23 January 2014
EMA/CHMP/71722/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Mabthera

International non-proprietary name: RITUXIMAB

Procedure No. EMEA/H/C/000165/X/0083

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

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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
CHOP	cyclophosphamide, vincristine, doxorubicin, prednisone
CI	confidence interval
CLL	chronic lymphocytic leukemia
CMC	chemistry, manufacturing, and controls
CR	complete response
CRR	complete response rate
Cru	unconfirmed complete response
CSR	clinical study report
Ctrough	trough or minimum serum concentration
CVP	cyclophosphamide, vincristine, prednisone
DLBCL	diffuse large B-cell lymphoma
ECLIA	electrochemiluminescence immunoassay
ELISA	enzyme-linked immunosorbent assay
FC	fludarabine and cyclophosphamide
FL	follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
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
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

Pursuant to Article 19 and Annex I of Commission Regulation (EC) No 1234/2008, Roche Registration Limited submitted to the European Medicines Agency (EMA) on 3 December 2012 an application for an extension of Marketing Authorisation.

The extension of the Marketing Authorisation concerns a new route of administration (subcutaneous injection) associated with a new strength 1400 mg and a new pharmaceutical form: solution for injection.

Roche Registration Ltd is already the MAH for MabThera 100 mg and 500 mg, concentrate for solution for infusion (EU/1/98/067/001-002).

The applicant applied for a part of the indication as approved for already authorised route/ pharmaceutical form / strengths, as follows:

- Non-Hodgkin's lymphoma (NHL)

  MabThera is indicated for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy.

  MabThera maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy.
  MabThera monotherapy is indicated for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy.

  MabThera is indicated 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 application submitted is composed of administrative information, quality data, non-clinical and clinical data based on applicants' own tests and studies.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision EMEA-000308-PIP01-08-M01 on the granting of a (product-specific) waiver and on the granting of a class waiver.

Information relating to orphan market exclusivity

N/A

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 18 December 2008. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

Mabthera has been given a Marketing Authorisation in EU on 2 June 1998.

1.2. Manufacturers

Manufacturers of the active substance

Genentech, Inc.
1000 New Horizons Way
Vacaville, CA 95688
USA

Genentech, Inc.
One Antibody Way
Oceanside, CA 92056
USA

Manufacturer responsible for batch release

Hoffmann - La Roche AG
Emil-Barrell-Strasse 1
D-79639 Grenzach-Wyhlen
Germany

1.3. Steps taken for the assessment of the product

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

Rapporteur: Jens Ersbøll Co-Rapporteur: Pieter de Graeff

- The application was received by the EMA on 3 December 2012.
- The procedure started on 30 January 2013.

- The Rapporteur's first Assessment Report was circulated to all CHMP members on 25 April 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 25 April 2013.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 16 May 2013.
- During the meeting on 30 May 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 30 May 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 September 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 24 October 2013.
- During the CHMP meeting on 21 November 2013, the CHMP agreed on a list of outstanding issues to be addressed by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 16 December 2013.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 9 January 2014.
- The Rapporteurs circulated the final Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 21 January 2014.
- During the meeting on 23 January 2014, 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 to MabThera.

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 1998 and is at present indicated in the treatment of NHL, CLL, and rheumatoid arthritis. The currently marketed formulation of rituximab is concentrate for solution for infusion (available as 100 mg/10 mL or 500 mg/50 mL single-use vials), and once the solution is prepared it is administered as an intravenous (IV) infusion.

The recommended dose of rituximab for adult patients in the approved NHL indications is 375 mg/m^2 body surface area (BSA) per cycle as induction treatment either as monotherapy at weekly dosing intervals for 4 weeks or in combination with chemotherapy at dosing intervals every 3 weeks for up to 8 cycles, and as maintenance treatment at 2- or 3-monthly dosing intervals for 2 years. The recommended dose of rituximab for patients with CLL is 375 mg/m^2 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. To minimize the potential for infusion-related toxicity, it is recommended to premedicate patients with acetaminophen/paracetamol and an antihistamine before each infusion, and to initiate the infusions at a rate of 50 mg/h for the first infusion or 100 mg/h for subsequent infusions. In the absence of infusion-related toxicity, the rate can be increased steadily to a maximum rate of 400 mg/h, but in the case of infusion-related toxicity the infusion should be interrupted or the rate slowed.

Based on these recommendations, the first infusion typically requires 4 – 6 hours and subsequent infusions require 2 – 4 hours. The first infusion is generally administered over a longer duration as a result of the risk of infusion-related toxicities, and some patients require even slower rates for this initial exposure. The second and subsequent infusions at the recommended infusion rate are generally well tolerated.

The MAH hereby applied to introduce a subcutaneous formulation in which rituximab has been concentrated 12-fold to 120 mg/mL with the addition of recombinant human hyaluronidase (rHuPH20) 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.

Premedication consisting of an anti-pyretic and an antihistaminic, e.g. paracetamol and diphenhydramine, should always be given before each administration of MabThera as specified in SmPC section 4.2. Premedication with glucocorticoids should be considered if MabThera is not given in combination with glucocorticoid-containing chemotherapy for treatment of non-Hodgkin's lymphoma.

Administration is by a subcutaneous injection in the abdominal wall over approximately 5 minutes.

The recommended dose of MabThera subcutaneous formulation used for adult patients is a subcutaneous injection at a fixed dose of 1400 mg irrespective of the patient's body surface area.

Before starting MabThera subcutaneous injections, all patients must always receive beforehand, a full dose of MabThera by intravenous infusion, using MabThera intravenous formulation

Combination therapy

The recommended dose of MabThera in combination with chemotherapy for induction treatment of previously untreated or relapsed/ refractory patients with follicular lymphoma is: first cycle with MabThera intravenous formulation 375 mg/m^2 body surface area, followed by subsequent cycles with MabThera subcutaneous formulation injected at a fixed dose of 1400 mg per cycle for up to 8 cycles.

MabThera should be administered on day 1 of each chemotherapy cycle, after administration of the glucocorticoid component of the chemotherapy if applicable.

The posology was proposed as follows:

Maintenance therapy

- Previously untreated follicular lymphoma

The recommended dose of MabThera subcutaneous formulation used as a maintenance treatment for patients with previously untreated follicular lymphoma who have responded to induction treatment is: 1400 mg once every 2 months (starting 2 months after the last dose of induction therapy) until disease progression or for a maximum period of two years.

- Relapsed/refractory follicular lymphoma

The recommended dose of MabThera subcutaneous formulation used as a maintenance treatment for patients with relapsed/refractory follicular lymphoma who have responded to induction treatment is: 1400 mg once every 3 months (starting 3 months after the last dose of induction therapy) until disease progression or for a maximum period of two years.

- Monotherapy: Relapsed/refractory follicular lymphoma

The proposed dose of MabThera monotherapy used as induction treatment for adult patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy is: first cycle with MabThera intravenous formulation 375 mg/m^2 body surface area, followed by subsequent cycles with MabThera subcutaneous formulation injected at a fixed dose of 1400 mg per cycle, once weekly. In total: 4 weeks. For retreatment with MabThera monotherapy for patients who have responded to previous treatment with MabThera monotherapy for relapsed/refractory follicular lymphoma using the subcutaneous formulation, the recommended dose is 1400 mg once weekly for four weeks.

2.2. Quality aspects

2.2.1. Introduction

A new MabThera dosage form for subcutaneous injection has been developed (referred to as MabThera SC) and Roche is seeking approval for it with this Extension Application. The new SC formulation contains rHuPH20, a recombinant human hyaluronidase which enables the subcutaneous injection of large volumes and acts as a permeation enhancer.

The complete composition of MabThera subcutaneous formulation is: 120 mg/mL rituximab in histidine/histidine hydrochloridetrehalose, polysorbate 80, L-methionine and rHuPH20.

This line extension builds on the existing experience with rituximab drug substance. The manufacturing process for rituximab drug substance is, with one exception, identical between the currently approved rituximab IV process and the applied rituximab SC process.

The SC formulation is concentrated to a higher protein content and buffer exchanged with another buffer in the final ultrafiltration/diafiltration step of the process.

Hyaluronidase (rhuPH20) is produced in CHO cells. rhuPH20 is a novel excipient and detailed information on the manufacture and control is presented in the dossier. However, rhuPH20 has been recently reviewed, as a novel excipient in the following procedure; Trastuzumab SC, EMEA/H/C/278/X/60. Trastuzumab SC is also marketed by Roche Registration Ltd. Manufacture and the manufacturing process for rhuPH20 at Avid is similar to the material to be used in Trastuzumab SC and MabThera SC. The Trastuzumab SC procedure received a CD in 2013.

2.2.2. Active Substance

Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody representing a glycosylated immunoglobulin with human IgG1 constant regions and murine light-chain and heavy-chain variable region sequences. The antibody is produced by Chinese hamster ovary (CHO) cell suspension culture and purified by affinity chromatography and ion exchange, including specific viral inactivation and removal procedures.

Manufacture

Manufacturers of the active substance

The facility used for the cGMP manufacture and testing of Rituximab SC Drug Substance is listed below. The manufacturing site responsible for the rituximab SC manufacture (Vacaville) is already responsible for the manufacture of the currently approved rituximab IV.

Genentech, Inc.
1000 New Horizons Way
Vacaville, CA 95688
USA

Genentech, Inc.
One Antibody Way
Oceanside, CA 92056
USA

The fermentation and harvest process of the rituximab SC manufacturing process is identical to the currently approved process for rituximab IV.

The rituximab SC purification process is also identical to the purification process of rituximab IV, except for the final ultrafiltration/diafiltration (UFDF) step which has been modified to achieve a higher Drug Substance concentration (120 mg/mL)

The raw materials that are new to the rituximab SC drug substance process, compared to the currently approved rituximab IV process, are; L-Histidine, L-Histidine Hydrochloride, Monohydrate, L-Methionine, α,α-Trehalose Dihydrate.

The final formulation (except for the addition of rHuPH20) is made on the drug substance level and all the excipients comply with Ph Eur requirements. Certificate of analysis for all excipients in the formulation of drug substance is provided and demonstrates a satisfactorily low bioburden.

Control of critical steps and intermediates in the rituximab SC drug substance manufacturing process is identical with the ones currently approved for Mabthera drug substance. No additional CPPs were identified for the rituximab SC UFDF step compared to the currently approved rituximab IV process. This is acceptable, given that the process step in its nature is unchanged.

The applicant has provided adequate data to demonstrate process validation of the modified steps, i.e. the UFDF step and the changes in DS formulation. In addition, removal of impurities was re-assessed, and satisfactory information has been provided with regard to validation of the efficacy of the UFDF membrane cleaning procedures, UFDF filter leachables, and drug substance re-filtration. A maximum number of three re-filtrations is proposed. Refiltration to remove contaminants such as bioburden outside established limits or foreign matter is not permitted.

The proposed hold times for the UFDF pool and diluted UFDF pool have been validated.

Specification

The proposed specification, the methods and the limits proposed for release of rituximab SC drug substance are partly based on the Rituximab IV process and is overall acceptable. A number of limits are changed due to formulation changes, i.e. colour, clarity, pH, content of polysorbate protein content and bacterial endotoxinsConsidering the highly concentrated protein solution, a separate specification for aggregates was requested and has been introduced.

The same reference standards are used as for analysing rituximab IV.

Stability

The stability data submitted support a 24 months shelf-life when stored at –20°C.

Comparability exercise for Active Substance

The analytical comparability program of rituximab SC drug substance encompasses both the currently licensed release assays as well as extended characterization methods These studies sufficiently demonstrate that rituximab SC have analytical characteristics that are highly comparable to rituximab DS manufactured by the IV process. The level of impurities in rituximab SC DS and rituximab IV DS are essentially comparable or below the detection limitHowever, the residual amount is well below the acceptance level that is based on a safety risk assessment.

2.2.3. Finished Medicinal Product

The complete composition of MabThera subcutaneous formulation is: 120 mg/mL rituximab inL-histidine/histidine hydrochloride, trehalose, polysorbate 80, L-methionine, and rHuPH20. One vial of the final product contains 1400 mg of rituximab in 11.7 ml solution (120 mg/mL)

Pharmaceutical Development

The development of this subcutaneous formulation uses a new technology based on an excipient, recombinant human hyaluronidase (rHuPH20), which acts as permeation enhancer, allowing larger volumes to be comfortably administered via the SC route. While the intravenous infusions typically require 2-4 hours, the subcutaneous formulation injections into the abdominal region will take approximately 5 to 7 minutes to administer. Recombinant rHuPH20 is considered a novel excipient

(conform to a recent trastuzumab application) and the applicant has also provided a full dossier with details of manufacture, characterisation and control, accordingly.

The objective of the formulation development program was to develop a stable high concentrated liquid formulation for the subcutaneous administration of rituximab. A step-wise approach was used for formulation development as it started by a formulation screening study followed by a stability study with selected formulation candidates and a formulation robustness study.

The choice and concentrations of the excipients has been adequately justified by extensive formulation studies.

The overall manufacturing process of the clinical lots is similar to the commercial process; only the formulation process differs in material and size of the compounding vessel and size of the receiving vessel. Batch analysis data of the clinical and commercial batches are provided and show that these materials are comparable.

Data from characterization studies demonstrate that the presence of rHuPH20 in MabThera SC formulation has no impact on rituximab quality.

Adventitious agents

The rituximab IV adventitious agent controls and virus validation studies are also applicable to rituximab SC as the upstream manufacturing process is identical as well as the recovery steps used to purify and formulate rituximab with the exception of the UFDF step (no claimed virus reduction). The provided TSE information is reassuring.

Manufacture of the product

Manufacturer responsible for batch release

Hoffmann - La Roche AG
Emil-Barrell-Strasse 1
D-79639 Grenzach-Wyhlen
Germany

The manufacturing process consists of thawing rituximab SC and hyaluronidase, mixing and sterile filtration and filling. Pooling of thawed rituximab bulks from multiple active substance storage containers is performed into a sterilized mixing/compounding vessel in order to yield the required batch size for the fill process. Subsequently to the transfer in the mixing/compounding vessel, the rituximab bulk solution is homogenized by stirring. The rHuPH20 solution is slowly poured into the compounding vessel to the rituximab bulk solution and mixed further to obtain a homogenized formulated MabThera SC finished product bulk solution.

Following bioburden reduction filtration, the formulated MabThera SC bulk solution is transferred into a steam sterilized receiving/transport vessel. The bioburden reduction filtration is performed with steam sterilized membrane filters. The resulting filtered finished product bulk solution is submitted to the final sterile filtration prior to filling into vials.

The process validation data presented in the dossier suggest that the Mabthera SC drug product manufacturing process is well controlled and consistent.

The need for up to three freeze/thaw cycles of the rituximab SC Drug Substance bulk and the rHuPH20 bulk for manufacturing the final bulk solution has been justified.

Product specification

The proposed specifications and methods are partly based on the Rituximab IV process.. The new methods are described in sufficient detail and adequate system suitability criteria and validation data have been presented. By request a separate specification for aggregates has been introduced and a number of limits has been tightened and are now in line with the batch analysis data of the clinical lots, process capability and analytical method variation.

The same reference material is used in the analytical testing of rituximab SC Drug Substance and MabThera SC Drug Product. This reference material is also used for rituximab IV. For testing of the rHuPH20 activity in MabThera SC Drug Product the same reference standard is used as for the recombinant human hyaluronidase (rHuPH20) analytics.

Stability of the product

The primary packaging consist of a 15 mL colorless USP/Ph. Eur., Type I glass vial, sealed with a butyl rubber stopper laminated with fluoro-resin film, and crimped with an aluminum overseal fitted with a plastic flip-off disk . Satisfactory information has been provided on the primary packaging materials. They are of standard quality, suited for packaging sterile-liquid products and comply with relevant pharmacopeia requirements.

Based on the stability data provided a shelf-life of 30 months when stored at 2-8°C is acceptable for Mabthera SC drug product.

Novel excipient: recombinant human hyaluronidase (rHuPH20)

The rHuPH20 degrades hyaluronan under physiological conditions and acts as a spreading factor *in vivo.* Thus, when combined or co-formulated with certain injectable drugs, rHuPH20 facilitates the absorption and dispersion of these drugs by temporarily clearing a path through the connective tissue in the subcutaneous space.

Recombinant human hyaluronidase is a glycosylated single chain protein with up to 447 amino acids.

Manufacture

Overall, description of the upstream (cell expansion and main fermentation) and downstream process (solvent/detergent, four column purifications, nanofiltration and filling) is given and IPCs stated. The steps, control parameters, test methods used for control, and acceptance criteria are indicated.

Detailed information about inoculum expansion, bioreactor operation and harvesting processes and the respective in-process controls are provided. Description of the single steps of the purification process is given. Respective maximum hold times are defined. Information about buffer volumes, flow rates, in process controls, maximum target mass, and collection mode is sufficient. The acceptance criteria for in-process controls are considered acceptable. Lists for the major equipment used during purification, chemical composition, sterilization method and equipment are provided. All equipment except for the viral inactivation tank and chromatography columns is single use. Each step in the filling, storage, and shipping steps is described adequately, along with in-process controls and tests that are monitored.

The specifications for the raw materials used for the fermentation, purification, and the bulk formulation process are provided. Description of the generation of the host cell line and the cell banking system is in line with the demands of the ICH guidelines Q5B, Q5D and CHMP 3AB1A. Critical parameters were defined based on the ICH Q7A definition of a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within pre-determined criteria (operating range) to ensure that the rHuPH20 meets its specification. The critical controls and the numerical limits are considered acceptable.

The process validation protocol was developed based upon the expectation as defined by the "Guidance for Industry: Process Validation". The rHuPH20 lots were manufactured under Good Manufacturing Practices.

The process was validated at full commercial scale with a five batch campaign. All five consecutive runs met the requirements for conformance with regard to run-to-run process performance and product quality attributes, as defined in the process qualification (PQ) protocol. The data confirmed that the process is robust and in a state of control. Information concerning general properties of the IMP, Manufacturing Process, Process Controls and specifications are in agreement with the demands of the guideline ICH Q6B.

The current manufacturing process of rHuPH20 was developed using an amplified cell line. The generation of the host cell line and the cell banking system is described in satisfactory detail. Comprehensive information on the cloning and establishment of the MCB and WCB has been provided. The MAH has adequately characterised the MCB, WCB and EoP cells for phenotype, genotype and safety. The applicant has also calculated the total number of generation required between MCB and EoP cells and shown that this is within the *in vitro* cell age as calculated in small scale stability studies with extended MCB passaging.

Detailed biophysical and biochemical characterization of seven HUB batches using state-of-the-art methods is provided.

Impurities present in rHuPH20 purified bulk may result from product related impurities, process related impurities or microbiological impurities. Process related impurities are eliminated throughout the manufacturing process to an acceptable low level.

Specification

The specification for hyaluronidase has been suitably justified and is supported by consistent data from multiple lots. The specification contains tests for pharmacopoeial methods as well as specific methods to ensure safety and quality with respect to identity, purity, quantity, potency.

The proposed specification for rHuPH20 is considered adequate to confirm the high quality of the excipient. Validation of analytical procedures used for the release or stability of rHuPH20 was performed in accordance with the principles outlined in ICH Q2 (R1).

Stability

The description of the container closure system for hyaluronidase is considered appropriate.

The stability testing is conducted in line with the recommendations of the ICH Guideline Q5C. These data support the shelf-life at the recommended storage for the rHuPH20 at -80 °C up to 30 months.

Adventitious agents

The parental CHO cell line and the cell banks (MCB, WCB, and EOP) were all generated using synthetic media and there are no materials of animal origin used in the process. In addition, the media used to propagate the cell banks did not contain bovine serum albumin or trypsin. It is noted that the Insulin used is produced on yeast. In its manufacture, bovine materials are used. The supplier provided a declaration that they comply with the TSE requirements in the EU.

Five process steps were identified as virus clearance steps and were scaled-down and evaluated. Results of virus removal studies demonstrated that the additive effect of different steps give good assurance of virus clearance ability.

On the viral distribution, and carryover studies the applicant presented data which demonstrated that for both new and aged resins, that virus distribution and carry over seem consistent. The viral clearance study was used to assess the viral inactivation/removal for selected chromatography steps at highest protein load capacities (worst case). The virus log reduction values (LRVs) were comparable between the maximum compared to the typical load conditions, except the Xenotropic Murine Leukemia Virus (X-MuLV) removal by a column. The MAH states that the inequality of the mass balance data is partially due to inactivation during washes; however, this has not been demonstrated directly. The CHMP recommended conducting additional viral inactivation studies to determine the mechanism of action of X-MuLV inactivation during the respective chromatography used in the manufacture of rHuPH20 to fully validate the inactivation process.

Post-approval change management protocol: Additional manufacturing site for the novel excipient rHuPH20

The initially submitted manufacturer of rHuPH20 does not have the manufacturing capacity to deliver the forecasted amount of rHuPH20 material for the products currently under licensing review on a mid- and long-term basis. In planning for this potential, an additional manufacturer has been developed to provide supply of rHuPH20. rHuPH20 enzyme sourced from both manufacturers has been used in the MabThera SC clinical trials.

The applicant submitted a post-approval change management protol for the addition of the second manufacturer of rHuPH20. This was agreed at the Scientific Advice meeting with DKMA on March 28, 2012.

The applicant has detailed as to how it is assured that the facilities, manufacturing process and operations of second manufacturer are in line with the principles of EU GMP.

The Post-Approval change management protocol contains a description of process change and process controls, description of analytical changes, risk assessment, studies already performed (including comparability assessment), studies to be performed, and submission of upcoming data. Almost all data needed for licensing of the second supplier are provided with this application, the exception being the production of a series of additional consecutive batches to further demonstrate consistency. The full information for these additional consecutive batches will be provided after the data are available. No additional analytical characterisation or stability studies will be performed for the these additional batches from the second manufacturer.

The comparability between the rHuPH20 produced at both manufacturing sites was assessed on full scale development and clinical batches as well as on PQ batches. The design of the comparability studies is considered adequate.

In conclusion, the analytical comparability exercise adequately demonstrates that the quality attributes of rHuPH20 from both manufacturers are highly similar and sufficiently ensure equivalent safety and function of the excipient.

Considering the quality of the data presented and assessed in this report, the approach of the company is considered reasonable. By request specific activity acceptance criteria for the different chromatography steps in the change management protocol were introduced.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Quality Development

Information on development, manufacture and control of the new pharmaceutical form (solution for injection); has been presented in a satisfactory manner.

The manufacturing process is overall, well described. The in-process control (IPC) tests are described and deemed suitable for controlling and monitoring the manufacturing process.

Appropriate general information about the novel excipient rHuPH20 has been provided. The potency assay is adapted from the USP method for activity. The differences between the in-house method and the USP assay are stated and are acceptable.

Based on the submitted information the HCP assay cannot be regarded as fully validated. However, any potential risk from the rHuPH20 is conceivably small due to the small quantities of rHuPH20 in the final Finished Product. Nevertheless, the MAH is recommended to quantitatively validate that the current HCP assay reliably measures CHO proteins present in the rHuPH20. Should this validation reveal that the generic ELISA is not capable of this, a process specific ELISA should be developed.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The changes to the rituximab SC process are clearly outlined. Only change in the rituximab SC process, compared to the currently approved rituximab IV process is the higher concentration of drug substance in the UFDF step.

The change (higher concentration) of the UFDF step has not lead to any changes in the control system, which is considered acceptable.

Comparability of rituximab SC vs currently approved rituximab IV drug substance is addressed

Based on the submitted data, the application for Mabthera SC is recommended for approval based on quality grounds.

Overall, information on manufacture and control of the active substance, finished product and novel excipient (rHuPH20) has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important quality characteristics.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

rHuPH20, first manufacturer

1. It is recommended that the MAH should quantitatively validate that the current HCP assay is capable of detecting the majority of HCP present in the rHuPH20. Should this validation reveal that the generic ELISA is not capable of this, a process specific ELISA should be developed.

Additional manufacture of rHuPH20; second manufacturer

2. It is recommended that the MAH will review the unclarified harvest enzyme activity acceptance criteria of the process after collecting additional data from more commercial batches and reassess the acceptance criteria based on a larger data set.

rHuPH20, both manufacturers

3. It is recommended that the MAH re-evaluate the specific activity limits of the different chromatographic steps of the rHuPH20 manufacturing process at both sites after manufacture of more commercial batches.

2.3. Non-clinical aspects

2.3.1. Introduction

2.3.2. Pharmacology

The non-clinical development program for rHuPH20 has previously been submitted by the MAH as part of the application for a SC formulation of trastuzumab (Herceptin® EMEA/H/C/000278/X/0060), and is submitted and assessed also via this procedure.

In addition to studies performed with rHuPH20 alone, the following studies have been performed in support of the SC extension application for rituxmab:

- Comparative anti-tumour efficacy of IV and SC rituximab formulations (Report no 1049779)
- SC pharmacokinetics of rituximab/rHuPH20 formulation in mice (Report no 1049704), minipigs (1029903) and Cynomolgus monkey (1036353)
- 8-week repeat-dose SC toxicity in Cynomolgus monkeys (Report no 1029890)
- Local tolerance in rabbits following SC administration of a rituximab/rHuPH20 formulation (Report no 1031874)

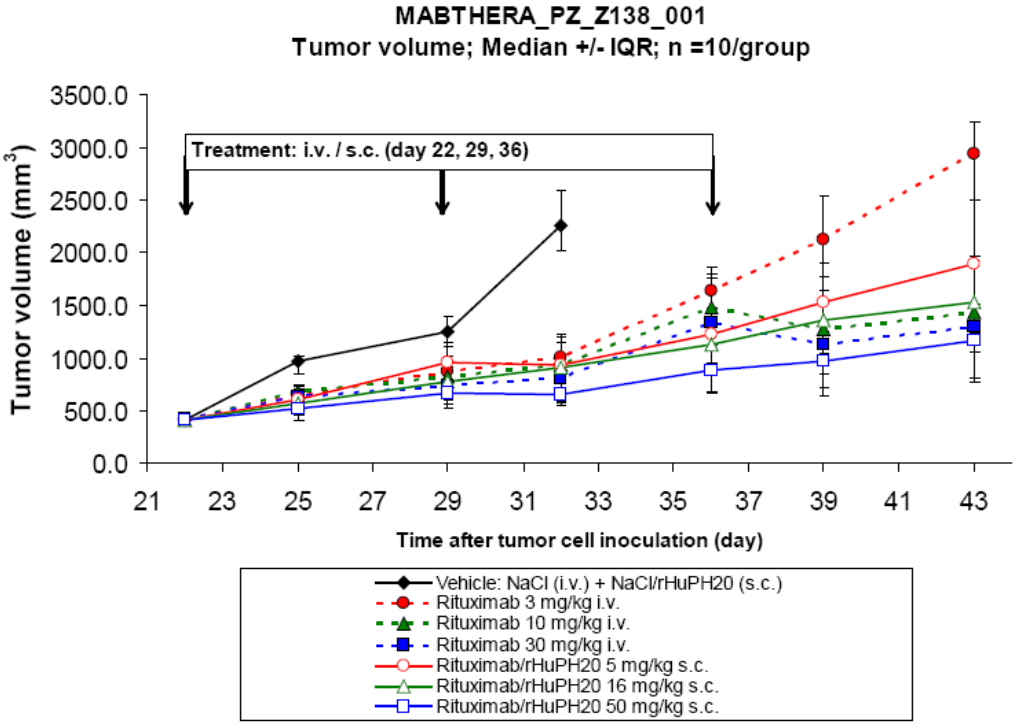
Besides rHuPH20, the excipients in the SC rituximab solution are well-known and included in the Ph. Eur.

