labels for ritiximab IV and SC advise contraception for all patients receiving rituximab, and all those receiving treatment with chemotherapy agents or methotrexate.~~ ~~Label for rituximab SC recommend that patients who conceive whilst treated with rituximab SC should discontinue treatment with the SC formulation. Change to the IV formulation should only be considered if the possible benefit of continued treatment with rituximab outweighs the potential risk to the developing foetus.~~ ~~Differentiation of IV and SC package material.~~	
Off-label use of the subcutaneous formulation (NHL/CLL SC formulations)	Section 4.4 of the EU SmPC states: The use of MabThera subcutaneous formulation as monotherapy in patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy cannot be recommended as the safety of the once weekly subcutaneous administration has not been established. The information provided in the Section 4.4 pertains to the use of MabThera subcutaneous formulation in the approved indications "Treatment of non Hodgkin lymphoma (strength 1400 mg) ~~only~~ and Treatment of Chronic Lymphocytic Leukemia (strength 1600 mg)". ~~For information related to the other indications, please refer to the SmPC of MabThera IV formulation.~~	Educational material for healthcare professionals.
Administration route error (NHL/CLL SC formulations)	Section 4.2 of the EU SmPC states: It is important to check the medicinal product labels to ensure that the appropriate formulation (intravenous or subcutaneous formulation) is being given to the patient, as prescribed. MabThera subcutaneous formulation is not	Educational material for healthcare professionals.

	intended for intravenous administration and should be given via subcutaneous injection only.	
Use in Pregnancy and Lactation (All Indications)	Section 4.4 of the EU SmPC states: IgG immunoglobulins are known to cross the placental barrier. B cell levels in human neonates following maternal exposure to MabThera have not been studied in clinical trials. There are no adequate and well-controlled data from studies in pregnant women, however transient B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to rituximab during pregnancy. For these reasons MabThera should not be administered to pregnant women unless the possible benefit outweighs the potential risk. Whether rituximab is excreted in human milk is not known. However, because maternal IgG is excreted in human milk, and rituximab was detectable in milk from lactating monkeys, women should not breastfeed while treated with MabThera and for 12 months following MabThera treatment. ~~Due to the long retention time of rituximab in B cell depleted patients, women of childbearing potential should use effective contraceptive methods during treatment and for 12 months following MabThera therapy.~~	None.
Immunogenicity and Autoimmune Disease (RA and GPA/MPA only)	Section 5.1 of the EU SmPC states: The presence of HACA may be associated with worsening of infusion or allergic reactions after the second infusion of subsequent courses. ~~EU SmPC section 4.8 states: Worsening of infusion or allergic reactions and failure to B cell deplete following rituximab cannot be excluded in HACA positive patients after repeated exposure to rituximab on the basis of available data.~~	None.
Long Term Use in GPA/MPA Patients (GPA/MPA)	Section 5.1 of the EU SmPC states: ~~Continued immunosuppressive therapy may be especially appropriate in patients at risk for relapses (i.e. with history of earlier relapses and Granulomatosis with polyangiitis, or patients with reconstitution of B-lymphocytes in addition to PR3- ANCA at monitoring). When remission with MabThera has been achieved, continued immunosuppressive therapy may be considered to prevent relapse.~~ The efficacy and safety of MabThera in maintenance therapy has not	None.

	been established."	
Immunogenicity associated with the subcutaneous formulation (NHL/CLL SC formulations)	The product label describes the incidence of HACA and anti-rHuPH20 antibody formation in patients receiving rituximab subcutaneous in clinical trials.	None.
Effect of greater exposure in patients with low BSA after fixed-dose SC administration (NHL/CLL SC formulations)	None.	None.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The SAWYER study has provided evidence that administration of rituximab SC is non-inferior with regard to Ctrough when compared to rituximab IV. Thus, efficacy and safety seem to be comparable and the benefit of rituximab SC for CLL is mainly driven by a more convenient route of administration.

Uncertainty in the knowledge about the beneficial effects

Administration of rituximab IV is usually preceded by administration of antipyrexic and/or antihistaminergic drugs as pre-treatment and this has been applied in the SAWYER study. It was considered of interest to clarify whether more/equal/less pre-treatment is necessary when changing routes of administration from IV to SC. The role of pre-treatment with antipyrexic and/or antihistaminergic drugs in relation to rituximab SC administration do not raise any further objections.

Risks

Unfavourable effects

In addition, rituximab SC has a safety profile which is acceptable when compared to rituximab IV. The SAWYER study has demonstrated that administration of rituximab SC carries with it a higher risk of cutaneous AEs than does IV administration. Indeed, AEs related to the SOCs of *skin and subcutaneous tissue disorders* and *musculoskeletal and connective tissue disorders* were more prominent in the SC cohort as were injection site erythema and injection site pain. However, these AEs were generally of low Grade severity.

Uncertainty in the knowledge about the unfavourable effects

Long term safety data are lacking and will be provided by the submission of clinical study reports from ongoing trials (see Annex II). Final CSR from BO25341 will include reports on long term safety in relation to BSA (as measure for exposure variation) and to gender.

An improvement of the rHuPH20 activity assay, to reduce the assay variability, is on-going and this is highly recommended. Preliminary validation data do support that the improved assay will have a lower variability compared to the currently used version of the assay.

Administration route error associated with the SC formulation is considered a potential risk (see RMP) which can be managed with sufficient differentiation of the outer carton (addition of the indication, a peel off sticker, colour coded cartons, etc.). Also, the educational material reflects these two packages and informs adequately about the different indications.

Benefit-risk balance

Importance of favourable and unfavourable effects

The SAWYER study has provided evidence that administration of rituximab SC is non-inferior with regard to Ctrough when compared to rituximab IV. In addition, rituximab SC has a safety profile which is acceptable when compared to rituximab IV. Thus, efficacy and safety seem to be comparable and the benefit of rituximab SC for CLL is mainly driven by a more convenient route of administration.

It is considered adequately shown that the favourable effects generally outweigh the unfavourable effects of MabThera 1600 mg SC for CLL.

Benefit-risk balance

The Benefit/Risk of MabThera 1600 mg solution for subcutaneous formulation injection in the treatment of adult patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia in combination with chemotherapy is considered positive.

Discussion on the benefit-risk balance

Rituximab is currently approved in an IV administration for the treatment of CLL. However, IV administrations of rituximab are given as infusions over several hours. The possibility of administering rituximab by the SC route would provide for a more convenient and less time-consuming administration regimen. This holds the possibility of enhancing the treatment experience for both patients, doctors and nurses and might serve to improve the resource utilization at the treatment facility.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that MabThera is not similar to obinutuzumab, ofatumumab and ibrutinib within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix X.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of MabThera *1600 mg solution for subcutaneous formulation injection in the treatment of adult patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia in combination with chemotherapy* is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.