The preclinical safety studies for rituximab SC were conducted in accordance with the respective ICH guidances and in accordance with GLP.

Primary pharmacodynamic studies

Anti-tumor efficacy of IV and SC rituximab formulations in the human Z138 NHL (MCL) xenograft SCID mouse model (1049779)

The pharmacodynamic effects of the SC rituximab formulation (containing rHuPH20) was compared to those of rituximab administered IV in a xenograft model implanting Z138 Mantel cell lymphoma cells into female SCID beige mice (n=10/group). Animals were treated with SC and IV doses giving rise to similar rituximab trough levels (5, 16 and 50 mg/kg SC corresponding to 3, 10 and 30 mg/kg IV, respectively) on day 22, 29 and 36 after tumour cell inoculation. The applied SC rituximab formulation contained 4600 U/mL rHuPH20 in 0.9% saline and the injection was performed SC. The treatment effects on tumour growth are shown in the figure below.



No statistically significant differences in anti-tumour efficacy were observed for corresponding IV and SC rituximab dosages. Serum analysis showed that rituximab levels of corresponding IV and SC doses were in the same range showing maximum 2 fold deviation. Still, the rituximab serum trough concentrations were generally slightly higher following SC administration.

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies have been submitted in support of this application.(see discussion on preclinical pharmacology).

Safety pharmacology programme

No safety pharmacology data been submitted in support of this application (see discussion on preclinical pharmacology).

Pharmacodynamic drug interactions

No pharmacodynamic drug interactions studies have been submitted in support of this application (see discussion on preclinical pharmacology).

2.3.3. Pharmacokinetics

Newly submitted studies evaluated the pharmacokinetics of rituximab following IV and/or SC administration in SCID beige mice, Göttingen minipigs and Cynomolgus monkeys.

Both SCID mice and Cynomolgus monkeys have been used in support of the original MAA for the IV formulation of rituximab via inclusion in pharmacodynamic and toxicity studies, respectively. Rituximab shows affinity for Cynomolgus monkey CD20 and depletion of Cynomolgus monkey B cells has been demonstrated following both IV and SC administration of 10 mg/kg rituximab.

An overview of the conducted studies is given in Table 2 below.

Table 2. The pharmacokinetic studies performed in support of the current extension application

Species and strain	Route of administration	Rituximab doses	rHuPH20 doses (IU/mL)	Study no (report no)
Beige SCID mouse	IV	30 mg/kg	-	1049704
	SC	30 mg/kg	6000	
Cynomolgus monkey	SC	20 mg/kg	6000	1036353
Göttingen minipig	IV	10 mg/kg	-	1029903
	SC	14 and 28 mg/kg	2650, 7170	

In the mouse study, 30 mg/kg rituximab with 6000 IU/mL rHuPH20 was administered SC. Furthermore, a Cynomolgus monkey pharmacokinetic study applying SC administration of 20 mg/kg rituximab in a formulation with 6000 IU/mL rHuPH20 was performed. The results are summarized in Table 3 and 4 below.

Table 3. The pharmacokinetic parameters for rituximab following IV and/or SC administration to mice and monkeys

Report no	Species	N	Dose (mg/kg)	Route	C_{max} (µg/mL)	T_{max} (h)	AUC (h*µg/mL)
1049704	Beige SCID mouse	2/time point/d	30	IV	828	-	122,000

Report no	Species	N	Dose (mg/kg)	Route	C_{max} (µg/mL)	T_{max} (h)	AUC (h*µg/mL)
	(female)	ose route		SC	300	2	76,700
1036353	Cynomolgus monkey (male)	3	20	SC	300	24	64,700

Table 4. The pharmacokinetic parameters for rituximab following IV and/or SC administration to mice and monkeys

Report number	Species	N	Dose (mg/kg)	Route	$t_{½, el}$ (h)	Vss (L/kg)	Cl* (mL/min/kg)	F (%)
1049704	Female Beige SCID mouse	2/time point/dose route	30	IV	217	0.0745	0.0041	-
				SC	202	-	0.00652	62.9
1036353	Cynomolgus monkey (male)	3	20	SC	53.0-64.6 (329)**	-	0.00502	-

** CL SC: CL/F, tabulated in mL/min, CL IV: CL*
*** The variability of $t_{½}$ was large, where one animal showed $t_{½}$ of 329 h whereas the remaining two animals were in the range of 53.0-64.6 h*

The pharmacokinetic study in mice showed a relatively high bioavailability of 62.9%. Bioavailability was not evaluated in the Cynomolgus monkey study since no IV arm was included in the study design. However, based on the rituximab serum trough levels obtained in the IV and SC Cynomolgus monkey 8-week toxicity studies, the rituximab bioavailability following SC administration of 20 mg/kg rituximab appeared comparable to if not higher than following IV administration (also 20 mg/kg) (see also Toxicology).

An overview of the pharmacokinetic study conducted in Göttingen minipigs can be found in tables 5 and 6 below. A 120 mg/mL rituximab formulation was administered SC to each animal. In Groups 2 to 4 the dose volume was 1 mL per animal, however, in Group 5 the animals received 2 mL SC. SC rituximab formulations with two different concentrations of rHuPH20 (2650 and 7170 IU/mL according to the certificates of analysis) was tested. The dose regimen resulted in average doses of 10 mg/kg rituximab IV in Group 1 (no rHuPH20 included), and approximately 14 mg/kg rituximab in the SC dosed groups receiving 1 mL/animal (groups 2-4), and 28 mg/kg in the group receiving 2 ml/animal (group 5).

As can be derived from table 5, the C_{max} was increased following administration of 1 mL rituximab formulation containing rHuPH20 (group 3) when compared to the formulation containing no rHuPH20 (group 2), and T_{max} occurred earlier (24 hours compared to 48 hours without rHuPH20), indicating that rHuPH20 indeed did facilitate faster absorption of rituximab. While increasing the excipient concentration from 2650 to 7160 IU/mL did not further increase the systemic rituximab absorption, an doubling of C_{max} and AUC was observed when the injection volume of the rHuPH20 containing rituximab formulation was increased from 1 to 2 mL.

Table 5. Overview of the minipig pharmacokinetic study

Report no Species N	Route	Dose group: mg/kg rituximab	SC dose volume (mL)	rHuPH20 conc (IU/mL)	C_{max} (µg/mL)	T_{max} (h)	AUC (h*µg/mL) 0-672h
1029903 Göttingen minipig 5 females/ group*	IV	1: 10 mg/kg	-	0	203	0.08	33,700
	SC	2: 14 mg/kg	1	0	82.6	48	24,100
	SC	3: 14 mg/kg	1	2650	110	24	32,700
	SC	4: 14 mg/kg	1	7170	110	24	26,300
	SC	5: 28 mg/kg	2	2650	230	36	52,800

**only 3 animals in the IV group as 2 were excluded from the toxicokinetic calculations and 4 animals in group 4 (240 mg rituximab per animal)*

As shown in table 6, Group 2, receiving 14 mg/kg rituximab with 2000 IU/mL rHuPH20 dosed at 1 ml per animal, showed the highest bioavailability (F=70.7± 28.1 %). Doubling of the dose volume, or increasing the rHuPH20 content to 6000 U/mL resulted in bioavailability similar to the rituximab formulation without any rHuPH20 (57-58% and 52.4 % respectively).

Table 6. Summary table showing the pharmacokinetic parameters evaluated in the minipig study in support of the extension application

Report no Species N	Route	Dose group: mg/kg rituximab	SC dose volume (mL)	rHuPH20 conc (IU/mL)	t½, el (h)	Vss (L/kg)mL)	Cl* (mL/min/kg)	F (%)
1029903 Göttingen minipig 5 females/ group*	IV	1: 10 mg/kg	-	0	241	0.0848	0.0044	-
	SC	2: 14 mg/kg	1	0	199	-	0.0924	52.4
	SC	3: 14 mg/kg	1	2000	267	-	0.0516	70.7
	SC	4: 14 mg/kg	1	6000	154	-	0.0854	57.4
	SC	5: 28 mg/kg	2	2000	145	-	0.0771	57.8

** CL SC: CL/F, CL IV: CL*

120 mg/mL rituximab was administered SC as follows: Groups 2-4: 1 mL/animal, Group 5: 2 mL/animal

only 3 animals in the IV group as 2 were excluded from the toxicokinetic calculations and 4 animals in group 4 (240 mg rituximab per animal)

Distribution

No distribution studies have been submitted.

Metabolism

No dedicated studies on the metabolism/catabolism of rituximab SC have been submitted.

Excretion

No dedicated studies on the excretion of rituximab SC have been submitted.

Pharmacokinetic drug interaction studies

No pharmacokinetic drug interaction studies have been submitted with the SC formulation of rituximab.

2.3.4. Toxicology

Single dose toxicity

Single -dose toxicity studies have not been submitted.

Repeat dose toxicity

An 8-week repeat-dose toxicity study was performed with the new SC formulation including the rHuPH20 excipient (2000 IU/mL) to bridge to the previously performed IV studies with rituximab. A dose of 20 mg/kg/week rituximab SC was evaluated and the treatment period was followed by a 13 week recovery period. The following parameters were evaluated during the study; clinical signs (including qualitative food consumption), body weights, ophthalmic findings, ECG findings, blood pressure measurements, immunophenotyping, haematology, clinical chemistry, urine analysis, organ weights, macroscopic necropsy findings, histopathological examinations, anti-drug antibody determination, anti-rHuPH20 antibody analysis and toxicokinetics evaluation. No toxicities were observed, and the SC formulation was well tolerated. At terminal kill, one female in the control group showed acute inflammation at the injection site, whereas 5 animals in the treated group showed slight sub-acute inflammation at the injection site. The study pathologist found these lesions to be within the expected findings of a SC injection study, and did not attribute the findings to be related to the test item. One male in the 20 mg/kg/week group showed markedly elevated GLDH and moderately increased ALT values on Day 52, which correlated to a slightly increased liver weight at necropsy as well as marked hepatocellular necrosis. No infectious agent was observed histologically, but antibodies against hepatitis A were detected in serum from this animal. Therefore it was stated that a relationship to treatment is rather unlikely for this finding.

Table 7. Summary table showing the major findings made in the 8-week SC repeat dose toxicology study performed in Cynomolgus monkeys

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOAEL (mg/kg/day)	Major findings
Report No: 1029890 GLP	Cynomolgus monkey 5 M/F Terminal Kill: 3 M/F Recovery kill: 2M/F	0, 20 mg/kg/week SC	8 weeks treatment 13 week recovery	20 mg/kg/week	20 mg/kg: B-cell depletion (pharmacodynamic effect)

M; male, F; female, SC; SC injection

As in the previously submitted 8-week IV study, no toxicologically significant findings apart from the B-cell depletion were observed following SC administration of rituximab containing rHuPH20.

The Applicant provided a table presenting the serum trough levels from the IV study performed in support of the original MAA, and the values obtained following SC administrations in the present study (see Table 8). The values are similar especially following the first dosing cycle, at which point in time no anti-rituximab antibodies have been formed. From Day 36 and 99 following SC administration of rituximab (males and females respectively) low or no exposure levels of rituximab were observed. This was attributed to an accelerated clearance due to an immune response against rituximab in several monkeys. As AUC values had not been determined in the IV study, no AUC comparison was possible.

Table 8. Comparison of rituximab serum trough levels in the IV and SC 8-week toxicity studies with rituximab in Cynomolgus monkeys following administration of 20 mg/kg/week rituximab (range and (mean) in µg/mL).

	Day 8 (1st dosing cycle)		Day 50 (7th dosing cycle)	
Study	**Male**	**Female**	**Male**	**Female**
IV study	74.6-88.8 (80.9)	75.7-96.2 (87.7)	0-138.6 (84.5)	0-111.2 (64.7)
SC study	111-120 (115)	99.0-120 (106)	<0.5-1.41 (0.282)	<0.5-274 (151)

- **Toxicokinetics**

Table 9. Summary table of the AUC exposures obtained in Cynomolgus monkeys negative for anti-rituximab antibodies included in the 8-week SC repeated dose toxicity study.

Study ID	Weekly Dose Rituximab	Day	Animal AUC (µg.h/ml)	
			♂	♀
1029890	20 mg/kg	1 43	243000 6590*	22700 40200**

* n=1, ** n=4

- **Interspecies comparison**

Table 10. Summary table showing the interspecies comparison of Cynomolgus monkey, rabbit and human

Species	Cynomolgus Monkey	Rabbit	Patients[a]
Treatment duration	8 weeks	Single dose	Maximum of 2 years
Dosing frequency	Once weekly	Single dose	Once every 3 weeks for 8 cycles followed by a maintenance period of once every 2 months or once every 3 months
Dose	20 mg/kg corresponding to 240 mg/m^2	60 mg 20 mg/kg[b] corresponding to 240 mg/m^2	1400 mg 20 mg/kg 736 mg/m^2
Reference	Report No. 1029890	Report No.1031874	Pivotal Study BO22334
Cmax (µg/mL) (mean of males and females)	Day 1: 202 Day 43: 196	ND	Cmax (geometric mean) at Cycle°7 of the induction phase with dosing every 3 weeks: 236.82
$AUC_{(0\text{-}168h)}$ (µg.h/mL) (mean of males and females)	Mean AUC after dosing on Day 43 calculated for a 3 week exposure interval: 100500	ND	AUC (geometric mean) at Cycle°7 of the induction phase with dosing every 3 weeks: 90694
Margin of safety for mg/m^2	0.3[a]	0.3[a]	-
Margin of safety for AUC at steady state over a 3 week interval	1.1	NA	-

[a] *Based on a maximum expected SC dose of 1400 mg rituximab for a 70 kg patient with a body surface area of 1.9 m^2*
[b] *Based on a 3 kg rabbit*
NA – not available, ND- not determined

Genotoxicity

No genotoxicity studies have been submitted (see discussion on non-clinical aspects).

Carcinogenicity

No carcinogenicity studies have been submitted (see discussion on non-clinical aspects).

Reproduction Toxicity

No reproductive and developmental toxicity studies have been submitted (see discussion on non-clinical aspects).

Toxicokinetic data

Local Tolerance

The local tolerance of rituximab SC (containing rHuPH20) was evaluated in a dedicated study in rabbits (Report number 1031874), as well as in the 8 week SC toxicity study performed in Cynomolgus monkeys (Report number 1029890).

In the rabbit local tolerance study, 6 rabbits were either dosed SC with 60 mg rituximab SC formulation (including 2000 IU/mL rHuPH20) per site or vehicle (0.9% NaCl) at a volume of 0.5 mL/site. Three rabbits were killed 24 hours after dosing, and the last 3 rabbits were killed 96 hours after dosing. A histopathological evaluation was performed of the injection sites as well as both axillary and inguinal lymph nodes representing draining and non-draining lymph nodes. No changes attributable to the treatment with the rituximab SC formulation were observed.

In the repeat-dose toxicity study in Cynomolgus monkeys (20 mg/kg/week, 0.167 mL/kg), the SC injection sites were evaluated histopathologically at terminal kill. One female in the control group (vehicle including rHuPH20) showed acute inflammation at the injection site, whereas 5 animals in the treated group showed slight sub-acute inflammation at the injection site. The study pathologist found these lesions to be within the expected findings of a SC injection study, and did not attribute the findings to be related to the test item, and therefore the rituximab SC formulation appeared to be well tolerated in the repeat-dose treatment in the cynomolgus monkey.

Other toxicity studies

Recombinant human hyaluronidase (rHuPH20)

The excipient rHuPH20 is a transiently active, locally-acting permeation enhancing enzyme that allows for the SC delivery of therapeutics that has been delivered IV. The mode of action of the rHuPH20 is to locally depolymerize the substrate, hyaluronan (or hyaluronic acid), at the site of injection in the skin. Hyaluronan is a repeating polymer of N-acetyl glucosamine and glucuronic acid that contributes to the soluble gel-like component of the extracellular matrix of the skin. Depolymerisation of hyaluronan by hyaluronidase is accomplished by hydrolysis of the repeating polysaccharide polymer. This depolymerisation of hyaluronan results 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, e.g., dose volume of 11.7 mL for the clinical dose of the rituximab SC formulation.

The non-clinical development program for rHuPH20 have been submitted previously by the Applicant in the extension application for a SC formulation of Herceptin (EMEA/H/C/000278/X/0060), and the pharmacology and toxicology studies have been assessed in this procedure.

In addition to the studies performed with rHuPH20 alone, the Applicant has also submitted 7 studies in the present application that have been performed with trastuzumab/rHuPH20. These studies are not assessed in the current procedure, as they have been assessed in the previously submitted extension application the SC formulation of Herceptin.

An overview of the non-clinical studies conducted with rHuPH20 alone and in combination with trastuzumab is given in Table 11 and 12 below.

Table 11. Overview of the non-clinical studies performed with rHuPH20 alone

Study type	Report number	Title
Pharmacodynamic	1040359	Dose dependent systemic evaluation of rHuPH20 in a dye dispersion assay in nude mice
	1040360	Dose dependent effects of intradermal rHuPH20 on distal sites of injection in the nude mouse
	1040361	Effects of an anti-rHuPH20 neutralizing antibody on dye dispersion with rHuPH20 enzyme in nude mice

	1040357	rHuPH20 (Lot No. HUB07010EB) in vivo dispersion assay with trypan blue
	1040356	Dermal reconstruction following administration of rHuPH20 (Lot No. HUB07010EB)
	1040355	Dose response of co-mixture delivery of rHuPH20 versus single dose sequential delivery of rHuPH20 in the mouse dye dispersion model
Pharmacokinetic Validation	1047778	Partial validation of a method for the determination of hyaluronidase activity in cynomolgus monkey plasma using spectrophotometric detection
	1047777	Quantitative determination of hyaluronidase activity in mouse plasma using microplate-based method with a biotinylated hyaluronic acid substrate
	107776	Qualitative determination of antibodies to rHuPH20 in cynomolgus monkey K_2EDTA plasma using a bridging ELISA
	107775	Method for determination of neutralizing activity titer against hyaluronidase in cynomolgus monkey plasma
Pharmacokinetic Absorption	1041746	A multi-dose pharmacokinetics study of rHuPH20 administered by IV and SC injection in female cynomolgus monkeys
	1040393	Evaluation of the pharmacokinetics of two Halozyme test articles following a single IV dose in CD-1 mice
	1017117	A 39-week toxicity study of rHuPH20 administered SC in cynomolgus monkeys with a recovery phase
Pharmacokinetic distribution	1040358	Biodistribution of rHuPH20 in the skin, lymphatics, and plasma after intradermal administration in the mouse
Toxicology	1034926	A 7-day repeat dose IV and SC toxicity study of rHuPH20 in cynomolgus monkeys
	1017117	A 39-week toxicity study of rHuPH20 administered SC in cynomolgus monkeys with a recovery phase
	1037039	SC dose-range developmental toxicity study of rHuPH20 in mice
	1034927	SC developmental toxicity study of rHuPH20 in mice
	1034928	SC developmental and perinatal/postnatal reproduction toxicity study of rHuPH20 in mice, including a postnatal behavioural/functional evaluation

Table 12. Summary of the submitted non-clinical studies evaluating rHuPH20 in combination with trastuzumab

Study type	Report number	Title
Pharmacodynamic	1032485	Antitumor activity of a Herceptin IV and Herceptin SC formulation containing rHuPH20 against Calu-2NSCLC xenografts in female Balb/c nude mice
Pharmacokinetic	1029906	SC bioavailability of trastuzumab/rHuPH20 co-formulations in Göttingen minipigs
	1032235	Pharmacokinetics of trastuzumab after IV and SC administration of trastuzumab to BALB/c nu/nu mice
	1031088	Pharmacokinetics of trastuzumab after SC administration of trastuzumab/rHuPH20 to cynomolgus monkey
	1043726	SC bioavailability study of trastuzumab-rHuPH20 formulations in Göttingen minipigs – compartmental pharmacokinetic evaluation
Toxicology	1027259	A 13-week SC injection toxicity and toxicokinetic study in cynomolgus monkeys with a 17-week recovery phase
	1030364	Local tolerance study after single SC administration in the male rabbit

2.3.5. Ecotoxicity / environmental risk assessment

No environmental risk assessment studies have been submitted (see Discussion on non-clinical aspects.

2.3.6. Discussion on non-clinical aspects

As could be expected, a comparative study in a tumour xenograft mouse model showed that there was no significant difference in anti-tumour efficacy of IV and SC administered rituximab when doses giving rise to similar serum trough levels were administered. The pharmacodynamic action of rituximab is adequately characterised and further studies on safety pharmacology are not required.

In general the methods of PK analysis for rituximab and anti-rituximab antibodies are considered to be adequate.

Newly submitted studies evaluated the pharmacokinetics of rituximab following IV and/or SC administration in SCID beige mice, Göttingen minipigs and Cynomolgus monkeys.

Bioavailability following SC administration of 30 mg/kg rituximab with 6000 IU/mL rHuPH20 to SCID mice was 62.9% while the T_{max} and half-life was 2 and 202 hours, respectively.

In Cynomolgus monkeys, T_{max} and half-life occurred at 24 hours and from 53 to 329 hours post-dosing following administration of a SC rituximab (20 mg/kg) formulation containing 6000 IU/mL rHuPH20 (n=3). Bioavailability was not evaluated as part of the study. However, based on the rituximab serum trough levels obtained in the IV and SC Cynomolgus monkey 8-week toxicity studies, the rituximab bioavailability following SC administration of appeared comparable to if not higher than following IV administration of 20 mg/kg rituximab.

The pharmacokinetics of SC rituximab formulations containing 2650 and 7170 IU/mL of the excipient rHuPH20 was evaluated in minipigs. The minipig was chosen for SC formulation testing, as the structure of the subcutis in this species resembles the human more than the other more traditionally used laboratory species like rat, rabbit, dog or monkey (Rose et al 1977).

Addition of rHuPH20 to the SC formulation increased the rituximab C_{max} and T_{max} occurred earlier (24 hours compared to 48 hours without rHuPH20), indicating that rHuPH20 indeed did facilitate faster absorption of rituximab. The rituximab formulation containing 2650 IU/mL rHuPH20 was associated with the highest bioavailability (F=71% while increasing the rHuPH20 content to 7170 IU/mL or doubling the dose volume from 1 to 2 mL resulted in overall bioavailability (57-58%) comparable to the formulation with no rHuPH20 added (54%). However, the validity of this finding was questioned since the clearance and consequently half-life of rituximab was significantly different in the group receiving rituximab in combination with 2650 IU/mL rHuPH20 when compared to the other SC study groups. Moreover, the large inter-individual variation in rituximab bioavailability is noticeable hence the bioavailability ranged from 52 to 98% and from 28 to 93% in minipigs administered rituximab formulations containing 2650 and 7170 IU/mL rHuPH20, respectively (See discussion on clinical aspects). The SC dose volume was limited to 1 to 2 mL per minipig, whereas in the clinical setting a dose volume of 11.7 mL per SC administration of rituximab is to be applied.

No distribution studies have been submitted. The SC delivery of IgG is generally considered to be absorbed via the lymphatic system, before reaching the systemic circulation (Lobo et al, 2004). Once in systemic circulation the IgG undergoes similar distribution relative to that observed following IV administration, and hence rituximab SC is expected to show similar tissue distribution behaviour as rituximab after IV administration. Therefore the lack of any new distribution studies is acceptable.

The lack of any dedicated studies of excretion of rituximab SC is acceptable, as the monoclonal antibody is expected to undergo proteolysis and the resulting amino acids are excreted or recycled.

IgG catabolism is described in the literature; IgGs are to be cleared from the body predominantly via catabolism and that the binding to the neonatal Fc receptor (FcRn) has a key role in maintaining IgG homeostasis by protecting the IgG from catabolism (Lobo et al 2004). As uptake of IgGs from the interstitial space into the lymphatic system and subsequent back transport into blood circulation also occurs following IV administration as part of the normal distribution and re-circulation process of IgGs (Lobo et al, 2004), metabolic processes unique to SC administration of an IgG are considered to be unlikely.

Overall the catabolism processes of rituximab administered SC are expected to be similar to those after IV administration. No dedicated studies on the excretion of rituximab SC have been submitted. IgG antibodies undergo minimal renal or biliary excretion (Lobo et al, 2004) however they are expected to undergo catabolism by proteolysis in the lysosymes. The resulting amino acids and small peptides may subsequently be excreted or added to the endogenous amino acid pool.

The lack of any dedicated PK drug interaction studies is acceptable, as the potential for PK drug interaction is expected to be similar to that of the IV formulation of rituximab, and the use of rituximab administered IV is well established.

The only finding in the 8-week repeat-dose toxicity study of rituximab SC was the expected pharmacodynamic effect, namely B-cell depletion. Hence no new additional toxicities were observed following SC injection of rituximab formulation containing approximately 2000 IU/mL rHuPH20, when compared to the IV administration of rituximab. The dose of 20 mg/kg rituximab IV (performed in support of the original MAA) and SC resulted in comparable trough levels after first dose illustrating the relatively high bioavailability of the SC formulation.

Based on allometric scaling, the obtained margin of safety following 8-week repeat dose treatment of Cynomolgus monkey is only 0.3, however based on obtained AUC_{0-168h} (mean of both sexes) the margin of safety is slightly higher (1.1-fold). Still, the dose level of 20 mg/kg in the animal study is similar to the IV doses applied in the repeat dose study in cynomolgus monkeys submitted for the original MAA, complete and prolonged B-cell depletion was achieved in monkeys demonstrating expected activity in these animals, and the clinical use of rituximab is well established, hence the lack of any significant safety margin is not considered of concern.

Formal scientific advice has been provided by the CHMP on the adequacy of the non-clinical program for rHuPH20 (EMEA/CHMP/SAWP/806036/2009). The proposed abbreviated program (no studies on metabolism, genotoxicity and carcinogenicity) was considered acceptable provided that no untoward findings emerged in the studies. The lack of any genotoxicity evaluation and carcinogenicity studies for rituximab SC is acceptable and in line with the relevant guidance ICH S6 (R1). This information has been reflected in section 5.3 of the SmPC.

The lack of reproductive and developmental studies with the rituximab SC formulation is considered to be justified. It is not expected that rituximab given SC will give rise to any additional reproductive findings not already observed following IV administration, and the excipient rHuPH20 has been studied separately in an embryo-fetal development study as well as a peri- and post-natal development study in mice. Reproductive organs were examined as part of the 8-week repeat-dose SC toxicity study with rituximab SC in Cynomolgus monkey and no adverse findings were noted. In the repeated dose toxicity study (39-week SC) in cynomolgus monkeys studying rHuPH20, no abnormalities were seen in reproductive organs, semen parameters, testosterone or LH levels and menstrual cycling. Due to the low overall doses of rHuPH20 (≤ 0.21 mg/m^2) to be used in patients receiving rituximab SC and the general lack of measurable rHuPH20 systemic exposure in man, the risk for effects on embryonic/fetal development subsequent to rituximab SC dosing is considered to be low.

Therefore it is agreed that additional reproductive toxicity studies will not add significantly to the current knowledge. Relevant information has been included in the SmPC section 5.3 and in section 4.6 it is stated that “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”.
The rituximab SC formulation including rHuPH20 was well tolerated in the rabbit local tolerance study as well as in the 8 week SC repeat-dose toxicity study in Cynomolgus monkey. A slight inflammatory response was observed in the repeat-dose toxicity study, however, the findings were within the range to be expected following SC administration and changes were also seen in the control group.

The non-clinical studies conducted with the excipient rHuPH20 have been assessed previously via the line extension application for Herceptin (EMEA/H/C/000278/X/0060). Administration of rHuPH20 was neither associated with adverse findings in a 39-week SC repeat-dose toxicity study in Cynomolgus monkeys nor in a mice SC pre- and post-natal development study. Increased resorptions, decreased litter size and decreased fetal weight were observed in a SC embryo-fetal development study conducted in mice with a NOAEL of 3 mg/kg/day (9 mg/m^2/day).

No environmental risk assessment studies have been submitted; this is in line with the relevant guideline (EMEA/CHMP/SWP/4447/00).

2.3.7. Conclusion on the non-clinical aspects

The preclinical programme on the subcutaneous formulation of Mabthera is considered satisfactory. Resulting information has been adequately reflected in the SmPC.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

- Tabular overview of clinical studies

Table 1 Overview of the Rituximab SC Clinical Development Program

Study	Title	Rituximab dose and route of administration	Patients enrolled	Study status / Data for submission (Data at cut-off date)
BP22333 (SparkThera)	A two-stage phase Ib study to investigate the PK, safety and tolerability of rituximab SC formulation in patients with FL as part of maintenance treatment.	Stage 1: 375 mg/m^2 IV vs 375, 625, 800 mg/m^2 SC (q2m/q3m, single cycle at maintenance C2 or later). Stage 2: 375 mg/m^2 IV vs 1400 mg SC (q2m/q3m, multiple cycles from maintenance C2 onwards).	Stage 1: N= 124 Stage 2: N= 157	Stage 1 and 2: - primary analysis completed - follow-up ongoing - PK, safety (March 07, 2012) - immunogenicity (March 07, 2012)
BO22334 (SABRINA)	A two-stage phase III, international, multicentre, randomized, controlled, open-label study to investigate the PK, efficacy and safety of rituximab SC in combination with CHOP or CVP versus rituximab IV in combination with CHOP or CVP in patients with previously untreated FL followed by maintenance treatment with	Stage 1 and 2: induction: 375 mg/m^2 IV vs 1400 mg SC (q3w R-CHOP or R-CVP: C1 375 mg/m^2 IV all patients; C2-8 IV vs SC); patients with at least PR at end of induction receive maintenance: 375 mg/m^2 IV vs 1400 mg SC (q2m maintenance with IV or SC as randomized to	Stage 1: N= 127	Stage 1: - induction treatment completed, maintenance ongoing - PK (March 14, 2012) - safety, efficacy, (April 11, 2012) - immunogenicity (April 11, 2012[cleaned data], and additional data available up to June 12, 2012)

	either rituximab SC or rituximab IV.	induction)		
BO25341 (SAWYER)	An adaptive, comparative, randomized, parallel-group, multicentre, phase Ib study of SC rituximab versus IV rituximab both in combination with chemotherapy (fludarabine and cyclophosphamide) in patients with previously untreated CLL.	Part 1: 1400, 1600, 1870 mg SC (single infusion at C6, q4w in combination with FC) Part 2: 500 mg/m^2 IV vs SC dose to be determined (q4w R-FC: C1 375 mg/m^2 IV all patients; C2-6 IV vs SC)	Part 1: N=64	Part 1: - treatment completed, follow-up ongoing - safety, immunogenicity (April 04, 2012)

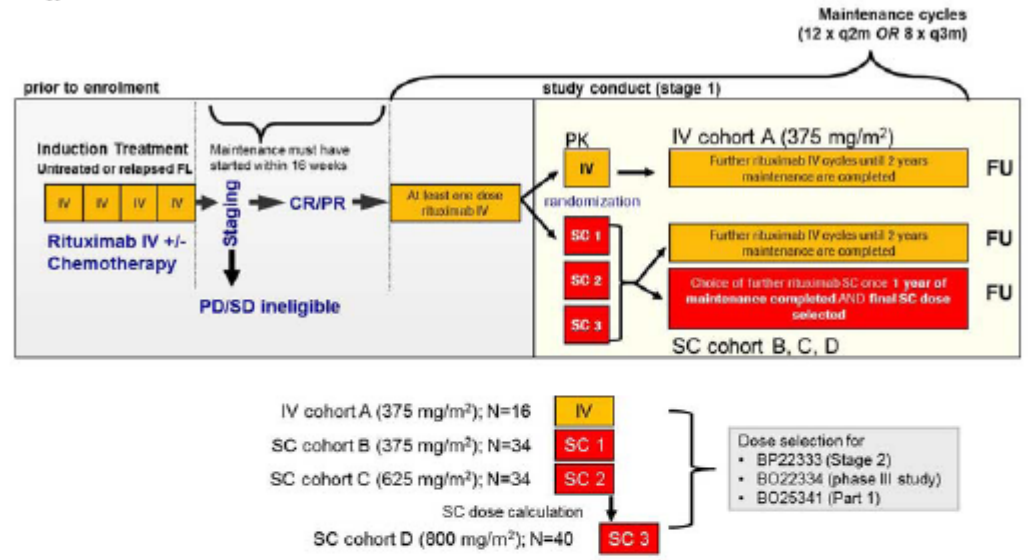
C: cycle; CHOP: cyclophosphamide, vincristine, doxorubicin, and prednisone; CLL: chronic lymphocytic leukemia; CVP: cyclophosphamide, vincristine, and prednisone; FC: fludarabine and cyclophosphamide; IV: intravenous; FL: follicular lymphoma; PK: pharmacokinetics; PR: partial response; q2/3m: every 2 or 3 months; q3/4w: every 3 or 4 weeks; SC: subcutaneous

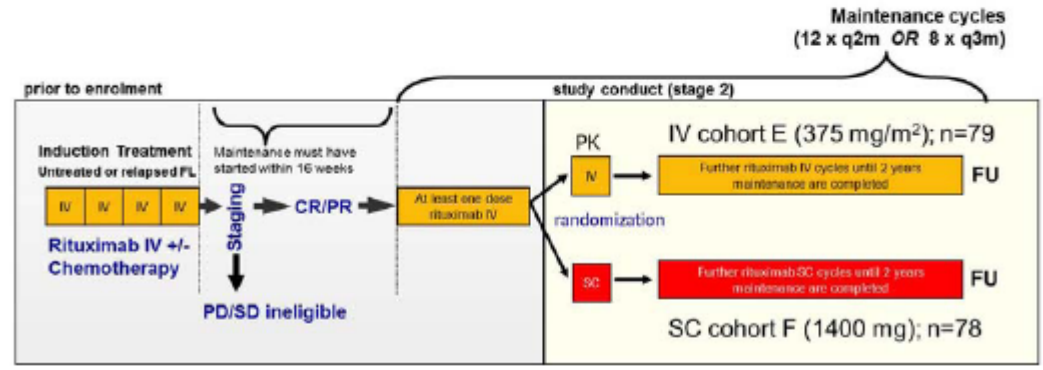
2.4.2. Pharmacokinetics

Clinical pharmacology data to support the registration of rituximab SC (R-SC) in the approved NHL indications are available from two randomized studies:

Study BP22333 (SparkThera):

Figure 1 BP22333: Study Design





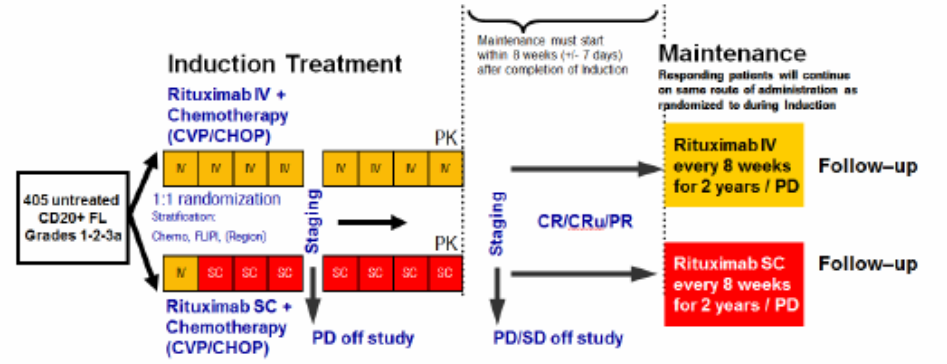
CR=complete response; FL=follicular lymphoma; FU=follow-up; IV=intravenous; PD=progressive disease; PK=pharmacokinetics; PR=partial response; q2/3m=once every two/three months; SC=subcutaneous; SD=stable disease.

A two-stage, randomized, open-label, multicenter adaptive Phase Ib study to investigate the PK, safety, and tolerability of R-SC formulation in patients with FL as part of maintenance treatment. The primary objective of Stage 1 (dose selection) was to determine a R-SC dose that yielded comparable serum trough concentrations (Ctrough) to rituximab IV (R-IV) in the FL maintenance population. The primary objective of Stage 2 (dose confirmation) was to demonstrate comparable Ctrough of R-IV and R-SC (using the SC dose determined in Stage 1), as assessed by a non-inferiority test with a lower boundary above 0.8 for the two-sided 90% confidence interval. The FL maintenance patient population was chosen to determine the R-SC dose and to statistically demonstrate Ctrough comparability because the PK variability among this patient population was expected to be lower in these patients compared with those in the induction setting (as a result of the lower tumor load in responders who are eligible for maintenance). In the dose-selection part, exposure to R-SC was limited to one single administration during the maintenance period to prevent potential underexposure of patients who were currently being maintained in remission on R-IV, and a modeling approach was used to derive information on the R-SC PK characteristics. Once the final

SC dose had been selected in Stage 1, patients randomized to an SC cohort and who had received rituximab IV maintenance treatment for at least 4 cycles for the q3m regimen or 6 cycles for the q2m regimen (i.e., at least 1 year IV maintenance) were given the option to switch to the final selected SC dose for their remaining cycles of maintenance treatment (SC extension phase).

Study BO22334 (SABRINA):

Figure 2 BO22334: Overall Study Design for Stage 1 and Stage 2



A total of 405 patients were to be randomized in the study: approximately 125 patients in Stage 1, and approximately 280 patients in Stage 2.

CHOP = cyclophosphamide, vincristine, doxorubicin, and prednisone; CR = complete response; CRu = unconfirmed complete response; CVP = cyclophosphamide, vincristine, and prednisone; FL = follicular lymphoma; IV = intravenous; PD = progressive disease; PK = pharmacokinetics; PR = partial response; SC = subcutaneous; SD = stable disease.

A two-stage, randomized, controlled, open-label, multicenter Phase III study to investigate the PK, efficacy, and safety of R-SC in combination with cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) or cyclophosphamide, vincristine, prednisolone (CVP) versus R-IV in combination with CHOP or CVP (induction treatment) in patients with previously untreated FL followed by maintenance treatment with either R-SC or R-IV. The primary objective of Stage 1 was to estimate the ratio of Ctrough(SC)/Ctrough(IV) at Cycle 7 of induction treatment, 21 days after administration. The primary analysis for Stage 1 was scheduled when PK data were available from approximately 100 patients who had completed Cycle 7 (induction). At the cut-off date of March 14, 2012, PK data were available from 113 patients (of 127 patients enrolled). Results of the PK analysis were reported together with safety, immunogenicity, and efficacy results from Stage 1.

The study is ongoing: patients in Stage 1 are continuing in the maintenance phase, and enrollment to Stage 2 has been initiated (280 patients planned). Stage 2 aims to provide additional efficacy and safety data of R-SC compared with R-IV, using the R-SC dose established in Stage 1. Dense sampling for PK/PD assessments was carried out during the first cycle in study BP22333. Thereafter sampling was performed pre-dose in the following cycles and during follow-up every 3 months until 9 months after the last dose of maintenance treatment. Assessment of rHuPH20 was also performed in this study from samples taken 4 times on day 1 and 2.

2.4.1. Methods

Analytical methods

Measurement of rituximab concentration and rHuPH20 activity

Rituximab assay

A validated enzyme-linked immunosorbent assay (ELISA) was used to measure rituximab concentrations in serum. The reporting range established during the partial validation performed at Covance was 5.0 – 128 ng/ml and 5.0 – 150 ng/ml at QPS.

rHuPH20 assay

A validated microplate-based colorimetric assay was used to measure rHuPH20 activity in plasma by biotin/ streptavidin methodology.

Detection of Anti-Rituximab and Anti-rHuPH20 Antibodies

Anti-Rituximab Antibody Assays

A validated bridging ELISA was used to detect and confirm the presence of anti-rituximab antibodies in serum. The assay uses a two-tiered approach: 1) a screening assay, which detects anti-rituximab antibodies (screen-positives), and 2) a confirmatory assay, which contains an immunodepletion (competitive binding) step to assess the specificity of initial positive results (confirmed positives).Positivity for anti-rituximab antibodies was assessed by photometric absorbance. The neutralization potential of anti-rituximab antibodies was measured by B-cell depletion, as a direct measurement of drug activity based on its mode of action; this was a more appropriate marker for loss of in vivo activity rather than an in vitro neutralizing antibody assay.

Anti-rHuPH20 Antibody Assay

A validated bridging electrochemiluminescence immunoassay (ECLIA) was used to detect and confirm the presence of anti-rHuPH20 antibodies in plasma.

Neutralizing Anti-rHuPH20 Antibody Assay

A validated United States Pharmacopeia (USP) turbidimetric method was used to detect neutralizing anti-rHuPH20 antibodies in plasma.

Pharmacokinetic data analysis

The Phase Ib Study BP22333 included patients who had responded to induction and had received 1 to 11 cycles of rituximab IV as part of a q2m or q3m maintenance dosing regimen, and PK data were modeled using NONMEM to allow a comparison to be made between rituximab SC and rituximab IV at Cycle 2 maintenance. In the Phase III Study BO22334, observed data were used to determine PK parameters at Cycle 7 of induction in combination with CHOP or CVP chemotherapy. The observed PK data were derived using Phoenix Winnonlin. As a result of these differences, the PK results across studies cannot be directly compared.

In both studies (BP22333 and BO22334), rituximab PK parameters (Ctrough, AUC_T, Cmax) were derived from actual rituximab serum concentrations according to standard non-compartmental

analysis (NCA) methods using Winnonlin Version 6.2 (Pharsight, Mountain View, California, United States). AUCT parameters were derived using the linear trapezoidal method and actual sampling times for all patients. At least three concentration timepoints were used for the calculation of a terminal rate constant. All NCA PK parameters were summarized using descriptive statistics, including arithmetic means, standard deviations, geometric means, coefficients of variation (CV), medians, and ranges. Less than 0.5% of post-dose observations had values below the quantification limit (BQL) . These values were excluded from the analysis as it was not deemed necessary to apply likelihood-based method for handling of the BQL data.

Peripheral blood CD19+ lymphocyte counts (B cells) were summarized for the safety analysis population (SAP) using descriptive statistics (SI units: × 109 cells/L), including mean, standard deviation, median, and range (minimum and maximum values). The normal range was defined as 0.08 – 0.616 × 109 cells/L.

Statistical analysis

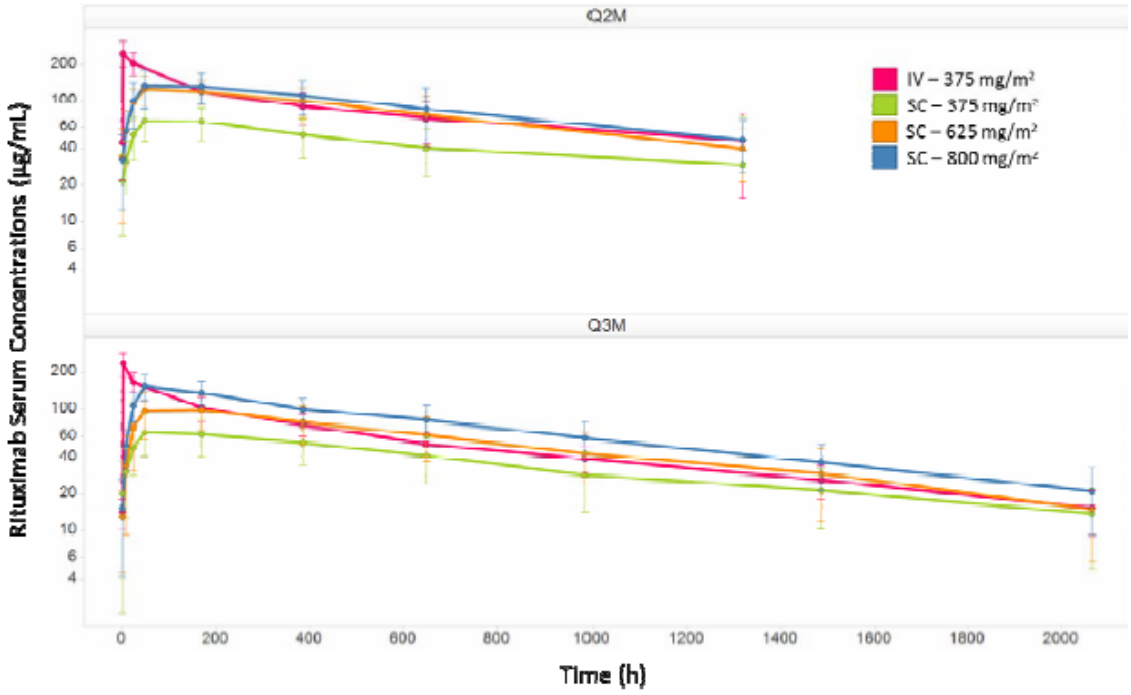
A non-inferiority test was applied to demonstrate comparability of the predicted rituximab Ctrough and AUCT levels for both routes of administration (the lower limit of the 90% double sided confidence interval of the ratio Ctrough SC / Ctrough IV or AUCT SC / AUCT IV is above 0.8) at cycle 7 of induction, cycle 10 (cycle 2 of maintenance treatment) and cycle 18 (the last cycle of the maintenance treatment).

2.4.2. Results

- **Dose selection – study BP22333**

In study BP22333, pharmacokinetics of rituximab was compared in FL patients following administration of 350 mg/m^2 IV, 350 mg/m^2 SC, 625 mg/m^2 SC and 800 mg/m^2 SC in the maintenance phase in order to derive a SC dose that would lead to a comparable mean C_{trough} between rituximab IV and rituximab SC administration. Following SC administration, rituximab concentrations increased slowly and reached the peak at around 3.0 days post-dose. During this phase, SC concentrations were maintained below the IV ones and then reached the same magnitude of exposure at the time of maximal concentrations

Figure **1**.



IV = intravenous; SC = subcutaneous; SD = standard deviation.

Figure 1. Study BP22333 stage 1 dose selection: Rituximab serum concentration (observed Mean (± SD) – time profiles for the q2m and q3m regimens.

The AUCT was clearly lower with rituximab SC 375 mg/ m^2 as compared to IV. The data suggested a dose of between 625 and 800 mg/ m^2 rituximab SC would be required to achieve non-inferiority to rituximab IV with a high variability of Ctrough > 50%. See table 3 for a comparison of mean rituximab serum parameters for each cohort.

Table 2. Study BP22333 stage 1 dose selection: Rituximab serum PK parameters (Mean (%CV)).

Cohort	Dose	Regimen	n	C_{trough} (μg/mL)[a]	t_{max} (h)[b]	C_{max} (μg/mL)	AUC_{τ} (day • μg/mL)
A	IV 375 mg/m^2	q2m	9	46.1 (66.2)	–	243 (24.1)	4730 (31.4)
A	IV 375 mg/m^2	q3m	7	15.3 (41.1)	–	238 (21.4)	4320 (22.1)
B	SC 375 mg/m^2	q2m	17	18.5 (62.5)	48.5 (47.2-192)	70.2 (30.8)	2340 (39.0)
B	SC 375 mg/m^2	q3m	17	13.7 (64.5)	165 (44.8-384)	68.0 (32.9)	2900 (41.1)
C	SC 625 mg/m^2	q2m	18	39.8 (47.0)	48.9 (45.9-48.9)	130 (25.8)	4440 (34.2)
C	SC 625 mg/m^2	q3m	16	14.9 (62.2)	168 (23.1-382)	105 (35.7)	4210 (39.4)
D	SC 800 mg/m^2	q2m	22	47.2 (46.4)	118 (23.9-384)	144 (29.8)	4980[c] (38.4)
D	SC 800 mg/m^2	q3m	18	21.2 (56.1)	48.1 (44.8-383)	156 (21.7)	5690 (27.3)

AUC_{τ} = area under the serum concentration – time curve for dosing interval; C_{max} = maximum serum concentration; C_{trough} = trough or minimum serum concentration; CV = coefficient of variation; IV = intravenous; q2m = once every 2 months; q3m = once every 3 months; SC = subcutaneous; t_{max} = time of maximum serum concentration.

[a] C_{trough} (Cohort A q2m n = 9; Cohort A q3m n = 6 as C_{trough} was missing for Patient 1720; Cohort B q2m n = 16 due to C_{trough} for Patient 1816 taken during infusion so excluded; Cohort B q3m n = 15 as C_{trough} was missing for Patients 1242 and 1420; Cohort C q2m n = 17 as C_{trough} was missing for Patient 1633; Cohort C q3m n = 13 as C_{trough} was missing for Patients 1722, 2740, and 2920; Cohort D q2m n = 21 as C_{trough} was missing for Patient 2290; Cohort D q3m n = 17 as C_{trough} was missing for Patient 1570.

[b] Median (min-max).

[c] n = 21 due to AUC for Patient 2290 not determined.

Source: CSR BP22333, Table 9.

Fixed dose selection

The applicant considered the therapeutic range of rituximab wide enough to select a fixed dose over dosing based on BSA. A modeling approach was used to determine a fixed dose that would result in non-inferior C_{trough}. The structural model combined a two-compartment model with time-varying clearance (see methods pharmacokinetic analysis). Serum C_{trough} and AUCτ values were simulated 100 times by comparing rituximab IV 375 mg/m^2 with various fixed doses of rituximab SC between 1100 and 1400 mg and assuming a BSA distribution of 1.92 m^2 ± 0.24 m^2. The dose selection was performed on C_{trough} concentrations at Cycle 7 of the induction period and at Cycle 2 of the maintenance period. A non-inferiority test was applied to each of the 100 replicates, and the percentage of replicates with a positive non-inferiority test corresponded to the probability of success of the trial. The probability of success, the expected geometric mean C_{trough}SC/C_{trough}IV ratio, the lower and higher bounds of the 90% confidence interval of the geometric mean ratio with their [P5-P95] confidence interval comparing the 375 mg/m^2 IV dose and the 1400 mg dose in the induction and maintenance settings are summarized in table 3.

Simulation showed that a rituximab SC dose of 1400 mg tested in 75 patients would result in ≥ 80% probability of success in both the induction (92%) and maintenance settings (92% and 84% in q2m and q3m, respectively). At this dose for maintenance treatment, the mean expected C_{trough} ratio, the lower bound, and the higher bound were 1.33, 1.01, and 1.76, respectively, for the q2m regimen; and 1.36, 1.00, and 1.86, respectively, for the q3m regimen. At this dose for induction treatment, the mean expected C_{trough} ratio, the lower bound, and the higher bound were 1.34, 1.03, and 1.47, respectively, for the q3w regimen. With the fixed dose of 1400 mg rituximab SC, the probability of success of a non-inferiority test on AUCτ during the induction and maintenance periods was higher than 95%. At this dose for maintenance treatment, the mean expected AUCτ ratio, the lower bound, and the higher bound were 1.28, 1.09, and 1.49, respectively, for the q2m regimen; and 1.28, 1.11, and 1.49, respectively, for the q3m regimen. At this dose for induction treatment, the mean expected AUCτ ratio, the lower bound, and the higher bound were 1.26, 1.05, and 1.52, respectively, for the q3w regimen.

Table 3. Dose selection: Probability of Success and Ctrough Ratios during the Maintenance Period Cycle 2.

SC Dose and Regimen	Probability of Success	Mean Ratio [P5-P95]	Lower Bound [P5-P95]	Upper Bound [P5-P95]
1100 mg q2m (n=70)	51%	1.07 [0.83-1.40]	0.81 [0.62-1.06]	1.42 [1.09-1.85]
1200 mg q2m (n=70)	71%	1.16 [0.87-1.44]	0.88 [0.65-1.09]	1.55 [1.17-1.93]
1300 mg q2m (n=70)	80%	1.27 [0.93-1.59]	0.95 [0.70-1.22]	1.69 [1.22-2.10]
1300 mg q2m (n=75)	83%	1.26 [0.90-1.57]	0.95 [0.68-1.19]	1.66 [1.19-2.04]
1300 mg q3m (n=75)	75%	1.27 [0.93-1.66]	0.93 [0.68-1.24]	1.72 [1.25-2.24]
1400 mg q2m (n=75)	92%	1.33 [1.00-1.79]	1.01 [0.76-1.35]	1.76 [1.32-2.34]
1400 mg q3m (n=75)	84%	1.36 [0.98-1.81]	1.00 [0.71-1.34]	1.86 [1.34-2.48]

C_{trough} = trough or minimum serum concentration; P5 = 5th percentile; P95 = 95th percentile; q2m = once every 2 months; q3m = once every 3 months; SC = subcutaneous.

Since the IV dose is given by BSA and that the SC dose is a fixed dose, the simulation results were compared between extreme BSA categories to ensure that the non-inferiority of the SC versus the IV was present across the entire body-weight range. The low BSA category corresponded to BSA below percentile 5th (<1.51) and the high BSA category corresponded to BSA above percentile 95th (≥ 2.33). The results of the C_{trough} geometric mean ration (C_{trough}SC/C_{trough}IV) for the two BSA categories in the induction and maintenance setting are presented in Table 4. Non-inferior concentrations are expected in SC arm compared to IV over the whole range of BSA. However, in patients with low BSA, mean C_{trough} Rituximab levels were 68-102% higher following SC administration compared to IV dosing.

Table 4. Dose selection: Probability of success and Ctrough ratios for a fixed SC dose of 1400 mg (BSA 1.92 ± 0.25 m2 and low (5%) BSA <1.51 m2 and high (95%) BSA>2.33 m2, and 75 patients/arm).

Setting	Probability of success	Mean ratio (P5-P95)	Low BSA (<1.51 m^2) (P5-P95)	High BSA (>2.33 m^2) (P5-P95)
Induction	91%	1.34 (1.02-1.72)	1.68 (1.48-1.91)	1.13 (1.01-1.27)
Maintenance Q2m	92%	1.33 (1.00-1.79)	1.71 (1.50-1.95)	0.96 (0.85-1.08)
Maintenance Q3m	84%	1.36 (0.98-1.81)	2.02 (1.74-2.34)	0.96 (0.84-1.11)

Dose Confirmation: study BP22333 Stage 2 - maintenance

The objective of Stage 2 was to confirm the rituximab SC dose identified in Stage 1 by demonstration of comparability of the predicted C_{trough} of rituximab SC and rituximab IV, as assessed by a non-inferiority test with a lower boundary above 0.8 for the two-sided 90% confidence interval. The PK evaluable population was N = 76 from the rituximab IV group (Cohort E) and N = 77 from the rituximab SC group (Cohort F).

The predicted geometric mean C_{trough} values at Cycle 2 (maintenance) were higher in the rituximab SC arm than the rituximab IV arm (Table 5). For the q2m and the q3m regimens, the geometric mean ratio C_{trough}SC/C_{trough}IV values were 1.24 and 1.12, respectively, with corresponding lower limit of the two-sided 90% confidence interval of 1.02 and 0.86, respectively. Both of these

lower-limit values are greater than the pre-specified non-inferiority margin of 0.8. Therefore, non-inferiority for the primary endpoint was met. The AUC_{tau} ratio (AUC_{tau}SC /AUC_{tau}IV) indicates that rituximab exposure increases by 35% after SC administration compared to IV in average.

Table 5. BP22333: Summary of Statistics for Predicted C_{trough}, AUC and C_{max} during the Maintenance Period (gMean (95%CI)).

regimen	Q2m		Q3m		Ratio SC/IV	
route	IV 375 mg/ m^2 N=37	SC 1400 mg N=41	IV 375 mg/ m^2 N=34	SC 1400 mg N=34	Q2m	Q3m
C_{trough}	25.9 (21.5-31.3)	32.2 (28.0-37.1)	10.9 (8.4-14.1)	12.1 (10.1-14.6)	1.24 (1.02-1.51)	1.12 (0.86-1.45)
AUC	4012 (3721-4326)	5430 (4980-5921)	3947 (3662-4255)	5320 (4880-5799)	1.35 (1.23-1.49)	1.35 (1.23-1.48)
Cmax*	202 (137-333)	204 (85-484)	183 (126-304)	182 (74-396)	n.c.	n.c.

*gMean (range); n.c. not calculated

The mean C_{max} for rituximab SC and for rituximab IV were comparable following q2m and q3m regimen. The median t_{max} in the rituximab SC arm was approximately 3 days as compared to the t_{max} occurring at or close to the end of the infusion for the rituximab IV arm.

Dose Confirmation: study BO22334 Stage 2 - induction

The primary endpoint in Stage 1 was the estimated ratio of observed rituximab serum C_{trough}SC/C_{trough}IV at Cycle 7 of induction treatment. The primary analysis was performed on observed rituximab serum C_{trough} values from Cycle 7, measured 3 weeks after the Cycle 7 dose (pre-dose Cycle 8).

The mean and geometric mean C_{trough} values at pre-dose Cycle 8 were higher among the rituximab SC group than the rituximab IV group (Table 6). The geometric mean ratio C_{trough}SC/C_{trough}IV value was 1.62 with a corresponding lower limit for the two-sided 90% confidence interval of 1.36. Hence, non-inferiority for the primary PK endpoint was demonstrated for induction. The coefficients of variation (CV) for C_{trough} at Cycle 7 were 43.2% in the rituximab SC group and 36.7% in the rituximab IV group, demonstrating comparable variability in the two groups. Rituximab exposure increases by 38% after SC administration compared to IV in average (Table 6).

Table 6. Dose confirmation induction phase study BO22334: summary of Ctrough and AUC at Cycle 7, Stage 1.

PK Parameter	Rituximab IV			Rituximab SC			Geometric Mean Ratio[a] [90% CI]
	n	Geometric mean	CV (%)[b]	n	Geometric mean	CV (%)[b]	
C_{trough} (µg/mL)	48	83.1	36.67	54	134.6	43.17	1.62 [1.36;1.94]
AUC (µg • day/mL)	58	2734.2	28.03	55	3778.9	33.72	1.38 [1.24;1.53]

CI = confidence interval; CV = coefficient of variation; IV = intravenous; PK = pharmacokinetic; SC = subcutaneous.

[a] Geometric mean ratio adjusted for tumor load at baseline.

[b] Coefficients of variation (CV) calculated on the original scale.

Source: CSR BO22334, Table 12.

Using the covariate PopPK model, a secondary analysis was performed using the predicted PK parameters for analysis of C_{trough}. For C_{trough}, the geometric mean was 135.4 µg/mL for the rituximab SC group compared with 87.8 µg/mL for the rituximab IV group. The resulting GMR C_{trough}SC/C_{trough}IV) value was 1.54 with a corresponding lower limit for the two-sided 90% confidence interval of 1.32, which is above the pre-specified non-inferiority margin of 0.8. Further support that rituximab SC was not inferior to rituximab IV route was obtained by ORR analysis.

For AUC, the predicted geometric mean was 3898 µg•day/mL for the rituximab SC group compared with 2726 µg•day/mL for the rituximab IV group. For Cmax, the predicted geometric mean was 234.5 µg/mL for the rituximab SC group compared with 247.6 µg/mL for the rituximab IV group. The median terminal elimination half-life was 29.7 days.

2.4.3. Pharmacokinetics in target population

Rituximab PK was described in the final population PK model, including all data from studies BP22333 and BO22334, by a two-compartment model. Clearance was presented as a sum of a non-specific time-independent clearance (CLinf) and time dependent target-mediated clearance (CLt) that exponentially decreased with time, due to depletion of peripheral CD19+ lymphocytes (B-cells).

The estimates of time-independent clearance (194 mL/day), inter-compartment clearance (773 mL/day), central compartment volume (4370 mL), and peripheral compartment volume (3880 mL) were in the range typical for monoclonal antibodies. The estimate of absorption rate constant was 0.340 L/day and bioavailability was 71.0%. High initial time-dependent clearance (535 mL/day in addition to time- independent clearance) can possibly be attributed to the target-mediated elimination. This clearance component decreased with time, with a half-life of about 12 and 30 days for Study BO22334 and Study BP22333, respectively. The median terminal elimination half-life was 29.7 days with a range of 9.9 to 91.2 days.

All clearance and volume parameters increased with body size. These dependencies were described by the power functions of body surface area with the power coefficients of 1.31 and 1.38 for

clearance and volume parameters, respectively. Among other covariate dependencies, central volume increased with age and absorption rate constant decreased with age (for age >60 years), but these dependencies were shown to result in negligible changes in rituximab exposure. The PK of rituximab did not depend on gender and baseline albumin concentrations.

Anti-drug antibodies (ADA) were detected in only 13 (3%) patients, and they did not influence the steady-state clearance. The diagnostic plots suggested a possible effect on the time dependent part of clearance (CLT). While inclusion of this effect in the model indicated an increase of CLT in subjects with ADA, the model that accounted for this effect did not result in the decrease of the inter-subject variability. Also, the effect size was estimated with very large uncertainty, with the confidence intervals that included the null values. Thus, the effect was not included in the final model.

2.4.4. Special populations

- **Impaired renal and hepatic function**

Data on renal and hepatic function were not submitted (see discussion on Cluinical Pharmacology).

- **Gender**

Among the 403 patients, there were 181 (45%) male patients and 222 (55%) female patients.

C_{trough} and AUC rituximab values at cycle 7 were higher in females than in males, but when corrected for BSA, gender was no covariate for rituximab pharmacokinetics (data not shown).

- **Race**

Most of the patients were White (87%), while the majority of non-White patients were of other race (11% of the total). In terms of ethnicity, only 31 patients (8%) were Hispanic. Thus, the dataset was not representative to allow the analysis of the race or ethnicity dependence of PK parameters.

- **Weight**

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. The mean weight and BSA of the population were 74.4 kg (range: 43.9 – 130 kg) and 1.83 m^2 (range: 1.34 – 2.48 m^2), respectively.

BSA was identified as the main covariate affecting clearance and volume in the pop-PK model. All clearance and volume parameters increased with the body size. Stratification by body size shows gmean C_{trough} ratio of 2.25, 1.65, and 1.21 in patients with a BSA of 1.4, 1.9, and 2.4 m^2, respectively. The corresponding AUCT ratios were 1.96, 1.45, and 1.09. When patients were grouped in three subpopulations, patients with the lowest 33rd percentile BSA had on average a 66% higher exposure to rituximab following SC administration compared to IV route. Patients with BSA between 33-66percentile or >66^{th} percentile had on average 17% and 32% higher rituximab exposure. Results from this analysis are summarized in Table 7.

Table 7. Summary of PK Parameters by BSA Subgroup in induction phase study BO22334.

	C_{trough} at Cycle 7			AUC at Cycle 7		
	Geometric Mean		Geometric Mean Ratio (SC/IV) [90% CI]	Geometric Mean		Geometric Mean Ratio (SC/IV) [90% CI]
	Rituximab IV	Rituximab SC		Rituximab IV	Rituximab SC	
BSA						
Low (n)	66.69 (16)	132.04 (24)	1.869 [1.178,2.965]	2607.27 (16)	4428.93 (23)	1.661 [1.330,2.073]
Medium (n)	71.74 (26)	99.29 (15)	1.394 [1.057,1.839]	2774.50 (25)	3240.44 (15)	1.172 [0.971,1.414]
High (n)	79.53 (16)	103.87 (20)	1.364 [1.149,1.621]	2785.44 (16)	3491.56 (17)	1.318 [1.151,1.510]

AUC = area under the serum concentration – time curve; CI = confidence interval; C_{trough} = trough or minimum serum concentration; IV = intravenous; n = number of patients contributing to summary statistics; SC = subcutaneous.

Patients were grouped into one of three subpopulations: low (BSA ≤ 33rd percentile), medium (BSA between 33rd and 66th percentiles) and high (BSA ≥ 66th percentile)

Source: CSR BO22334, Table 13 (pk001c7bsa_I_001, pk002c7bsa_I_001).

- **Elderly**

Among other covariate dependencies, central volume increased with age and the absorption rate constant decreased with age (for patients aged >60 years). However, these age dependencies were shown to result in negligible changes in rituximab exposure (data not shown).

- **Tumour load at baseline**

As would be expected, baseline tumour size and B-cell counts affected the initial (time-dependent) clearance, but inclusion of these effects did not result in the decrease of the inter-subject variability. Also, the parameters for these effects were estimated with very large uncertainty, with the confidence intervals that included the null values. Thus, these effects were not included in the final model.

Subgroup	C_{trough} at Cycle 7			AUC at Cycle 7		
	Geometric Mean		Geometric Mean Ratio (SC/IV) [90% CI]	Geometric Mean		Geometric Mean Ratio (SC/IV) [90% CI]
	Rituximab IV	Rituximab SC		Rituximab IV	Rituximab SC	

Tumor Load at Baseline*						
Low (n)	92.32 (14)	135.35 (22)	1.461 [1.152,1.852]	2974.19 (18)	3878.36 (20)	1.312 [1.106,1.555]
Medium (n)	91.70 (20)	171.26 (14)	1.861 [1.538,2.253]	2765.13 (21)	4479.73 (16)	1.620 [1.401,1.874]
High (n)	65.06 (14)	110.80 (18)	1.704 [1.056,2.749]	2493.56 (19)	3186.23 (19)	1.275 [1.017,1.599]

- **Anti-rituximab antibodies**

Effect of anti-rituximab antibodies on pharmacokinetics of rituximab was evaluated. During Stage 1 of Study BP22333, there were no positive HACA samples at any time-point (among 124 patients tested). During Stage 2, only one of 154 patients tested (0.6%) had positive HACA results, both at baseline (prior to receiving any rituximab in the study) and at later time-points. Patient 2207 had positive HACA results during his first study cycle. HACA titers of 2.51 at baseline, and 2.81 at Day 22, and Day 85 were recorded. The overall rate for anti-rituximab antibody positivity, including baseline and post-baseline, was 1% (1/77) for the rituximab SC group and 0% (0/77) for the rituximab IV group.

In Study BO22334, blood samples for the analysis of anti-rituximab antibodies were collected from all patients immediately prior to the administration of rituximab at each cycle during induction (i.e., every 3 weeks for 8 cycles) and maintenance treatment (i.e., every 8 weeks for 2 years), and every 12 weeks after the last rituximab administration until 96 weeks after the last rituximab administration (i.e., 8 follow-up visits). Of the 124 patients with samples available at baseline, 114 patients (57 patients per arm) tested negative for HACA at baseline. Of these 114 patients, 1 patient in each arm had a transient positive result post-baseline (i.e., a positivity rate of 2% per arm when restricted to patients who were negative at baseline).

- **Anti-rHuPH20 antibodies**

In study B22333 stage 1, 7 of the 108 patients treated with rituximab SC had a positive result for anti-rHuPH20 antibodies; hence, the overall rate of anti-rHuPH20 positivity in Stage 1 was 6.5% (Ib025_s001). Six (5.5%) of these patients tested positive at baseline; that is, prior to the subcutaneous administration of rituximab. Titers recorded at baseline in patients in Stage 2 ranged from 2 to 32. No neutralizing antibody activity was detected.

The overall rate for anti-rHuPH20 antibody positivity (including baseline and post-baseline) in the study was 13% (8/62 patients) for the SC arm and 14% (9/65 patients) for the IV arm. The majority of the patients testing positive showed a positive result already at baseline, that is, prior to the administration of any study drug. The rate of baseline positivity was 10% (6/59 patients) in the SC arm and 11% (7/64 patients) in the IV arm. Of the patients who were anti-rHuPH20 antibody negative at baseline (53 in the SC arm and 57 in the IV arm), antibodies were observed at later time-points in 2/53 patients (4%) in the SC group (Patients 2156 and 2881) and 2/57 patients (4%) in the IV group (Patients 1542 and 2756). All of the confirmed-positive samples in Study BO22334 were negative for the presence of neutralizing antibodies.

2.4.5. rHuPH20 Pharmacokinetics

In study BP22333, plasma rHuPH20 concentrations were measured at predose and at 30 minutes, 1 hour, and 24 hours postdose, in a total of 185 patients treated with rituximab SC: n = 34 in Cohort B, n = 34 in Cohort C, and n = 40 in Cohort D (Stage 1); and n = 77 in Cohort F (Stage 2). Plasma rHuPH20 concentrations were below the limit of quantification (BLQ, < 0.3125 U/mL) for all sampling timepoints in all but one of the 185 patients with available data, indicating that the use of rHuPH20 as a permeation enhancer for rituximab results in a very low likelihood of observing quantifiable systemic exposure to the enzyme.

Given the low likelihood of systemic rHuPH20 exposure in patients and the short half-life of rHuPH20, it is unlikely rHuPH20 will accumulate in the plasma with the planned marketed regimen.

2.4.6. Pharmacodynamic results – B-cell count

Peripheral blood CD19+ lymphocyte counts (B cells) were summarized for the safety analysis population (SAP) using descriptive statistics (SI units: $\times 10^9$ cells/L), including mean, standard deviation, median, and range (minimum and maximum values). The normal range was defined as $0.08 - 0.616 \times 10^9$ cells/L.

B-cell count: Study BP22333 maintenance phase

B-cell depletion was defined as peripheral blood CD19+ lymphocyte count < 80 cells/mm^3. Available data from 124 patients in Stage 1 and 154 patients from Stage 2 showed effective B-cell depletion (CD19+ lymphocyte counts) in all patients analysed at baseline. This finding was expected as the dataset consists entirely of peripheral blood counts from patients who were receiving rituximab in the maintenance setting, and who had responded to a minimum of four cycles of 375 mg/ m^2 rituximab IV in induction and who also had received at least one cycle of rituximab IV in the maintenance setting prior to enrolment into the study.

B-cells were still depleted in 26 patients (14 IV and 12 SC) enrolled in Stage 2 with data available at the 3-month follow-up visit. Data of only 5 patients are available at the 9-month follow-up visit. B-cells started to recover in 3 patients. This is consistent with the trend seen previously in patients with haematological malignancies treated with rituximab IV, where B-cell recovery begins within 6 months of treatment and generally returns to normal levels within 12 months after completion of therapy.

B-cell count: Study BO22334 induction phase

In Study BO22334, patients with previously untreated FL entered the study and received their first cycle of rituximab intravenously. Absolute CD19+ lymphocyte counts were available from 102 patients at baseline (pre-dose Cycle 1; 51 in the rituximab SC arm and 54 in the rituximab IV arm), with median CD19+ lymphocyte counts were around the lower limit of the normal range: 0.12×10^9 cells/L (rituximab SC) and 0.05×10^9 cells/L (rituximab IV). Significant depletion of peripheral B cells was observed in both groups following the first cycle of rituximab IV treatment, and B-cell levels continued to deplete with additional cycles of induction treatment in both SC and IV groups

2.4.7. Discussion on clinical pharmacology

The clinical pharmacology was adequately addressed.
Data describing the pharmacokinetics and pharmacodynamics was obtained from two studies, BP22333 and BO22334. The assay measuring rituximab in serum used in studies BP22333 and BO22334 were adequately validated and there was no impact on the assay on the presence of rHuPH20. Assays used for measuring rHuPH20 activity, anti-rituximab antibodies, anti-rHuPH20 antibodies and neutralizing anti-rHuPH20 antibodies have been satisfactorily validated.
Standard and appropriate PK analysis methods were used and only 0.5% of post-dose rituximab concentrations were below the quantification limit.

The intended injection site is the abdominal wall; no other sites were investigated in the clinical studies. Dose-selection was based on data from stage 1 in study BP33222 where doses of 375 - 800 mg/m^2 were evaluated. Model simulation of PK data obtained from this study form the basis for the choice of the fixed dose of 1400 mg.

A non-compartmental analysis of PK data suggested that a dose between 625 and 800 mg/m2 would be required to achieve non-inferiority of R-SC to R-IV with a high variability of Ctrough > 50%, this is justified by concentration-time data from Stage 1 of study BP22333. The PK model simulated the impact of various fixed doses (1100-1400 mg) on Ctrough and AUC in patients in the induction and maintenance settings and the fixed dose of 1400 mg R-SC in the model provided the highest probability of success on the expected geometric mean ratio and the lower and upper limit of the 90% confidence interval for Ctrough and AUC and was carried on to the Stage 2 of Study BP22333, the dose confirmation part to be compared to R-IV 375 mg/m2, q2m or q3m. Results showed that the PK model (combining PK data from stage 1 and 2) predicted Ctrough and AUC values were similar to the observed values. The modelling of PK data showed that the primary outcome, lower limit of Ctrough > 0.8, was achieved. GMR (90% CI) of Ctrough at q2m was 1.24 (95%CI 1.02-1.51) and at q3m 1.12 (90% CI 0.86-1.45). GMR (90% CI) for AUC was at q2m 1.35 (95% CI 1.23-1.49) and for q3m 1.35 (90% CI 1.23-1.48). The median Cmax of both the q2m and q3m regimen were similar for the i.v. and s.c. administration.

The results from study BO22334, stage 1, where the dosing regimen was q3w (induction treatment) instead of q2m and q3m (maintenance treatment), confirmed the results from study BP22333. Rituximab SC was non-inferior to rituximab IV regarding Ctrough with a GMR 1.62 (90% CI 1.36-1.94) with the upper limit exceeding 1.25%/1.37%. Exposure was higher in terms of AUC with SC administration (1.38; 90% CI 1.24-1.53).

Overall, the flat dose of 1400 mg R-SC for the maintenance and induction treatment of FL provided Ctrough concentrations which were non-inferior to 375 mg/m^2 R-IV. The bioequivalence guideline (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) states that for highly variable drugs, where the intra-subject variability > 30%, the acceptance criteria for BE (80-125%) can be widened to a maximum of 69.84-143.19 for Cmax. However; for AUC the criteria should be within 80-125% regardless of variability. The present application does not fulfil the BE criteria in a strict sense but was supported by clinical endpoints (Study BO22334).

Volume of distribution was in the range normally seen with other antibodies, i.e. 3-4 L. In the popPK analysis the central volume in the SC route of administration was increased by 48.9%; however this did not impact the overall description of the data. It is generally accepted that monoclonal antibodies are eliminated by catabolism or target-mediated processes and not by hepatic metabolic

clearance or renal excretion. The initial clearance was as expected higher due to higher tumour burden at the start (target mediated clearance) than at later times at steady-state (non-specific clearance) where the tumour burden has diminished. The median terminal the half-life was 29.7 days (range 9.9-91.2 days).

The most important covariate was body surface area. Subgroup analysis (induction setting, q3w) showed that R-SC was non-inferior to R-IV in terms of Ctrough and AUC, meaning that patients with both low and high BSA sustained an acceptable level of rituximab in the blood. Exploratory analysis on the impact of BSA on safety and efficacy revealed no evidence that patients, with low BSA and therefore relatively higher rituximab concentration would present with more adverse events compared to patients with higher BSA. Likewise, patients with high BSA and relatively lower rituximab concentration showed no signs of reduced efficacy. The PK of rituximab, when administered subcutaneously, is not supposed to be influenced by renal and hepatic impairment and no such studies were conducted.

Mabthera was granted a full waiver for paediatric studies in the context of the NHL indication therefore the PK of rituximab in children was not evaluated (see section 4.2 of the SmPC).

In conclusion, the PK of R-SC was comparable to R-IV. R-SC was non-inferior to R-IV in terms of the primary endpoint Ctrough in Study BP22333 (cycle 2, maintenance treatment) and Study BO22334 (cycle 7, induction treatment). The increased exposure seen with R-SC compared to R-IV did not raise safety concerns, but this should be considered in the light of the limited number of patients involved in general and in particular the limited number of patients that have received the proposed posology in combination with a relatively short follow-up (see also safety section for further information and discussion). There may also be a very high estimated exposure upon rituximab SC monotherapy in the patients with the stage III-IV FL with refractory disease or upon the ≥ 2 relapse, where the patients are planned to receive Rituximab SC every week for 4 weeks. This would involve a Ctrough of at least 1.9 times that of rituximab IV, with an even higher exposure in patients with a low BSA. This also in relation to the uncertainty on the consequences for safety of this estimated high exposure. Based on this concern expressed by the CHMP, the Applicant withdrew this part of the indication. This has been considered acceptable provided the applicant mentions in section 4.4 of the SmPC that it is not recommended to treat patients that meet the indication of “MabThera monotherapy in the treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy.” with MabThera SC. In addition, the Applicant has updated the educational material to address this issue.

R-SC was as effective in the depletion of B-cells as R-IV as measured by CD19+ lymphocyte counts that remained depleted throughout study BP22333. In study BO22334, during the induction treatment, B-cell levels continued to fall. The overall response rate (ORR) at the end of the induction period was evaluated according to different subgroups comparing R-SC and R-IV. No statistical significant difference between R-SC and R-IV in terms of ORR was seen for Ctrough (low, medium, high), AUC (low, medium, high), BSA (low, medium, high), gender, CHOP/CVP and tumour load (low, medium, high). Overall, the pharmacodynamics is not different between sc and iv formulation.

Extrapolation of data between indications within the scope of NHL, seems possible as pharmacology of rituximab is not expected to be different in the relapsed, stage III-IV FL patients, even considering the different dosing interval of once a week as compared to every 3 weeks. However,

the concomitant estimated mean Ctrough levels have a considerably higher ratio of 1.9, which means it is even higher in subjects with low BSA. Such a high exposure has not been tested in the current studies, whereas underexposure in the various HL indications will not be an issue, (to be further discussed under Clinical safety)

2.4.8. Conclusions on clinical pharmacology

PK data from study BP33222- stage 1 form the basis for the model simulation and the choice of the fixed dose of 1400 mg (see section 4.2

In the absence of comparative safety data in the stage III-IV FL treatment setting with once a week rituximab SC 1400 mg for 4 weeks the proposed indication was revised not to include monotherapy and a statement in section 4.4 of the SmPC that it is not recommended to treat patients in the context of the indication of "MabThera monotherapy in the treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy."

The CHMP considers the following measures necessary to address the issues related to pharmacology (See also discussion on Clinical Efficacy):

- Submission of The MAH will provide the clinical study reports from the clinical trials BP22333, BO22334 and BO25341 including reports on long-term safety in relation to BSA (as a measure for exposure variation) and to gender as follows:

2.5. Clinical efficacy

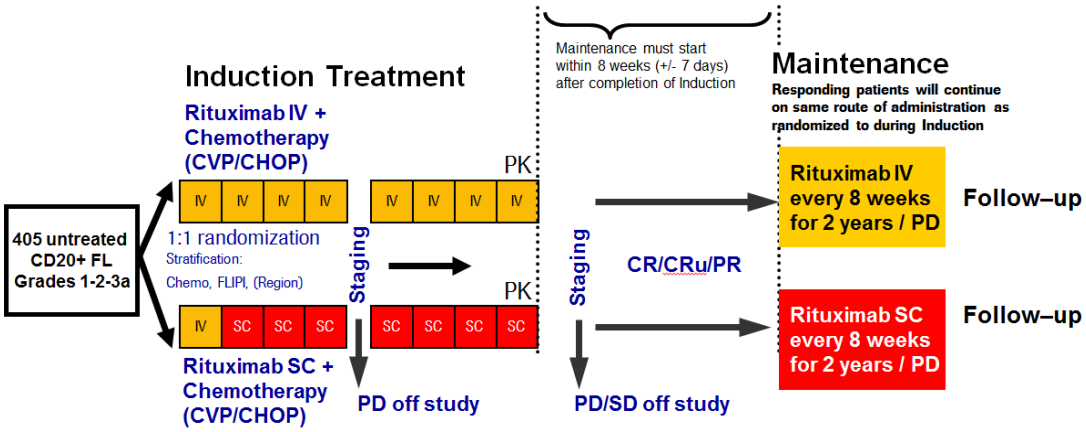
2.5.1. Dose response studies

2.5.2. Dose – finding was part of study BP33222 -Stage 1 as discussed in the Clinical Pharmacology section. These PK data form the basis for the model simulation and the choice of the fixed dose of 1400 mg. Main study

Study BO22334

Study BO22334 is a two-stage phase III, international, multicenter, randomized, controlled, open-label study to investigate the PK, efficacy and safety of rituximab SC in combination with CHOP or CVP versus rituximab IV in combination with CHOP or CVP in patients with previously untreated FL followed by maintenance treatment with either rituximab SC or rituximab IV.

Figure 1: BO22334: Overall Study Design for Stage 1 and Stage 2



Methods

Study Participants

Previously untreated patients aged ≥ 18 years with CD20-positive FL Grade 1, 2, or 3a were randomized.

Treatments

Patients were randomized into the following two treatment groups:

Rituximab SC: first cycle rituximab IV (375 mg/m^2) plus 7 cycles of rituximab SC in combination with up to 8 cycles of CHOP or CVP chemotherapy administered every 3 weeks. Rituximab SC was given at a fixed dose of 1400 mg as determined in the Phase Ib study BP22333. Patients achieving at least partial response (PR) at the end of induction entered rituximab SC maintenance therapy once every 8 weeks for 96 weeks.

Rituximab IV: 8 cycles of rituximab IV in combination with up to 8 cycles of CHOP or CVP chemotherapy administered every 3 weeks. Patients achieving at least PR at the end of induction entered rituximab IV maintenance therapy once every 8 weeks for 96 weeks. Rituximab IV was used at the standard dose of 375 mg/m^2.

Objectives

The primary objective of Stage 1 was to estimate the ratio of C_{trough} of rituximab obtained at Cycle 7, 21 days after SC administration to that obtained after IV administration ($C_{trough(SC)}/C_{trough(IV)}$ during Cycle 7 of induction treatment).

Outcomes/endpoints

The primary endpoint of Stage 1 was to estimate the ratio of trough serum concentrations of rituximab obtained at Cycle 7, 21 days after SC administration to that obtained after IV administration ($C_{trough(SC)}/C_{trough(IV)}$ during Cycle 7 of induction treatment).

Secondary endpoints of Stage 1 included additional PK parameters, B-cell depletion, safety, and the following efficacy parameters:

ORR, comprising CR, CRu and PR, at the end/completion of induction treatment

Complete response rate (CRR, comprising CR and CRu) at the end/completion of induction treatment

ORR and CRR at the end/completion of maintenance treatment

Time-to-event efficacy endpoints: progression-free survival (PFS), event-free survival (EFS), and overall survival (OS).

Patients had a final response assessment based on clinical examination and CT scans after completion of induction therapy. Patients achieving CR, CRu, or PR according to the International Working Group response criteria for lymphoma entered the rituximab maintenance phase of the study and continued to receive either rituximab SC (1400 mg) or rituximab IV (375 mg/m^2), depending on which treatment group they were initially randomized to, every 8 weeks for 96 weeks.

All efficacy endpoints were analyzed according to the ITT population.

Sample size

Under the assumption of a coefficient of variation (CV) equal to 0.56 and assuming that the true PK of rituximab sc formulation is 5% above the rituximab iv formulation (ie mean Ctrough, sc to be above 5% above ctrough, iv) 50 patients in each treatment arm were adequate in order to achieve 80% power with one-sided alpha of 0.05 (ie. 2-sided 90% CI). Assuming that 20% of patients would not have valid PK data at cycle 8 pre-dose, a total of approximately 125 patients were to be enrolled into stage 1 of the study. Approximately 125 patients were to be enrolled in sttage1 plus an additional 125 enrolled patients to obtain 100 evaluable patients in case an adjustment of the rituximab SC dose was needed followed by approximately 280 patients to stage 2 (once recruitment for Stage 1 was completed and the rituximab sc dose confirmed.

In stage 1 an interim PK futility analysis was planned after 35 patients in each treatment arm had completed cycle 7 of induction treatment. The interim analysis followed a group sequential design proposed by Lan –DeMets with an alpha spending function according to O'Brien and Flemming. If the results showed overwhelming evidence of futility of rituximab sc over iv the sc dose would need to be adjusted and an additional 125 patients would be enrolled in Stage 1. Otherwise, recruitment of stage 1 would be accomplished as planned.

A total of 405 patients to be randomized in the study: approximately 125 patients in Stage 1, and approximately 280 patients in Stage 2.

Randomisation

Screening/baseline tests were performed within 28 days before randomization. A central randomization procedure was used for all patients that fulfilled the entry criteria at screening. Patients were stratified by underlying chemotherapy backbone during induction treatment (CHOP, CVP), Follicular Lymphoma International Prognostic Index (FLIPI) (low-risk, intermediate-risk, high-risk) and regions (Europe and North America, South and Central America, Asia). Study visits were planned on the first day of drug administration of each new treatment cycle. Assessments included clinical tumor assessment, physical examination, vital signs, weight, hematology, serum chemistry, urinalysis, rituximab PK samples, peripheral blood sample for flow cytometry testing,

anti-rituximab antibody sample (HACA), and anti-rHuPH20 antibody sample (HAHA). PK assessments are performed at pre-specified time points. Assessment of tumor response was performed according the International Working Group response criteria for non-Hodgkin's lymphomas.

Patients underwent interim staging after receiving 4 cycles of induction immunochemotherapy. Response assessment was based on clinical examination and computed tomography (CT) scans. Patients achieving a complete response (CR), unconfirmed complete response (CRu), or a PR, or with stable disease (SD) according to the International Working Group response criteria for lymphoma (Cheson et al., 1999) continued induction treatment. Patients receiving CHOP chemotherapy could receive an additional 2 or 4 cycles of CHOP according to investigator discretion. Patients receiving CVP chemotherapy received an additional 4 cycles of chemotherapy. Rituximab (SC or IV, respectively) was administered for a total of 8 cycles during induction therapy for all patients.

Blinding (masking)

Study BO22334 was an open-label study.

Statistical methods

Response rates (ORR and CRR) at the end/completion of induction treatment were analyzed in frequency tables including 95% two-sided Pearson – Clopper confidence intervals (CIs) by treatment group For the difference in response rates, 95% two-sided CIs (Hauck – Andersen) were calculated.

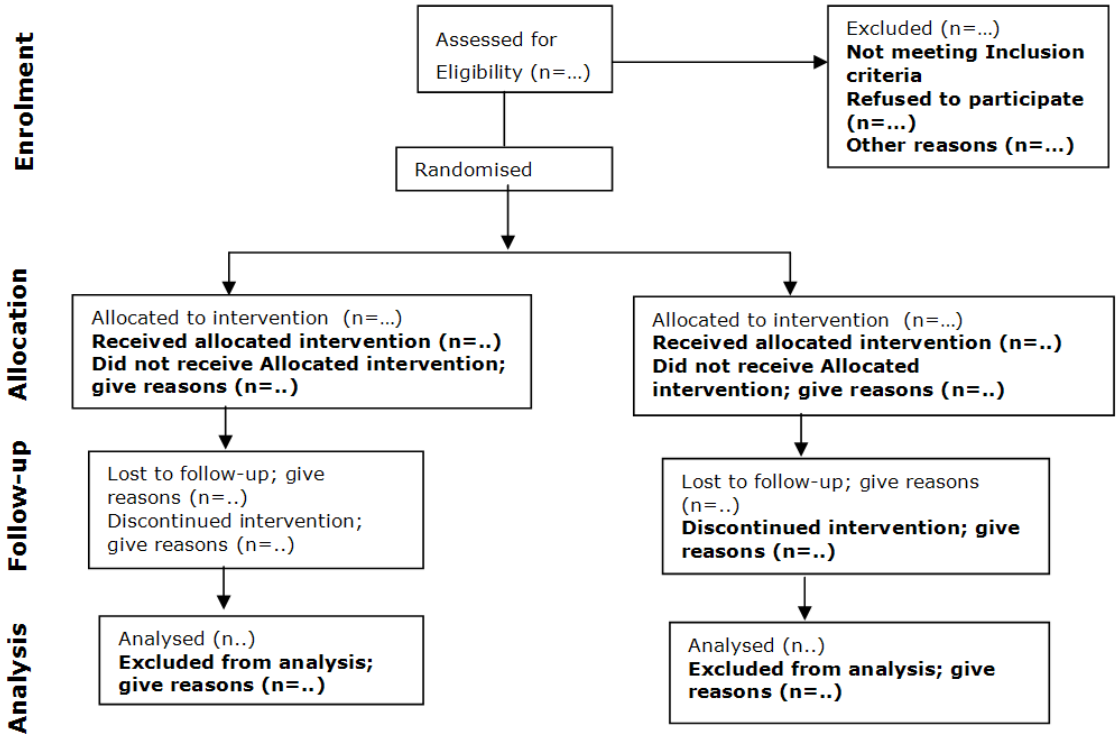
All efficacy endpoints were analyzed according to the intent-to-treat (ITT) population which included all patients being randomized into the study irrespective of whether they received study drug or not. Patients were analyzed according to the treatment to which they were assigned.

A numerical comparison of point estimates and 95% CIs for ORR for both treatment groups was deemed appropriate, given the anticipated non-inferior C_{trough} levels with rituximab SC compared with rituximab IV.

Results

- **Participant flow**

Participant flow



Recruitment

Discontinuations during induction and maintenance		
Reason for discontinuation	Rituximab SC	Rituximab IV
Safety reasons (n)	**2**	**2**
Death(n)	**1** (MI)	-
Efficacy (n)	**2** (2 PD)	**2** (1 PD, 1 SD)
Other reasons (n)	**2** (2 physician's decision)	**2** (1 physician's decision, 1 lost to follow up)
Furthermore (n)	**1** (Patient decided to discontinue shortly after the first rituximab dose (which was IV according to the protocol))	-

Conduct of the study

The study was conducted in accordance with the declaration of Helsinki and GCP guidelines.

An IMC independent from the study management team was established which performed the interim PK futility after 35 patients were completed cycle 7 of induction treatment.

Baseline data

Overall, the treatment arms were balanced with respect to age, height, and weight at induction baseline. The median age was 57.0 years (range 35 – 85 years) in the rituximab IV arm and 54 years (range 28 – 85 years) in the rituximab SC arm. The median height in each treatment arm was 167 cm (range 141 – 192 cm in the rituximab IV arm and 145 – 188 cm in rituximab SC arm), and the median weight was 71.5 kg (range 43.9 – 118.0 kg) in the rituximab IV arm and 70.0 kg (range 45.0 – 116.4 kg) in the rituximab SC arm.

The median BSA was 1.82 m^2 (range 1.34 – 2.30 m^2) in the rituximab IV arm and 1.74 m^2 (range 1.37 – 2.32 m^2) in the rituximab SC arm. Overall, more female patients than male patients were randomized in this study (68/127 [54%] females vs. 59/127 [46%] males). However, more patients were male in the rituximab IV arm (33/64 [52%]), whereas there were more female patients in the rituximab SC arm (37/63 [59%]) (Table 1).

The baseline stratification characteristics of chemotherapy and FLIPI risk groups were well-balanced between the two treatment arms. The greatest proportion of patients comprised of the intermediate and high-risk FLIPI groups (39% and 40%, respectively). The majority of patients had Ann Arbor Stage IV lymphoma at study entry, with 37/64 patients (58%) in the rituximab IV arm and 39/63 patients (62%) in the rituximab SC arm. The greatest proportion of patients had Grade 2 FL (59/127 patients [46%]), followed by Grade 1 (39/127 patients [31%]) and Grade 3/3a (29/127 patients [23%]). Slightly more patients in the rituximab IV arm had Grade 2 FL (35/64 [55%] patients) compared to the rituximab SC arm (24/63 [38%] patients).

Table 1 BO22334: Baseline Patient Characteristics – Stage 1 (ITT)

	Rituximab IV + Chemo N = 64	Rituximab SC + Chemo N = 63	Total N = 127
Age (years)			
Mean	56.5	54.0	55.3
SD	11.42	13.29	12.39
Median	57.0	54.0	55.0
Min-Max	35 - 85	28 - 85	28 - 85
n	64	63	127
Age Category (years)			
<65	50 (78%)	50 (79%)	100 (79%)
>=65 - <=70	6 (9%)	5 (8%)	11 (9%)
>70	8 (13%)	8 (13%)	16 (13%)
n	64	63	127
Gender			
MALE	33 (52%)	26 (41%)	59 (46%)
FEMALE	31 (48%)	37 (59%)	68 (54%)
n	64	63	127
Weight (kg)			
Mean	74.845	71.931	73.400
SD	15.0238	16.7784	15.9223
Median	71.500	70.000	71.000
Min-Max	43.90 - 118.00	45.00 - 116.45	43.90 - 118.00
n	64	63	127
Height (cm)			
Mean	168.07	166.42	167.25
SD	9.660	9.203	9.435
Median	167.00	167.00	167.00
Min-Max	141.0 - 192.0	145.0 - 188.0	141.0 - 192.0
n	64	63	127
Body Surface Area (sqm)			
Mean	1.843	1.795	1.819
SD	0.1992	0.2320	0.2167
Median	1.820	1.740	1.805
Min-Max	1.34 - 2.30	1.37 - 2.32	1.34 - 2.32
n	63	63	126
Ethnicity			
HISPANIC	18 (32%)	13 (24%)	31 (28%)
NON-HISPANIC	38 (68%)	42 (76%)	80 (72%)
n	56	55	111
Race			
AMERICAN INDIAN/ALASKA NATIVE	1 (2%)	1 (2%)	2 (2%)
ASIAN	4 (7%)	4 (7%)	8 (7%)
OTHER RACE	4 (7%)	4 (7%)	8 (7%)
WHITE	48 (84%)	45 (83%)	93 (84%)
n	57	54	111
Tobacco Use History			
NEVER	33 (52%)	31 (49%)	64 (50%)
CURRENT	12 (19%)	19 (30%)	31 (24%)
PREVIOUS	19 (30%)	13 (21%)	32 (25%)
n	64	63	127
Chemotherapy Combination			
CHOP	40 (63%)	40 (63%)	80 (63%)
CVP	24 (38%)	23 (37%)	47 (37%)
n	64	63	127

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
DM16 31AUG2012:13:55:16

Source: CSR BO22334, Table 10 (adapted from dm001_i001).

Numbers analysed

The efficacy analyses were based on the ITT population for Stage 1, comprising all patients who completed the randomization process irrespective of whether they received study drug or not. The

ITT population comprised 127 patients: 64 patients in the rituximab IV arm and 63 patients in the rituximab SC arm.

One patient randomized to the rituximab SC arm, discontinued shortly after the first rituximab IV administration and was analyzed under the rituximab IV arm for analyses performed on the safety analysis population (SAP: 65 patients in the rituximab IV arm and 62 patients in the rituximab SC arm).

Outcomes and estimation

Efficacy Results for Study BO22334

A total of 54/64 patients (84.4%, 95% CI [73.1%,92.2%]) in the rituximab IV arm achieved an overall response (including CR, CRu and PR) compared with 57/63 patients (90.5%, 95% CI [80.4%,96.4%]) in the rituximab SC arm. A difference in ORR of 6.10% (95% CI [-6.3%,18.5%]) was observed in favor of the rituximab SC arm.

A complete response (CR or CRu) was achieved by 19/64 patients (29.7%) in the rituximab IV arm and 29/63 patients (46.0%) in the rituximab SC arm. A difference in CRR of 16.34% (95% CI [–1.2%,33.9%]) was observed in favor of the rituximab SC arm.

Patients with stable disease (SD), progressive disease (PD), missing information, and invalid information (ie, defined as any response assessment performed more than 56 days after the last cycle of rituximab, or after the first rituximab cycle of the maintenance phase, or after the start of new anti-lymphoma treatment were classified as non-responders. The rate of non-response was 15.6% (10/64 patients) in the rituximab IV arm compared with 9.5% (6/63 patients) in the rituximab SC arm, and comprised SD (4.7% in rituximab IV arm vs. 3.2% in rituximab SC arm), PD (1.6% vs. 0.0%, respectively), missing information (3.1% vs. 3.2%, respectively), and invalid information (6.3% vs. 3.2%, respectively).

Table 2 BO22334: Tumor Response Rate at End of Induction – Stage 1 (ITT)

	Rit. IV + Chemo (N=64)		Rit. SC + Chemo (N=63)
Responders$	54 (84.4 %)		57 (90.5 %)
Non-Responders	10 (15.6 %)		6 (9.5 %)
95% CI for Response Rates*	[73.1; 92.2]		[80.4; 96.4]
Difference in Response Rates		6.10	
95% CI for Difference in Response Rates#		[-6.3; 18.5]	
p-Value (Chi-squared Test)		0.3002	
Odds Ratio		1.76	
95% CI for Odds Ratio		[0.60;5.17]	
Complete Response (CR and CRu)	19 (29.7 %)		29 (46.0 %)
95% CI for CR and CRu Rates*	[18.9; 42.4]		[33.4; 59.1]
Difference in CR and CRu Rates		16.34	
95% CI for Difference in CR and CRu Rates#		[-1.2; 33.9]	
p-Value (Chi-squared Test)		0.0575	
Odds Ratio		2.02	
95% CI for Odds Ratio		[0.97;4.19]	
Partial Response (PR)	35 (54.7 %)		28 (44.4 %)
95% CI for PR Rates*	[41.7; 67.2]		[31.9; 57.5]
Difference in PR Rates		-10.24	
95% CI for Difference in PR Rates#		[-28.5; 8.0]	
p-Value (Chi-squared Test)		0.2484	
Odds Ratio		0.66	
95% CI for Odds Ratio		[0.33;1.33]	
Stable Disease (SD)	3 (4.7 %)		2 (3.2 %)
95% CI for SD Rates*	[1.0; 13.1]		[0.4; 11.0]
Progressive Disease (PD)	1 (1.6 %)		0 (0.0 %)
95% CI for PD Rates*	[0.0; 8.4]		[0.0; 5.7]
Not Evaluated/Missing (NE) &	2 (3.1 %)		2 (3.2 %)
95% CI for NE Rates &	[0.4; 10.8]		[0.4; 11.0]
Invalid Response Assessments ^	4 (6.3 %)		2 (3.2 %)

Response: End of Induction-Derived (RSPEIND)
$ Patients with end of treatment response of CR, CRu 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.
^ A response is classified as invalid (and as a 'Non-Responder') if the response assessment:
(1) was more than 56 days after the last Rituximab intake,
(2) was after the first Rituximab intake of the maintenance phase, or
(3) was after the start of new anti-lymphoma treatment.

Program : $PROD/cdt3490c/c22334a/rr001.sas
Output : $PROD/cdt3490c/c22334e/reports/rr001_I_001.out
29JUN2012 11:51

Source: CSR BO22334, Table 14 (rr001_I_001)

Ancillary analyses

Table 4 summarizes the results of the subgroup analyses of overall response rates by C_{trough} (high vs. medium vs. low), AUC (high vs. medium vs. low), BSA (high vs. medium vs. low), gender (male vs. female), chemotherapy regimen (CHOP vs. CVP), and tumor load at baseline (high vs. medium vs. low). In the majority of the subgroups analyzed, the ORR point estimates were numerically higher among patients treated with rituximab SC than those treated with rituximab IV. Point estimates for ORR were numerically lower in the rituximab SC arm for patients with high C_{trough}, low BSA, and female patients. The interpretation of the subgroup analysis is limited by the small

sample size and wide 95% confidence intervals associated with the point estimates for ORR within each subgroup.

Table 3 BO22334: Subgroup Analysis of Overall Response Rate at End of Induction - Stage 1 (ITT)

	Overall Response Rate (CR, CRu, PR) at End of Induction		
Subgroup	**Rituximab IV [95% CI]**	**Rituximab SC [95% CI]**	**Difference [95% CI]**
C_{trough}[1]			
Low	22/25 (88.0%) [68.8%,97.5%]	9/9 (100.0%) [66.4%,100.0%]	12.00% [-6.6%,30.6%]
Medium	16/18 (88.9%) [65.3%,98.6%]	17/17 (100.0%) [80.5%,100.0%]	11.11% [-6.8,29.0%]
High	5/5 (100.0%) [47.8%,100.0%]	26/28 (92.9%) [76.5%,99.1%]	-7.14% [-26.9,12.6%]
Area Under the Curve (AUC)[1]			
Low	26/28 (92.9%) [76.5%,99.1%]	10/10 (100.0%) [69.2%,100.0%]	7.14% [-7.6%,21.9%]
Medium	21/24 (87.5%) [67.6%,97.3%]	13/13 (100.0%) [75.3%,100.0%]	12.50% [-4.9%,29.9%]
High	5/6 (83.3%) [35.9%,99.6%]	30/32 (93.8%) [79.2%,99.2%]	10.42% [-31.7%,52.5%]
Body Surface Area (BSA)[1]			
Low	15/16 (93.8%) [69.8%,99.8%]	22/26 (84.6%) [65.1%,95.6%]	-9.13% [-31.0%,12.7%]
Medium	20/26 (76.9%) [56.4%,91.0%]	15/16 (93.8%) [69.8%,99.8%]	16.83% [-6.9%,40.5%]
High	18/21 (85.7%) [63.7%,97.0%]	20/21 (95.2%) [76.2%,99.9%]	9.52% [-10.8%,29.9%]
Gender			
Male	27/33 (81.8%) [64.5%,93.0%]	25/26 (96.2%) [80.4%,99.9%]	14.34% [-2.9%,31.6%]
Female	27/31 (87.1%) [70.2%,96.4%]	32/37 (86.5%) [71.2%,95.5%]	-0.61% [-18.6%,17.4%]
Chemotherapy Backbone			
CHOP	34/40 (85.0%) [70.2%,94.3%]	37/40 (92.5%) [79.6%,98.4%]	7.50% [-7.7%,22.7%]
CVP	20/24 (83.3%) [62.6%,95.3%]	20/23 (87.0%) [66.4%,97.2%]	3.62% [-19.3%,26.5%]
Tumor Load at Baseline[1]			
Low	18/19 (94.7%) [74.0%,99.9%]	22/23 (95.7%) [78.1%,99.9%]	0.92% [-15.1%,16.9%]
Medium	21/24 (87.5%) [67.6%,97.3%]	17/18 (94.4%) [72.7%,99.9%]	6.94% [-13.2%,27.1%]
High	15/21 (71.4%) [47.8%,88.7%]	18/22 (81.8%) [59.7%,94.8%]	10.39% [-17.8%,38.5%]

1 Patients were grouped, based on C_{trough}, AUC, BSA, or tumor load, into one of three subpopulations: low (BSA or tumor load $\leq$ 33rd percentile), medium (BSA or tumor load between 33rd and 66th percentiles), and high (BSA or tumor load $\geq$ 66th percentile).
Source: CSR BO22334, Table 15 (rr002_I_001, rr003_I_001, rr005_I_001, rr006_I_001, rr007_I_001, rr008_I_001)

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of efficacy for trial BO22334

Title: Sabrina study			
Study identifier	Study BO22334, stage 1		
Design	A two-stage phase III, international, multicenter, randomized, controlled, open-label study to investigate the PK, efficacy and safety of rituximab SC in combination with CHOP or CVP versus rituximab IV in combination with CHOP or CVP in patients with previously untreated FL followed by maintenance treatment with either rituximab SC or rituximab IV.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		**February 04, 2010 (first patient screened) to June 12, 2012 (data snapshot date)** not applicable not applicable
Hypothesis	Non-inferiority		
Treatments groups	Rituximab SC		Rituximab SC: first cycle rituximab IV (375 mg/m^2) plus 7 cycles of rituximab SC in combination with up to 8 cycles of CHOP or CVP chemotherapy administered every 3 weeks. Rituximab SC was given at a fixed dose of 1400 mg as determined in the Phase Ib study BP22333. Patients achieving at least partial response (PR) at the end of induction entered rituximab SC maintenance therapy once every 8 weeks for 96 weeks. N = 63 rituximab SC arm (n = 40 receiving CHOP, n= 23 receiving CVP)
	Rituximab IV		Rituximab IV: 8 cycles of rituximab IV in combination with up to 8 cycles of CHOP or CVP chemotherapy administered every 3 weeks. Patients achieving at least PR at the end of induction entered rituximab IV maintenance therapy once every 8 weeks for 96 weeks. Rituximab IV was used at the standard dose of 375 mg/m^2. N = 64 rituximab IV arm (n = 40 receiving CHOP, n= 24 receiving CVP)
Endpoints and definitions	Primary endpoint	C though	The primary objective of Stage 1 was to estimate the ratio of C_{trough} of rituximab obtained at Cycle 7, 21 days after SC administration to that obtained after IV administration ($C_{trough(SC)}/C_{trough(IV)}$ during Cycle 7 of induction treatment).

	Secondary endpoint	ORR	comprising CR, CRu and PR, at the end/completion of induction treatment
	Secondary endpoint	CRR	comprising CR and CRu at the end/completion of induction treatment
Database lock	**June 12, 2012 (data snapshot date)** The snapshot date of June 12, 2012 was chosen when all patients had completed their final assessment following completion of induction treatment.		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (ITT)		
	Secondary endpoint ORR*	Rituximab **IV** + chemo	Rituximab **SC** + chemo
		54/64 (84.4%)	N = 57/63 (90.5%)
		95% CI [73.1; 92.2]	95% CI [80.4; 96.4]
		P-value (Chi-sq. test) 0.3002	
	Secondary endpoint CRR*	Rituximab **IV** + chemo	Rituximab **SC** + chemo
		19/64 (29.7 %)	29/64 (46.0%)
		95% CI [18.9 ; 42.4]	95% CI [33.4; 59.1]
		P-value (Chi-sq. test) 0.0575	
Notes	*Response rates (ORR and CRR) at the end/completion of induction treatment were analyzed in frequency tables including 95% two-sided Pearson – Clopper confidence intervals (CIs) by treatment group For the difference in response rates, 95% two-sided CIs (Hauck – Andersen) were calculated. Other important secondary endpoints as Time-to-event efficacy endpoints (progression-free survival (PFS) and overall survival (OS) are not available at this time.		

Analysis performed across trials (pooled analyses and meta-analysis)

Study BO22334 is the only study from which efficacy data are available in support of the registration of rituximab SC

Clinical studies in special populations

No new studies in special populations have been performed

Supportive studies

No supportive studies have been performed

2.5.3. Discussion on clinical efficacy

The Applicant has submitted an extension application for registration of a new formulation of rituximab for subcutaneous injection (rituximab SC) at a fixed dose of 1400 mg.

Design and conduct of clinical studies

To investigate the efficacy of rituximab SC one study (study BO22334) was included. Study BO2234 is a two-stage phase III, international, multicenter, randomized, controlled, open-label study to investigate the PK, efficacy and safety of rituximab SC in combination with CHOP or CVP versus rituximab IV in combination with CHOP or CVP in patients with previously untreated FL followed by maintenance treatment with either rituximab SC or rituximab IV. The basis for submission for the line extension application was only data from stage 1 of the study (induction treatment). Stage 2 (maintenance therapy) is ongoing. Stage 1 of the phase III study BO22334 has been conducted to demonstrate non-inferiority of rituximab SC 1400 mg to rituximab IV 375 mg/m^2 in terms of C_{trough} in FL induction and by extrapolating in the NHL indication. To evaluate the potential impact of the SC route of administration on the anti-lymphoma activity of rituximab in stage 1 of the study, a numerical comparison of point estimates and 95% CIs for ORR for both treatment groups at the end of induction was chosen as the primary parameter to exclude major differences in efficacy between rituximab SC and rituximab IV. This approach was found acceptable given the anticipated non-inferior C_{trough} levels with rituximab SC compared with rituximab IV. The design of the study is found adequate. The population did not include children <18 years of age.

Efficacy data and additional analyses

It was concluded from the clinical pharmacology data that R-SC was non-inferior to R-IV in terms of the primary endpoint Ctrough in Study BP22333 (cycle 2, maintenance treatment) and Study BO22334 (cycle 7, induction treatment). However; the overall exposure, in terms of AUC, was about 40% higher in the R-SC compared to the R-IV.

The efficacy results from study BO22334 showed that an ORR = 84.4%, 95% CI [73.1; 92.2] in the rituximab IV arm and 90.5%, 95% CI [80.4; 96.4] for the rituximab SC army, P-Value (Chi-squared Test) = 0.3002. The numerical comparison of point estimates and 95% CIs for ORR for both treatment groups at the end of induction did not show major differences between rituximab SC and rituximab IV. The numerical comparison of point estimates and 95% CIs for ORR for both treatment groups at the end of induction did not show major differences between rituximab SC and rituximab IV.

Furthermore, a CRR of 29.7 %, 95% CI [18.9 ; 42.4] was observed for the IV arm and 46.0%, 95% CI [33.4; 59.1] for the SC arm, P-value (Chi-sq. test) = 0.0575. The higher percentage of CRR in the rituximab SC arm compared to the rituximab IV arm may be due to the bigger exposure with the SC formulation.

Data generated in patients with follicular lymphoma can be extrapolated to the other NHL indications using the same dose and regimens. In this aspect it is agreed that extrapolation of the *induction* efficacy results in FL to treatment of CD20+diffuse large B-cell NHL can be done, due to the same regimen and dose. However, concerning the proposed maintenance therapies and the induction therapy in combination with chemotherapy, the regimens are different from the induction monotherapy therapy in relapsed stage III-IV follicular lymphoma. For the latter, extrapolation was not considered sufficiently evident by the CHMP, and further justification was requested. The underlying assumption of the PK bridging approach was that attaining rituximab serum Ctrough levels with the SC formulation at least as high as those achieved with established IV dose would result in a non-inferior degree of target-site saturation and the same degree of efficacy, regardless of the route of administration. The idea is that the target tissue is never underexposed in

comparison to an already established exposure reached by IV dosing, i.e. there is, from a scientific perspective, not a higher chance of development of resistance. Another underlying assumption of this clinical bridging approach is that the anti-lymphoma activity of rituximab would not depend on the underlying B-cell malignancy. The effect size of rituximab in FL appears sufficiently large in order to be a "sensitive model" to detect potential differences between rituximab SC and IV as regards efficacy. Based on the comparative IV/SC PK data in study BO2234, the PK following weekly administration can be modelled. As pharmacology of rituximab is not expected to be different in the relapsed, stage III-IV FL patients, extrapolation seems possible even considering the different dosing interval of once a week as compared to every 3 weeks. However, the concomitant estimated mean Ctrough levels have a considerably higher ratio of 1.9, which means it is even higher in subjects with low BSA. Such a high exposure has not been tested in the current studies. This would mean that underexposure in the various HL indications will not be an issue, but the safety profile corresponding to an unequivocally high Ctrough level may be. This would prevent the extrapolation to the stage III-IV FL indication at this time. Comparative safety data in the stage III-IV FL treatment setting with once a week rituximab SC 1400 mg for 4 weeks, are not available at this time, this part of the indication was withdrawn. It is of importance to highlight the reasons for excluding this indication and appropriate statements that it is not recommended to treat patients that meet the indication of "Mabthera monotherapy in the treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy" with Mabthera SC are included in section 4.4. The educational material should also reflect this issue (see RMP).

Efficacy endpoints are only included as secondary endpoints in the provided results from stage 1 of the study BO22334. The endpoints ORR, CRR, PFS and OS are accepted as relevant efficacy endpoints, however; only ORR and CRR are provided. The most compelling endpoints; PFS and OS are not available at this point in time. Due to the increased exposure of rituximab SC long term safety issues which potentially could influence the overall survival cannot be excluded. Timelines with regard to the provisions of PFS and OS data have been agreed.

2.5.4. Conclusions on the clinical efficacy

Submission of results on time –related endpoints on an on-going basis is agreed as follows:

Study	Availability of Interim/Primary/Updated CSR	Availability of Final CSR
BP22333		
Stage 1 Stage 2	CSR BP22333[a] October 2012 (both stages)	Q2/2014 (both stages)
BO22334		
Stage 1	Interim CSR BO22334[a] October 2012 (Stage 1 only)	Q3/2018 (both stages)
Stage 2	Updated CSR BO22334[b] by end of Q3/2014 (both stages)	
BO25341		
Part 1 Part 2	Primary CSR BO25341[c] by end of Q4/2014 (both parts)	Q4/2018 (both parts)

a Submitted as part of the Line Extension Application.
b To report analysis of primary endpoint (overall response rate at end of induction) for Stage 2 and available safety and immunogenicity data from both stages of the ongoing study.
c To report analysis of primary endpoint (C_{trough} non-inferiority) for Part 2 and available safety and immunogenicity data from both parts of the ongoing study.

2.6. Clinical safety

Safety data in support of the registration of rituximab solution for subcutaneous injection (rituximab SC) 1400 mg are available from three studies, as in table 1. Data are presented per individual trial.

Table 23. Summary of studies contributing to safety evaluation of rituximab SC.

Study No. (Phase)	Title	Rituximab Dose and Route of Administration	Patients Enrolled	Study Status / Data Cut-Off Date
BP22333 (SparkThera) Phase Ib	A two-stage phase Ib study to investigate the pharmacokinetics, safety and tolerability of rituximab subcutaneous formulation in patients with follicular lymphoma as part of maintenance treatment	Stage 1 dose selection: 375 mg/m^2 IV vs 375, 625, 800 mg/m^2 SC (q2m/q3m, single cycle at maintenance C2 or later); Stage 1 SC extension phase: 1400 mg SC (dose determined in Stage 1) for 1–5 cycles; Stage 2: 375 mg/m^2 IV vs 1400 mg SC (q2m/q3m, 1–11 cycles from maintenance C2 onwards)	N=124 (Stage 1) N=157 (Stage 2)	Stage 1 and Stage 2 primary analysis completed, follow-up ongoing Safety data cut-off: 7 March 2012
BO22334 (SABRINA) Phase III	A two-stage phase III, international, multicenter, 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	Stage 1 and Stage 2: induction: 375 mg/m^2 IV vs 1400 mg SC (q3w R-CHOP or R-CVP: C1 375 mg/m^2 IV all patients; C2–8 IV vs SC); patients with at least PR at end of induction receive maintenance: 375 mg/m^2 IV vs 1400 mg SC (q2m maintenance with IV or SC as randomized to induction)	N=127 (Stage 1)	Stage 1 induction treatment completed, maintenance ongoing Safety data cut-off: 12 June 2012
BO25341 (SAWYER) Phase Ib	An adaptive, comparative, randomized, parallel-group, multicenter, phase Ib study of subcutaneous rituximab versus intravenous rituximab both in combination with chemotherapy (fludarabine and cyclophosphamide) in patients with previously untreated CLL	Part 1: 1400, 1600, 1870 mg SC (q4w R-FC, single cycle SC at C6) Part 2: 500 mg/m^2 IV vs 1600 mg SC (dose determined in Part 1) (q4w R-FC: C1 375 mg/m^2 IV all patients; C2–6 IV vs SC)	N=64 (Part 1)	Part 1 treatment completed, follow-up ongoing Safety data cut-off: 4 April 2012

C: cycle; CHOP: cyclophosphamide, vincristine, doxorubicin, and prednisone; CLL: chronic lymphocytic leukemia; CVP: cyclophosphamide, vincristine, and prednisone; FC: fludarabine and cyclophosphamide; IV: intravenous;
NHL: non-Hodgkin's lymphoma; PR: partial response; q2/3m: every 2 or 3 months; q3/4w: every 3 or 4 weeks; SC: subcutaneous.

Patient exposure

A total of 1413 cycles of rituximab SC were administered to 303 patients across the three studies (table 24 and 25), of which 1215 cycles were with the 1400 mg dose. Among 182 patients with NHL who received at least one cycle of rituximab SC at the final selected dose of 1400 mg, 165 patients received at least three sequential cycles of rituximab SC 1400 mg, and 130 patients received five sequential cycles of rituximab SC 1400 mg. Overall, 70 patients were treated with rituximab SC 1400 mg for at least 12 months: 63 patients in Stage 2 of Study BP22333, and 7 patients in Stage 1 of Study BO22334.

Table 24. Exposure to rituximab across studies.

No. of Cycles of Rituximab[d]	BO22334[a]		BP22333[b]						BO25341				Total Patients Receiving R-SC across Studies
	Stage 1		Stage 1[c]				Stage 2		Part 1				
	R-SC 1400 mg	R-IV	R-SC 375 mg/m^2	R-SC 625 mg/m^2	R-SC 800 mg/m^2	R-IV	R-SC 1400 mg	R-IV	R-SC 1400 mg	R-SC 1600 mg	R-SC 1870 mg	R-SC 1000 mg	
1	0 (*0*)	1	19 (*2*)	22 (*4*)	24 (*2*)	1	2	6	16 (*0*)	17 (*0*)	22 (*0*)	1 (*0*)	**123**
2	0 (*0*)	2	1 (*5*)	3 (*4*)	1 (*3*)	1	5	2	– (*16*)	– (*17*)	– (*22*)	– (*1*)	**10**
3	0 (*0*)	0	0 (*2*)	3 (*4*)	2 (*5*)	2	3	1	–	–	–	–	**8**
4	1 (*0*)	1	7 (*2*)	2 (*2*)	6 (*0*)	0	3	3	–	–	–	–	**18**
5	2 (*1*)	1	2 (*1*)	0 (*6*)	3 (*3*)	0	4	4	–	–	–	–	**10**
6	1 (*2*)	1	5 (*1*)	4 (*3*)	4 (*3*)	1	14	21	–	–	–	–	**29**
7	2 (*1*)	1	– (*7*)	– (*1*)	– (*6*)	3	7	9	–	–	–	–	**8**
8	20 (*2*)	4	– (*3*)	– (*0*)	– (*1*)	0	5	6	–	–	–	–	**7**
9	17 (*20*)	18	– (*3*)	– (*0*)	– (*0*)	0	15	8	–	–	–	–	**35**
10	13 (*17*)	17	– (*2*)	– (*2*)	– (*5*)	3	12	9	–	–	–	–	**29**
11	4 (*13*)	14	– (*6*)	– (*8*)	– (*12*)	5	7	9	–	–	–	–	**20**
12	2 (*4*)	3	–	–	–	–	–	–	–	–	–	–	**4**
13	0 (*2*)	2	–	–	–	–	–	–	–	–	–	–	**2**
Total Patients	**62**	65	**34**	**34**	**40**	16	**77**	77	**16**	**17**	**22**	**1**	**303**

a Number of cycles received in induction and maintenance settings. All patients received rituximab IV at the first cycle (see also footnote d).
b Number of cycles received in maintenance setting.
c SC extension phase: 43 patients received at least one dose of 1400 mg in Stage 1 of study BP22333.
d No. of cycles of rituximab IV and/or SC administrations provided in parentheses (*italicized*).
Data source: tt002_S_001 (BO22334); tt002_S_001, t_ahr001_S_001, tt002_S_002 (BP22333); ae002_s001 (BO25341).

Table 25. Extent of exposure across studies.

	BO22334		BP22333						BO25341				Total across Studies
	Stage 1		Stage 1				Stage 2		Part 1				
	R-SC 1400 mg	R-IV	R-SC 375 mg/m^2	R-SC 625 mg/m^2	R-SC 800 mg/m^2	R-IV	R-SC 1400 mg	R-IV	R-SC 1400 mg	R-SC 1600 mg	R-SC 1870 mg	R-SC 1000 mg	
No. of Patients Treated[a]	62	65	34	34	40	16	77	77	16	17	22	1	**461 patients**
Patients with ≥ 1 cycle of R-SC[b]	62	–	34	34	40	–	77	–	16	17	22	1	**303 patients**
No. of Cycles of R-SC[b]	545	–	89	69	95	–	558	–	16	17	23	1	**1413 cycles**
No. of Cycles of R-SC 1400 mg[b]	545	–	45	24	27	–	558	–	16	0	0	0	**1215 cycles**
Median Observation Time (months)[c]	8.87	8.74	22.0	18.7	22.0	23.3	14.9	14.9	7.4	7.3	9.0	10.0	–
Median Time in Follow-Up (months)[d]	2.6 n=4	4.0 n=5	6.1 n=27	6.1 n=29	3.4 n=36	4.5 n=15	0.3 n=34	0.3 n=32	1.9 n=16	1.8 n=17	5.9 n=22	6.3 n=1	–

a Data source: ae008_s001 (BO22334); ae008_s001, ae008_s002 (BP22333); ae002_s001 (BO25341).
b Data source: tt002_S_001 (BO22334); t_ahr001_s_001, tt002_s_002 (BP22333); ae002_s001 (BO25341).
c Data source: ot002_S_001 (BO22334); ot001_s_001, ot001_s_002 (BP22333); pd007_s001 (BO25341).
d Data source: ah003_s001 (BO22334); adh17_s001, adh17_s002 (BP22333); ah005_s001 (BO25341). 1 month=30.4375 days.

Study BP22333

In Stage 1 of study BP22333, the Stage 1 SAP comprised 124 patients (16 patients rituximab IV 375 mg/m^2 [Cohort A], 34 patients rituximab SC 375 mg/m^2 [Cohort B], 34 patients rituximab SC 625 mg/m^2 [Cohort C], and 40 patients rituximab SC 800 mg/m^2 [Cohort D]). At the time of clinical cut-off (March 07, 2012), the median observation time was 22 months. A total of 43 patients participated in the optional SC extension phase (15 patients Cohort B, 12 patients Cohort C, and 16 patients Cohort D), and opted to receive rituximab SC 1400 mg for their remaining cycles of maintenance treatment. These patients were analysed according to the randomized treatment initially received.

In Stage 2 of study BP22333, at the time of clinical cut-off (March 07, 2012), the median observation time was 15 months among the Stage 2 SAP (77 patients rituximab SC vs 77 patients rituximab IV). The treatment groups were generally well balanced in terms of median treatment duration (14.8 months rituximab SC vs 13.8 months rituximab IV). The median number of cycles of rituximab received was 8 in the rituximab SC group and 6 in the rituximab IV group (randomization was not stratified according to previous numbers of rituximab IV cycles prior to study entry). Patients receiving rituximab SC 1400 mg (fixed dose) had a higher median cumulative dose of rituximab than patients receiving rituximab IV 375 mg/m^2 (i.e. 9800 mg rituximab SC vs 4620 mg rituximab IV). The median duration of the rituximab SC administration was 5.9 minutes.

Study BO22334

In Stage 1 of study BO22334, at the time of reporting (database snapshot date: June 12, 2012), the median duration of observation for the Stage 1 SAP (62 patients rituximab SC vs 65 patients rituximab IV) was approximately 9 months and similar across the treatment groups (8.8 months rituximab SC vs 8.7 months rituximab IV). The median duration of treatment was similar across both treatment groups (8.6 months rituximab SC vs 8.5 months rituximab IV). The median number of cycles of rituximab received was 10 in both groups, and the median cumulative dose of rituximab received was 13190 mg in the rituximab SC group (fixed dose) and 6667 mg in the rituximab IV group (BSA-adjusted dose). The median duration of rituximab SC administration was 6.1 minutes. Exposure to chemotherapy was similar across treatment groups among patients receiving CHOP (N=80) and among those receiving CVP (N=47).

Study BO25341

In Part 1 of CLL study BO25341, 64 patients were enrolled to receive rituximab IV at Cycle 5 and a test dose of rituximab SC at Cycle 6 of treatment, in combination with FC chemotherapy. Five patients discontinued treatment prior to Cycle 5, including one patient who died soon after enrolment. Three patients were withdrawn after their rituximab IV infusion at Cycle 5 and hence did not receive rituximab SC at Cycle 6. One patient enrolled to receive 1870 mg rituximab SC at Cycle 6 received only 1000 mg rituximab SC in error. The SAP at Cycle 6 comprised 56 evaluable patients (16 patients rituximab SC 1400 mg, 17 patients rituximab SC 1600 mg, 22 patients rituximab SC 1870 mg, and 1 patient rituximab SC 1000 mg). At the time of clinical cut-off (April 04, 2012), the median duration of observation was 7.4 months.

Adverse events

The safety data from the three studies (BP22333, BO22334 and BO25341) are summarized individually, since the studies differed substantially in terms of study design, indication (NHL vs

CLL), treatment setting (induction vs maintenance), extent of prior exposure to rituximab, dosage and duration of treatment.

An overview of safety of rituximab SC 1400 mg compared with rituximab IV 375 mg/m2 in the two NHL studies (Stage 2 of Study BP22333 and Stage 1 of Study BO22334) is presented in table 26. The table summarizes the key safety findings in the induction setting, when previously untreated NHL patients received rituximab-CHOP/rituximab-CVP immunochemotherapy (Study BO22334, Stage 1), and in the maintenance setting, when patients responding to prior induction treatment received rituximab maintenance (Study BP22333, Stage 2). Some broad trends can be seen across the studies as follows: Aside from the occurrence of administration – related reactions (ARRs), the rituximab SC 1400 mg and rituximab IV 375 mg/m^2 treatment groups in each study were balanced with respect to the proportion of patients experiencing AEs, Grade ≥ 3 AEs, SAEs and AEs leading to withdrawal. One death was recorded in each of the rituximab SC treatment groups, and both deaths were considered unrelated to study treatment. The difference in the safety profile regarding ARRs across the SC and IV treatment groups reflects the expected change in the ARR profile as a result of the subcutaneous route of administration. An ARR was defined as any AE occurring during or within 24 h of infusion/injection that was considered by the investigator to be related to the study drug.

Table 26. Overview of safety in NHL studies BP22333 (Stage 2) and BO22334 (Stage 1).

Total patients with at least one:	BP22333, Stage 2 (MAINTENANCE)[a]		BO22334, Stage 1 (INDUCTION)[b]	
	Rituximab IV 375 mg/m^2 N=77 No. (%)	Rituximab SC 1400 mg N=77 No. (%)	Rituximab IV 375 mg/m^2 +Chemo N=65 No. (%)	Rituximab SC 1400 mg +Chemo N=62 No. (%)
AE	61 (79)	61 (79)	57 (88)	57 (92)
total number of AEs	*257*	*291*	*363*	*528*
Grade≥3 AE	13 (17)	14 (18)	30 (46)	29 (47)
Serious AE	11 (14)	9 (12)	14 (22)	14 (23)
ARR	3 (4)	24 (31)	21 (32)	31 (50)
AE leading to withdrawal	4 (5)	4 (5)	3 (5)	2 (3)
AE leading to death	0 (0)	0 (0)	0 (0)	1 (2)
Deaths	0 (0)	1 (1)	0 (0)	1 (2)

Results based on the respective safety analysis populations for the two studies. Investigator text for Adverse Events encoded using MedDRA version 15.0. Percentages are based on N. Multiple occurrences of the same adverse event in one individual counted only once. An ARR was defined as any AE occurring during or within 24 h of infusion/injection that was considered by the investigator to be related to the study drug.

a Study BP22333: Deaths are derived from the Death page.

b Study BO22334: Deaths are derived from the Death page. Withdrawals derived from Study Completion page. Safety results are predominantly from the induction period.

The key AE findings for study BP22333 are summarized below:

In Stage 2 of study BP22333, 79% of patients per treatment group experienced at least one AE. The incidence of Grade ≥3 AEs, SAEs, and AEs leading to withdrawal of treatment was also balanced following treatment with rituximab SC or rituximab IV. There were no fatal AEs in either treatment group. ARRs were reported more commonly in the rituximab SC group (difference 27%). However, all ARRs were non-severe and non-serious events and mainly local injection site reactions reflecting the expected change of the ARR profile when switching to the subcutaneous route of administration. The overall profile of AEs reported in Stage 2 of the study was similar following treatment with either rituximab SC or rituximab IV.

The AE with the highest incidence was administration-related reactions (ARRs: 31% rituximab SC vs 4% rituximab IV). By system organ class (SOC), the most commonly reported AEs occurred in the SOC infections and infestations (43% rituximab SC vs 56% rituximab IV). Other SOCs in which AEs were commonly reported included gastrointestinal disorders (31% rituximab SC vs 17% rituximab IV), injury, poisoning and procedural complications (36% rituximab SC vs 12% rituximab IV; which includes ARRs), and musculoskeletal and connective tissue disorders (25% rituximab SC vs 22% rituximab IV). The majority of events reported across the treatment groups were NCI-CTCAE Grade 1 or 2 events. The treatment groups were balanced with respect to the incidence of Grade ≥3 AEs (18% rituximab SC vs 17% rituximab IV). The highest incidence of Grade ≥3 AEs was reported in the SOC blood and lymphatic system disorders (3% rituximab SC vs 6% rituximab IV). Besides Grade ≥3 neutropenia (3% [2 patients] per group), the incidence of other Grade ≥3 AEs reported was no more than 1% (i.e. 1 patient). No Grade 5 events were recorded.

Key AE findings for study BO22334 are:

In Stage 1 of study BO22334, the proportion of patients reporting AEs was comparable between the rituximab SC group and the rituximab IV group (92% vs 88%, respectively). The proportion of patients with Grade ≥3 AEs and SAEs was comparable across treatment groups. There was one Grade 5 AE of myocardial infarction that was considered unrelated to treatment in a patient treated with rituximab SC. ARRs were more common among patients treated with rituximab SC (difference 18%) (Section 5.4), however, the ARRs were mainly mild or moderate injection site reactions that are considered expected when switching to the subcutaneous route of administration. The overall safety profile of rituximab SC was similar to that of rituximab IV, and no new clinically relevant safety signals were identified.

Key AE findings for the single cycle administration in study BP22333 and study BO25341 are:

During the single cycle of randomized treatment in Stage 1 of study BP22333, aside from ARRs, the incidence and types of AEs were similar across treatment groups. There were no clear trends related to event incidence or intensity/seriousness and dose of study drug administered (rituximab SC 375, 625, or 800 mg/m^2). The most common AE by preferred term was ARRs (1/16 patients rituximab IV, 7/34 patients rituximab SC 375 mg/m^2, 8/34 patients rituximab SC 625 mg/m^2, and 9/40 patients rituximab SC 800 mg/m^2). The majority of events reported were Grade 1 or 2 events. There were very few Grade 3 AEs recorded (1/16 patients rituximab IV [appendicitis], 2/34 patients rituximab SC 375 mg/m^2 [neutropenia and diarrhoea], and 2/40 patients rituximab SC 800 mg/m^2 [influenza and lung infection]), with no Grade ≥3 AEs reported in the intermediate-dose (rituximab SC 625 mg/m^2) group. There were no Grade 4 or Grade 5 AEs recorded.

During the single cycle of rituximab SC in Part 1 of CLL study BO25341, more patients experienced at least one AE with higher doses of rituximab SC (7/16 patients rituximab SC 1400 mg, 10/17 patients rituximab SC 1600 mg, and 18/22 patients rituximab SC 1870 mg [and 1/1 patient rituximab SC 1000 mg]). However, a similar variation was observed at the previous cycle (Cycle 5, IV administration), during which patients were dosed according to BSA. The majority of events in each treatment group at Cycle 6 were Grade 1 or 2 events. The treatment groups were balanced with respect to the incidence of Grade ≥3 AEs (3/16 patients rituximab SC 1400 mg, 4/17 patients rituximab SC 1600 mg, and 3/22 patients rituximab SC 1870 mg [and 1/1 patient rituximab SC 1000 mg (dosing error)]). The highest incidence of Grade ≥3 AEs was reported in the SOC of blood and lymphatic system disorders, with neutropenia experienced by 2/16 patients in the rituximab SC

1400 mg group and 3/22 patients in the rituximab SC 1870 mg group. No Grade 5 events were recorded.

Serious adverse event / deaths / other significant events

There were no Grade 5 AEs in Stage 1 or Stage 2 of study BP22333. A total of 21 SAEs were reported for 20 patients in Stage 2 of study BP22333 (9/77 patients [12%] rituximab SC vs 11/77 patients [14%] rituximab IV). Of note, the incidence of each preferred term was not reported in more than one patient per treatment group. There was one pregnancy reported, in a 40-year-old patient randomized to receive rituximab SC 1400 mg in Stage 2 of study BP22333. The patient became pregnant while on study and later experienced a spontaneous abortion (SAE). The patient had received eight cycles of maintenance treatment with rituximab SC on study prior to the event. Cycle 9 was delayed due to this event but was administered at a later point.

A total of 54 SAEs were reported for 28 patients during Stage 1 of study BO22334 (14/62 patients [23%] rituximab SC vs 14/65 patients [22%] rituximab IV). By SOC, the most commonly reported SAEs overall were infection and infestations (6% rituximab SC vs 9% rituximab IV) and blood and lymphatic system disorders (11% rituximab SC vs 5% rituximab IV). The most commonly reported SAE was febrile neutropenia (10% [6 patients] rituximab SC vs 3% [2 patients] rituximab IV). Two of the six patients in the rituximab SC arm who reported febrile neutropenia had experienced SAEs of febrile neutropenia during the first cycle (rituximab IV). One of these patients reported a total of 14 SAEs: the patient experienced a massive pleural effusion on Study Day 2 that required a thoracotomy with sequelae, including pneumonia, post-operative pain, and infection, all of which were reported as SAEs.

Among the SAEs reported among all patients in the rituximab SC group during Cycle 1 (when receiving rituximab IV), only SAEs of febrile neutropenia and abdominal pain were reported later during Cycles 2 – 8 of induction (with rituximab SC). During the single cycle of randomized treatment in Stage 1 of study BP22333, three patients experienced SAEs (1 patient rituximab IV [appendicitis], 1 patient rituximab SC 625 mg/m^2 [peripheral artery angioplasty], and 1 patient rituximab SC 800 mg/m^2 [angina pectoris]). No SAEs were reported in the low-dose (rituximab SC 375 mg/m2) group. During the single cycle of rituximab SC treatment in Part 1 of CLL study BO25341, two patients in the rituximab SC 1600 mg group experienced SAEs (diarrhoea and cholecystitis, respectively). No SAEs were reported in the other rituximab SC dose groups.

Deaths

In Stage 2 of study BP22333, there was one death reported: a 63-year-old woman randomized to the rituximab SC 1400 mg group was withdrawn from the study because of progressive disease and later died due to disease progression. The death occurred after the patient was withdrawn from the study and approximately 8 months following the last treatment with study drug, and was not considered related to the study drug.

Two deaths were reported in Stage 1 of study BO22334, both among patients in the rituximab SC group. A 64-year-old female patient experienced a Grade 5 AE of myocardial infarction following Cycle 5 of treatment; the death was considered unrelated to study drug. A 62-year-old female patient, who was withdrawn from the study after Cycle 9 (first cycle of maintenance) due to progressive disease, subsequently died due to disease progression.

There were no Grade 5 AEs recorded in Part 1 of CLL study BO25341 during the single cycle of rituximab SC treatment. There was one death of unknown reason in study BO25341 soon after the patient's enrolment to the study and prior to receiving study drug.

Laboratory findings

Haematology

Study BP22333

There were no consistent trends or patterns of changes in haematology parameters. There were few relevant shifts from baseline.

Study BO22334

The majority of patients in both treatment arms showed no change in NCI-CTCAE grade for haematology test parameters during Stage 1. The number of patients whose haematology values worsened during Stage 1 and shifted to NCI-CTCAE Grade 3/4 is summarized in table 27. The highest number of shifts to Grade 3/4 was observed for neutropenia for both treatment arms. The number of shifts to Grade 3/4 for lymphopenia and leukopenia was higher in the rituximab SC arm compared with the rituximab IV arm.

Table 27. BO22334: Summary of newly occurring Grade ≥3 laboratory values during Stage 1 (SAP).

Parameter	Rituximab IV + Chemo N = 65			Rituximab SC + Chemo N = 62		
	n	Grade 3 n (%)	Grade 4 n (%)	n	Grade 3 n (%)	Grade 4 n (%)
Hemoglobin (decrease)	65	-	-	62	2 (3)	0
White blood cell (decrease)	65	8 (12)	2 (3)	62	9 (15)	5 (8)
White blood cell (increase)	65	-	-	62	1 (2)	-
Platelets (decrease)	65	-	1 (2)	62	-	2 (3)
Lymphocytes (decrease)	64	9 (14)	2 (3)	62	14 (23)	3 (5)
Neutrophils (decrease)	64	13 (20)	10 (16)	61	12 (20)	12 (20)

Source: CSR BO22334, Table 28
IV = intravenous; SC = subcutaneous.
Missing and non-numeric values were excluded from the analysis.

Serum Chemistry

Study BP22333

Uric acid levels displayed a consistent shift from baseline for rituximab SC across all dose groups. In Stage 1, there were 7, 6, and 6 patients in Cohorts B through D, respectively, who experienced a shift from Grade 0 at baseline to Grade 3 at end of treatment. There were no similar shifts for Cohort A. In Stage 2, there were 8 and 14 patients in Cohorts E and F, respectively, who experienced a shift from Grade 0 at baseline to Grade 3 at end of treatment. These shifts were not considered as medically relevant.

Other chemistry parameters did not show consistent trends or change patterns.

Study BO22334

There were very few shifts to Grade 3/4 for blood chemistry parameters, and for these parameters, there was little difference between the two treatment arms.

B-cells

Study BP22333

A summary of B-cell depletion for patients in Stage 2 of Study BP22333 is presented. Analysis of CD19+ lymphocyte subsets showed suppression of B-cells in both study arms at baseline and continued B-cell suppression throughout the study.

Available data from 124 patients in Stage 1 and 154 patients in Stage 2 confirmed effective depletion of $CD19^+$ cells in all patients at baseline. This is to be expected as the dataset consists entirely of peripheral blood counts from patients who had responded to a minimum of four cycles of 375 mg/m^2 rituximab IV in induction and also had at least one cycle of rituximab IV in the maintenance setting prior to enrollment into the study.

In Stage 1, available $CD19^+$ lymphocyte counts from patients at the 9-month follow/up visit showed an increase in B-cell levels at this time point compared with previous time points, with median counts of 0.05 $\times 10^9$ cells/L (Cohort A, n=6), 0.03 $\times 10^9$ cells/L (Cohort B, n=16), 0.02 $\times 10^9$ cells/L (Cohort C, n=15), and 0.03 $\times 10^9$ cells/L (Cohort D, n=7).

Among those patients enrolled in Stage 2 with available $CD19^+$ lymphocyte counts at the 9-month follow-up visit, an increase in B-cell levels could be seen in 3 rituximab IV patients and 2 rituximab SC patients at that time point, with median B-cell counts of 58 cells/mm^3 (range 0 - 75 cells/mm^3) and 33 cells/mm^3 (range 1 - 65 cells/mm^3), respectively. Although the sample size is limited, the results are consistent with the trend seen previously in patients with haematological malignancies treated with rituximab IV, where B-cell recovery begins within 6 months of treatment and generally returns to normal levels within 12 months after completion of therapy; although in some patients, this may take longer.

Study BO22334

Data on B-cell levels showed similar trends across the treatment arms, with significant depletion of peripheral B-cells following the first cycle of rituximab IV and continued depletion with additional cycles of induction treatment.

Absolute $CD19^+$ lymphocyte counts were available from 102 patients at baseline (pre-dose Cycle 1; 48 patients in the rituximab SC arm and 54 patients in the rituximab IV arm), with median $CD19^+$ cell counts of 0.12 $\times 10^9$ cells/L (range 0.00 - 27.12 $\times 10^9$ cells/L) for the rituximab SC arm and 0.05 $\times 10^9$ cells/L (range 0.01 - 25.48 $\times 10^9$ cells/L) for the rituximab IV arm (normal range: 0.08 - 0.616 $\times 10^9$ cells/L). Analysis of $CD19^+$ lymphocyte counts following Cycle 1 (IV) showed effective depletion of B-cells in both treatment arms by Cycle 2, with median counts of 0.00 $\times 10^9$ cells/L in both treatment arms pre-dose at Cycle 2 (range 0.00 - 8.23 $\times 10^9$ cells/L [rituximab SC arm] and 0.00 - 0.34 $\times 10^9$ cells/L [rituximab IV arm]). Median counts pre-dose at Cycle 3 were 0.00 $\times 10^9$ cells/L in both treatment arms (range 0.00 - 0.05 $\times 10^9$ cells/L [rituximab SC arm] and 0.00 - 0.11 $\times 10^9$ cells/L [rituximab IV arm]). Median B-cell counts remained zero in subsequent cycles indicating continued B-cell depletion over the treatment period.

Safety in special populations

Intrinsic

Demographic variables

Study BP22333

In Stage 1 events were experienced by a higher proportion of patients in the >70 years of age group for Cohort E than Cohort F (93% and 60%, respectively). The two cohorts were generally well balanced in terms of AEs by all other patient characteristics examined.

In Stage 2 Grade ≥3 AEs were experienced by a higher proportion of patients in the >70 years of age group for Cohort E than Cohort F (5 patients [36%] and 1 patient [10%], respectively). Within each cohort, a higher proportion of male patients than female patients experienced AEs with a Grade ≥3 (25% vs. 11% for Cohort E, and 28% vs. 11% for Cohort F).

The two cohorts in stage 2 were generally balanced with respect to incidence of SAEs by the various subgroups. For the gender category, more male patients than female patients experienced SAEs (19% of males in each cohort, compared with 11% and 7% of females in Cohorts E and F, respectively); a similar trend was observed for Grade ≥3 AEs. For patients aged >70 years, a greater proportion of patients in Cohort E than in Cohort F reported SAEs (4 patients [29%] versus 1 patient [10%], respectively).

Study BO22334

The treatment groups were generally well balanced in the subgroups for age, gender and race. More females than males experienced SAEs in both treatment groups (31% vs 12% for rituximab IV, and 28% vs 15% for rituximab SC).

Study BO25341

AEs in Study BO25341 are summarized by age, gender, and race for Cycle 5 and Cycle 6. The treatment groups were well balanced in terms of AEs with respect to demographic characteristics.

Body Surface Area

In moving from a BSA-adjusted dosing approach with the IV formulation to a fixed-dose approach with the SC formulation, there is a risk that patients with low BSA may be over-exposed to rituximab, which could lead to potential safety concerns with rituximab SC, and that patients with high BSA could be under-dosed, which could lead to potential concerns around the clinical efficacy of rituximab SC. Therefore, key safety findings (all-grade AEs, Grade ≥ 3 AEs, and SAEs) were analysed in subgroups by BSA at baseline.

Study BP22333

In Stage 2 of Study BP22333, AEs, Grade ≥3 AEs, and SAEs were summarized separately for patients with low BSA and high BSA in Cohorts E and F (see table 28) Low BSA was defined as BSA ≤1.6 m^2 for female patients or ≤1.9 m^2 for male patients, and high BSA was defined as BSA >1.6 m^2 for female patients or >1.9 m^2 for male patients. There were 25 patients from Cohort E and 22 patients from Cohort F with low BSA, whereas the high BSA subgroup was larger with 52 patients from Cohort E and 55 patients from Cohort F.

BSA did not affect the incidence of overall adverse events, as the treatment groups remained balanced. In the low BSA group, overall event incidence was 80% and 86% for Cohorts E and F, respectively. Similarly, in the high BSA group, overall event incidence was 79% and 76%, respectively.

BSA did not affect the incidence of Grade ≥3 AEs, as the treatment groups remained balanced. In the low BSA group, overall event incidence was 12% and 14% for Cohorts E and F. Similarly, in the high BSA group, overall event incidence was 19% and 18%, respectively.

There were no obvious differences in incidence and type of SAE with respect to the treatment cohort or BSA category. In the high BSA subgroup, SAEs were reported for 15% and 13% of patients in Cohorts E and F, respectively. In the low BSA subgroup, SAEs were reported for 12% and 9% of patients in Cohorts E and F, respectively.

Table 28. BP22333, Stage 2: Number of patients (%) with at least 1 AE, SAE or Grade ≥3 AE by BSA subgroups (SAP)

	Cohort E Rituximab IV 375 mg/m^2 N=77	Cohort F Rituximab SC 1400 mg N=77
AEs by Body Surface Area*		
Low	20/25 (80%)	19/22 (86%)
High	41/52 (79%)	42/55 (76%)
SAEs by Body Surface Area*		
Low	3/25 (12%)	2/22 (9%)
High	8/52 (15%)	7/55 (13%)
Grade ≥ 3 AEs by Body Surface Area*		
Low	3/25 (12%)	3/22 (14%)
High	10/52 (19%)	10/55 (18%)

* Low BSA was defined as BSA ≤1.6 m^2 for female patients or ≤1.9 m^2 for male patients. High BSA was defined as BSA >1.6 m^2 for female patients or >1.9 m^2 for male patients.

Study BO22334

For Stage 1 of Study BO22334, the number of AEs in subgroups based on BSA at baseline is presented in table 29. BSA subgroups in this study were defined based on the 33rd and 66th percentiles for BSA at baseline among the study population. The number of patients in these subgroups was relatively small (total 42 patients per BSA category from both treatment arms). However, the groups were well-balanced in terms of all AEs, SAEs, and Grade ≥ 3 AEs irrespective of BSA at baseline. Patients with the lowest BSA having the highest exposure following rituximab SC administration did not appear to experience a higher incidence in AEs compared to the rituximab IV arm. There was no clear relationship between these subgroups and risk of experiencing an AE.

Table 29. BO22334: Number of patients (%) with at least 1 AE, SAE or Grade ≥3 AE by BSA subgroups (SAP)

	Rituximab IV 375 mg/m^2 +Chemo	Rituximab SC 1400 mg +Chemo	Total
AEs by Body Surface Area*			
Low	14/16 (88)	24/26 (92)	38/42 (90)
Medium	23/27 (85)	14/15 (93)	37/42 (88)
High	19/21 (90)	19/21 (90)	38/42 (90)
SAEs by Body Surface Area*			
Low	3/16 (19)	5/26 (19)	8/42 (19)
Medium	9/27 (33)	7/15 (47)	16/42 (38)
High	2/21 (10)	2/21 (10)	4/42 (10)
Grade ≥ 3 AEs by Body Surface Area*			
Low	8/16 (50)	15/26 (58)	23/42 (55)
Medium	15/27 (56)	7/15 (47)	22/42 (52)
High	7/21 (33)	7/21 (33)	14/42 (33)

* Patients were grouped based on BSA into one of three subpopulations: low BSA ≤ 33rd percentile, medium BSA between 33rd and 66th percentiles, and high BSA ≥ 66th percentile.

Exploratory logistic regression analysis of safety by BSA

Overall, the median BSA among the study population in Study BO22334 was 1.81 m^2 (range 1.34 – 2.32 m^2): median BSA was 1.82 m^2 (range 1.34 – 2.30 m2) in the rituximab IV arm and 1.74 m^2 (range 1.37 – 2.32 m^2) in the rituximab SC arm.

To evaluate the assumption of homogeneity of the risk of having a SAE during the course of the study between rituximab SC and rituximab IV with BSA, the interaction term between BSA (low/medium/high) and treatment effect (rituximab SC vs. rituximab IV) was included in a logistic regression model (table 30). The interaction term was non-significant for the risk of experiencing a SAE or a Grade ≥3 AE (p = 0.8422 and p = 0.5773, respectively), concluding that the treatment effects are homogeneous among the BSA categories.

To assess the nature and direction of the interaction from a clinical perspective, the risk of experiencing a SAE or a Grade ≥3 AE during the course of the study was examined for each BSA category. An overall assessment of the incidence of AEs across the three studies did not suggest a consistent association between BSA and risk of AEs (SAEs or Grade ≥3 AEs).

Table 30. BO22334: Subgroup analysis of safety by BSA.

	Interaction[a]	Rituximab IV 375 mg/m^2 +Chemo N=65[b]	Rituximab SC 1400 mg +Chemo N=62	Odds Ratio [95% CI]
Body Surface Area (m^2)				
median		1.820	1.740	
range		1.34–2.30	1.37–2.32	
SAEs[c]				
Low		3/16 (18.75%)	5/26 (18.75%)	1.03 [0.21;5.06]
Medium	0.8422	9/27 (33.33%)	7/15 (46.67%)	1.75 [0.48;6.37]
High		2/21 (9.52%)	2/21 (9.52%)	1.00 [0.13;7.85]
Grade≥3 AEs[c]				
Low		8/16 (50.00%)	15/26 (57.69%)	1.36 [0.39;4.77]
Medium	0.5773	15/27 (55.56%)	6/15 (40.00%)	0.53 [0.15;1.92]
High		7/21 (33.33%)	7/21 (33.33%)	1.00 [0.28;3.61]

a p value from likelihood ratio test related to interaction BSA (low, medium, high)×treatment effect (rituximab SC vs. rituximab IV).

b Patient 1857 was not analyzed in rituximab IV treatment group due to missing BSA, thereby reducing the sample size from N=65 to N=64 for the subgroup analysis.

c Adverse events with missing onset date are excluded.

Of note: results of subgroup analyses should be regarded with caution, given the possibility of confounding by other baseline prognostic variables that could be associated with low BSA (e.g., older age, advanced disease, comorbidities), the risk of false-positive findings resulting from multiple comparisons, sample size within subgroups (and therefore low statistical power), effects of co-administered chemotherapy, and the open-label study design.

Study BO25341

In study BO25341, low BSA was defined as BSA ≤1.6 m^2 for female patients or ≤1.9 m^2 for male patients, and high BSA was defined as BSA >1.6 m^2 for female patients or >1.9 m^2 for male patients. Overall, there were 16 patients in the low BSA subgroup and 47 patients in the high BSA subgroup.

From the available data, there were no obvious differences in incidence and type of Grade ≥3 AEs or SAEs with respect to the dose cohort or BSA category.

Extrinsic

No clinical information related to the safe use of rituximab SC during pregnancy or lactation or in children is available.

Immunological events

Administration-related reactions

Administration-related reactions (ARRs) were considered as AEs of special interest. An ARR was defined as any AE occurring during or within 24 h of infusion/injection that was considered by the investigator to be related to the study drug. Across all studies, ARRs were reported more frequently

after administration of rituximab SC than rituximab IV. ARRs consisted primarily of injection site reactions such as pain, swelling, and redness, and were generally of a mild (Grade 1 or 2) and transient nature. The imbalance regarding ARRs reflects the expected change in ARR profile associated with the SC route of administration and is assessed to be a change that is not medically relevant to the overall safety profile of rituximab.

Below the ARRs are described per contributing study.

Study BP22333, Stage 2

The incidence of ARR events was higher among patients in the rituximab SC group than in the rituximab IV group (24/77 patients [31%] vs 3/77 patients [4%], respectively). The most frequently occurring events were those in the SOCs of general disorders and administration site conditions (18% rituximab SC vs 3% rituximab IV), followed by skin and subcutaneous tissue disorders (17% rituximab SC vs 0% rituximab IV), and musculoskeletal and connective tissue disorders (6% rituximab SC vs 0% rituximab IV). Erythema was the most common ARR reported (13% rituximab SC), followed by injection site erythema and myalgia (each 5% rituximab SC). All remaining AEs were reported in < 5% of patients. All ARRs in the rituximab SC group were Grade 1 events, while those that occurred in the rituximab IV group were assessed with an intensity of Grade 1 or 2.

Study BO22334, Stage 1

The incidence of ARRs was higher in the rituximab SC group than in the rituximab IV group (31/62 patients [50%] vs 21/65 patients [32%], respectively). The most commonly reported ARRs among patients in the rituximab SC group were injection site erythema (6 patients [10%]), erythema (5 patients [8%]), pruritus (4 patients [6%]), and rash (4 patients [6%]).

The majority of ARRs in both treatment groups were Grade 1 or 2 in intensity (95% rituximab SC vs 98% rituximab IV). One patient in the rituximab IV group experienced a Grade 3 ARR of vomiting and was subsequently withdrawn from the study after repeated vomiting following their IV infusions at Cycles 4, 5, and 6. Three patients in the rituximab SC group experienced Grade 3 ARRs. Two of these patients experienced a Grade 3 ARR following their first SC injection at Cycle 2 (Grade 3 injection site rash and Grade 3 dry mouth). Both patients continued to receive further rituximab SC treatment without further Grade ≥3 ARRs. The third patient experienced Grade 3 urine output decrease and tumour lysis syndrome (which was also considered serious), however, both these events were experienced on Study Day 2 following the Cycle 1 IV infusion, prior to receiving rituximab SC.

Safety at Single Cycle of Rituximab SC

During the single cycle of randomized treatment in Stage 1 of study BP22333, the incidence of ARRs was higher among rituximab SC cohorts (7/34 patients rituximab SC 375 mg/m^2, 8/34 patients rituximab SC 625 mg/m^2, and 9/40 patients rituximab SC 800 mg/m^2) than for rituximab IV (1/16 patients). The most frequently occurring ARRs were those in the SOC of skin and subcutaneous tissue disorders. Erythema was the most common ARR (2/34 patients rituximab SC 375 mg/m^2, and 5/34 patients rituximab SC 625 mg/m^2); no erythema events were reported in the IV group or in the highest rituximab SC dose group. All ARRs that occurred during the single cycle of treatment were Grade 1 or 2 events.

During Cycle 6 of treatment in CLL study BO25341, ARRs were experienced by 12 patients (2/16 patients rituximab SC 1400 mg, 5/17 patients rituximab SC 1600 mg, and 5/22 patients rituximab SC 1870 mg). The majority of events were related to the injection site (i.e. injection site pain, erythema, discoloration, and oedema). Other ARRs included abdominal pain (1/16 patients rituximab SC 1400 mg) and nausea (1/17 patients rituximab SC 1600 mg). Each of these events was assessed as Grade 1 or 2.

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). Previous experience with rituximab IV showed the development of anti-rituximab antibodies to be an event of low incidence in NHL patients, i.e. 1.1% developed anti-rituximab antibodies. Retreatment of patients positive for anti/rituximab antibodies showed good results and no correlation was seen between the presence of this type of antibodies and loss of efficacy.

The change of route of administration may influence the immunogenic potential of drugs; therefore the MAH included in the clinical program for rituximab SC 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.

An analysis was performed to assess the impact of anti-rituximab and anti-rHuPH20 antibodies on AEs, ARRs, and events within the MedDRA SMQ Anaphylactic reactions (wide) in each of the studies.

Anti-rituximab antibodies

Regarding the safety analysis population from study BP22333, there were no positive human anti-chimeric antibody (HACA) samples at any time point during Stage 1,and only one patient had positive HACA results during Stage 2, both at baseline (pre-dose) and at later time points. The patient received a total of four rituximab SC doses as part of the study. Further HACA samples were not taken as the patient experienced disease progression and was withdrawn from study prior to entering follow-up. The PK parameters for this patient were within the expected range, and human antihuman antibody (HAHA) results were negative at the same time points.

In study BO22334, ten of 124 (8.1%) patients had a positive HACA prior to receiving rituximab (2 patients in the rituximab SC arm vs. 8 patients in the rituximab IV arm). Four patients (2 in rituximab SC arm vs. 2 in rituximab IV arm) had a positive HACA after baseline. Two of these patients (1 patient in each treatment arm) had a positive HACA result at Cycle 2 following a positive HACA result at baseline. The PK data for the patient in the rituximab SC arm were within the normal expected range. The patient in the rituximab IV arm was withdrawn from the study with disease progression following Cycle 2. The other two patients (1 in each treatment arm) had a positive HACA result following negative HACA results at baseline (i.e. at pre-dose Cycle 3), and the PK data for both of these patients were within the normal expected range. All other samples taken during the course of the study up until the clinical cut-off were negative for HACAs.

Regarding the safety population from study BO25341, only one patient (in the 1870 mg rituximab SC dose group) among 59 patients tested had a positive result for HACA, at his follow-up month 6 visit. This patient achieved a complete response at the end of treatment, and his rituximab serum

levels at the follow-up month 6 visit were below the limit of quantification, as seen for most patients at this visit. The patient had a rituximab PK profile as expected for Cycle 5, but during Cycle 6 his PK profile was lower than that for other patients who received the 1870 mg dose. At the time of clinical cut-off, there were no reports or indications of worsening of disease.

Anti-rHuPH20 antibodies

Study BP22333

For the safety analysis population during Stage 1, six patients in Cohorts B through D (1, 2, and 3 patients, respectively) had positive human anti-human antibody (HAHA) samples at baseline (prior to having received any rHuPH20). Five of these six patients also had a positive HAHA sample at one or more subsequent time points. By the 9-month follow-up visit, positive HAHA samples were recorded for 1 patient in each of Cohorts B and C. Positive HAHA samples were further tested using a neutralizing antibody assay. None of the patients who had positive HAHA samples tested positive for neutralizing antibodies.

For the safety analysis population during Stage 2, five patients (6%) in the rituximab SC arm had positive HAHA samples at baseline. All five patients also had positive HAHA samples at later time points. In addition, one patient in the rituximab SC arm had a positive HAHA result at Visit 2, Day 1 following negative HAHA results at baseline. The sensitivity of the HAHA assay is 1 ng/mL, with an expected "false positive" rate with a range of 4 – 11%. Positive HAHA samples were further tested using a neutralizing antibody assay. None of the patients who had positive HAHA samples tested positive for neutralizing antibodies.

Study BO22334

Thirteen of 123 (10.6%) patients (6 in the rituximab SC arm vs. 7 in the rituximab IV arm) had a positive HAHA result at baseline (pre-dose Cycle 1). This false-positive rate (10.6%) was within the expected range for this initial screening assay (4 – 11%). None of the patients with positive HAHA samples tested positive for neutralizing antibodies.

During the course of the study until the clinical cut-off date, the number of patients with a positive screening assay for HAHAs ranged between 9 – 17% in the rituximab IV arm and 4 – 8% in the rituximab SC arm. The results of the neutralizing antibody assay were negative at all time points for these patients.

Study BO25341

Six of 56 patients (10.7%) had positive results for HAHAs. Four of these patients had a positive result for every time point where results are available, including at pre-dose Cycle 6 (i.e. prior to receiving their dose of rituximab SC). One patient in the 1400 mg rituximab SC dose group had a positive HAHA result at pre-dose Cycle 6 but was negative at all subsequent time points (results available until the follow-up month 3 visit). One patient in the 1870 mg rituximab SC dose group had a positive HAHA result at the Day 56 follow-up visit whilst having negative results for all other samples up to and including the sample at follow-up month 9. None of the patients who had positive HAHA samples tested positive for neutralizing antibodies.

Safety related to drug-drug interactions and other interactions

Patients Retreated with Rituximab SC

Forty-three patients participated in the optional SC extension phase in Stage 1 of study BP22333 (15/34 patients from rituximab SC 375 mg/m^2 cohort [Cohort B], 12/34 patients from rituximab SC 625 mg/m^2 cohort [Cohort C], and 16/40 patients from rituximab SC 800 mg/m^2 cohort [Cohort D]).

The incidence of AEs was similar across the three SC dose cohorts (8/15 patients from Cohort B, 5/12 patients from Cohort C, and 9/16 patients from Cohort D). By SOC, the most commonly reported AEs occurred in the SOC infections and infestations (4/15 patients from Cohort B, 2/12 patients from Cohort C, and 4/16 patients from Cohort D). All preferred terms within this SOC were reported with an incidence of a single patient. The most commonly reported AE during the SC extension phase was administration-related reaction, recorded for 2/15 patients from Cohort B and 1/16 patients from Cohort D. None of the ARRs reported were severe.

Two patients from Cohort B and two patients from Cohort C experienced Grade ≥3 AEs during the SC extension phase. These AEs were pneumonia and neuralgia (Cohort B) and pyrexia and lung adenocarcinoma (Cohort C). With the exception of neuralgia, all of these severe AEs were also considered to be serious AEs. No Grade ≥3 AEs or SAEs were recorded for patients in Cohort D during the SC extension phase.

Medication Error / Overdosage

One patient received an overdose of rituximab as a result of a medication error in Stage 1 of study BO22334. A 58-year-old female patient was randomized to the rituximab IV group and received 50 mL of rituximab IV (500 mg/50 mL) and 19 mL of rituximab SC (2280 mg) intravenously at her second cycle of maintenance treatment (Cycle 10). As a result, she received a total of 2780 mg of rituximab by IV infusion in addition to approximately 28000 U rHuPH20. The patient felt well with no obvious complications and was closely monitored afterwards. The patient is continuing with rituximab treatment. Potential risks associated with medication errors and mitigation of those risks are addressed in the updated RMP.

Discontinuation due to adverse events

Multiple cycles administered of the rituximab SC formulation

In Stage 2 of study BP22333, a total of eight patients (4/77 patients [5%] per group) were withdrawn from treatment due to an AE. In the rituximab SC group, patients were withdrawn from treatment due to AEs of malignant melanoma (Grade 4 and considered an SAE); breast cancer (considered an SAE); hypersensitivity (Grade 3); and rash vesicular (Grade 2). In the rituximab IV group, patients were withdrawn from treatment due to AEs of enterovesical fistula (Grade 2);

leukopenia (Grade 3); thrombocytopenia (Grade 4 and considered an SAE); and agranulocytosis (Grade 4 and considered an SAE).

In Stage 1 of study BO22334, five patients were withdrawn from treatment due to AEs (2/62 patients [3%] rituximab SC vs 3/65 patients [5%] rituximab IV). In the rituximab SC group, one patient discontinued treatment due to dysphonia after Cycle 1 and another patient died due to the SAE of myocardial infarction following Cycle 5. In the rituximab IV group, single patients were withdrawn from treatment due to AEs of vomiting (after Cycle 6); pneumonia (after Cycle 5, considered to be an SAE), and increased levels of alanine aminotransferase, blood alkaline phosphatase and gamma-glutamyltransferase (after Cycle 2).

Single cycle administration of the rituximab SC formulation

Over Stage 1 of study BP22333, there was one patient withdrawn from treatment due to an AE (all SAEs) in each of the rituximab SC cohorts (lung adenocarcinoma, spinal cord compression, and squamous cell carcinoma). Importantly, the SAEs leading to withdrawal occurred after the patients had received further maintenance cycles by IV infusion.

In Part 1 of CLL study BO25341, there were no AEs that led to withdrawal from study following treatment administration at Cycle 6. Three patients who did not receive rituximab SC were withdrawn from the study due to AEs (2 patients due to neutropenia, and 1 patient due to Guillain-Barre Syndrome).

Post marketing experience

Rituximab SC is not a marketed formulation.

2.6.1. Discussion on clinical safety

The safety data from the three studies (BP22333, BO22334 and BO25341) were summarized individually, since the studies differed substantially in terms of study design, indication (NHL vs CLL), treatment setting (induction vs maintenance), extent of prior exposure to rituximab, dosage and duration of treatment.

Overall, in study BP22333 the proportion of patients who experienced one or more AEs was similar following treatment with either rituximab SC or rituximab IV (e.g., 79% of patients in each arm for Stage 2). The incidence of severe AEs (CTC Grade $\geq$ 3), SAEs and AEs leading to withdrawal of treatment was also balanced following SC and IV treatment. There were no treatment-related fatal AEs in either treatment regimen.

The incidence of ARRs was higher in the rituximab SC cohorts than in the rituximab IV cohorts, primarily due to a higher incidence of cutaneous reactions, no ARRs were considered serious or severe. With the exception of ARRs, the overall profile of AEs reported was similar following treatment with either rituximab SC or rituximab IV.

In study BO22334, there were no new clinically relevant safety signals during Stage 1 and the safety profile of the rituximab SC and rituximab IV treatment arms was similar. The proportion of patients reporting an AE of any grade during the study was 88% in the rituximab IV arm compared

with 92% in the rituximab SC arm. The total number of AEs reported was higher in the rituximab SC arm than the rituximab IV arm (528 vs. 363, respectively). However, the majority of AEs reported in the rituximab SC arm and the rituximab IV arm were Grade 1 or 2 in intensity (86% vs. 89%, respectively). The proportion of patients with Grade ≥ 3 AEs and SAEs was similar across treatment arms. No new safety signals were observed. A higher incidence of ARR events the majority being Grade ≤ 2 and were primarily cutaneous reactions with local site reactions.

Overall in study BO25341 Cycle 5, the three rituximab SC treatment groups were balanced with respect to the number of patients experiencing at least one AE, and the majority of events in each treatment group consisted of CTC Grade 1 or 2 events. In Cycle 6, more patients experienced at least one AE with higher doses of rituximab SC (7 patients [44%], 10 patients [59%] and 18 patients [82%] for the 1400 mg, 1600 mg and 1870 mg rituximab SC groups, respectively). However, this apparent dose effect must be considered in light of the low patient numbers and a similar variation in Cycle 5 (IV administration), where more patients in the 1870 mg rituximab SC group experienced AEs. In both Cycle 5 and Cycle 6, the treatment groups were balanced with respect to the incidence of Grade ≥ 3 AEs and SAEs. ARRs were experienced by more patients in Cycle 6 (rituximab SC) than Cycle 5 (rituximab IV), the majority were related to the injection site (i.e. injection site pain, erythema, discolouration and edema) and were Grade ≤ 2.

Study BO25341 compared several SC doses, although not in the target indication, implying a dose-relationship of the adverse events, and is considered as a potential signal towards a dose-dependent effect, especially for neutropenia/leukopenia and for erythema and other administration-related reactions. This is included in the RMP.

A higher incidence of febrile neutropenia was observed for the rituximab SC arm in study BO22334: From Cycles 2 to 8 of induction treatment (i.e., patients receiving either IV or SC rituximab, plus combination chemotherapy), neutropenia was reported in 20/64 patients (31%) in the IV cohort and 21/62 patients (34%) in the SC cohort (thus not being of a real difference). Of those, 12/64 patients (19%) in the IV cohort and 15/62 patients (24%) in the SC cohort experienced severe events. *Febrile* neutropenia was reported in 2/64 patients (3%) in the IV cohort and 5/62 patients (8%) in the SC cohort. The difference in incidences (2/64 vs 5/64) is inconclusive as to whether it is a chance effect and highlights the difficulties of assessing the data.

The incidence of administration-related reactions (ARRs) was higher in the rituximab SC cohorts than in the rituximab IV cohorts, primarily due to a higher incidence of cutaneous reactions, none of them serious or severe. This finding was consistent throughout the studies. While clinically manageable, it is nevertheless relevant in light of the primary claim for the SC formulation, i.e. convenience for the patient and the healthcare professional. Administration-related reactions and local events like erythema, pruritis, and also systemic reactions like cough or dyspnoea were reported and can be considered related to the subcutaneous administration of rituximab SC

As regards the fixed dose schedule, there is a risk that patients with low BSA may be over-exposed to rituximab, which could lead to potential safety concerns with rituximab SC, and that patients with high BSA could be under-dosed, which could lead to potential concerns around the clinical efficacy of rituximab SC. In patients with low BSA, the geometric mean ratio in study BO22334 at Cycle 7 was higher than in the medium BSA and high BSA subgroups. However, there were no important differences between the rituximab IV and rituximab SC groups in terms of SAEs or Grade ≥ 3 AEs. An overall assessment of the incidence of AEs across the three studies did not suggest a consistent association between BSA and risk of AEs (SAEs or Grade ≥ 3 AEs), neither from a statistical nor from

a clinical perspective. From the data available rituximab SC does not seem to have a differential safety profile in the different BSA subgroups specific to rituximab. As rituximab primarily targets B-cells and tumour cells, it may not necessarily depend on body weight or BSA.

As regards immunogenicity, , this has been among the main potential concerns for subcutaneously administered rituximab. The immunogenicity or rituximab SC was remarkably low. The most probable explanation is that rituximab targets B-cells and thus the main effector for producing anti-rituximab antibodies; thus, rituximab reduces its own immunogenicity by a pharmacodynamic effect. The immunogenicity of rituximab for example in rheumatoid arthritis (lower doses), may be different and although this indication is not applied for, it is an important risk as regards potential off-label use and is reflected in the RMP.

Occurrence of anti-rHuPH20 antibodies was infrequent and appeared not to be linked to any apparent safety finding.

In the event that specific anti-rHuPH20 antibodies are generated in patients, their biologically relevant impact could potentially include autoimmunity responses resulting in attenuation of fertility via one or more mechanisms. In adult males, anti-sperm antibodies could theoretically interfere with sperm maturation, motility, or transport. In females, anti-sperm antibodies could impede progress through the cervix and uterus, facilitate sperm agglutination, or block normal processes that facilitate sperm-egg interactions. However, current literature suggests no cause and effect relationship exists between presence of anti-sperm antibodies and infertility in humans. The Applicant will provide follow-up data from immunogenicity analyses on anti-rHuPH20 antibodies as part of all three studies. An effect is unlikely but not known at this stage.

While the immunogenicity of rituximab SC was low, with the current dataset, it cannot be excluded if re-administration of rituximab SC for further cycles in the further course of treatment could be hampered, e.g. be linked to occurrence of safety issues or loss/lack of efficacy. There was no association between the detection of HACAs and adverse events, efficacy, pharmacokinetics, or pharmacodynamics parameters. Further data will be submitted to confirm this aspect (see RMP)

It should be noted that these data and conclusions cannot be extrapolated to immunogenicity in rheumatoid arthritis (not applied for). There are no data on patients treated with rituximab SC that were previously treated already with the SC route of administration; the specific question of HACA incidence (and potential consequences) after re-administration of rituximab SC upon relapse can only be addressed within the scope of post approval studies as set out in the Annex II.

In conclusion, patients receiving rituximab SC 1400 mg had a higher median cumulative dose, compared with those receiving rituximab IV, and thus a higher exposure. This was also observed for trastuzumab SC. The overall assessment of safety was challenging due to the limited safety database, the underlying severe disease condition, the short follow-up, and different disease characteristics in the three studies submitted. The current safety database for rituximab SC does not give rise to specific concerns.

2.6.2. Conclusions on the clinical safety

No new adverse drug reactions have been seen with the safety profile with rituximab sc.

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

- The MAH will provide the clinical study reports from the on-going trials BP22333, BO20334 and BO25341 including reports on long-term safety in relation to BSA (as a measure for exposure variation) and to gender

Study		Availability of Interim/Primary/Updated CSR	Availability of Final CSR
BP22333			
	Stage 1 Stage 2	CSR BP22333[a] October 2012 (both stages)	Q2/2014 (both stages)
BO22334			
	Stage 1	Interim CSR BO22334[a] October 2012 (Stage 1 only)	Q3/2018 (both stages)
	Stage 2	Updated CSR BO22334[b] by end of Q3/2014 (both stages)	
BO25341			
	Part 1 Part 2	Primary CSR BO25341[c] by end of Q4/2014 (both parts)	Q4/2018 (both parts)

a Submitted as part of the Line Extension Application.
b To report analysis of primary endpoint (overall response rate at end of induction) for Stage 2 and available safety and immunogenicity data from both stages of the ongoing study.
c To report analysis of primary endpoint (C_{trough} non-inferiority) for Part 2 and available safety and immunogenicity data from both parts of the ongoing study.

- The MAH will study immunogenicity of rituximab SC in further courses of treatment, including impact on safety and efficacy; Request for scientific advice procedure 4Q 2014

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice (annex 7) on the submitted Risk Management Plan (version 10.1):

PRAC Advice

The RMP is acceptable provided that the Applicant agrees to update the educational material in Annex 11 with the approved indication for MabThera subcutaneous formulation and as commented above, and furthermore delete the wording “Fixed-dose for treatment of NHL only” from the packaging and the vials of the MabThera SC formulation product.”

The applicant submitted (on the 17th of January of 2014) an RMP (version 11) and Educational Material following the comments of the joint Rapporteurs assessment report and the PRAC report, after the evaluation of responses to CHMP day 180 LoOI.

The submitted update of the Risk Management Plan (version 11) is summarised below:

- **Safety concerns**

Important Identified Risks	Acute Infusion-Related Reactions[a] Infections[a] Impaired Immunisation Response[a] PML[a] Neutropenia (including prolonged)[a] HBV Reactivation[a] Tumor Lysis[b] Serious Viral Infections[b] GI Perforation[b] PRES[b] Hypogammaglobulinaemia[c] Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis[a] Local cutaneous reactions (SC formulation only)[e]
Important Potential Risks	De Novo HBV[c] Opportunistic Infections[a] Malignant Events[c] Impact on Cardiovascular Disease[c] GI Perforation [c] Prolonged B-cell depletion[a] Grade 3/4 and serious blood and lymphatic system AEs in >70year patients[b] AML/MDS[b] Second malignancies[b] Off label use in autoimmune disease[c] Off label use in pediatric patients[a] Relapses[d] Embryofetal toxicity resulting from systemic exposure to rHuPH20[e] Off-label use of the subcutaneous formulation[e] Administration route error[e]

Missing Information	Use in Pregnancy and Lactation[a] Immunogenicity and Autoimmune Disease[c] Long term use in GPA/MPA patients[d] Immunogenicity associated with the subcutaneous formulation[e] Effect of greater exposure in patients with low BSA after fixed-dose SC administration[e]

- **Pharmacovigilance plans**

Study	Protocol Version	Protocol Status	Planned Date for Submission of Interim Data	Planned Date for Submission of Final Data
ML19514 (local marketing study)	2.0	ongoing	N/A	2010 as poster at ASH Preparation final manuscript ongoing
ML18434 (local marketing study)	Amendment 2	ongoing	2007	Data from this trial will be made available within 12 months of study completion
BSRBR	-	ongoing	Interim data included in PBRER 1053866 (Jan 2014 submission)	Q4 2014
ARTIS	-	completed	N/A	Final report included in PBRER 1053866 (Jan 2014 submission)
RABBIT	-	ongoing	N/A	Planned Submission of Final Data for RABBIT – Q4 2015
WA27893	2	ongoing	n/a	April 2018
GRAID II	0.4	ongoing		Within 12 months of end of study, anticipated to be 2015

Study	Protocol Version	Protocol Status	Planned Date for Submission of Interim Data	Planned Date for Submission of Final Data
WA25615	3	on-going		The common closeout date will occur 18 months after the enrollment of the last patient. At screening, all patients will be assessed for eligibility according to the inclusion and exclusion
RAVELOS	1.0	First Patient In: Q3, 2012	Q2, 2013	Q2, 2015
BA28478 (MabThera autoimmune drug utilization study) PASS	1.0	ongoing	None planned	Study start planned Q1 2014 and Final Report submission Q4 2016
Plasma Exchange and Glucocorticoids for Treatment of Anti-Neutrophil Cytoplasm Antibody (ANCA)-Associated Vasculitis (PEXIVAS)		on-going	Started in 2010 with a plan to complete in 2016	tbc
Multicenter, randomized, controlled trial comparing rituximab with azathioprine as maintenance therapy in relapsing ANCA-associated vasculitis (MAINRITSAN I)		on-going	Started in 2008, estimated study completion date December 2013, final data collection date for primary outcome measure in June 2013	tbc
Maintenance of Remission Using Rituximab in Systemic ANCA-associated Vasculitis II (MAINRITSAN II)		on-going	Started in November 2012, estimated study completion date February 2018, final data collection date for primary outcome	tbc

Study	Protocol Version	Protocol Status	Planned Date for Submission of Interim Data	Planned Date for Submission of Final Data
			measure in August 2017	
An International, Open Label, Randomised Controlled Trial Comparing Rituximab With Azathioprine as Maintenance Therapy in Relapsing ANCA-associated Vasculitis (RITAZAREM)		on-going	Start date December 2012, estimated study completion date December 2016, final data collection date for primary outcome measure in December 2016	tbc
National Czech Registry of AAV patients	ongoing	on-going	tbc	Planned study start in Q1 2014. Protocol and submission timelines under discussion with external vendor
Addenbrooke's Vasculitis and Lupus Clinic, Cambridge University Hospital (UK)	ongoing	on-going	tbc	Planned study start in Q1 2014. Protocol and submission timelines under discussion with external vendor
BO25341	D	on-going	None	CSR 2015
BO22334	A	on-going	data included in version 9.1 of the EU RMP	CSR Q2 2018
BP22333	D	on-going	data included in version 9.1 of the EU RMP	2013

- **Risk minimisation measures**

Safety Concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important Identified Risks		
Acute Infusion Related Reactions[a]	RA Routine: Section 4.4 of the EU SmPC states: MabThera is associated with infusion reactions, which may be related to release of cytokines and/or other chemical mediators.	Education for Healthcare professionals

Safety Concern	Routine risk minimisation measures	Additional risk minimisation measures
	Premedication with intravenous glucocorticoid significantly reduced the incidence and severity of these events Routine: for WG and MPA patients, glucocorticoids are given in combination with rituximab as part of the specified indication.	
Infections[a]	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.	Additional: Patient alert card was implemented and educational material is provided above.
Impaired Immune Response[a]	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
PML[a]	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	Additional: Patient alert card was implemented and educational material is provided above.
Neutropenia[a]	Section 4.8 of the EU SmPC states: In clinical	None

Safety Concern	Routine risk minimisation measures	Additional risk minimisation measures
	trials with MabThera monotherapy given for 4 weeks, haematological abnormalities occurred in a minority of patients and were usually mild and reversible. Severe (grade 3/4) neutropenia was reported in 4.2 %, anaemia in 1.1 % and thrombocytopenia in 1.7 % of the patients.	
HBV Reactivation[a]	Section 4.4 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/Rituxan as per institutional guidelines. Patients with active hepatitis B disease should not be treated with MabThera/Rituxan. 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
Tumor Lysis Syndrome[b]	Section 4.4 of the EU SmPC states: Patients with a high tumour burden or with a high number (≥25 x 10^9/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	None

Safety Concern	Routine risk minimisation measures	Additional risk minimisation measures
	frequently manifests itself within one or two hours of initiating the first infusion. Patients with a history of pulmonary insufficiency 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[b]	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
GI Perforation[b]	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
PRES[b]	Cases of posterior reversible encephalopathy syndrome (PRES) / reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms include visual disturbance, headache, seizures and	None

Safety Concern	Routine risk minimisation measures	Additional risk minimisation measures
	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.	
Hypogamma-globulinaemia[c]	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 paediatric patients are unknown.	None
SJS/ TEN[a]	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 permenantly discontinued.	None

Safety Concern	Routine risk minimisation measures	Additional risk minimisation measures
De Novo HBV[c]	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 HBsAg-status 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[a]	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

Safety Concern	Routine risk minimisation measures	Additional risk minimisation measures
Malignant Events[c]	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 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.	None
Impact on Cardiovascular Disease[c]	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
GI Perforation[c]	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
Prolonged B-cell depletion[a]	Section 4.8 of the EU SmPC states: In the clinical trial evaluating MabThera maintenance treatment, median IgG levels 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).	None
Grade 3/4 and serious blood and lymphatic system Aes	*Patient subpopulations - MabThera*	None

Safety Concern	Routine risk minimisation measures	Additional risk minimisation measures
in >70year patients[b]	*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.	
AML/MDS[b]	Section 4.4 of the EU SmPC states: immunomodulatory drugs may increase the risk of malignancy.	None
Second malignancies[b]	Section 4.4 of the EU SmPC states: immunomodulatory drugs may increase the risk of malignancy.	None
Off label use in autoimmune disease[c]	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 is maintained to reflect appropriate information related to off-label use.	None
Off label use in pediatric patients[a]	The MAH does not consider that additional risk minimisation measures are required for off label use in pediatric patients as the MAH notes that the wording in the label was recently strengthened for this topic.	None
Relapse[d]	EU SmPC Section 5.1 Pharmacodynamic Properties 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 Granulomatosis with polyangiitis and Microscopic polyangiitis. 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).	None
Local cutaneous reaction (SC only)	Local cutaneous reactions were very common in patients receiving MabThera subcutaneous in clinical trials; reported in up to 50% of	None

Safety Concern	Routine risk minimisation measures	Additional risk minimisation measures
	patients at some time during treatment. Symptoms included pain, swelling, induration, haemorrhage, erythema, pruritus and rash (see section 4.8). 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.	
Important Potential Risks		
Embryofetal toxicity resulting from systemic exposure to rHuPH20 (rituximab SC)[e]	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.	None

Safety Concern	Routine risk minimisation measures	Additional risk minimisation measures
Off-label use of the subcutaneous formulation[e]	Section 4.4 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 SC in the approved indication "Treatment of NHL only". For information related to the other indications, please refer to the SmPC of MabThera IV formulation	Educational material
Administration route error[e]	section 4.2 SmPC: 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 intended for intravenous administration and should be given via subcutaneous injection only.	Educational material

Safety Concern	Routine risk minimisation measures	Additional risk minimisation measures
Missing Information		
Use in Pregnancy and Lactation[a]	Section 4.6 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. 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[c]	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 safety in GPA/MPA patients[d]	EU SmPC Section 5.1 Pharmacodynamic Properties 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 been established."	None

Safety Concern	Routine risk minimisation measures	Additional risk minimisation measures
Immunogenicity of the SC formulation[e]	The product label describes the incidence of HACA and anti-rHuPH20 antibody formation in patients receiving rituximab SC in clinical trials.	None
Effect of greater exposure in patients with low BSA after fixed-dose SC administration[e]	Not applicable	None

The CHMP endorsed the PRAC advice and the updated RMP (version 11) without changes.

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Rituximab as add-on to chemotherapy has become standard of care for neoplastic B-lymphocyte derived diseases such as follicular lymphoma, large cell B-cell lymphomas and chronic lymphocytic leukaemia. The new SC formulation in which rituximab has been concentrated 12-fold to 120 mg/mL by the addition of recombinant human hyaluronidase (rHuPH20) in order to facilitate the SC administration, is studied in a phase III, international, multicenter, randomized, controlled, open-label study (study BO22334) compared to the iv formulation on top of standard chemotherapy CHOP or CVP in patients with previously untreated FL followed by maintenance treatment with either rituximab SC or rituximab IV. At present only data from stage 1 of the study (induction treatment) has been presented. Stage 2 (maintenance therapy) is ongoing.

The SC formulation of rituximab is considered at least as effective as the IV formulation as shown by the efficacy results from study BO22334; ORR = 84.4%, 95% CI [73.1; 92.2] in the rituximab IV arm and 90.5%, 95% CI [80.4; 96.4] for the rituximab SC arm, P-Value (Chi-squared Test) = 0.3002. A CRR of 29.7 %, 95% CI [18.9; 42.4] was observed for the IV arm and 46.0%, 95% CI [33.4; 59.1] for the SC arm, P-value (Chi-sq. test) = 0.0575. The numerical comparison of point estimates and 95% CIs for ORR for both treatment groups at the end of induction did not show major differences between rituximab SC and rituximab IV. Similar efficacy is also supported by PK data.

Data generated in patients with follicular lymphoma can in principle be extrapolated to the other NHL indications using the same dose and schedule for rituximab. In that aspect it is agreed that

extrapolation of the induction efficacy results in FL to treatment of CD20+diffuse large B-cell NHL can be done.

Uncertainty in the knowledge about the beneficial effects.

While ORR and CRR are acceptable primary endpoints for the comparison of efficacy of the two rituximab formulations, time-dependent endpoints, such as PFS and OS are not available at present. Such data will be provided as part of the final study reports.

The rituximab SC regimen for FL as maintenance therapy and as induction therapy combined with chemotherapy, are different from the regimen for induction monotherapy in the relapsed stage II-IV FL setting, i.e. maintenance rituximab SC 1400 mg once every 2 months in previously untreated FL, maintenance rituximab SC 1400 mg once every 3 months for relapsed-refractory FL vs rituximab 1400 mg SC as monotherapy for relapsed/refractory stage II-IV FL every week for 4 weeks) and extrapolation to the induction monotherapy setting is not evident, therefore the this indication has been excluded from the treatment with the sc formulaiton.

Risks

Unfavourable effects

A total of 1413 cycles of rituximab SC were administered across the three studies submitted, 1215 cycles of which were with the 1400 mg dose. Patients receiving rituximab SC 1400 mg had a higher median cumulative dose, compared with those receiving rituximab IV, which puts further emphasis on a comparative assessment of a potential impact of this on safety.

The incidence of administration-related reactions (ARRs) was higher in the rituximab SC cohorts than in the rituximab IV cohorts, primarily due to a higher incidence of cutaneous reactions, none of them serious or severe. This finding was consistent throughout the studies. While clinically manageable, it is nevertheless relevant in light of the primary claim for the SC formulation, i.e. convenience for the patient and the healthcare professional. ARRs and local events, like erythema, pruritis, and also systemic reactions, like cough or dyspnoea, were reported and can be considered related to the subcutaneous administration of rituximab SC. This is reflected in the SmPC.

Uncertainty in the knowledge about the unfavourable effects

The incidence of febrile neutropenia was higher with sc as compared to the IV formulation, but this finding should be confirmed when a larger safety data base is available.

Immunogenicity of subcutaneously administered rituximab was generally remarkably low, most probably due to administration of a B-cell depleting dose. However, uncentainties still exist and it cannot be excluded that re-administration of rituximab SC for further cycles in the further course of treatment could be hampered, due to occurrence of safety issues or loss/lack of efficacy and long-term immunogenicity especially upon re-exposure with rituximab later in the treatment course when initial cycles have been completed and the patient later relapses needs to be further elucidated. As a post-approval measure, a proposal regarding the investigation of immunogenicity upon re-administration of rituximab SC after relapse and will be discussed in the scope of Scientific Advice (Q4/2014).

Long term safety data are warranted and will be provided as agreed through relevant post authorization measures (See Annex II).

Benefit-risk balance

Importance of favourable and unfavourable effects

The applicant has demonstrated at least similar efficacy for the SC formulation of rituximab when the product is used in combination with standard chemotherapy for follicular lymphoma. This effect can be extrapolated to patients with large B-cell lymphomas since dose and schedule for rituximab are identical. SC administration of rituximab appears to be more convenient for the patients although it is not a major difference as all cytostatic agents should still be administered via the IV route.

The incidence of administration-related reactions (ARRs) was higher in the rituximab SC cohorts than in the rituximab IV cohorts, primarily due to a higher incidence of cutaneous reactions, none of them serious or severe. Administration-related reactions and local events like erythema, pruritis, and also systemic reactions, like cough or dyspnea, were reported and can be considered related to the subcutaneous administration of rituximab SC.

Benefit-risk balance

The benefit – risk balance of the subcutaneous formulation of Mabthera to be used for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy; as maintenance therapy for the treatment of follicular lymphoma patients responding to induction therapy and 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; is positive.

Discussion on the benefit-risk balance

Rituximab is standard of care for three important B-cell derived neoplastic diseases. The new SC formulation could be seen as an improvement in terms of patient care as compared to the IV formulation. At least equal efficacy has been demonstrated and, except from local reactions, the safety profile is considered similar at this time. Further data on efficacy in terms of time related endpoints, long term safety and immunogenicity of the subcutaneous formulation of rituximab will be provided from on-going trials.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by concensus that the risk-benefit balance of Mabthera in the treatment of Non-Hodgkin's lymphoma (NHL), Chronic lymphocytic leukaemia (CLL) and Rheumatoid arthritis is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal products on "restricted" medical prescription, reserved for use in certain specialised areas (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and 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 agreeed 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

<u>Subcutaneous formulation</u>

All healthcare professionals administering MabThera subcutaneous formulation will be provided with an Educational Material (« step by step guide » and « comparison card ») to minimise the risk of off label use and administration route error.

- **Obligation to conduct post – authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
Submission of clinical study reports from the clinical trials BP22333, BO22334 and BO25341 including reports on long-term safety in relation to BSA (as a measure for exposure variation) and to gender as follows:	
CSR BP22333 (both stages)	Q2/2014
Updated CSR BO22334[a] (both stages)	Q3/2014
Final CSR BO22334 (both stages)	Q3/2018
Primary CSR BO25341[b] (both parts)	Q4/2014
Final CSR BO25341 (both parts)	Q4/2018
a To report analysis of primary endpoint (overall response rate at end of induction) for Stage 2 and available safety and immunogenicity data from both stages of the ongoing study. b To report analysis of primary endpoint (C_{trough} non-inferiority) for Part 2 and available safety and immunogenicity data from both parts of the ongoing study.	
Development of a proposal regarding the investigation of immunogenicity upon re-administration of rituximab SC after relapse which will be discussed in the context of Scientific Advice.	Q4/2014

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable