Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Rituximab

Proprietary Product Name: MabThera

Sponsor: Roche Products Pty Ltd

February 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ACPM	Australian Committee of Prescription Medicines
AE	Adverse event
ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under The Curve
BILI	Total Bilirubin (Serum Concentration)
BMI	Body Mass Index
BSA	Body Surface Area
CI	Confidence Interval
CL	Clearance
CLL	Chronic Lymphocytic Leukaemia
C_{max}	Maximum Concentration
CR	Complete Response
CRF	Case Report Form
DOR	Duration Of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event free survival
EORTC	European Organization Research on the Treatment of Cancer
EU	European Union
FDA	Food and Drug Administration

Abbreviation	Meaning
FL	Follicular Lymphoma
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
GLP	Good Laboratory Practice
HR	Hazard ratio
ICH	International Committee on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRC	Independent review committee
ITT	Intent-to-treat
LC/MS/MS	Liquid chromatography/mass spectrometry/mass spectrometry
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NONMEM	Nonlinear Mixed Effects Model
OMA	Office of Medicines Authorisation
ORR	Objective response rate
OS	Overall survival
PD	Pharmacodynamic(s)
PFS	Progression-free survival
PI	Principal investigator
PK	Pharmacokinetic(s)
PP	Per protocol
Q2M/3M	Two monthly/three monthly
QoL	Quality of life
QTc	Interval from beginning of QRS complex to end of the T wave; QT corrected

Abbreviation	Meaning
rHuPH20	Recombinant human hyaluronidase
SAE	Serious adverse event
SGOT	Serum glutamic-oxaloacetic transaminase
SOC	System organ class
t1/2	Terminal elimination half-life
TEAE	Treatment-emergent adverse event
TEAV	Treatment-emergent abnormal laboratory values
T_{max}	Time of maximum observed plasma concentration
ULN	Upper limit of normal
VAS	Visual analog scale
Vd	Volume of distribution
Vss	Volume of distribution at steady state
WHO	World Health Organization

I. Introduction to product submission

Submission details

Type of submission:	Major variation (new strength and route of administration) and changes to Product Information
Initial decision:	Partially approved[1]
Date of initial decision:	28 April 2016
Final decision:	Approved[2]
Date of final decisions:	25 November 2016
Date of entry onto ARTG	2 December 2016
Active ingredient(s):	Rituximab
Product name(s):	MabThera
Sponsor's name and address:	Roche Products Pty Limited PO Box 255, Dee Why NSW 2099
Dose form(s):	Solution for injection
Strength(s):	100 mg/10 mL and 500 mg/50 mL for intravenous infusion 1400 mg/11.7 mL for subcutaneous injection Proposed: 1600 mg / 13.4 mL for subcutaneous injection
Container(s):	Single use vial
Pack size(s):	1 or 2 vials
Approved therapeutic use:	[Cancer indications only shown]: MabThera rituximab 100 mg/10mL injection vial and 500 mg/50mL injection vial: *Non-Hodgkin's Lymphoma: MabThera is indicated for treatment of patients with: CD20 positive, previously untreated, Stage III/IV follicular, B-cell non-Hodgkin's lymphoma. CD20 positive, relapsed or refractory low grade or follicular, B-cell non-Hodgkin's lymphoma, CD20 positive, diffuse large B-cell non-Hodgkin's lymphoma, in combination with chemotherapy. Chronic Lymphocytic Leukaemia: MabThera is indicated for the treatment of patients with CD20 positive chronic lymphocytic leukaemia (CLL) in combination with chemotherapy.* MabThera SC (1400 mg/11.7mL)

[1] Changes to PI and change in dosing frequency for previously untreated maintenance NHL patients with IV formulation were approved.
[2] Mabthera SC 1600 mg for CLL and change in dosing frequency for previously untreated maintenance NHL patients with SC formulation approved.

	Mabthera SC is indicated for treatment of patients with: - CD20 positive, previously untreated, Stage III/IV follicular, B-Cell non-Hodgkin's lymphoma, - CD20 positive, relapsed or refractory low grade or follicular, B-cell non-Hodgkin's lymphoma, CD 20 positive, diffuse large B-cell non-Hodgkin's lymphoma, in combination with chemotherapy.
Route(s) of administration:	Intravenous (IV) and Subcutaneous (SC)
Dosage:	Dependent on indication. See Product Information (Attachment 1) for details.
ARTG number (s):	AUST R 60318, 60319 and 207334.

Product background

This AusPAR describes the application by the sponsor to register a new strength via the subcutaneous route of administration for MabThera to treat chronic lymphocytic leukaemia (CLL). The proposed new strength is 1600 mg/13.4 mL Solution for subcutaneous (SC) injection.

The sponsor has also applied to make changes to the PI for both the MabThera SC 1400 mg formulation and MabThera IV formulation (dose calculated on body surface area) to increase the dosage frequency of the dose in maintenance treatment of non-Hodgkin's lymphoma (NHL) from 3 monthly to 2 monthly, in patients with previously untreated follicular lymphoma who have responded to induction treatment. In addition, the sponsor wishes to make changes to the PI requiring data evaluation for both MabThera SC and IV based on the BO22334/SABRINA and BP22333/SparkThera studies in NHL.

MabThera is currently approved as the following products: *(oncology indications only shown)*

- *100 mg/10 mL and 500 mg/50 mL Vials, Concentrate Solution for intravenous infusion for CLL and NHL*
- *1400 mg/11.7 mL Solution for Injection for subcutaneous injection (NHL)*

Currently, the MabThera IV formulation is indicated for the treatment of patients with CD20 positive CLL in combination with chemotherapy.

Both the MabThera IV and SC formulations are currently also registered for Non-Hodgkin's Lymphoma (NHL) as follows:

For treatment of patients with:

- CD20 positive previously untreated, Stage III/IV follicular, B-cell NHL;
- *CD20 positive, relapsed or refractory low grade or follicular, B-cell NHL;*
- *CD20 positive, diffuse large B-cell NHL in combination with chemotherapy.*

CLL is one of the chronic lymphoproliferative disorders and is characterised by a progressive accumulation of functionally incompetent lymphocytes, which are usually monoclonal in origin. In Australia, the average of age of onset is 70, with a male preponderance (61.8%, 2012 Australian Institute of Health and Welfare statistics). There is a sharp rise in incidence with increasing age; in the United Kingdom (UK) between 2010 and 2012, an average of 43% of cases were diagnosed in men and women aged 75 and over (Cancer Research UK statistics).

While some patient subsets have survival rates that are similar to the normal population, others who present with early stage disease and poor risk prognostic markers (for example 17p deletion (del(17p)), TP53 mutations, CD38 positivity, un-mutated segments of the immunoglobulin heavy chain variable [IGHV] genes) have a less favourable prognosis. Patients with del(17p) are at high risk of either not responding to initial treatment or relapsing soon after achieving remission. Consequently, these risk factors should be included as stratification factors at randomisation in order to ensure an even distribution within each arm in clinical trials assessing the efficacy of a therapeutic intervention.

Therapy is offered to patients with early stage and poor risk disease (usually in a clinical trial if possible) and symptomatic CLL with the goals of ameliorating symptoms and improving progression-free (PFS) and overall survival (OS). With the possible exception of allogeneic hematopoietic cell transplantation, CLL cannot be cured by current treatment options.

In Australia, the currently registered chemotherapy treatments for CLL include fludarabine, cyclophosphamide, bendamustine and chlorambucil; all of which may be used in combination with rituximab. In addition, the PI3-kinase inhibitor, idelalisib, was approved in 2015 for use in combination with rituximab based on a different rituximab regimen from that used in combination with fludarabine based regimens.[3] Of relevance to this application, rituximab is approved for use only in combination with chemotherapy for CD20 positive CLL, not as monotherapy, although in clinical practice, monotherapy is sometimes used.

Rituximab in combination with either fludarabine (+/- cyclophosphamide) (FR or FCR) or bendamustine (BR) is usually recommended as first line therapy in patients < 70 years of age, without significant comorbidities, while BR is also considered appropriate for patients > 70 years or age or younger patients with comorbidities. Rituximab in combination with idelalisib (PI3 kinase inhibitor) was registered based on clinical trials conducted specifically in patients with CLL who were older with more co morbidities and considered unable to tolerate chemo-immunotherapy. Of note is that the regimen used for rituximab in combination with idelalisib was different from that with other combination regimens.

Thus rituximab is potentially used as part of a combination regimen to treat all patients with CLL, both in the first line or upon relapse, including those with significant comorbidities and advancing age.

Rituximab (IV formulation) is also registered for the following indications in non-malignant conditions in Australia:

- *Rheumatoid Arthritis*

  In combination with methotrexate, for the treatment of adult patients with severe, active rheumatoid arthritis who have had an inadequate response or intolerance to at least one tumour necrosis factor (TNF) inhibitor therapy.

- *Granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis*

[3] Idelalisib (Zydelig) in combination with rituximab is indicated for the treatment of patients with CLL/small lymphocytic lymphoma (SLL) including patients with 17p deletion or TP53 mutation, upon relapse after at least one prior therapy in patients for whom chemoimmunotherapy is not considered suitable.
Zydelig is not recommended for first-line treatment of CLL/SLL.
Zydelig is indicated as monotherapy for the treatment of patients with follicular lymphoma which is refractory to at least two prior systemic therapies.

(MPA) in combination with glucocorticoids, for the induction of remission in patients with severely active granulomatosis with polyangiitis (GPA, also known as Wegener's granulomatosis) and microscopic polyangiitis (MPA).

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 6 October 1998 (MabThera IV). MabThera SC received initial registration in Australia on 28 May 2014.

At the time the TGA considered the application for MabThera SC 1600 mg for use in CLL , similar applications had been submitted to the European Union (EU) on 5 November 2014 and New Zealand on 6 July 2015 and were currently under review.

Table 1: Regulatory status of MabThera SC 1600 mg for use in CLL

Country	Status
EU	Approved; positive CHMP opinion April 2016 and decision 25 May 2016. Indication: MabThera is indicated in adults in combination with chemotherapy for the treatment of patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia (CLL). Only limited data are available on efficacy and safety for patients previously treated with monoclonal antibodies including MabThera or patients refractory to previous MabThera plus chemotherapy.
New Zealand	Under review.

Product information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

Drug substance (active ingredient)

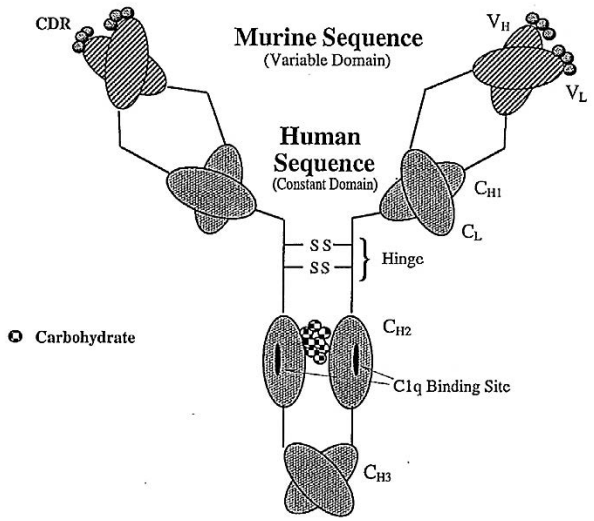
The active ingredient is identical to that used for the currently registered products:

- MabThera rituximab 100 mg/10 mL injection vial (AUST R 60318).
- MabThera rituximab 500 mg/50 mL injection vial (AUST R 60319).
- MabThera SC rituximab 1400 mg/11.7 mL injection vial (AUST R 207334).

Structure

The drug substance has the following structure (Figure 1):

Figure 1: Chemical structure of MabThera



The variable region consists of murine sequences and the constant domains are human sequences. The variable and constant domains are labeled.

Manufacture

This substance is manufactured from cell supernatant taken from an antibody producing Chinese Hamster Ovary (CHO) cell line. Cell banking processes are satisfactory. All viral/prion safety issues have been addressed including use of animal-derived excipients, supplements in the fermentation process and in cell banking.

The manufacturing process has not changed as compared to that of MabThera SC 1400 mg dosage format.

Physical and chemical properties and specifications

The physical and chemical properties and specifications have not changed as compared to those of MabThera SC 1400 mg dosage format.

Stability

Stability data have been generated under real time/stressed conditions to characterise the stability/degradation profile of the substance.

Drug product

The formulation of the MabThera SC 1600 mg product is identical to that of the currently registered MabThera SC 1400 mg product.

The formulation of MabThera SC consists of 120 mg/mL rituximab in histidine/histidine hydrochloride monohydrate, trehalose dihydrate, methionine, recombinant human hyaluronidase (rHuPH20) andpolysorbate 80.

Manufacture

The product is manufactured by thawing frozen drug substance and mixing with the required excipients including hyaluronidase. After compounding, the drug product bulk solution is filtered (0.2 µm filter) into a steam-sterilized receiving/transport vessel.

Specifications

Table 2 describes the manufacturing specifications for the proposed product.

Table 2: Manufacturing specifications for MabThera

Sterility: Final container	Corresponds to European Pharmacopeia, US Pharmacopeia and Japanese Pharmacopoeia
Bacterial endotoxins	Maximum 20 EU/mL

Stability

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Photostability data indicates that the product is not photostable.

The data supports the 30 month shelf-life of MabThera SC drug product when stored at 2 to 8°C, protected from light.

Biopharmaceutics

Biopharmaceutic data have not been assessed in the quality evaluation.

Quality summary and conclusions

The administrative, product usage, chemical, pharmaceutical, microbiological data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

There are no outstanding issues from the quality evaluation.

The quality evaluator recommends that MabThera SC rituximab (rch) 1600 mg/13.4 mL solution for injection (AUST R 235147) should be approved.

Batch release conditions of registration for clinical delegate

It is a condition of registration that, as a minimum, the first five independent batches of MabThera SC rituximab (rch) 1600 mg/13.4 mL solution for injection (AUST R 235147) imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Office of Laboratories and Scientific Services (OLSS).

The sponsor should supply:

1. Certificates of Analysis of all active ingredient (drug substance) and final product.
2. Information on the number of units to be released in Australia with accompanying expiry dates for the product and diluents (if included).
3. Evidence of the maintenance of registered storage conditions during transport to Australia.
4. 3 containers (usually 3 to 5 vials) of each batch for testing by the Therapeutic Goods Administration OLSS together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

The rationale for the development of the new SC strength is stated by the sponsor to be to add a valuable therapeutic option for CLL patients resulting in reduced administration time and increased comfort and convenience that may result in improved treatment compliance.

There was no evidence to show that there was an unmet need for this route of administration. This is especially important given that patients already have IV access (for the other concomitant chemotherapies) and that there are perceived issues with adding a bolus of fluid into the SC tissues of an already unwell population group, currently having IV therapy anyway.

Contents of the clinical dossier

The clinical dossier included the following data to support each of the changes proposed:

New strength of MabThera SC (1600 mg/13.4mL) for use in CLL:

- One new clinical trial, BO25341 (SAWYER) that builds on the earlier approval of MabThera SC 1400 mg in NHL. BO25341 is an adaptive, comparative, randomised, parallel-group, multi-centre, Phase Ib study of SC rituximab versus IV rituximab both in combination with chemotherapy (fludarabine and cyclophosphamide), in patients with previously untreated CLL.
- A population PK analysis of part I of study BO25341 was provided to inform dose selection for Part 2 of the study. Validation study reports were also provided including a description of the rituximab enzyme-linked immunosorbent assay (ELISA) assay for concentration measurements.
- The SAWYER study was also supported by safety and efficacy evaluation of Mabthera IV in CLL from Study ML17102 (CLL8). This pivotal CLL registration study using IV rituximab on a dose/m^2 basis was provided as a protocol only (in error). (The final study report was later re-submitted in response to Section 31 questions).

Change in dosing frequency

This change was supported by information from Study MO18264 (PRIMA) supporting the increased frequency of dosing from every 3 months to every 2 months.

Product information update:

This change was supported by information from

- Study BP22333 (SparkThera): A two- stage phase Ib study to investigate the pharmacokinetics, safety, and tolerability of rituximab subcutaneous formulation in patients with follicular lymphoma (FL) as part of maintenance treatment

- Study BO22334 (SABRINA): A two-stage Phase III, 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.

Submission of these two study reports also fulfilled commitments made by Roche during the TGA evaluation of the MabThera SC 1400 mg application.

Paediatric data

The submission did not include new paediatric data. The PI states

> *The safety and effectiveness of MabThera in paediatric patients have not been established. Hypogammaglobinaemia has been observed in paediatric patients treated with MabThera, in some cases severe and requiring long-term immunoglobulin substitution therapy. The consequences of long term B cell depletion in paediatric patients are unknown.*

There is an agreed Paediatric Investigation Plan (PIP) in Europe. The agreed PIP is for the diffuse large B cell lymphoma condition. There is a class waiver for the CLL condition.

This is appropriate.

Good clinical practice

The new pharmacokinetic (PK) study (BO25341/SAWYER) was conducted in compliance with Good Clinical Practice.

Pharmacokinetics

Studies providing pharmacokinetic data

Three studies with pharmacokinetic (PK) data were submitted in this application.

1. Study BO25341 (SAWYER): An adaptive, comparative, randomised, parallel-group, multi-centre, Phase Ib study of subcutaneous (SC) rituximab versus intravenous (IV) rituximab both in combination with chemotherapy (fludarabine and cyclophosphamide) in patients with previously untreated CLL. This study had 2 Parts and primary and secondary endpoints in each Part. Essentially, Part 1 was designed to undertake a PK analysis to optimise the choice of dose for the Part 2 Study. Part 2 was thus informed by a population PK model using data from Part 1.
2. Study BP22333 (SparkThera): A Two- Stage Phase Ib study to investigate the pharmacokinetics, safety, and tolerability of rituximab subcutaneous formulation in patients with follicular lymphoma (FL) as part of maintenance treatment.
3. Study BO22334 (SABRINA): A two-stage Phase III, 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.

There were no other studies on PK, no bioequivalence, no food effects, no PK studies in special populations and no PK drug interaction studies.

Evaluator's conclusions on pharmacokinetics

The minimum plasma concentration (C_{trough}) and exposure of SC rituximab 1600 mg compared to 500 mg/m^2 rituximab IV was not inferior statistically. The clinical relevance of the log transformed ratio of 1.1 and the significance of the rHuPH20 data is unknown.

However using data from a PK study to derive efficacy benefits (or even safety), in the evaluator's opinion, requires evidence on the relationship of the PK parameters to safety and efficacy of rituximab (which was not clear in the submission) nor evidence of a study with appropriate efficacy or safety endpoints and sample size.

In the BP22333 study, the PK data were weak, with simulation data not backed up by actual PK parameters. Without efficacy data the benefit of reducing from 3 to 2 months is unknown. There were certainly potential issues noted around accumulation with the 2 month maintenance schedule instead of 3.

Pharmacodynamics

Studies providing pharmacodynamic data

B-cell depletion and repletion

B cell repletion has been discussed in the PK section for the BP22333 study (it was noted that repletion is quicker in the SC arm) (Attachment 2). For the BO25341 study, pharmacodynamic markers from blood samples included peripheral blood CD19+ B cell counts measured before each administration of study drug (Cycle 5 and 6 for Part 1 and all cycles for Part 2) and during follow-up until 2years after last treatment. B-cell depletion was defined as < 80 cells/mm^3.

In part 1, baseline B-cell counts before treatment started was not available as patients had already started treatment with rituximab IV prior to entering the PK study. At pre-dose Cycle 5 (when subjects had only had the IV rituximab), a high proportion (94%) of patients were already B-cell depleted and > 90% of patients remained so until the 6 month follow-up visit. Patients' B-cells began to replete by the 9 month follow-up visit. At this time point, the proportion of patients who were B-cell depleted had dropped to 66% and continued to decrease during subsequent visits. At the 12, 15, 18, 21 and 24 month follow-up visits, the proportion of B-cell depleted patients was 52% (25/48 patients), 43% (17/40), 36% (15/42), 32% (13/41) and 21% (9/42), respectively.

In part 2, following the first cycle of treatment, patients began to deplete B-cells, with 28% of patients B-cell depleted at pre-dose Cycle 2. A continuous increase in the proportion of B-cell depleted patients was observed with subsequent cycles of treatment and by Cycle 6, 96% of patients were depleted in the two treatment arms. Patients remained B-cell depleted until the Month 9 follow-up visit. At this time point, the proportion of patients who were B-cell depleted had dropped to 66% as for Part 1. At the 12 month follow-up visit the proportion of B-cell depleted patients was 41% (16/39 patients). The pattern of B-cell depletion was said to be similar in the two treatment arms.

Evaluator's conclusions on pharmacodynamics

For the BO25341 study, effect on B-cell depletion is stated to be similar across the two groups (IV and SC). However, it is important to see that data, as it was noted to be shorter in the BP22333 study.

Dosage selection for pivotal studies supporting SC 1600 mg in CLL

The dosage selected for the Part 2 of the Phase I study was based on PK modelling of Phase I data in study BO25341 (SAWYER)

This appears to be a reasonable approach for a Phase I study. The concern regarding calling the Phase I data pivotal efficacy and safety data has been previously noted.

The choice of the 1600 mg dose was not made clear using efficacy and safety data. The 1600 mg dose was chosen because it would enable achievement of the primary endpoint that is, non-inferior $C_{troughs}$, but the relative difference in peak plasma concentration (C_{max}) and exposure (area under the concentration versus time curve (AUC)) (safety and efficacy)was not clear.[4]

Efficacy

Studies providing efficacy data

Efficacy endpoints for the subcutaneous formulation of 1600 mg of rituximabin CLL were measured in the Phase Ib Study BO25341.

Study BO25341

This study has been described in Section 4 of Attachment 2 Extract from the CER.

The efficacy parameters of response rate at 3 months of follow up and minimal residual disease (MRD) were exploratory secondary endpoints. Time-to-event endpoints (progression free survival (PFS), event free survival (EFS) and overall survival (OS)) were not analysed because these data are not yet mature.

Reducing the dosing interval from 3 to 2 months for MabThera IV and SC in NHL

Efficacy data was not provided in BP22333. The change in dosing frequency was supported by the PRIMA study (MO18264).

Analyses performed across trials (pooled analyses and meta-analyses)

There were no efficacy pooled analyses or meta-analyses.

Evaluator's conclusions on efficacy

1. The proportion of patients with a tumour response at 3 months of follow up as reported by the investigator was similar in the rituximab IV and rituximab SC treatment arms. Complete responses were also similar. The efficacy results were similar in the per protocol dataset to the ITT dataset.

   Overall, in the Phase I study there are numerical improvements in some of the surrogate markers of efficacy such as tumour size and there were no consistent difference between the SC and the IV administration routes.

   The sponsor is requested to provide data to show the relationship of the efficacy surrogates to OS and PFS in CLL.

2. The simulations of PK for Cycle 2 in BP22333 showed accumulation of the drug. Further, actual data is needed to confirm the PK simulations. Improved efficacy was not able to be shown as efficacy was not an endpoint.[5] Therefore even disregarding

[4] A Comparison of AUC across the tested doses in Part 1 was included in the study report.
[5]Study BP 22333 was not submitted to support the change in dosing frequency.

the concern regarding accumulation, efficacy has not been shown. What was shown in Part 2 however, and which was of concern, was the rapid repletion of B cells in the SC arm.

The evaluator concludes that the evidence does not support a reduced dosing interval for dosing in NHL.

Safety

Studies providing safety data

The following studies provided evaluable safety data: BO25341(SAWYER) provided data in CLL. BP22333 (SparkThera) and BO22334/SABRINA provided data in NHL and were provided to support PI updates and to fulfil a TGA commitment.

Patient exposure

Part 1

Median treatment duration with MabThera 1600 mg was identical (29 days) in the three rituximab treatment sub-cohorts.

All patients in the 3 rituximab SC treatment sub-cohorts received treatment with IV rituximab (500 mg/m^2) during Cycle 5. During Cycle 6, 16 patients received rituximab 1400 mg SC, 17 patients received rituximab 1600 mg SC and 22 patients received rituximab 1870 mg SC.

Part 2

Patients in the IV and SC arms had similar median treatment duration (4.7 and 4.9 months respectively) and most patients (83%) received all 6 cycles.

Table 3: Part 2 Exposure to Chemotherapy (Safety Analysis Population)

	Rituximab IV		Rituximab SC	
Chemotherapy	Number of Cycles median (range)	Cumulative dose (mg) median (range)	Number of Cycles median (range)	Cumulative dose (mg) median (range)
Cyclophosphamide				
IV	6 (1 - 6)	7705 (1000-9432)	6 (1 – 6)	7462.5 (1020-10677.7)
Oral	6 (2 – 6)	7575 (2000-9900)	6 (2 – 6)	7500 (2700-9900)
Combined	6 (1 – 6)	7650 (1000-9900)	6 (2 – 6)	7500 (2100-10677.7)
Fludarabine				
IV	6 (1 – 6)	774.0 (100-936)	6 (2 – 6)	780.9 (210-1090.6)
Oral	6 (2 – 6)	1155 (300-1500)	6 (2 – 6)	1160 (420-1620)
Combined	6 (1 – 6)	846 (100-1500)	6 (2 – 6)	828 (210-1620)

Postmarketing data

This was summarised in the Risk Management Plan (RMP) document. As a result there are significant changes to the RMP which have been summarised.

Comment: These are appropriately incorporated.

It is relevant that the Medication Error tables have been updated with current data from the global safety database (cut-off date 28 July 2014) and the clinical database (cut-off date 31 July 2014). The data included is now from interventional clinical trials.

Evaluator's conclusions on safety

In Study BO25341, the SC increasing dose sub-cohorts showed that the number of patients who experienced at least one adverse event (AE) (of any grade) increased with increasing doses.

It is noted that of the 4 deaths which were judged as treatment related, the two in the SC arm were judged as related to treatment (progressive multifocal leukoencephalopathy (PML) and Herpes Zoster). There is a numerical increase in serious AEs (SAEs) in the SC arm in the febrile neutropenia category, as well as increased incidence of neutropenia, injection site pain and swelling and general erythema, abdominal pain, general erythema, pyrexia, arthralgia, bone pain and respiratory tract infection in the SC group compared to the IV group.

A higher incidence of AEs in females was noted, although the reverse was seen for SAEs.

A safety benefit or trend to benefit (for example, as could potentially be seen with immunogenicity) was not seen with the different route of administration.

In the BP22333 study, a much higher incidence of administration related reactions (ARR) was seen.

First round benefit-risk assessment

First round assessment of benefits

The benefits of SC rituximab in the proposed usage of CLL are:

- An alternative mode of administration.

The data is early and a potential inferior effect on PFS and OS is possible[6].

There has been no benefit demonstrated in the request to move the therapy from 3 to 2 months in previously untreated maintenance NHL patients.

First round assessment of risks

The risks of SC rituximab in the proposed usage are:

- Higher incidence of AEs especially ARRs.

Reactions of any grade were reported with higher incidence in the rituximab SC arm (36/85 patients [42%]) compared with the rituximab IV arm (2/89 patients [2%]) in CLL.

Higher rates of injection site erythema, injection site pain, injection site swelling and injection site bruising compared to the IV route.

Of the 4 deaths which were judged as 'treatment related', the two in the SC arm were judged as related to treatment (PML and Herpes Zoster).

First round assessment of benefit-risk balance

Overall, the SC route appears to have a similar effect on some of the surrogates of efficacy (such as tumour response). Whether or not this translates into as good as, better or worse PFS or OS is unknown[6].

[6] The sponsor submitted updated data on PFS and OS with their section 60 appeal documents.

The AE profile is on balance worse, with higher incidences of AEs particularly local discomfort and erythema and ARRs. The sponsor's statement that SC could potentially be more convenient was not evidenced. This is unlikely if the other drugs are given IV, however may be of interest if these drugs are only given orally.

Thus on balance, the benefit-risk balance is currently unfavourable for the SC formulation in CLL but could become favourable with PFS or OS data[6].

The evidence to support the request to shorten dosing from 3 to 2 months was noted.[7] Furthermore, the simulations suggested that accumulation may be an issue with 2 monthly dosing of this drug.

First round recommendation regarding authorisation

- Unfavourable in the 1600 mg dose for CLL.
- Lack of data to support shortening the maintenance course of therapy.[7]
- Unfavourable for the reduction of dosing interval for NHL maintenance from 3 to 2 months.

Clinical questions

1. There was no evidence to show that there was an unmet need for the SC route of administration. This is especially important given that patients already have IV access (for the other concomitant chemotherapies) and that there are perceived issues with adding a bolus of fluid into the SC tissues of an already unwell population group currently having IV therapy anyway. Can the sponsor please clarify the need for this route of administration?
2. Can the sponsor summarise the numbers of death with SC use likely or highly likely to be related to drug use since its availability for use in other conditions (for example, NHL) occurred?
3. Information on Study MO18264 to support the increased frequency of dosing and results from the Study Ml17102 was not able to be located. Can the sponsor please provide those?
4. The two questions on patient and nurse preference appeared exploratory. Can the sponsor provide information on the validation (internal and external) of the survey?
5. Comparative figures between the two groups for the Part 2 data PD endpoint of B-cell depletion were not available. Can this be provided? Further the relationship of B-cell depletion to PK parameters is requested.
6. The relationship of CR to patient relevant outcomes such as PFS and OS was not provided. Can the sponsor provide this please?
7. Noting the differences in AEs between men and women, can the sponsor link these events to AUC data?
8. Please provide evidence to link the PK parameters (trough and AUC) to efficacy.
9. Please provide information on evaluation and interpretation of the antibody data.

[7] Proposed new dosing is once every 2 months rather than once every 3 months and treatment duration is unchanged (i.e. up to 2 years)

10. Please provide data discussing the clinical significance of log transformed difference in ratio of 1.1 between the SC and IV groups in terms of exposure (although statistically significant).
11. MO18264 was not submitted with this application. Can it be provided please?
12. The relationship between planned end date, data analysis and data snapshot in the results section was difficult to follow in the study report.
13. The choice of the 1600 mg dose, using efficacy and safety data was not made clear. The 1600 mg dose for Part 2 was chosen because it would enable achievement of the primary endpoint, that is non-inferior $C_{troughs}$, but the relative difference in C_{max} and AUC (safety and efficacy) was not clear.
14. Please provide evidence to show the relationship of SC to IV in term of convenience.
15. The numbers and percentages do not appear to be consistent, for example 2 patients is equal to 12% but 2 patients is also 9% in the Safety data.
16. Can the sponsor please provide information on the relative frequency in incidence of human anti-human antibodies (HAHAs) and human anti-chimeric antibodies (HACAs) in IV and SC doses?
17. Does the sponsor have time-to-event endpoint (PFS, EFS and OS) data for this study yet?
18. Information on Study MO18264 to support the increased frequency of dosing and results from the Study ML17102 were not able to be located.
19. Can the sponsor please add incidence and clinical relevance of HAHA and HACA antibodies to the RMP?

Second round evaluation of clinical data submitted in response to questions

The sponsor's responses and the evaluator's comments regarding the clinical questions are shown in detail in Attachment 2 to this AusPAR.

Second round benefit-risk assessment

The benefit-risk balance of replacing IV with SC rituximab in CLL is unfavourable. This is based on:

- Unknown relationship between C_{trough} and PFS and OS in SC formulation
- Unknown comparison of SC with current therapy (IV rituximab) to PFS and OS
- Lack of externally and internally validated data showing improvement in Quality of Life (QoL) in patients or healthcare resources in patients having SC administration
- Shorter time to repopulate B cells in SC compared with IV formulation
- Increased dose (500 mg/m^2 to 1600 mg per cycle of therapy (cycles 2-6).

There is evidence showing benefit of 2 monthly maintenance therapy with IV rituximab, however outcomes with 2 months compared to 3 is not available. Therefore this change in maintenance dose is not recommended due to absence of comparative safety and toxicity evidence.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (EU-RMP Version 13.0 dated 9 October 2014, Data Lock Point (DPL) 9 October 2014) and an Australian Specific Annex Version 5.0 (dated March 2015) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown in Table 4.

Table 4: Summary of ongoing safety concerns

Important identified risks	Infusion-related reactions (All indications) Infections (including serious infections) (All indications) Impaired immunisation response (All indications) Progressive multifocal leukoencephalopathy (All indications) Neutropenia (including prolonged) (All indications) Hepatitis B reactivation (All indications) Stevens-Johnson syndrome/toxic epidermal necrolysis (All indications) Hypogammaglobinaemia (RA and GPA/MPA) Tumour lysis syndrome (NHL/CLL) Serious viral infections (NHL/CLL) Gastrointestinal perforation (NHL/CLL) Local cutaneous reactions (NHL/CLL SC formulations)
Important potential risks	Posterior reversible encephalopathy syndrome (All indications) Opportunistic infections (All indications) Prolonged B-cell depletion (All indications) Off label use in paediatric patients (All indications) Malignant events (RA and GPA/MPA) Impact on cardiovascular disease (RA and GPA/MPA) Gastrointestinal perforation (RA and GPA/MPA) Off label use in autoimmune disease (RA and GPA/MPA) Relapses (GPA/MPA) Acute myeloid leukaemia and myelodysplastic syndrome (NHL/CLL) Second malignancies (NHL/CLL) Increased risk of Grade 3/4 and serious blood and lymphatic system adverse events in > 70 year patients (CLL)

	Embryofetal toxicity resulting from systemic exposure to rHuPH20 (NHL/CLL SC formulations) Off-label use of subcutaneous formulation (NHL/CLL SC formulations) Administration route error (NHL/CLL SC formulations)
Missing information	Use in pregnancy and lactation (All indications) Immunogenicity and autoimmune disease (RA and GPA/MPA) Long term use in GPA/MPA patients (GPA/MPA) Immunogenicity associated with the subcutaneous formulation (NHL/CLL SC formulations) Effect on greater exposure in patients with low BSA after fixed-dose SC administration (NHL/CLL SC formulations)

Abbreviations: CLL - Chronic lymphocytic leukaemia; GPA - Granulomatosis with polyangiitis; MPA – Microscopic polyangiitis; NHL – Non-Hodgkin's lymphoma; RA – Rheumatoid Arthritis; SC – Subcutaneous.

Pharmacovigilance plan

The sponsor proposes routine and additional pharmacovigilance activities.

Risk minimisation activities

The sponsor proposes routine and additional risk minimisation activities.

Reconciliation of issues outlined in the RMP report

Table 5 summarises the TGA's first round evaluation of the RMP, the sponsor's responses to issues raised by the RMP evaluator and the evaluator's comments on the sponsor's responses.

Table 5: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
Safety considerations may be raised by the nonclinical and clinical evaluators through the TGA's consolidated request for further information and/or the Nonclinical and	The clinical evaluator made the following comment on the RMP: 'The Safety Specification in the draft Risk Management Plan is satisfactory. However additional pharmacovigilance for febrile neutropenia, HACA and HAHA (incidence and effect on response) is warranted.' Roche also acknowledges the clinical question regarding adding information on incidence and clinical relevance of human anti-human antibodies (HAHAs) and human anti-chimeric antibodies (HACAs) to the RMP. Roche provides the following response to	The sponsor's response is considered satisfactory from a RMP perspective; however, this issue is deferred for final determination by the

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	these two issues. *HACAs and HAHAs* Roche refers the RMP evaluator to the response to Clinical question. In summary, Roche believes the current management of this safety concern is adequate. 'Immunogenicity associated with the subcutaneous formulation (NHL/CLL SC formulations)' is currently included in the RMP list of safety concerns as Missing Information. The Pharmacovigilance Plan will further assess the incidence and clinical relevance of the development of HAHAs and HACAs through routine pharmacovigilance and additional pharmacovigilance activities (BP22333 and BO22334/SABRINA studies). *Febrile neutropenia* This safety concern is encompassed by the existing Identified Risk of 'Neutropenia (Including Prolonged)'. Routine Pharmacovigilance is currently practiced for this risk. Roche doesn't believe there is any new safety information to change the current management of this risk. Please note that the TGA nonclinical evaluation report was received on 25 September 2015. Roche does not believe there is any new information of relevance to the RMP.	Delegate.
The information presented in the RMP indicates that the current application is under review in the EU (Submission date: 5 November 2014). The sponsor should provide any update on the status of this application for consideration by	The application for MabThera 1600 mg solution for SC injection for use in CLL remains under review in the EU. The sponsor has received the Day 120 List of Questions from the Committee for Medicinal Products for Human Use (CHMP). The CHMP has raised no major objections to approval of the application. The overall benefit/risk of MabThera 1600 mg for CLL is considered positive pending the sponsor's response to the comments raised as part of the Day 120 List of Questions.	The sponsor's response is acceptable from a RMP perspective.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
the TGA.		
The sponsor has advised of numerous ongoing and planned pharmacovigilance activities. The sponsor should provide any updates on the status of these activities subsequent to the data lock point of this RMP (9 October 2014).	Roche does not have any updates at this time to the information provided in EU-RMP version 13.0 and the Australian Specific Annex regarding ongoing and planned pharmacovigilance activities.	The sponsor's response is noted, recognising that any updates will be included in future RMP submissions.
It is noted that the submitted healthcare professional and patient education materials are outdated and do not reflect the changes associated with this application. Educational materials should be updated to reflect any relevant changes associated with this application.	The proposed Australian educational materials in relation to the SC formulation will be updated to reflect the 1600 mg strength proposed with this application prior to launch of the presentation, assuming the application is approved. The EU educational materials provided with EU-RMP version 13.0 are current.	The sponsor's commitment to update the educational materials is acceptable from a RMP perspective. The materials should be submitted to the TGA for review prior to distribution

Summary of recommendations

Issues in relation to the RMP

There are no outstanding issues in relation to the RMP for this submission.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Key changes to the updated RMP

The provided EU-RMP with ASA is the current one (EU-RMP Version 13.0, dated 9 October 2014, DLP 9 October 2014; ASA Version 5.0, dated March 2015).

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is: Implement RMP (Version 13.0, dated 9 October 2014, DLP 9 October 2014) with Australian Specific Annex (Version 5.0, dated March 2015) and any future updates as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations[8]:

Quality

The quality evaluator had no objections to registration of the new formulation based on quality grounds.

It is noted in the information provided by the sponsor regarding the status of the European Medicines Agency (EMA) application that additional stability data have been requested. If not already supplied to the TGA, the Delegate requests that these data also be provided to the TGA (See *Questions for sponsor* below) as well as the reasons why the EMA requested these additional data.[9]

Nonclinical

There are no nonclinical studies provided to support the new MabThera SC 1600 mg strength formulation for use in CLL patients and nonclinical data to support changes to the dosing frequency from 3 monthly to 2 monthly in NHL patients for both the MabThera IV and SC formulations. Thus, the approval of the higher strength MabThera SC (1600 mg) formulation for use in CLL patients and changes to the dosing regimen for MabThera SC and IV use in NHL patients will rely on clinical and pharmaceutical data.

Clinical

The clinical evaluator has reviewed the submitted data (see Scope of clinical submission above) and evaluated them using TGA adopted EMA Guidelines as follows:

- *Guideline on the evaluation of anticancer medicinal products in man*.
- *Points to consider on application with 1. Meta-analyses; 2. One pivotal study.*

[8]See also *Section 60 appeal* and *Final Outcome* below for summarises and final decision.
[9] Data were submitted with section 60 appeal.

- Cancer in Australia an Overview 2014 http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=60129550202 (accessed at the time of the evaluation)
- Chronic lymphotic leukaemia (CLL) incidence statistics. Cancer Research UK. http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-cll/incidence#heading-One (accessed at the time of evaluation).

Clinical evaluator's recommendation

The clinical evaluator recommended that the application not be approved for the extension of indications for the new MabThera SC formulation, or for the increase in maintenance for the treatment of NHL using the MabThera SC formulation.

Paediatric data

The submission did not include paediatric data.

Pharmacokinetics/pharmacodynamics

Study BO25341/SAWYER to support registration of the SC formulation for use in CLL.

Study BO25341

A Phase Ib adaptive, comparative, randomised, parallel group, multicentre study of SC rituximab versus IV rituximab both in combination with chemotherapy (fludarabine and cyclophosphamide), in patients with previously untreated CLL was undertaken. This study had 2 Parts and primary and secondary endpoints in each Part. Essentially Part 1 was designed to undertake a PK analysis to optimise the choice of dose for Part 2 of the study. Part 2 was thus informed by a population PK model using data from Part 1 and its primary endpoint was to establish non-inferiority of the C_{trough} of the SC compared with the IV formulation. Randomisation was stratified according to Binet stage and route of administration of the fludarabine and cyclophosphamide (FC) chemotherapy.

Delegate comments on study design

1. FCR is reserved in Australia (and elsewhere) for younger patients with good performance status. The Australian website eviq.org.au states the following regarding FCR: 'this is a very immunosuppressive therapy caution required in: pre-treated patients, those with pre-existing cytopaenias, those with a history of opportunistic infections and the elderly'. Accordingly, the inclusion criteria required an Eastern Cooperative Oncology Group (ECOG)[10] performance status of 0 or 1, and the median age in Part 1 of the study was approximately 58 years (exact median not provided) and 60 years of age in Part 2.

[10] ECOG Performance Status: The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used: 0 - Fully active, able to carry on all pre-disease performance without restriction; 1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours; 3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours; 4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair; 5 – Dead

2. Fit, young, previously untreated patients are not representative of the general population with CLL. Generalisability of any findings to the much more commonly encountered older and more frail population is a major limitation in this study.
3. The doses of fludarabine and cyclophosphamide could be oral or IV; the former were variable according to the discretion of the investigator and the IV schedule was consistent with that used in Australia. There was a protocol amendment to stratify for route of administration of FC but the data are not presented on outcomes according to these different regimens.
4. No stratification by key predictive and prognostic molecular and cytogenetic factors known to affect response and survival was undertaken in Part 1 or Part 2 of this study. Retrospective evaluation of this was hampered by missing data which would be likely to influence outcomes within the trial, although efficacy was only an exploratory endpoint.
5. As stated in the company study report 'Efficacy endpoints analyses were considered exploratory. There was no formal statistical testing.' There was no pre planned interim analysis; the time of reporting is referred to as a 'data snapshot'.
6. The safety and efficacy of the SC MabThera was not investigated with any of the other options for combination with rituximab currently registered in Australia.
7. There are no safety data presented on the local effect of repeated injections of a significant volume SC, and the impact of repeated use of hyaluronidase, particularly in an elderly population.
8. The Delegate was unable to locate any clinical data to support the claimed improved PK of rituximab in combination with hyaluronidase versus rituximab alone; no clinical data to justify the increase in hyaluronidase for this increased dose of SC rituximab were presented.
9. The study design was to demonstrate PK, not safety and efficacy for the proposed usage. The following design issues will limit the power to detect any potential efficacy and/or safety differences due to the differing route of administration and exposure to rituximab:
    a. small numbers of patients in each arm
    b. fit, younger population without significant comorbidities
    c. previously untreated patients
    d. high absolute response rates to first line treatment (efficacy)
    e. high toxicity of the chemotherapy backbone (safety) with high background treatment-emergent adverse event rates
    f. relegation of efficacy endpoints to exploratory status

Delegate comment: The proposed study in support of registration has significant internal and external validity issues:

1. Internal validity
    a. Non-inferiority of the trough is being used as a surrogate endpoint for clinical benefit and safety for registration purposes. The study has not been designed to determine the risk of the resulting higher exposure, particularly for safety.
    b. The study was not designed statistically to demonstrate safety and efficacy; indeed, the efficacy endpoints which were exploratory and data are not presented on PFS, OS as the sponsor states these are immature still.

c. Patients could receive either oral or IV regimens, with a variable dose strategy of 30 to 40 mg/m^2 of fludarabine in the oral regimen. No data are presented on the study patients' safety and efficacy outcomes by regimen type, compliance with the oral regimen (for example tablet counts) nor the toxicities according to the route of administration selected.

d. There was no stratification for factors known to influence response rates and survival.

e. No data are presented to demonstrate the safety and efficacy of SC rituximab with other combinations chemotherapy or targeted agents. This is a significant deficiency of the application given the questionable generalisability of the findings from a younger, fitter population < 70 years of age being treated for the first time with a very immunosuppressive regimen which would not be deemed suitable for half the patients presenting with CLL in Australia. Nor does it provide support for the safety and efficacy in a previously treated population.

2. External validity

The study has significant limitations as:

a. Very few patients were > 70 years of age and the median age was more than 10 years younger than the mean age of onset in CLL in Australia.

b. The patients represent a less common subset of those presenting with CLL; that is younger, fitter receiving first line treatment.

c. No data are presented for those with pre-treated CLL and who have a more marginal benefit of adding rituximab to FC (as stated in the PI) and for whom greater exposure to rituximab may pose a higher immunosuppressive risk.

d. No data are presented to represent combinations with other chemotherapy to support extension to the broad indication currently approved for the IV regimen.

e. There were only 25% of women in the study, with 25 in total treated with the proposed formulation.

Therefore, any safety and efficacy data generated in this population will not necessarily be generalisable to more heavily pre-treated populations nor a more frail population, who would be included in an extension of indications currently proposed. No other data with different regimens are proposed in support of the subcutaneous dosing strategy.

Study BO25341

Part 1Pilot dose selection

In Part 1, a single cycle of rituximab SC was administered to select a dose of rituximab SC that would result in rituximab C_{trough} values comparable to those achieved with the IV regimen.

In Cycle 5 (and previous cycles), patients received rituximab IV and subsequently in Cycle 6 rituximab IV was replaced by a single rituximab SC dose (the first sub-cohort received 1870 mg rituximab SC and thereafter two sub-cohorts, with 1400 mg and 1600 mg rituximab SC doses, were sequentially opened).

Figure 2: Part 1. Pilot dose finding study Cohort A

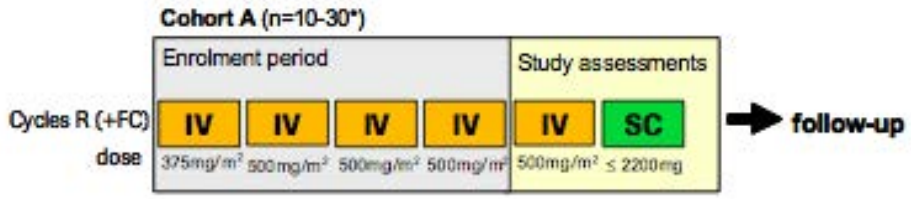
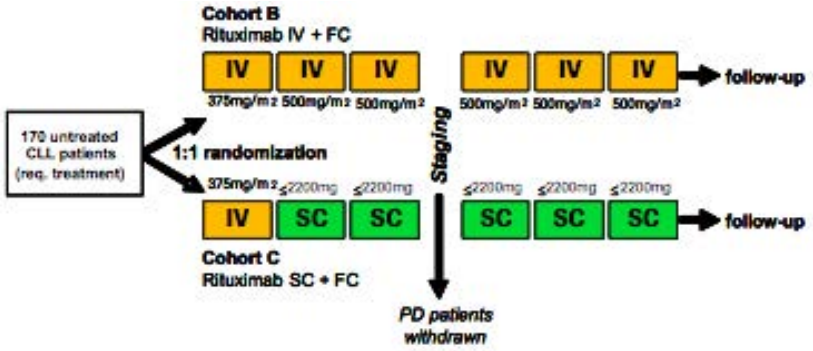


Figure 3: Part 2 Study with primary endpoint of demonstrating C-trough non-inferiority between fixed dose 1600 mg SC versus IV rituximab.



Objectives of Part 1

Primary

- To confirm a selected SC rituximab dose results in C_{trough} levels that are comparable with IV rituximab

Secondary

- To describe the rate of incidence of injection related reactions during the SC rituximab cycle
- To describe patient and nurse preference regarding SC or IV administration.

Objectives of Part 2

Primary

- To establish non-inferiority in observed C_{trough} levels between the confirmed SC rituximab dose and the reference IV rituximab dose, as assessed by a non-inferiority test with a lower boundary above 0.8 for the 90% confidence interval.

Secondary (stated as exploratory in the Statistical Analysis Plan)

- To evaluate safety parameters among patients for SC versus IV rituximab
- To assess physician/nurse opinions on time savings and convenience with SC versus IV rituximab

Shared secondary objectives for Parts 1 and 2

- To assess additional PK parameters, including AUC from time 0 to the end of the dosing interval ($AUC_{0-\tau}$), C_{max}, time to C_{max} (T_{max}) and half-life ($t_{1/2}$) of both SC and IV rituximab
- To compare the immunogenicity of SC versus IV rituximab
- To examine peripheral blood B-cell levels and B-cell depletion and repletion with SC rituximab compared with IV rituximab
- Exploratory assessment of the efficacy of SC rituximab compared to IV rituximab, including Response rate [Complete Response (CR), Complete Response with incomplete bone marrow recovery (CRi), Partial Response (PR), EFS, EFS and OS.

Part 1

- 64 patients enrolled sequentially to Cohort A; 56 patients treated:
  - 16 patients in rituximab 1400 mg SC sub-cohort
  - 17 patients in rituximab 1600 mg SC sub-cohort

– 23 patients in rituximab 1870 mg SC sub-cohort

Statistics describing demographics of this part of the trial are not given for the entire group. Of 55 who received treatment, the median age was approximately 58 with no figure given for those > 65 years ('most were under 65'), 27% were women, body surface area (BSA) ranged from 1.55 to 2.33m^2.

Delegate comment: Patients only received a single SC dose so no meaningful safety data apart from administration related reactions can be determined. Efficacy is not evaluable due to confounding.

Outcome of Part 1

The Population PK evaluator noted the report does not provide a final conclusion as to what dose level should be used. However, it appears that SC doses between 1400 to 1650 mg are likely to be non-inferior to the IV dose.

The dose of 1600 mg was selected for Part 2 based on non-inferiority of the C_{trough} and comparability of the AUC after using population PK modelling identified the initial 1870 mg SC dose was too high.

The TGA's Pharmaceutical Subcommittee advised that after consideration of the sponsor's responses, the following matters are still concerns directly related to the population pharmacokinetic evaluation:

- The impact on the model of the clearance of the outliers (2 noted).
- The impact of high anti-rituximab antibody levels on the quantification of small concentrations of rituximab.

Delegate comment: The sponsor indicated in their response that the main goal of the analysis was to recommend a dose that would 'match (or exceed)' the exposure (C_{trough} and AUC_T) of the IV formulation (to establish 'non-inferiority'); it appears to be accepted that there would be a much higher exposure and higher trough for the vast majority of patients compared with the IV route and BSA dosing strategy.

Part 2

176 patients were randomised to Cohort B and C. 174 patients were treated: 87 patients in Cohort B and 87 patients in Cohort C.

Cohort B

87 patients treated on Day 1 of a 28 day cycle: 375 mg/m^2 IV rituximab, followed by Day 1 500 mg/m^2 IV rituximab for up to 5 further cycles to a maximum of 6 cycles. FC was administered as per investigator choice of oral or IV regimen below.

Cohort C

87 patients treated on Day 1 of a 28 day cycle with 375 mg/m^2 IV rituximab + FC, followed by SC rituximab at the dose determined from Part 1 of the study (1600 mg) + FC for up to 5 further cycles.

In Part 2 of the study, the median age was 60 years, (range 25 to 78) with 8% subjects > 70 years of age; 25% were women; BSA ranged from 1.41 to 2.42 m^2. The treatment arms were well balanced with respect to BSA and age. There was a significant gender imbalance between the arms: 60% in the IV arm were men versus 71% in the SC arm.

Delegate comment:

1. Only 25 women received the dose proposed for registration, the 1600 mg SC formulation, in this randomised part of the study –.

2. 73% of patients receiving the 1600 mg SC dose were < 65 years of age (range 25 to 74), only 8 patients over the age of 70 and 15 aged between 65 and 70 were treated with 1600 mg SC rituximab in the randomised part of the study; it is noted that these patients must have been very fit to be considered for the FCR regimen. This is not representative of the general CLL population requiring treatment, either in terms of age or performance status.

The following information on the FC component of the regimen is taken from the CSR and contains some inconsistencies in the scheduling of cyclophosphamide (the two doses are presented with both stated as oral; should the Days 1 to 3 be IV?), on which the sponsor is requested to comment (see Questions for sponsor below):
Fludarabine was administered either as 24 mg/m^2 orally on Days 1 to 5 of all cycles or 30 to 40 mg/m^2 orally on Days 1 to 3 of all cycles.
Cyclophosphamide was administered either as an IV infusion at 250 mg/m^2 on Days 1 to 3 of all cycles or orally as part of an approved dosing regimen as follows:

- 150 mg/m^2 orally on Days 1 to 5 of all cycles
- 200 to 250 mg/m^2 orally on Days 1 to 3 of all cycles.

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

Delegate comment: 30% received oral chemotherapy, with doses of either route varied according to local practice. All of which may affect toxicity and tolerability as well as efficacy. Compliance is also uncertain with oral formulations. This 'real world' approach to dosing is a risk in a small study already lacking power to demonstrate efficacy and safety and underscores that this trial is not designed to demonstrate safety and efficacy.

Outcome of Part 2

The primary endpoint of the study, to demonstrate non-inferior C_{trough} of the 1600 mg rituximab SC dose compared with rituximab IV 500 mg/m^2 in CLL was met. Based on the geometric mean for C_{trough} measurements with dosing every 4 weeks (q4w) available in 77% of the ITT population, serum rituximab exposure was comparable between the rituximab IV 500 mg/m^2 and rituximab SC 1600 mg arms. The geometric mean ratio for observed C_{trough} of 1.53 (90% confidence interval (CI): 1.27, 1.85) for the q4w regimen was 20% higher than the predicted value from population PK analyses at Part 1 (1.21), although this was within the confidence interval. The lower limit of the two-sided 90% confidence interval was 1.27 which was much greater than the pre-specified non-inferiority margin of 0.8.

Delegate comment: The C_{trough}SC/C_{trough}IV was 1.53 which represents a 53% increase in trough for patients receiving the SC formulation, with the 90% CI lower limit being 27% and the upper limit being 85% higher than with IV formulation.

The secondary endpoint in Part 2 was the estimated ratio of observed rituximab serum AUC (SC)/AUC (IV) during Cycle 6. The geometric mean AUC_τ values for the IV and SC formulations were 3630 µg/day/mL (CV% 32.8) and 4088 µg/day/mL (CV% 34.6). These values yield a mean $AUC_{\tau(SC)}$ AUC_τ /$AUC_{\tau(IV)}$ AUC_τ ratio of 1.10 (90% CI 0.98 to 1.25).

Delegate comment:

a. Data for the Cycle 5 C_{trough} and AUC Cycle 6 are evaluable from 77% and 62% of the ITT population, respectively. The sponsor assumed a 20% drop out rate but the AUC missing data exceed that by nearly 2 fold. Given this is primarily a PK

study, these missing data are of concern and the implications of the missing data cannot be established. The clinical evaluator identified that AUC might be the better parameter for establishing non-inferiority due to the differential effect of absorption, distribution and elimination on C_{max}, T_{max} with the SC route, also likely to vary with age and body composition. Disease progression would not be expected to explain this based on the results from the previous trials of this regimen in CLL.

b. There is a wide degree of variability for the AUC, making individual exposure predictions difficult; using the mean AUC for each route of administration, almost all patients had a greater exposure to rituximab with the SC formulation.

c. No data to support the safety and efficacy of the resulting increased exposure to rituximab are presented. The Delegate notes that the sponsor presented a single publication in support of a wide therapeutic window in response to previous questions by the TGA when registering the 1400 mg SC formulation for NHL. However, this is considered inadequate to support this application and reliance on such evidence constitutes a hybrid literature-based submission and requires a literature search strategy agreed with the TGA prior to the submission of the application.

Pharmacodynamic effects

The pharmacodynamic effects of the SC versus IV route resulted in similar median rates of B cell depletion during treatment. However, at all the time points including baseline, there were significant missing data; up to 33% in the IV arm and up to 25% in the SC during the active treatment time and 6 month follow-up period.

Delegate comment: These missing data render the information unreliable as the missing data could reflect treatment failures. The need for efficacy to be a primary or secondary rather than exploratory endpoint is evident.

The TGA's Pharmaceutical Subcommittee considered the application at two separate meetings (recommendation No 2395 and 2402) and recommended that dosing be based on crossover data rather than population pharmacokinetics, and that data were lacking regarding bioavailability in the elderly who are likely to be the majority of patients. In addition, there was concern over the tolerability of such a large volume (13.4 mL for the 1600 mg dose) being administered SC to a largely elderly population.

The following are additional concerns to be considered in the clinical evaluation;

- Limited data of use in patients with CLL and implications on clinical safety.
- Limited information about the tolerability of the SC injection.
- The impact of less hospital observation time and potential for tumour lysis syndrome if first used (inappropriately) in patients with extremely high white cell counts.

Efficacy

All efficacy outcomes were stated to be exploratory and the study was not powered to detect differences in these outcomes. This, together with the fact that time-to-event endpoints (PFS, EFS and OS[6]) for Part 2 have not been analysed because these data are not yet mature is a significant deficiency which the Delegate considers precludes approval. Although the CSR states that '*these parameters will be analysed and presented in the final (follow-up) CSR*', this would not overcome the limitations of the study design to demonstrate efficacy for the new formulation.

No meaningful conclusions can be drawn from the 3 month efficacy data on response rates because:

1. This was a PK study and all efficacy endpoints were exploratory
2. Data from Part 1 are non-randomised, have different SC doses and are confounded by 5 out of 6 cycles being given IV. Data from Part 2 are somewhat less confounded as patients who completed the trial will have received one dose of IV and five SC doses.
3. Patients could have received oral or intravenous FC chemotherapy, with starting doses varying according to local practice; in addition, compliance is more uncertain with oral medications and there are no data were presented to address this. 30% received oral FC.
4. High response rates to the FC component of the regimen are seen in untreated patients and the study lacks power to detect any difference between the variable of route of administration of rituximab.
5. The subgroups determined by BSA were not pre-specified and in any case, the numbers are too small to provide assurance there is no significant difference between the formulations and dosing strategies.
6. The gender subgroups of men and women were not pre-specified and in any case, the numbers are too small to provide assurance there is no significant difference between the formulations and dosing strategies.
7. Of concern for such a small study, was that data were missing for 14% at the 3 month efficacy time point.

The data on minimal residual disease measurements are further limited by only 71.5% of patients having evaluable results.

Pharmacoeconomics and outcomes research related parameter analysis

Both patients and health care professionals indicated a preference for the SC formulation in Part 1 of the study, that is, after/during a single SC injection given at Cycle 6.

Delegate comment: This is based on a single administration of the SC formulation and appears to have been gathered at the time of administration.

In Part 2 of the study, nurse/physician 'opinion' not patients' opinion about time savings were sought at Cycle 6.

Delegate comments:

1. Patient reported outcomes were only measured in Part 1 after a single MabThera SC injection, but no patient, only health care professional input was sought regarding the impact of up to five SC injections of rituximab in Part 2. This is not adequate for a study purporting to provide improved patient convenience and quality of life.
2. There was no formal, objective measurement of the time taken for administration, for example, whether that was the patient's time in the unit or time spent by the health care professional administering the treatment.
3. No information is provided for those receiving oral FC compared with those receiving IV chemotherapy. It is not clear whether the providing MabThera SC is more relevant for the 30% of patients receiving oral chemotherapy compared with those receiving IV chemotherapy.
4. In response to the clinical evaluator's question about validation of the questionnaires used, the sponsor notes this was not undertaken prior to the

study. The Delegate is in agreement with the clinical evaluator that '*lacking this, any discussion on improved QoL or patient benefit for SC formulation is without substantiation*'.

Other endpoints

The sponsor claims in the letter of application that:

8. '*the median duration of the injection was around 7 minutes compared to several hours for IV administration*'.

Delegate comment: No data could be located to support this claim (see *Questions for sponsor* below). Furthermore, it is accepted practice in chemotherapy day wards to administer rituximab at a faster rate if the first cycle was tolerated well, thus the 'several hours' is not an accurate reflection of current clinical practice. If patients need a slower rate of infusion due to prior reactions, then it could be argued they are not candidates for a rapidly administered SC infusion that cannot be stopped. This has not been adequately tested in the trial presented.

9. '*The new SC strength will add a valuable therapeutic option for CLL patients resulting in reduced administration time and increased comfort convenience (sic) that may result in improved treatment compliance.*'

Delegate comment: The Delegate agrees that a reduced administration time would be appreciated by patients. It is not clear, however, that *'increased comfort convenience*' is provided by a treatment with higher rates of administration reactions. The sponsor has not provided any evidence in terms of the local effects of repeated administration of a large volume of SC formulation containing hyaluronidase, nor provided any adequate evidence of improved patient satisfaction to demonstrate any effect on '*comfort convenience*' and resulting improvement in compliance.

The safety of the proposed usage has not been demonstrated to allow patients to make a fully informed decision about consenting to this potentially faster route of administration.

Summary

The data collected and presented are from questionnaires that were not validated and do not contain patient reported outcomes beyond the single SC dose administered in Part 1 of the study, representing only 17 patients receiving a single SC dose of 1600 mg. This does not capture the effects of multiple dosing SC and whether this is acceptable or not to patients. Patient and physician preference is not informed by key information in the absence of clearly demonstrated efficacy and safety.

Efficacy discussion

The study presented in support of the proposed usage is from a PK study designed to establish PK endpoints. It is unclear whether C_{trough} is the optimal PK parameter, nor is it an adequate surrogate endpoint for clinical efficacy (or safety) for establishing non-inferiority that is generalisable across all CLL patients. This study is inadequate for clinical bridging given the complexity of the changes being introduced: a higher fixed dose, new dosing strategy and new formulation with a new route of administration. The conclusions that can be drawn are very limited by the small study numbers, missing data, and confounding effects of prior treatment with IV rituximab and potentially variable doses and routes of administration of the accompanying chemotherapy. Inadequate amounts and method of collection of data regarding patient and health care professionals' assessments of time savings and benefits do not support the sponsor's claim of increased convenience.

Safety data

No studies assessing safety as a primary outcome were presented in support of the proposed new formulation for the treatment of CLL, nor for the increased frequency of administration in the maintenance treatment of NHL.

Delegate comment: These are major deficiencies of the application.

Adverse events

Part 1

The limited safety data from the Part 1 study suggested that treatment-related AEs increased with increasing dose: (6 patients [38%], 8 patients [47%] and 14 patients [64%] for the 1400 mg, 1600 mg and 1870 mg rituximab SC sub-cohorts, respectively). ARRs, defined as any related AE which occurred during or within 24 hours of infusion/injection (that is, injection site pain, erythema, discoloration and oedema) were more common with increasing dose: 6% with 1400 mg dose, 29% with 1600 mg dose and 27% with the 1870 mg dose. This may be related to the larger volume being infused, as well as the larger dose of hyaluronidase. The final results of 42% ARR reported in the PI is substantially higher than the 20% seen with the 1400 mg SC dose used in NHL.

Delegate comment: These are the only data that allow comparison with the currently registered 1400 mg SC formulation and would suggest that the local safety profiles are not the same. It is unclear whether there is a maximum tolerated SC infusion volume.

Part 2

Increased ARRs occurred in the SC arm (31% versus 15%), while gastrointestinal and vascular disorders were reported less commonly (8% versus 18% and 5% versus 16% respectively). Of the ARRs, however, 4 were ≥ Grade 3 intensity: injection site erythema, anxiety, thrombocytopenia and urticarial. The latter two resulted in withdrawal from the study.

Delegate comment: No data are provided on whether the two patients who withdrew from the study due to adverse events continued with rituximab IV or stopped rituximab treatment altogether.

Due to the small numbers and lack of power of the study, the differences in other adverse event rates cannot be interpreted due to small numbers of patients in the trial. However, it was notable that women experienced more Grade ≥ 3 AEs than men with both the rituximab IV (42% versus 26%) arm and SC (36% versus 27%) formulations, respectively.

Delegate comment: Clarification of the actual grade of all 4 events is requested, as currently these are designated as '≥Grade 3'; as is the speed of onset of thrombocytopenia is important to understand for monitoring purposes and the sponsor is requested to provide this information. The sponsor is also requested to state whether this withdrawal was from the study or resulted in discontinuation of rituximab altogether. See *Questions for sponsor* below.

Similar to Part 1, there was a much higher rate of local cutaneous reactions in the SC arm (38% versus 2%) with severity ranging from Grade 1 to 3 in severity. These rates are higher than in the trastuzumab SC formulation (total infusion volume of 5 mL) and suggest a volume related effect.

Serious adverse events and deaths

Of 9 deaths in Part 2, 5 were in the SC arm and 4 in the IV arm. Five were attributed to progressive disease and four were attributed to infections; the two deaths considered treatment-related both occurred in the SC arm and were due to Herpes zoster and PML.

The most common SAE was febrile neutropenia (4 patients [4%] in the rituximab IV arm and 9 patients [11%] in the rituximab SC arm, respectively), followed by neutropenia (8 patients [9%] and 1 patient [1%]), pyrexia (1 patient [1%] and 3 patients [4%]), and anemia (3 patients [3%] and 0 patients).

Delegate's comment: Of the 4 deaths which had a judgement as to treatment related, the two in the SC arm were judged as related to treatment (PML and Herpes Zoster). Febrile neutropenia occurred more commonly.

Discontinuations

Withdrawals from Part 2 were similar in each arm (9/14 due to an AE in the SC arm versus 7/15 in the IV arm). It not clear if those who withdrew from the SC arm continued treatment with the IV formulation[11].

Antibody formation

Anti-rituximab antibodies (HACAs): In Part 1, all patients had received IV rituximab before commencing therefore no conclusions can be drawn. No inferences about the potential effect of neutralizing antibodies from response rates can be drawn as patients were receiving concomitant chemotherapy with a high likelihood of response to that treatment.

Anti-ruHuPH20 antibodies were detected in patients prior to receiving the SC formulation therefore this questions the specificity of the assay.

The potential for antibody formation including neutralizing antibodies remains an area of uncertainty.

Safety discussion

Limited data are available from Part 1 due to the small numbers receiving the proposed dose, and confounding from prior IV rituximab. However, there appears to be a clear dose related increase in adverse events, particularly ARRs. The role of the volume and/or constituents in the sharp increase in ARRs from the 11.7 to 13.4 mL used in NHL and CLL respectively is unclear. Patient reported outcomes are not available to assess this particular aspect. ARRs were also increased in Part 2, and in addition there were two deaths attributed to treatment in the SC and none in the IV arm, as well as higher rates of febrile neutropenia. There is uncertainty as to whether neutralizing antibodies occur at a higher rate. The study was not designed to demonstrate safety and this is a key deficiency of the application.

Risk management plan

The RMP evaluator recommended implementation of RMP (Version 13.0, dated 9 October 2014, DLP 9 October 2014) with Australian Specific Annex (Version 5.0, dated March 2015) and any future updates as a condition of registration. However, the Delegate does not currently support registration.

It is considered that the sponsor's response to the TGA's questions have adequately addressed all of the issues identified in the RMP evaluation report.

The opinion of the Advisory Committee for the Safety of Medicines (ASCOM) was not sought for this application.

[11] Sponsor clarifies that patients did not continue with IV if withdrawn from SC.

Risk-benefit analysis

Data deficiencies/limitations

The application might be considered approvable if the following deficiencies could be addressed:

1. There are no data from studies designed and powered to provide randomised, controlled data in support of efficacy and safety of the proposed usage. There was a reliance solely on PK non-inferiority as an endpoint and an unsubstantiated extrapolation of the relevance of that to efficacy and safety. There was no inclusion of a relevant pharmacodynamic endpoint to establish efficacy, for example B-cell depletion.

2. There were two treatment related deaths in the SC arm and an increase in febrile neutropenia suggesting a potentially inferior safety profile compared with the existing IV formulation.

3. There are no data reporting on the long term local effects of repeat dosing with a large volume of solution containing hyaluronidase. This is relevant for both the study provided to support registration with a larger volume for the treatment of CLL and the more frequent maintenance usage of SC MabThera in NHL.

4. The larger volume being administered and dose related increase in adverse event rates in the CLL study prevent generalisations from any NHL studies.

5. There are limited numbers of women (25) and patients either aged 65 to 70 (15) or >75 years of age (8) treated with the proposed dose. Given 43% of patients are > 75 years of age at diagnosis and women account for 39% of cases of CLL in Australia, this is too small a sample to size from which to make generalisations about safety and efficacy. In particular, women appear to have higher adverse event rates with rituximab, and the safety of increased exposure, especially over time has not been adequately demonstrated.

6. In Australia, approved regimens including rituximab are for use in all ages and stages of disease, thus the data presented here for a fit, previously untreated population have limited generalisability. Given the very high background rate of treatment-emergent adverse events, a large randomised controlled trial comparing the two formulations is required to demonstrate the safety and efficacy in this population.

7. Ideally any study designed to demonstrate safety and efficacy of SC rituximab should include more than one type of chemotherapy and also include targeted therapies, given emergence of the latter as key agents in treating CLL; combinations with rituximab are the subject of active investigation.

8. There are no long term data reporting the safety and efficacy of MabThera SC in either CLL or NHL.

9. The patient reported outcome data are too limited to support the acceptability of SC MabThera in this application. Validated questionnaires administered throughout the study are required to assess the claims of improved comfort, convenience and compliance claimed in the letter of application.

Thus, the effects of the new dosage form, route of administration, flat-dosing on safety and efficacy have not been demonstrated adequately. This could be addressed by conducting larger, randomised controlled trials which have safety and efficacy as primary and/or secondary endpoints. Ideally, such a trial would include patients who are representative of the broader population in which the new formulation would be used. Treatment combinations should include chemotherapy and targeted therapies.

Summary of issues

A single Phase Ib clinical trial with PK primary endpoints and 3 month surrogate exploratory efficacy endpoints is provided in support of the new dose strength, new dosing strategy of fixed dose rather than calculated by BSA, new formulation used at higher doses resulting in greater exposure than the approved intravenous formulation to treat CLL.

Significant internal and external validity issues limit the value of the data in support of the proposed usage.

1. Trial was conducted in younger, previously untreated patients with good performance status (that is, not representative of the broader population with CLL)
2. Small numbers were enrolled and it was not designed or powered to demonstrate safety and efficacy of the new dose formulation/strength/strategy.
3. All efficacy endpoints were exploratory, based on a 3 month 'data snapshot' of surrogate endpoints and the statistics were descriptive.
4. Efficacy data (PFS, OS) are immature and thus not presented.
5. No data on the local effect of the regular, large volumes of SC hyaluronidase containing solutions are presented.
6. The SC arm of the randomised part of the trial included:
    a. 25 women
    b. 15 patients aged 65 to 70
    c. 8 patients > 75 years

To avoid a lower C_{trough} with the SC formulation, a higher fixed dose based on population PK estimates was selected and has resulted in greater exposure than initially predicted. No data are presented from a study powered to demonstrate safety of this increased exposure.

The only treatment related deaths occurred in the SC arm and febrile neutropenia was increased in the SC arm.

Administration related reactions were much higher compared with SC versus IV (42% versus 2%) and increased sharply with increasing SC dose and volume: 42% in the CLL study (1600 mg SC dose, 13.4 mL) compared with 20% in the NHL study (1400 mg SC, 11.7 mL).

Patient reported outcomes are lacking to support the claim of increased patient convenience and acceptability, for short or long term usage.

The Delegate believes that a PK bridging study carried out in the fittest cohort of previously untreated patients presenting with a disease which most commonly affects an elderly population is inadequate to demonstrate efficacy and safety satisfactorily, given the complexity of the changes to the dosing strategy.

The sponsor also seeks to increase the maintenance dose frequency from 3 monthly to 2 monthly, including for the MabThera SC formulation. No direct long term data on safety and efficacy of increased MabThera SC infusion frequency are presented in support of this. Thus the Delegate does not support the changes to the PI for the SC formulation.

Proposed action

The Delegate does not support registration of the new strength for the treatment of CLL due to the lack of demonstrated safety and efficacy for this increased dose, the route of

administration and this proposed usage. In particular, there is a lack of data to support the longer term efficacy and safety of the SC formulation in either CLL or NHL. The latter was based on simulated data, with potential accumulation identified with the shorter 2 monthly dosing interval proposed. Additional clinical data are needed to demonstrate safety and efficacy. In the interim, there is an approved IV formulation available.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Whether Ctrough is the most appropriate PK parameter to establish non-inferiority for different routes of administration.
2. Whether the bridging data presented in the PK trial are sufficient to demonstrate safety and efficacy for the proposed usage.
3. The generalisability of the findings in this study with respect to age, gender, comorbidities, previous treatment given the wide approval for the IV formulation for use in combination with chemotherapy, regardless of stage of disease, prior treatments.

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Questions for the sponsor

1. The TGA requested information from the sponsor regarding an EU-related quality topic that the EMA had posed questions on during their review.
2. The information on the FC component of the regimen taken from the company study report contains some inconsistencies regarding the dosing of cyclophosphamide: the two doses schedules are both presented. Should the Days 1-3 be IV?
3. The sponsor is requested to provide a summary of the median time of infusion for the SC versus IV formulations with interquartile ranges in Part 2 of the BO25431 study.
4. For the 4 ARR events in Part 2 of Study BO25341, please clarify:
    a. The grade of each individual ARR.
    b. The timing of the onset of the observed thrombocytopenia, together with pre dose platelet levels and post dose platelet levels
    c. Whether the two withdrawals due to ARRs were from the study or resulted in discontinuation of rituximab altogether.

Response from sponsor

Background and comment on the delegate's proposed action

The application under review proposes to

1. register MabThera SC 1600 mg for chronic lymphocytic leukaemia (CLL) and
2. change the dosage frequency to 2 monthly, rather than 3 monthly, for both MabThera IV and SC for the maintenance treatment of non-Hodgkin's lymphoma (NHL).

The Delegate's preliminary assessment does not support registration of 1600 mg SC for CLL or changes to the maintenance dosing frequency for the SC formulation.

Roche considers that the MabThera SC 1600 mg has a favourable benefit-risk profile for CLL, comparable to that of the registered intravenous (IV) formulation, and is expected to increase clinician and patient convenience and healthcare resource utilisation. Roche considers the proposal for 2-monthly (q2m) dosing in the NHL maintenance setting is favourable for both MabThera IV and SC. This regimen is current standard practice in Australia and is supported by long-term safety and efficacy data. This response document describes the fundamentals of the development program for MabThera SC, provides the Sponsor position on questions posed to the ACPM and addresses additional specific questions posed by the Delegate to the Sponsor.

MabThera SC in CLL is part of comprehensive, consistent overarching program for MabThera SC

Study BO25341(SAWYER) is the primary study in this application designed to select (Part 1) and confirm (Part 2) the rituximab SC dose that would yield non-inferior C_{trough} compared with the rituximab IV CLL dose of 500 mg/m^2 given every 4 weeks. This study is part of an overall clinical development program for rituximab SC designed to establish the subcutaneous route of administration for rituximab for B-cell malignancies. In this context SAWYER should not be interpreted in isolation and should be considered together with the studies conducted to support the 1400 mg SC dose in NHL: BP22333/(SparkThera) and BO22334/SABRINA.

The clinical development program for rituximab SC in B-cell malignancies is a pharmacokinetic (PK) based clinical bridging approach enabled based on the fact that the active ingredient in MabThera IV and SC is identical and the well-established safety and efficacy of MabThera IV through clinical trials and years of post-marketing experience in broad NHL and CLL population groups. Due to the strong fundamentals underpinning the PK-bridging approach, a traditional efficacy/safety by indication development program that would be applicable to a new drug or indication is not necessary.

The clinical development program for rituximab SC is based on the assumption that serum rituximab levels after SC administration at least as high as after IV infusion would result in at least the same degree of efficacy, regardless of the route of administration or first-line or refractory settings. The development program for the rituximab SC formulation was based on PK-bridging to the corresponding established rituximab IV dose and dosing intervals for NHL and CLL. The dose and dosing interval of rituximab IV is different for NHL and CLL indications, therefore, separate PK-bridging studies for rituximab SC were conducted for NHL and CLL. The primary comparison of efficacy after SC and IV administration was conducted in the Phase III SABRINA study in NHL which evaluated the overall response rate (ORR) at the end of induction treatment and confirmed that the anti-lymphoma activity of rituximab was not impaired by a switch in route of administration. Efficacy endpoints in the SAWYER study were therefore secondary and intended to support the conclusions from the SABRINA study. The development program for rituximab SC was designed to answer 4 main research questions:

1. Does subcutaneously administered rituximab result in serum C_{trough} levels that are non-inferior to those of the IV formulation for the clinically established rituximab doses and dosing intervals?
2. Is the above possible when administered as a fixed dose?
3. Does the SC route of administration result in a new and medically relevant safety finding?
4. Does the SC route of administration impair the anti B-cell activity of rituximab?

1400 mg for use in NHL based on PK and safety data (including B-cell depletion and immunogenicity) from the SparkThera and SABRINA studies, together with efficacy data from SABRINA. SAWYER is a component of the overall rituximab SC program and provides

consistent additional data supporting the use of MabThera SC 1600 mg dose for the B-cell malignancy of CLL.

MabThera SC 1400 mg for NHL is now approved in over 35 countries worldwide. MabThera 1600 mg in CLL is at an advanced stage of review in the EU with no major clinical issues arising to date.

ACPM advice topics

Use of C_{trough} as the primary PK parameter to establish non-inferiority for different routes of administration

The clinical development program for rituximab SC was designed to select and confirm a dose and dosing intervals for rituximab SC that would yield non-inferior C_{trough} levels compared with rituximab IV. Hence, the sample size in Part 2 of the SAWYER study (170 patients; 85 per treatment arm) was based on the requirement to demonstrate C_{trough} non-inferiority. Adequate homogeneity across both treatment arms was achieved by inclusion and exclusion criteria that were similar to the pivotal first line CLL registration study for rituximab IV (ML17102/CLL-8) as well as stratifying treatment arms by Binet stage and route of chemotherapy.

The sponsor believes that C_{trough} is the most appropriate PK parameter because it is the most conservative PK parameter reflecting the degree of target site saturation at the end of a treatment interval. In contrast to C_{max}, C_{trough} measured in the blood reflects the degree of target site saturation after sufficient time is allowed for rituximab levels to reach equilibrium between the central and peripheral compartments, where relevant lymphoma/CLL lesions are located. Reaching equilibrium can take up to 5 days[12], which may explain why C_{trough} (includes effects of target-specific elimination of malignant B-cells) correlates with efficacy while C_{max} (excludes effects of target-specific elimination of malignant B-cells) does not correlate with efficacy.[13] When serum levels of rituximab after SC administration are at least as high as a trough reached after IV administration, target receptor saturation is maintained relative to rituximab IV and therefore the same degree of anti-B-cell activity is expected. AUC was considered an important secondary PK endpoint as it includes information on PK over the entire treatment interval, including the early phase.

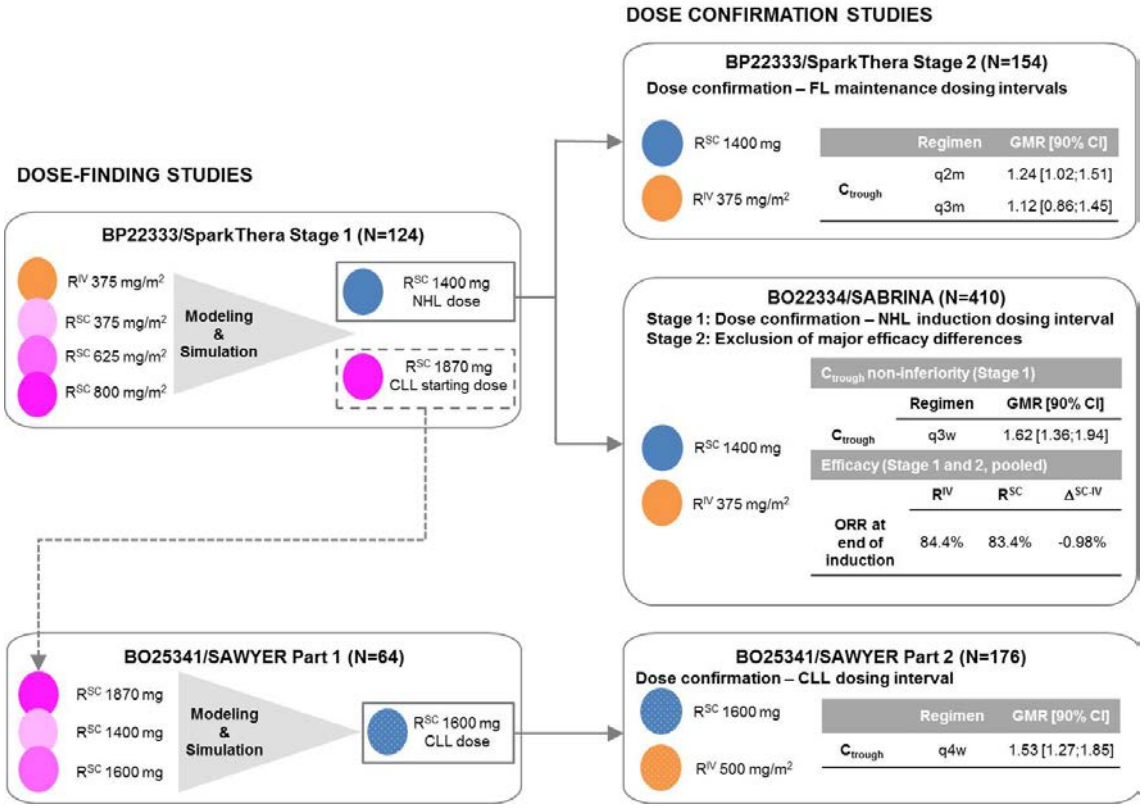
Prevention of underexposure of all patient subgroups was an important aim of the clinical development program.

The use of C_{trough} as the primary PK parameter is consistent with the approach taken for the approval of SC 1400 mg for NHL. In this program, first, the Phase Ib study SparkThera was conducted to identify a rituximab SC dose that allowed for comparable drug exposure to that achieved with the approved rituximab IV NHL dose (375 mg/m^2) and to investigate if we could consider fixed dosing. Subsequently, noninferiority in terms of C_{trough} with the selected dose of rituximab SC compared with rituximab IV was evaluated in Stage 2 of SparkThera in follicular lymphoma (FL) maintenance and in Stage 1 of SABRINA in NHL induction (Figure 4).

[12] Scheidhauer K, Wolf I, Baumgartl H-J et al. Biodistribution and kinetics of I-labelled anti-CD20 MAB IDEC-C2B8 (rituximab) in relapsed non-Hodgkin's lymphoma. Eur J Nucl Med. 2002;29:1276-1282.
[13] Tobinai K, Igarashi T, Itoh K et al. Japanese multicenter phase II and pharmacokinetic study of rituximab in relapsed or refractory patients with aggressive B-cell lymphoma. Ann Oncol. 2004;15:821-830.

Figure 4: Overview of PK-Bridging Clinical Development Program for Rituximab SC

A stepwise approach was adopted to select and confirm the rituximab SC doses, starting in NHL and followed by CLL.



Data from SAWYER demonstrated C_{trough} non-inferiority of MabThera SC 1600 mg compared with rituximab IV at the dose of 500 mg/m^2 given every 4 weeks (CLL dose and dosing interval).

Adequacy of the bridging data presented in the PK trial to demonstrate safety and efficacy for the proposed usage

Due to the large volumes of therapeutic rituximab doses, establishing the SC route of administration required the development of a formulation where rituximab is concentrated 12-fold (120 mg/mL) relative to the IV formulation and co-formulated with rHuPH20 (vorhyaluronidase alfa), a human recombinant hyaluronidase that transiently degrades interstitial hyaluronan at the injection site. The effects of rHuPH20 on the SC injection site are local and reversible due to the transient action of rHuPH20 (half-life of less than 30 minutes) and the rapid turnover of its substrate hyaluronan in the skin with a half-life of less than 2 days.[14] Rapid biosynthesis of hyaluronan restores the normal permeability of the SC tissue within 24 to 42 hours after hyaluronidase treatment.[15] The injection volume used in CLL is 13.4 mL for a 1600 mg dose; larger volumes were evaluated across the SC development studies (1870 mg/15.6 mL in Part 1 of SAWYER; 20 mL in Stage 1 of SparkThera) and were well tolerated.

[14] Frost GI. Recombinant human hyaluronidase (rHuPH20): An enabling platform for subcutaneous drug and fluid administration. Expert Opin Drug Delivery. 2007;4:427-440.
[15] Hechter O. Studies on spreading factors I. The importance of mechanical factors in hyaluronidase action in the skin. J Exp Med. 1947;85:77-97.
Bywaters EG, Holborow EJ, Keech MK. Reconstitution of the dermal barrier to dye spread after hyaluronidase injection. Br Med J. 1951;2:1178-1183.

Safety

A fixed (flat) dosing approach for SC was desirable in terms of improved convenience for healthcare providers with a lower risk of dosing errors compared with body surface area (BSA) adjusted dosing. The approach was supported by a published simulation study of 12 monoclonal antibodies, including rituximab, which showed the variability in PK would be no greater with a fixed-dose approach than with a BSA adjusted dosing approach.[16]

A prerequisite for establishing the SC route of administration and considering a fixed dosing approach was rituximab's well-established and manageable safety profile. Available data indicate that rituximab has a wide therapeutic window[17] and differences in exposure after SC versus IV administration are not likely to increase the risk of adverse events. Rituximab's dose-dependent toxicity is mainly linked to B-cell depletion, which is the desired pharmacodynamic effect; the terminal half-life of rituximab IV and SC is identical, meaning that higher accumulation after SC in not expected to change the B-cell repletion times and hence not expected to change long-term safety versus rituximab IV.

Safety data from SAWYER in CLL build on the safety data from the NHL SparkThera and SABRINA studies with MabThera SC 1400 mg and the experience with the IV formulation. The overall safety profile with rituximab SC 1600 mg was considered comparable to that with rituximab IV 500 mg/m^2 and importantly was as expected for this CLL patient population.

Part 2 of SAWYER, indicated that AUC (exposure) after rituximab SC was 10% higher with SC than with IV. A concern when changing from dosing based on BSA to a fixed dose is that this would result in higher exposure in patients with lower BSA (and thereby possibly a systematic overexposure of females and a lower exposure in patients with higher BSA). However, fixed dosing proved possible as the higher exposure in females was not related to an increased frequency of AEs and efficacy of rituximab remained unchanged in patients with higher BSA indicating sufficient rituximab exposure.

Neutropenia (all-grades) was reported in 58% of patients randomised to rituximab IV and 65% of patients randomised to rituximab SC, although clinically relevant AEs associated with neutropenia, such as febrile neutropenia and severe infections, were generally balanced between the SC and IV arms. There was a higher incidence of infection and infestation AEs in the SC arm compared with the IV arm overall; however, the incidence of Grade≥3 AEs and serious events was comparable. Furthermore, during Cycles 2-6, the incidences of all-grade, severe, and serious infections were comparable between the IV and SC treatment arms. Overall, the results are consistent with those of rituximab SC 1400 mg in NHL and generally comparable to the established safety profile of rituximab IV. The changes due to the SC route of administration were reflected in the higher frequency of local cutaneous reactions.

[16] Wang DD, Zhang S, Zhao H et al. Fixed dosing versus body size-based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol. 2009;49:1012-1024.
Bai S, Jorga K, Xin Y et al. A guide to rational dosing of monoclonal antibodies.
Clin Pharmacokinet. 2012;51;119-135.

[17] Maloney DG, Liles TM, Czerwinski DK et al. Phase I clinical trial using escalating single-dose infusion of chimeric anti-CD20 monoclonal antibody (IDEC-C2B8) in patients with recurrent Bcell lymphoma. Blood. 1994; 84: 2457-2466.
Coiffier B, Haioun C, Ketterer N et al. Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: A multicenter phase II study. Blood. 1992;92:1927-1932.
Keating M, O'Brien S. High-dose rituximab therapy in chronic lymphocytic leukemia. Semin Oncol. 2000;27:86-90.
O'Brien SM, Kantarijan H, Thomas DA et al. Rituximab dose-escalation trial in chronic lymphocytic leukemia. J Clin Oncol. 2001;19:2165-2170.

Pharmacoeconomic data from SAWYER show that there is a preference for rituximab SC as, from the perspective of physicians and nurses surveyed in the study, the formulation offers convenience and time savings compared with rituximab IV. This might be of particular relevance in view of the development of oral compounds in combination with anti-CD20 monoclonal antibodies in CLL indications that could result in establishing chemo-free and IV-free regimens in CLL. The SAWYER results are in line with those from the time-and-motion and PrefMab studies[18]) as well as those from SABRINA and from a retrospective survey on the administration of rituximab SC in SparkThera conducted at the end of 2011 to gain nurses' feedback on different aspects of the administration of rituximab SC .[19]

Efficacy

Efficacy parameters, including response rates and Minimal Residual Disease (MRD) in SAWYER were secondary and build on the conclusions from the pivotal Phase III SABRINA study in NHL as part of the rituximab SC development program in B cell malignancies. Data from SABRINA in NHL has already confirmed that the anti-lymphoma activity of rituximab was not impaired by the SC route of administration.

In SABRINA, the ORR at the end of induction was included as a primary parameter to exclude major differences in safety and efficacy between MabThera SC and IV.

The estimates of overall and complete response rates in SAWYER were largely comparable with overlapping 95% confidence intervals for the SC arm (ORR: 85.2% [76.1%; 91.9%]; CRR: 26.1% [17.3%; 36.6%]) and the IV arm (ORR: 80.7% [70.9%; 88.3%]; CRR: 33.0% [23.3%; 43.8%]), supporting the conclusion of SABRINA of comparable efficacy when non-inferior C_{trough} is achieved. Despite the small sample size and exploratory nature of the efficacy comparison, it is important to note that the point estimates for ORR in the CLL study are in the order of those observed in a similar patient population treated with rituximab IV (ORR: 85.8%; CRR: 36.0%) in the registration study CLL-8 evaluating R-FC versus FC alone.[20] In addition, data from Part 2 showed MRD-negative rates of 66% in the rituximab IV arm and 53% in the rituximab SC arm, in line with the rates reported for R-FC in the CLL-8 study (63%;[21]).

Data on B-cell depletion and repletion/recovery showed similar trends across treatment groups and are in line with previously reported results in patients with hematological malignancies treated with rituximab IV (MabThera Product Information). In Part 2, B-cell depletion was achieved by Cycle 4 in both SC and IV arms, and patients remained B-cell depleted until the 9-month follow-up visit when signs of repletion were seen.

[18]De Cock E, Kritikou P, Tao S et al. Time savings with rituximab subcutaneous (SC) injection vs. rituximab intravenous (IV) infusion: Final analysis from a time-and-motion study in 8 countries. Blood (ASH Annual Meeting Abstracts). 2013;122:#1724.
Rummel M, Min Kim T, Plenteda C et al. Patient preference for subcutaneous or intravenous administration of rituximab in previously untreated CD20+ non-Hodgkin lymphoma: Interim data from the PrefMab study. EHA 2014;#P467.

[19] Sayyed P, Shaw M, Schnetzler G. Practical experience with a new application mode of rituximab: a retrospective survey on the administration of subcutaneous rituximab among study nurses involved in the clinical development program. Haematologica. 2012;97(suppl 1):#1749

[20] Hallek M, Fischer K, Fingerle-Rowson G et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomized, open-label, phase 3 trial. Lancet. 2010;376:1164-1174.

[21] Böttcher S, Ritgen M, Fischer K et al. Minimal residual disease quantification is an independent predictor of progression-free and overall survival in chronic lymphocytic leukemia: a multivariate analysis from the randomized GCLLSG CLL8 trial. J Clin Oncol. 2012;9:980-988.

Extrapolation to broad usage in CLL

Differences of PK profiles for different routes of administration are influenced by the dose and dosing interval. True effects of the subcutaneous tissue on the PK, efficacy, and safety profile of rituximab are considered independent from the underlying B-cell malignancy. The sponsor therefore considers that PK findings in SAWYER are therefore applicable across all CLL subpopulations treated with a rituximab containing regime in which rituximab IV is given at a dose of 500 mg/m^2 with a dosing interval of every 4 weeks.

As noted earlier, homogeneity across both treatment arms in SAWYER was achieved by inclusion and exclusion criteria that were similar to the pivotal first line CLL registration study for rituximab IV (ML17102/CLL-8). Studies CLL 8 and the pivotal BO17072/REACH study (which supported approval in the relapsed/refractory setting), both investigated rituximab IV 500 mg/m^2 administered 4 weekly in combination with FC. Data from these studies together with extensive post marketing experience confirm the efficacy of MabThera in a broad CLL population.

As per the MabThera IV Product Information, benefits were seen in progression free survival in R-FC arms compared to FC arms alone in the first line CLL and relapsed /refractory CLL settings. The benefit in terms of PFS was consistently observed in most patient subgroups analysed according to disease risk at baseline (that is, Binet stages A-C). Survival analyses demonstrated improved survival in favour of the R-FC arms. In relapsed/refractory CLL patients, response rates of 70% or greater have been reported in small studies of multiple different chemotherapy regimens with MabThera.

The exploratory efficacy data from SAWYER are consistent with data from the pivotal IV registration studies in CLL. The demonstrated non-inferiority of $C_{trough,}$ exploratory efficacy in the SAWYER study combined with established efficacy with MabThera IV support the use of MabThera SC 1600 mg in a broad CLL population.

Overall conclusion

In summary, SAWYER is an integral part of the rituximab SC clinical development program and demonstrated C_{trough} non-inferiority of MabThera SC 1600 mg compared with rituximab IV at the dose of 500 mg/m^2 given every 4 weeks (CLL dose and dosing interval). The sponsor considers that MabThera SC 1600 mg has a favourable benefit-risk profile for CLL, comparable to that of the registered IV formulation, while reducing the treatment burden for patients and improving healthcare resource utilization at treatment facilities. This conclusion is reached taking into account the totality of safety and efficacy data of all rituximab SC clinical development studies, established efficacy with MabThera IV in CLL and PK, safety and efficacy data from SAWYER.

Question 1 response

The sponsor provided a summary to TGA regarding the EU quality topic including rationale for why this was not applicable in Australia. No additional quality data were provided by the sponsor.

Question 2 response

Dosing of cyclophosphamide in SAWYER was IV 250 mg/m^2 on Days 1 to 3 of all cycles or orally as 150 mg/m^2 on Days 1 to 5 of all cycles or 200 to 250 mg/m^2 on Days 1 to 3 of all cycles. Two different oral dose and schedules were included in the protocol based on various studies showing the efficacy of oral FC treatment in the CLL setting in 3 day or 5 day treatment regimens.[22,23,24,25]

Question 3 response

In Part 2, the median duration of rituximab SC administration in the SC treatment arm was 7.0 minutes (interquartile range 6 to 7 minutes), with the majority of SC injections (89%) being given in less than 9 minutes. In contrast, in the IV arm, the median duration for rituximab IV infusions, excluding infusions requiring dose modifications/interruptions, was 210 minutes (3.5 h) (interquartile range 150 to 245 minutes). The majority of infusions (62.6%) lasted between 180 and 300 minutes. In addition, 16.3% of the infusions were completed between 60 to 120 minutes and 14.6% of the infusions were completed between 120 to 180 minutes and no infusion was completed within 60 minutes (data on file).

Question 4 response

Details for the ARRs of Grade ≥ 3 observed in the SC arm during Cycles 2 to 6 in Part 2 are provided below:

- Patient A, Grade 3 urticaria: the event occurred at Cycle 3 Day 1, within 24 h after the end of injection. The patient discontinued study treatment with rituximab and continued to the follow-up phase.
- Patient B Grade 4 thrombocytopenia: occurred one day post SC injection at Cycle 2; the first rituximab administration (IV) was on 15 April 2013. The pre-dose platelet level on 28 May 2013 was 144,000/µL, reaching 93,000/µL on 24 June 2013. The patient discontinued study treatment with rituximab and entered survival follow-up.
- Patient C Grade 3 injection site erythema.
- Patient D Grade 3 anxiety.

Of note, the incidence of ARRs Grade ≥ 3 during Cycles 2 to 6 was balanced between the treatment arms: 4% in the IV arm (3/84 patients reporting 5 events) and 5% in the SC arm (4/85 patients reporting 4 events).

Change to dose frequency for NHL maintenance therapy

Roche's proposal to change the dosing frequency for rituximab (IV and SC) for NHL maintenance therapy from once every 3 months (q3m) to once every 2 months (q2m) in previously untreated patients follows the recommendation of TGA in an earlier application

[22] Forconi F, Fabbri A, Lenoci M et al. Low-dose oral fludarabine plus cyclophosphamide in elderly patients with untreated and relapsed or refractory chronic lymphocytic leukaemia. Hematol Oncol. 2008;46:247-251.
[23] Laurenti L, Tarnani M, De Padua L et al. Oral fludarabine and cyclophosphamide as front-line chemotherapy in patients with chronic lymphocytic leukemia. The impact of biological parameters in the response duration. Ann Hematol. 2008;87:891-898.
[24] Laurenti L, De Padua L, Tarnani M et al. Comparison between oral and intravenous fludarabine plus cyclophosphamide regime as front-line therapy in patients affected by chronic lymphocytic leukaemia: influence of biological parameters on the clinical outcome. Ann Hematol. 2011;90:56- 65.
[25] Mulligan SP, Gill DS, Turner P et al. A randomised dose de-escalation safety study of oral fludarabine, ±oral cyclophosphamide and intravenous rituximab (OFOCIR) as first-line therapy of fit patients with chronic lymphocytic leukaemia (CLL) aged ≥65 years. End of recruitment analysis of response and toxicity of the Australasian Leukaemia and Lymphoma Group (ALLG) and CLL Australian Research Consortium (CLLARC) CLL5 Study. Blood (ASH Annual Meeting Abstracts). 2012;120:#436.

(PM-2014-01461-1-4) and is supported by 6-year follow-up data from the pivotal rituximab IV Study MO18264/PRIMA (Report 1057423, submitted with PM-2014-01461-1-4). Roche was prompted to apply for this change based on the comments of the clinical evaluator in that application: '*However, in light of the longer-term safety data now available in Study MO18264, consideration may be given to the merits of increasing the approved dosing schedule of rituximab in the maintenance treatment of previously untreated advanced follicular lymphoma from every 3 months for 2 years, to every 2 months for 2 years to be in line with the dosing schedule used in the pivotal study and also the approved dosing regimen for this indication in other international jurisdictions. The recommended dosing schedule would then be in line with the available evidence from the pivotal study. The change would need to be subject to a separate application from the sponsor.'*

The evidence for the original approval for maintenance dosing was the EORTC 20981 study which used a q3m schedule of single 'booster' infusions to maintain rituximab levels above a threshold of 25 µg/mL.

Another Phase II study was subsequently reported in which the effect of individualised PK dosing of rituximab was evaluated in patients with B-cell lymphoproliferative disorders who had failed at least one prior therapy.[26] Patients received 4 weekly infusions of rituximab (375 mg/m^2) as induction therapy, and a repeat rituximab dose (375 mg/m^2) when serum levels fell to below 25 µg/mL. With this approach, single infusions of rituximab had to be administered every 2–4 months to maintain levels above 25 µg/mL. Based on this information, a more conservative schedule was chosen for the PRIMA study than that used in the EORTC 20981 study, with doses of rituximab given q2m during the maintenance phase.

This schedule was supported by data from the SAKK 35/98 trial[27] and later by PK data from the ECOG 4402 (RESORT) trial which showed that rituximab levels measured 12 weeks after rituximab induction (4 doses of 375 mg/m2 at weekly intervals) were < 25 ug/mL in nearly half (47%) the patients (median 26.9 µg/mL). The authors concluded that q3m administration would not be sufficient to maintain therapeutic levels (> 25 µg/mL) in a significant proportion of patients.[28]

The primary analysis of the pivotal study MO18264/PRIMA with a median follow-up of 25 months demonstrated that maintenance therapy with rituximab resulted in a clinically relevant and statistically significant improvement in the primary endpoint of investigator-assessed PFS as compared to no maintenance therapy. The overall safety of rituximab maintenance in the PRIMA study was consistent with its known safety profile in the maintenance treatment of patients with previously treated follicular lymphoma and in other malignant disease settings. Long-term data with over 6 years median follow-up confirmed the efficacy and safety results and the favorable benefit/risk profile of q2m rituximab maintenance.

This treatment regimen has become standard of care in the first-line FL setting and this regimen is PBS listed.

Additionally, Stage 2 of the rituximab SC Phase Ib study SparkThera in previously untreated and relapsed patients, receiving q2m or q3m maintenance, established that

[26] Gordan LN, Grow WB, Pusateri A et al. A phase II trial of individualized pharmacokinetic dosing of rituximab maintenance for patients with CD20-positive lymphoproliferative disorders. J Clin Oncol. 2005;23:1096-1102
[27] Ghielmini M, Schmitz SF, Cogliatti SB et al. Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly × 4 schedule. Blood. 2004;103:4416-4423.
[28] Kahl BS, Williams ME, Hong F et al. Preliminary pharmacokinetic (PK) analysis of Eastern Cooperative Oncology Group Protocol E4402: rituximab extended schedule or re-treatment trial (RESORT). Blood (ASH Annual Meeting Abstracts). 2007;110:#3420.

rituximab SC 1400 mg was non-inferior in terms of C_{trough} to rituximab IV 375 mg/m^2 for both dose intervals. With the exception of ARRs, which were more commonly reported in patients treated via the SC route, the overall safety profile observed was considered similar following treatment with either rituximab SC 1400 mg or rituximab IV 375 mg/m^2.

Furthermore, in the Phase III study SABRINA, PK samples were obtained in the induction phase (Cycles 1- 8) and in the 2 year maintenance phase of treatment (Cycles 9-20) where patients were administered q2m rituximab SC or IV. In both treatment arms, steady-state C_{trough} plasma levels were achieved by the third maintenance dose (Cycle 11) and steady state was maintained until the end of the maintenance phase. Based on the available data, Roche considers its proposal for q2m dosing in the NHL maintenance setting with the IV and SC formulations as favourable as this regimen is current standard practice in Australia for rituximab IV and is supported by long-term safety and efficacy data.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

- The evidence provided in the sponsor's submission did not satisfactorily establish the safety and efficacy of MabThera solution for subcutaneous injection containing 1600 mg/13.4 mL of rituximab.
- It is reasonable to increase the dosage frequency in maintenance treatment as part of first-line treatment of follicular lymphoma from 3 monthly to 2 monthly for the intravenous formulation only. The ACPM considered there was insufficient safety evidence to support this change for the proposed subcutaneous dosing. The ACPM noted there was no study on the effects of the increased frequency in dosing with the SC formulation.
- In making this recommendation the ACPM noted the data submitted did not fully support efficacy and safety of the proposed product and only included 12 weeks data, which was considered insufficient for proposed length of use.

Initial outcome[29]

Based on a review of quality, safety and efficacy, the TGA decided:

1. Not to approve the registration of new strength of MabThera (rituximab rch) 1600 mg/ 13.4 mL for SC administration for use in CLL on the grounds that quality, safety and efficacy have not been satisfactorily established for the purposes for which they are to be used;
2. Not to approve the registration of MabThera (rituximab rch) SC 1400 mg/ 11.7 mL with the new dosage frequency on the grounds that safety and efficacy have not been satisfactorily established;
3. To approve the registration of Mabthera (rituximab rch) for 100 mg/10 mL, and 500 mg/ 50 mL vial indicated for IV infusion with the new dosage frequency for maintenance therapy in previously untreated patients with follicular lymphoma who have responded to induction treatment, from once every 3 months to once every 2 months;

[29]See below in sections *Section 60 appeal* and *Final Outcome* for further information and final decision.

4. To vary the PI for MabThera containing rituximab rch 100 mg/ 10 mL and 500 mg/ 50 mL vial for infusion for the new dosage frequency for maintenance therapy in patients with previously untreated follicular lymphoma who have responded to induction treatment from once every 3 months to once every 2 months, as well as other agreed safety-related and editorial changes; and
5. To vary the PI for the MabThera SC (rituximab rch*)* 1400 mg 11.7 mL formulation based on the revision received on 21 March 2016 where the approved amendments are:
    a. editorial or safety related in nature;
    b. related to agreed updates for the studies for the already approved usage in non-Hodgkin's lymphoma but exclusive of any reference to new dosage frequency for maintenance therapy in patients with previously untreated follicular who have responded to induction treatment from every 3 months to once every 2 months, as this is not approved; and
    c. exclusive of any reference to the 1600 mg/ 13.4 mL formulation, as registration for this dose strength

Specific conditions of registration applying to these goods

The MabThera Risk Management plan (RMP), version 13.0, dated 9 October 2014, DLP 9 October 2014, with Australian Specific Annex (version 5.0, dated March 2015), and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Reasons for the delegate's decision

Safety and efficacy of proposed formulation MabThera 1600 mg/13.4 mL

The Delegate decided to refuse the application to register MabThera 1600 mg/13.4 mL for SC administration for the treatment of CLL on the basis that the safety and efficacy of the goods for the purposes for which they are to be used have not been satisfactorily established for the reasons provided below.

There are no data from studies designed and powered to provide randomised, controlled data to establish the efficacy and safety of the proposed usage.

The study provided (BO25341) was not designed statistically to demonstrate safety and efficacy; indeed, all efficacy endpoints which were exploratory and data are not presented on PFS, OS as the sponsor states these are immature still.

The efficacy data are inadequate as there was no stratification for factors known to influence response rates and survival, and these data were not available for all patients in the study when an attempt was made to measure these retrospectively. The effect of these missing data, together with the lack of stratification, does not enable a proper determination of efficacy, and therefore that consideration cannot be established.

No data are presented to demonstrate the safety and efficacy of SC rituximab with other combinations of chemotherapy, or at more advanced stages of the disease (for example, after prior treatments).

The single study submitted (BO25341) was designed to show non-inferiority of C_{trough} values between the 1600 mg subcutaneous and 375 mg/m^2 intravenous Mabthera formulations, and was not powered to demonstrate safety and efficacy. The effects on safety that resulted from the observed increase in C_{trough} resulting from the fixed dose of 1600 mg administered subcutaneously (as opposed to dosing on body surface area with the intravenous formulation) have not been assessed adequately.

In response to the Delegate's question in the overview for data reporting on the long term local effects of repeat dosing with a large volume of solution containing vorhyaluronidase in elderly patients, the sponsor provided reports from animal studies, review articles discussing potential usage of hyaluronidase (where one author[30] was anticipating infusion volumes of 2.5-7.5 mL, not the proposed 13.4 mL)), and a seminal paper on hyaluronidase written in 1947; none of which used the proposed formulation and which therefore do not satisfactorily establish safety of the proposed formulation and volume being administered.

Not only are these references inadequate to support safety of the proposed formulation of hyaluronidase in combination with rituximab but this approach to demonstrating safety (and/or efficacy) cannot be adopted at the pre ACPM stage, as stated specifically in the Delegate's Overview. Reliance upon literature to demonstrate safety or efficacy is a particular submission category and requires the sponsor to obtain agreement with the TGA to the literature search strategy proposed to ensure relevant and adequate representation of the literature. No such request was made; the literature used is thus not agreed as appropriate and representative. No request for a pre submission meeting to discuss the data and seek advice form the TGA regarding the sponsor's planned strategies for this submission was made by the sponsor prior to lodgement of the application.

The larger volume being administered and dose-related increase in adverse event rates in the CLL study prevent generalisations from any NHL studies.

This safety concern about repeated dosing remains unaddressed and is relevant in the decision not to approve the more frequent maintenance usage of MabThera SC 1400 mg/11.7 mL in NHL and the proposed usage of MabThera SC 1600 mg/13.4 mL in CLL.

The study lacks external validity required for extrapolation across the broad population and potential treatment regimens currently included in the approved indication for intravenous MabThera to treat CLL. Specifically, there were limited numbers of women (25) and patients either aged 65 to70 (15) or >75 years of age (8) treated with the proposed dose. Given 43% of patients are >75 years of age at diagnosis and women account for 39% of cases of CLL in Australia, this is too small a sample size from which to make generalisations about safety and efficacy. In particular, women appear to have higher adverse event rates with rituximab, and the safety of increased exposure with the MabThera 1600 mg/13.4 mL, especially over time has not been adequately demonstrated.

In Australia, approved regimens including rituximab are for use in all ages and stages of disease, thus the data presented here for a fit, previously untreated population have limited generalisability. Given the very high background rate of treatment-emergent adverse events, a large randomised controlled trial comparing the two formulations is required to demonstrate the safety and efficacy in this population.

No long term data reporting the safety and efficacy of subcutaneous administration of MabThera SC 1600 mg/13.4 mL or MabThera SC 1400 mg/11.7 mL in either CLL or NHL, respectively, were submitted to support the current application for use for either malignancy.

The patient reported outcome data from Study BO25341 were obtained in too few patients treated with the proposed dose (17 in total), using a questionnaire that had not been validated and at a single time point after receiving a single dose. The results consequently do not provide adequate support regarding the acceptability of MabThera SC 1600 mg/13.4 mL to support registration in this application. Validated questionnaires, preferably administered throughout an adequately powered, randomised controlled study

[30] Frost GI, Recombinant human hyaluronidase (rHuPH20): An enabling platform for subcutaneous drug and fluid administration. Expert Opin Drug Delivery 2007; 4:427-440

are required to assess the claims of improved comfort, convenience and compliance claimed as a benefit of this formulation in the letter of application.

Quality of proposed formulation MabThera 1600 mg/13.4 mL

The Delegate is not satisfied that the quality of the proposed new formulation for MabThera SC 1600 mg/13.4 mL has been satisfactorily established for the reasons provided below.

The sponsor did not provide any data (as requested in the Delegate's overview) to allow the Delegate, the quality evaluator or the ACPM to make an independent assessment to understand fully the EMA concerns [information redacted]. In the absence of the data, the TGA cannot make an independent assessment and cannot otherwise be satisfied that the quality of the product is established. As such, the Delegate cannot be satisfied that there is sufficient evidence to counter concerns regarding the quality of the manufacturing process.

As this was not the only deficiency leading to the Delegate's decision not to approve the application to register MabThera SC 1600 mg/13.4 mL, and the other matters have not been resolved by the sponsor's pre-ACPM response, the Delegate did not consider it would change the outcome of the application to have these data submitted after the ACPM. Any future applications or appeal processes to register MabThera SC 1600 mg/13.4 mL would need to provide these data for the TGA to be able to make a full assessment of the concerns raised by the EMA. The sponsor would also be required to state whether this has been a concern raised by any other regulatory authority with whom the proposed usage has been discussed.

Safety and efficacy of new dosage frequency for MabThera SC 1400 mg/11.7 mL

Due to there being no directly measured data provided in support of this proposed usage, and the presented modelling being insufficient to demonstrate safety and efficacy (there were concerns about potential accumulation), the Delegate decided not to approve the registration of MabThera SC 1400 mg/11.7 mL for the new dosage frequency on the grounds that safety and efficacy have not been satisfactorily established.

Quality, safety and efficacy of new dosage frequency for MabThera IV formulations

The Delegate is satisfied that the data presented in Study MO18264 (and evaluated as part of a previous application) support the safety and efficacy and therefore have decided to approve the registration of MabThera containing rituximab rch 100 mg/10 mL and 500 mg/50 mL vial for IV infusion for the new dosage frequency for maintenance therapy in previously untreated patients with follicular lymphoma who have responded to induction treatment, from once every 3 months to once every 2 months;

Variation to product information for new dosage frequency for MabThera IV formulations

The variations to the product information (PI) initially proposed in the sponsor's application were not considered acceptable; following amendments made during the course of the application, the Delegate now considers that the PI received on, and dated 22 March 2016 ("160322") is acceptable and have decided to approve the agreed variations to the PI for MabThera containing rituximab rch 100 mg/10 mL and 500 mg/50 mL vial for IV infusion for the new dosage frequency for maintenance therapy in patients with previously untreated follicular lymphoma who have responded to induction treatment from once every 3 months to once every 2 months, as well as other agreed safety-related and editorial changes.

Variation to product information for MabThera SC 1400 mL/11.7 mL

The variations to the product information (PI) initially proposed in the sponsor's application were not considered acceptable; following amendments made during the

course of the application, the Delegate now considers that the PI dated 22 March 2016 ("160322") and received on 23 March 2016 acceptable and have decided to approve variations to the PI for MabThera SC 1400 mL/11.7 mL, which are editorial and safety related in nature and otherwise related to the agreed updates for the studies for the already approved usage in non-Hodgkin's lymphoma; however, due to the lack of data demonstrating safety and efficacy and to ensure the PI is in accord with the Delegate's decision above, the Delegate decided not to approve the PI change requested by the sponsor to include the new dosage frequency for maintenance therapy for this dose formulation in patients with previously untreated follicular lymphoma who have responded to induction treatment from once every 3 months to once every 2 months;

The decisions outlined in the paragraphs above are based on the evaluation of the information and data provided with the original letter of application and all subsequent correspondence and submissions relating to the application, as outlined in the materials considered in making this decision.

Section 60 appeal

Following the initial decision described above, the sponsor sought a review under the provisions of Section 60 of the Therapeutics Goods Act. The Delegate of the Minister for the review decided to revoke the initial decision and substitute with a decision to include in the ARTG:

1) a new strength of MabThera SC (rituximab injection 1600 mg/13.4mL) for use in chronic lymphocytic leukaemia; and

2) a new dosage frequency for the approved MabThera SC (rituximab injection 1400 mg/11.7mL) strength for maintenance therapy in patients with previously untreated follicular lymphoma who have responded to induction treatment.

The Delegate of the Minister noted that paragraph 25(1)(d) of the Therapeutic Goods Act, which requires the goods to be evaluated with regard to whether the quality, safety and efficacy of the goods for the purposes for which they are to be used have been satisfactorily established, is of particular relevance.

The following is an excerpt from the Delegate of the Minister's Section 60 decision letter.

The Delegate of the Minister's findings of fact and reasons for decision

Based on review of the evidence listed above [in Initial Delegate's decision letter], the Delegate of the Minister made the following findings of fact:

Background

MabThera (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 mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity chromatography and ion exchange, including specific viral inactivation and removal procedures.

The IV preparation of MabThera was first registered by the TGA for use in CD20 positive B-cell lymphoproliferative disorders in 1998, and has since become an integral component of standard treatments for these disorders, in particular follicular and diffuse large B-cell NHL, and CLL. The safety and efficacy profile of this preparation has been extensively characterised.

MabThera subcutaneous formulation contains recombinant human hyaluronidase (rHuPH20), an enzyme used to increase the dispersion and absorption of co-administered substances when administered subcutaneously.

Rituximab binds specifically to the transmembrane antigen, CD20, a non-glycosylated phosphoprotein, located on pre-B and mature B lymphocytes. The antigen is expressed on >95 % of all B cell non-Hodgkin's lymphomas. CD20 is found on both normal and malignant B cells, but not on haematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissue. This antigen does not internalise upon antibody binding and is not shed from the cell surface. CD20 does not circulate in the plasma as a free antigen and, thus, does not compete for antibody binding.

Rituximab has shown to be highly specific to the CD20 antigen on B cells. Toxicity studies in cynomolgus monkeys have shown no other effect than the expected pharmacological depletion of B cells in peripheral blood and in lymphoid tissue.

Grouped concerns regarding safety and efficacy of proposed formulation MabThera SC 1600 mg/13.4mL for CLL.

In this section the Delegate of the Minister considered the TGA evaluation of MabThera 1600 mg/13.4 mL regarding safety and efficacy of the proposed formulation. The issue of quality with regard to this formulation is separately considered below.

There is a fundamental difference in the view of the sponsor and the [initial decision] Delegate regarding how the data in support of application PM-2012-04453-1-4 should be evaluated and interpreted, leading the Delegate to the view that a randomised controlled trial fully powered for efficacy comparing the IV and SC formulations is required to demonstrate safety and efficacy in CLL populations.
The sponsor states (item 4.4, page 17 of the appeal document) that:

'The TGA decision letter itemises many points central or corollary to the overall TGA conclusion that the pivotal SAWYER study of MabThera SC 1600 mg in CLL provided insufficient safety and efficacy data. The TGA requires a randomised controlled trial fully powered for efficacy comparing the two formulations to demonstrate safety and efficacy in the CLL population.

The TGA evaluation reports, ACPM minutes, PSC minutes and decision letter show that the TGA appear to have evaluated the application for MabThera SC 1600 mg for CLL based on the SAWYER data in isolation of the previously supplied SC data and viewed it in the light of a standard drug development program as opposed to the previously accepted PK-based clinical bridging development program.

The clinical overview of the application, responses to Section 31 questions and the pre –ACPM response pointed out that the SAWYER study should be viewed as an integral part of the overall MabThera SC development program.

In conclusion, consistent with the TGA accepted PK-based clinical bridging approach, the SAWYER study provided the evidence supporting the registration of MabThera SC 1600 mg for all MabThera IV approved CLL indications (Section 4.1 and Section 6). Roche believes that by approving MabThera SC 1400 mg for NHL, including NHL populations for which no clinical data were provided, while rejecting MabThera SC 1600 mg in CLL, TGA has introduced an inconsistency in their decision-making.'

Section 60 delegate's comment:

The sponsor argues that the MabThera SC clinical development program was based on bridging pharmacokinetic (PK) studies to the approved MabThera IV doses and dosing intervals for NHL and CLL, to ensure at least equivalent exposure to rituximab, with clinical bridging to exclude major differences in efficacy and safety associated with the SC route of administration. It is claimed that this does not require re-establishing the benefit-risk profile for MabThera SC in all of the approved MabThera IV indications.
It is noted that based on the results of the pivotal PK-based clinical bridging studies SparkThera (conducted in FL maintenance) and SABRINA, the TGA has previously approved MabThera SC 1400 mg with a broad NHL label (FL and DLBCL), identical to the

MabThera IV approved NHL indications. The sponsor contends that this demonstrates TGA acceptance of the PK-based clinical bridging development program without the need to re-establish the benefit risk profile of MabThera SC for each MabThera IV approved indication. Further, the sponsor asserts that this has introduced an inconsistency into the TGA decision-making process when considering the current application.
The sponsor states that the SAWYER study is pivotal to providing sufficient evidence to support the registration of the MabThera SC 1600 mg dose strength to treat patients with CLL. The efficacy and safety data from Part 2 of the SAWYER study, although based on a relatively small sample size, are stated to be consistent with the data from MabThera SC 1400 mg in NHL, confirming that the switch to the SC route of administration appears safe and does not impair anti- B-cell activity (SAWYER CSR with this application PM-2014-04709-1-4).
In this context, the Delegate addressed the Delegate's grouped concerns, identified by the sponsor in their appeal document, regarding safety and efficacy of the proposed formulation MabThera SC 1600 mg/13.4ml for CLL, taking into account the alternative view of the evaluation process presented by the sponsor. Reasons for section 60 Delegate's decision are summarised after each set of grouped concerns.

[Initial decision] Delegate's points 36, 37 and 47 of the decision letter

- There are no data from studies designed and powered to provide randomised, controlled data to establish the safety and efficacy of the proposed usage.
- The study provided (SAWYER, BO25341) was not designed statistically to demonstrate safety and efficacy – indeed, all efficacy endpoints were exploratory and data are not presented on PFS, OS as the sponsor states these are immature still.
- No long term data reporting the safety and efficacy of subcutaneous administration of MabThera SC 1600 mg/13.4 mL or MabThera SC 1400 mg/11.7mL in either CLL or NHL, respectively, were submitted to support the current application for use for either malignancy.

Sponsor's response

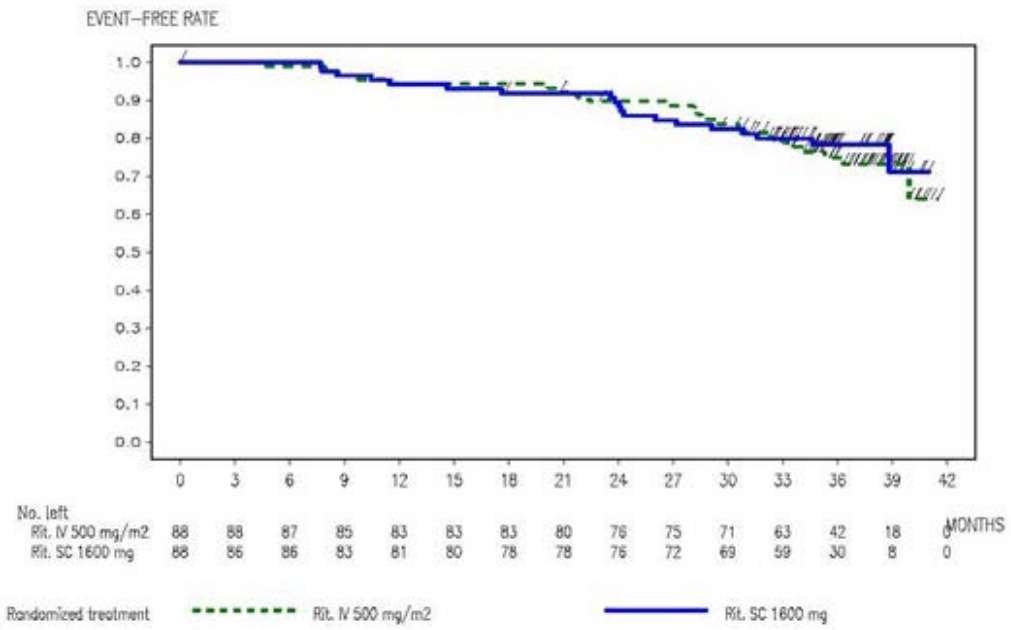
Long term follow up data from the SAWYER study were not mature at the primary analysis and were therefore not included in the submission. The sponsor has provided an updated analysis of the SAWYER data in which time-to-event points were analysed with a median follow up of approximately 36 months (Part 2), representing an increase of approximately 22 months compared with previously submitted data (with this application PM-2014-04709-1-4). An abbreviated clinical study report (CSR) including PFS, EFS and OS data from SAWYER were provided.

This data shows that the incidence of progression-related events (disease progression/relapse or death, whichever occurred first) was similar in the MabThera IV and SC arms (23/88 patients [26.1%] and 19/88 patients [21.6%], respectively). The hazard ratio was 0.89 (95% CI: 0.49; 1.64) with a wide confidence interval crossing 1 indicating no substantial difference in benefit to either the IV or SC arms.

Among patients who experienced an event 16/23 (69.6%) patients in the MabThera IV arm and 17/19 (89.5%) patients in the MabThera SC arm had experienced progression/relapse. Seven out of 23 patients (30.4%) in the MabThera IV arm and 2/19 patients (10.5%) in the MabThera SC arm had died.

The Kaplan–Meier curves are similar and overlapping for the two treatment arms. This is reproduced below (Figure 5). Because of the low number of events at the time of the updated analysis, the median PFS time could not be estimated for either treatment arm. The time-to-event analyses are claimed to further support similar efficacy between MabThera IV and SC.

Figure 5. Kaplan-Meier Plots for Progression-Free Survival – SAWYER Part 2 (Intent-to-Treat Population)



Delegate of the Minister's comment

It was noted in the resolutions of the ACPM Meeting 308 that: '*There appear to be more patients minimal residual disease negative in the IV arm of the[SAWYER] study than in the SC treatment arm*'

The Roche Primary Clinical Study Report – Protocol BO25341 contained in Module 5 of the original application PM-2012-04453-1-4 states that, based on PCR, after 3 months of follow-up, 64.5% (40/62) of patients in the IV arm and 53.1% (34/64) in the SC arm were MRD-negative, calculated on patients with a MRD response. The difference in MRD rates was 13%, but was not statistically significant, with a 95% CI of -30.9 to 4.9. However, data at time points up to 12 months of follow-up showed an apparent more rapid loss of MRD negativity in the SC arm, albeit with quite low numbers of patients available for analysis at 6 and 12 months.

The sponsor provided updated efficacy and safety data from the SABRINA study in NHL and an updated CSR including safety and PFS, EFS and OS data. Efficacy end points are reported with a median follow up of approximately 37 months representing an increase of approximately 22.5 months compared with data available when MabThera SC 1400 mg was approved. The updated safety data from the SABRINA study was consistent with previous reports – there were similar incidences of patients with at least one AE, Grade ≥3 AEs and serious AEs in MabThera SC and IV arms.

The Delegate accepted that the updated data from the SAWYER study gives no evidence of inferior clinical outcomes with the MabThera SC versus IV preparations, but are limited in reliability by the small patient numbers and inclusion of efficacy endpoints only as exploratory analyses.

The MRD data from the SAWYER study raises some concern regarding a potential signal of inferior outcomes, but it is noted that this did not reach statistical significance, and is based on very small patient numbers at later time points. It is acknowledged that the interpretation of MRD outcomes in CLL remains experimental, but an analysis of outcomes in the German CLL Study Group CLL8 trial[1] reported that higher MRD levels were associated with shorter progression-free and overall survival.

It is therefore of importance that updated data from the SAWYER and SABRINA studies (including MRD data related to outcomes in the SAWYER trial) are submitted to TGA for evaluation following completion of the final analyses, expected in 2018. This should be made a condition of any approval for ARTG registration.

[Initial decision] Delegate's point 38 of the decision letter:

- The efficacy data are inadequate as there was no stratification for factors known to influence response rates and survival, and these data were not available for all patients in the study when an attempt was made to measure these retrospectively. The effect of these missing data, together with the lack of stratification, does not enable a proper determination of efficacy, and therefore that consideration cannot be established.

Sponsor's response

The sponsor states that patients in Part 2 of the SAWYER study were stratified by Binet stage, but not for poor-prognosis genetic aberrations. However, the IV and SC arms were relatively well balanced for factors known to have an influence on prognosis in CLL, eg del(17p), del(11q). In Part 1 of the SAWYER study, patients were enrolled at different stages prior to their cycle 5 treatment, which made it impossible to collect baseline prognostic factors for these sub-cohorts. The sponsor contends that the balanced distribution of prognostic factors in Part 2 of the study suggests that this is likely to be the case also in Part 1.

Delegate of the Minister's comment:

The Delegate accepted that the possible imbalance in stratification of patients for prognostic factors in the SAWYER study is likely not to have materially affected the reliability of the reported outcomes. However, this does not alter the conclusion that the efficacy data from this study are limited in reliability by small patient numbers, open-label design and inclusion of efficacy endpoints only as exploratory analyses. This uncertainty should be reflected in the PI and CMI.

Point 39 of the [initial] decision letter:

- No data are presented to demonstrate the safety and efficacy of SC rituximab with other combinations of chemotherapy, or at more advanced stages of the disease (for example, after prior treatments).

Sponsor's response

The sponsor states that all patients enrolled in the SAWYER study were previously untreated CLL patients considered eligible for R-FC treatment according to the ESMO clinical practice guidelines (2015)[2] and NCCN guidelines v3.2016. Because the clinical development program was based on PK bridging to the approved MabThera IV doses and dosing intervals, it was not deemed necessary to investigate other chemotherapy combinations as well as other patient populations.

The sponsor contends that extrapolation outside the studied patient populations, still using the same dose and dosing interval, were accepted by the TGA when granting approval for a broad NHL label, even though data on all NHL populations was not provided.

Delegate of the Minister's comment:

This argument is essentially the same as that noted above regarding the difference in viewpoint between the sponsor and the Delegate concerning how the data in support of application PM-2012-04453-1-4 should be evaluated and interpreted. Other aspects of this issue are addressed further under a number of the points in this section.

[Initial decision] Delegate's point 40 of the decision letter:

- The single study submitted (BO25341) was designed to show non-inferiority of C_{trough} values between the 1600 mg subcutaneous and 375 mg/m^2 intravenous MabThera formulations, and was not powered to demonstrate safety and efficacy. The effects on safety that resulted from the observed increase in C_{trough} resulting from the fixed dose of 1600 mg administered subcutaneously (as opposed to dosing on body surface area with the intravenous formulation) have not been assessed adequately.

Sponsor's response

The sponsor states that MabThera has a well-established and manageable safety profile and wide therapeutic window with no detection of dose-limiting toxicity even after dose escalation up to 2250 mg/m^2 (4.5 times the established CLL dose). The wide therapeutic window is expected when considering MabThera's characteristics as an immunoglobulin targeting CD20. MabThera's dose-dependent toxicity is mainly linked to B-cell depletion, which is the desired pharmacodynamic effect of MabThera. The terminal half-life of MabThera IV and SC is identical, meaning that higher accumulation after MabThera SC is not expected to change the B-cell repletion times and hence long term safety versus MabThera IV. It was therefore not expected that a higher exposure after MabThera SC relative to IV, required to ensure non-inferior exposure to MabThera in all patient subgroups, would result in increased toxicity.

The sponsor further notes that the impact on safety of the increased exposure was similarly initially raised by the TGA during the review of application PM-2012-04453-1-4 for MabThera SC 1400 mg for NHL indications. It was concluded that safety had been satisfactorily established, stating in the AusPAR, *"in regard to the important general concern that increased exposure to rituximab may result in more toxicity, it is reassuring that subgroup analysis by BSA showed no worse toxicity in those with low BSA, in SparkThera. In the updated SABRINA data, there was no convincingly worse toxicity in those with low BSA using the SC approach"* (AusPAR for MabThera SC 1400 mg)".

The sponsor notes that the results of the SAWYER study further confirm that safety profile and incidence of AEs are comparable between SC and IV arms, in particular in the low BSA subgroup with the highest exposure to rituximab.

- In the SAWYER study the AUC over one cycle was 10% higher after MabThera SC administration than after IV administration. This compares with a corresponding approximate increase of 35% in AUC in the SparkThera and SABRINA studies in NHL.
- This higher exposure in the NHL setting was a consequence of the fact that the PK-bridging had to be across more than one dosing interval in NHL to demonstrate non-inferiority, whereas in CLL there was only one dosing interval. The GMR of C_{trough} SC/C_{trough} IV from the SAWYER study (1.53 with 90% CI 1.27; 1.85) was very similar to the C_{trough} SC/C_{trough} IV GMR ratio from the SABRINA study (1.62 with 90% CI 1.36-1.94 from Stage 1 and 1.52 with 90% CI 1.36-1.70 from stages 1 and 2) which was already accepted with approval of MabThera SC 1400 mg.

Based on the prior TGA decision regarding safety when similar C_{trough} SC/C_{trough} IV ratio were demonstrated, and the safety data from the SAWYER study which is broadly consistent with the data from the SABRINA study in patients with higher exposure, Roche contend that the effects of an increased exposure on safety in CLL patients have been adequately assessed.

Delegate of the Minister's comment

The Delegate accepted that rituximab has a long history of use in B-cell lymphoproliferative disorders that has led to a clear understanding of the safety profile of the IV preparation. The highly targeted nature of the product and lack of significant 'off-

target' toxicity suggest that additional toxicity as a result of a different route of administration (IV vs SC) is unlikely to materially change this safety profile.

The minimum effective dose of MabThera is not known with certainty, and the sponsor's claim of a wide therapeutic window without evidence of dose-limiting toxicity with considerable dose escalation beyond that in the current application is acceptable, although it is noted that the experience with higher doses is somewhat limited. Experience with overdosage of MabThera is limited but indicates no new or unexpected toxicity.

The development program for MabThera SC was predicated on ensuring non-inferior exposure to rituximab in all patient groups, with only a single fixed dose, using as a starting point a comparison with the usual BSA-adjusted IV doses that have previously been registered for use in NHL and CLL patient populations. As a consequence of this strategy, the SC dosage chosen results in a higher average patient exposure to rituximab, estimated by the geometric mean ratio of C_{trough} SC/C_{trough} IV, of the order of 1.53 times in the SABRINA study and 1.62 times in the SAWYER study when compared to the IV route. The terminal half-life of the IV and SC preparations are similar, suggesting that higher accumulation with the SC preparation would not be expected to substantially alter B-cell repletion times and therefore exacerbate safety considerations with respect to immunosuppression and infection.

Taking these aspects into consideration, the Delegate was on balance of the opinion that additional toxicity due to the degree of higher exposure demonstrated in the SABRINA and SAWYER studies is unlikely to alter significantly the safety profile of the SC preparation in comparison to the IV preparation. However, given that there is relatively little experience at present with clinical use of the higher dose SC preparation proposed for CLL populations, it would be prudent to reflect the possibility of unknown new toxicity arising from the increased exposure to and different route of administration of MabThera SC in comparison to MabThera IV in the approved Risk Management Plan (RMP), with timely notification of any new or emerging safety signal to TGA for review and possible action.

[Initial decision] Delegate's points 41, 42 and 43 of the decision letter:

- In response to the question in the overview for data reporting on the long term local effects of repeat dosing with a large volume of solution containing vorhyaluronidase in elderly patients, the sponsor provided reports from animal studies, review articles discussing potential usage of hyaluronidase (where one author was anticipating 26 infusion volumes of 2.5-7.5 mL, not the proposed 13.4 mL)[31], and a seminal paper on hyaluronidase written in 1947 – none of which used the proposed formulation and which therefore do not satisfactorily establish safety of the proposed formulation and volume being administered
- Not only are these references inadequate to support safety of the proposed formulation of hyaluronidase in combination with MabThera, but this approach to demonstrating safety (and/or efficacy) cannot be adopted at the pre-ACPM stage, as stated specifically in the Delegate's Overview. A reliance upon literature to demonstrate safety or efficacy is a particular submission category, and requires the sponsor to obtain agreement with the TGA to the literature search strategy proposed to ensure relevant and adequate representation of the literature. No such request was made, the literature used is thus not agreed as appropriate and representative. No request for a presubmission meeting to discuss the data and seek advice from the TGA regarding your planned strategies for this submission was made by you prior the lodgement of the application.

[31] Frost, Gregory I. Recombinant human hyaluronidase (rHuPH20): an enabling platform for subcutaneous drug and fluid administration. *Expert. Opin. Drug Deliv*. 2007;4(4):427-440.

- The larger volume being administered and dose-related increase in adverse event rates in the CLL study prevent generalisations from any NHL studies.

Sponsor's response

Roche has acknowledged the references provided did not use the proposed formulation and injection volume, but considers they provide valuable supportive information and are of a similar nature to the references used to support approval of MabThera SC 1400 mg. The references were used to support responses to specific questions posed in the [Initial decision] Delegate's Overview which the sponsor does not believe constitutes a specific literature based submission strategy.

The sponsor notes that the previously approved AusPAR for MabThera SC 1400 mg in NHL indications states *"No specific studies were submitted that assessed the ability to administer larger volumes via the SC route with the inclusion of hyaluronidase in the formulation. However, published data have indicated that the presence of hyaluronidase allows an increase in the SC infusion rate and administration of larger SC volumes, without swelling or tissue distortion (Bookbinder et al). Furthermore, the recombinant human hyaluronidase in the proposed SC formulation of rituximab is currently approved in the USA as an adjuvant to increase the dispersion and absorption of other injected drugs".*

The sponsor notes that 'the 13.4 mL injectable volume of MabThera SC 1600 mg is 1.6 mL less than that of the 15 mL vial of vorhyaluronidase alfa approved in Australia as a component of HYQVIA (10% normal immunoglobulin combined with vorhyaluronidase for subcutaneous injection). The most frequently reported adverse reactions identified during post-marketing use of vorhyaluronidase alfa in similar formulations for other products administered subcutaneously have been mild local injection site reactions such as erythema and pain. Oedema has been reported most frequently in association with large volume subcutaneous fluid administration (Australian PI for HyQvia approved 27 April 2016). The safety profile of MabThera SC was continuously established in the course of clinical development program comparing 1400 mg of MabThera SC versus 375 mg/m^2 MabThera IV in NHL (SparkThera and SABRINA) and 1600 mg of MabThera SC versus 500 mg/m^2 in CLL (SAWYER) indications. MabThera SC doses up to 2200 mg administered as a 15 mL injection were investigated (SparkThera study) with the incidence of adverse events comparable to MabThera IV, except for the events related to the change in the route of administration. The observed safety profile of MabThera SC in the overall clinical development program was also comparable to that of MabThera IV with the exception of local cutaneous reactions (expected due to the change in the route of administration) and was consistent across the pivotal studies (SparkThera, SABRINA and SAWYER) with incidence of treatment emergent adverse events (TEAEs) in IV and SC arms being 83% and 88%, 92% and 93% and 91% and 96% in each study respectively'.

Due to the fact that TGA had accepted the overall development program strategy and extrapolation for safety and efficacy between rituximab IV and SC with the approval of MabThera SC 1400 mg and because of extensive discussions with EU regulators who supported the overall SC development program, Roche did not feel that a pre submission meeting was required.

In conclusion Roche considers that the safety data submitted in the application are adequate to support the approval of the rituximab SC formulation, and that it is appropriate to consider safety data from patients with both CLL and NHL, and from NHL induction and maintenance settings, to support the application.

Delegate of the Minister s comment

The Delegate of the Minister reviewed the additional data submitted by the sponsor, as well as the literature cited by them in support of the safety of recombinant human

vorhyaluronidase when used as a permeabilising agent to facilitate better absorption with larger volumes of subcutaneous preparations.

Vorhyaluronidase is used for a similar purpose in a subcutaneously administered normal immunoglobulin preparation (HYQVIA - Normal Immunoglobulin Infusion 10% (Human) with Vorhyaluronidase alfa, Injection solution for subcutaneous use) that is registered on the ARTG. This preparation can be administered in high volumes subcutaneously.

In the pivotal publication reporting long-term tolerability, safety and efficacy of subcutaneous use of 10% normal immunoglobulin combined with vorhyaluronidase, a mean infusion volume of 292.2 mL was administered per infusion site with a local reaction frequency of 0.17, the majority of which were mild. No subject developed neutralizing antibodies to rHuPH20 (vorhyaluronidase).

The Delegate of the Minister was therefore of the opinion that the small increment in volume used in the CLL indication versus the NHL indication (13.4 mL versus 11.7 mL) is unlikely to result in a clinically significant increase in infusion-related adverse events. Further, the Delegate of the Minister accepted that it is unlikely that additional safety concerns will arise as a consequence of the slightly higher dose used in the CLL indication.

The Delegate of the Minister did not consider that whether a pre-submission meeting was requested was material to this review.

[Initial decision] Delegate's point 44 of the decision letter

- This safety concern about repeated dosing remains unaddressed and is relevant in the decision not to approve the more frequent maintenance usage of MabThera SC 1400 mg/11.7ml in NHL and the proposed usage of MabThera SC 1600 mg/13.4 mL in CLL.

Sponsor's response

The sponsor notes that MabThera SC 1400 mg in combination with chemotherapy is currently approved by the TGA for up to 7 cycles of dosing following first cycle dosing with MabThera IV in patients with previously untreated Stage III/IV follicular NHL (induction) and patients with DLBCL. It is also approved for up to 8 cycles of dosing at 3 monthly intervals as maintenance treatment in follicular lymphoma (the MabThera IV formulation is now approved for up to 12 cycles of treatment at two monthly intervals for the same patient population).

The key reasons why Roche believes repeated dosing with MabThera SC 1600 mg does not result in a safety concern are:

- The proposed dosing schedule for MabThera SC 1600 mg in CLL is for up to 5 cycles (first cycle is always given IV) which is shorter than the longest duration of dosing already approved for MabThera SC 1400 mg.
- Data from both the SABRINA and SAWYER studies show that the incidence of AEs is highest within the first cycle of dosing and decreases with subsequent cycles (see approved MabThera SC PI).
- In the SABRINA study in the NHL maintenance setting as well as the SAWYER study, the only driver for the difference in AE profile between the IV and SC formulations is administration- related reactions and local cutaneous reactions.

In conclusion, Roche does not agree that there is a safety concern about repeated dosing which remains unaddressed. Based on the clinical bridging approach, Roche's view is that no additional data are needed to demonstrate safety of MabThera SC in patients with CLL.

Delegate of the Minister's comment

The Delegate of the Minister accepted the sponsor's reasoning with regard to this point, and agree that it is unlikely that any additional safety concerns will arise as a consequence

of repeated dosing in patients with CLL, particularly as no maintenance phase of treatment is given in this condition.

[Initial decision] Delegate's points 45 and 46 of the decision letter

- The study lacks external validity required for extrapolation across the broad population and potential treatment regimens currently included in the approved indication for intravenous MabThera to treat CLL. Specifically, there were limited numbers of women (25) and patients either aged 65-70 (15) or >75 years of age (8) treated with the proposed dose. Given 43% of patients are >75 years of age at diagnosis, and women account for 39% of cases of CLL in Australia, this is too small a sample size from which to make generalisations about safety and efficacy. In particular, women appear to have higher adverse event rates with rituximab, and the safety of increased exposure with the MabThera 1600 mg/13.4mL especially over time has not been adequately demonstrated.
- In Australia, approved regimens including rituximab are for use in all ages and stages of disease, thus the data presented here for a fit, previously untreated population have limited generalisability. Given the very high background rate of treatment-emergent adverse events, a large randomised controlled trial comparing the two formulations is required to demonstrate the safety and efficacy in this population.

Sponsor's response

The sponsor refers to previous discussion regarding why they believe that a fully powered trial for safety and efficacy was not required in the CLL setting in the context of the overall development program for MabThera SC and consistency of results in the NHL and CLL settings with MabThera SC. Roche notes that '*Data from pivotal MabThera IV registration studies together with extensive post marketing experience confirm the efficacy of MabThera in a broad CLL population including first line and relapsed/refractory settings. In relapsed/refractory CLL patients, response rates of 70% or greater have been reported in small studies of multiple different chemotherapy regimens with MabThera* (approved MabThera PI)'.

The sponsor states that differences in PK profiles for different routes of administration are influenced by dose and dosing interval. True effects of the subcutaneous tissue on the PK, efficacy, and safety profile of rituximab are considered independent from the underlying B-cell malignancy. Roche therefore considers that PK findings in SAWYER are applicable across all CLL subpopulations treated with a rituximab containing regimen in which rituximab IV is given at a dose of 500 mg/m^2 with a dosing interval of every 4 weeks.

Roche agrees that the numbers of women and elderly in the study were low. The profile of reported AEs was comparable between SC and IV arms in both younger adults and elderly with no new safety concerns identified. Although there were slight imbalances in the incidence of all AEs in favour of males in the SAWYER study, this general imbalance was seen in both SC and IV arms. The difference in the incidence of Grade ≥ 3 AEs between males and females in both arms was mainly driven by blood and lymphatic system disorders. However, there were no differences between the treatment arms with respect to the incidence of Grade ≥ 3 AEs reported in female (29/36 patients [81%] in the rituximab IV arm versus 20/25 patients [80%] in the rituximab SC arm) or male patients (34/53 patients [64%] versus 39/60 patients [65%] respectively). The imbalances should be seen in light of the low patient numbers per subgroup.

The sponsor contends that acceptance by the TGA of the extrapolation from MabThera IV data to MabThera SC based on PK–clinical bridging with approval of MabThera SC 1400 mg in Australia for NHL indications, coupled with the consistency of the results from the SAWYER study in CLL with other SC studies, negates the need for a fully powered

randomised controlled trial including all subgroups and disease states to support approval of the same dosage form in CLL.

Delegate of the Minister's comment

The issue of whether the increase in exposure with MabThera SC will result in additional safety concerns has been already been discussed under Point 44 above.

Having considered all of the arguments put forward by the sponsor in response to the above points of concern raised by the Delegate in the [initial] decision letter, and taking into account the approval by the TGA in 2014 to register MabThera SC based on PK data, a bridging clinical study, and extrapolation of results from previous IV rituximab clinical studies, the Delegate of the Minister was on balance of the opinion that the need for a fully powered randomised controlled trial including all subgroups and disease states to support approval of the same dosage form in CLL has not been unequivocally established. However, there are some remaining concerns regarding the need for more mature results from the SABRINA and SAWYER studies that have been addressed above, as well as information in the PI and CMI that must be addressed before ARTG inclusion is approved. Additional risk management activities must also be negotiated.

[Initial decision] Delegate's point 48 of the decision letter

- The patient reported outcome data from Study B025341 were obtained in too few patients treated with the proposed dose (17 in total), using an un-validated questionnaire and at a single time point after receiving a single dose. The results consequently do not provide adequate support regarding the acceptability of MabThera SC 1600 mg/13.4mL to support registration in this application. Validated questionnaires, preferably administered throughout an adequately powered, randomised controlled study are required to assess the claims of improved comfort, convenience and compliance claimed as a benefit of this formulation in the letter of application.

Sponsor's response

The sponsor acknowledges that the preference data obtained from the SAWYER study were from un-validated questionnaires and obtained from a small sample size and are therefore considered as supportive data. They note that at the time of the planning and conduct of the SABRINA and SAWYER registration studies, there were no validated questionnaires to assess patients' preference for the MabThera route of administration. The use of un-validated questionnaires for the SAWYER and SABRINA studies to provide supportive data (exploratory end-points) is justified for the following reasons:

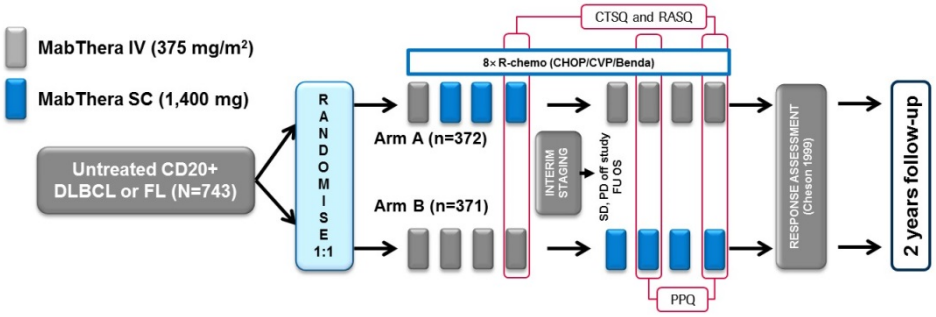
- A robust assessment of the patients' preference required a dedicated study with a cross-over design to account for intra-patient variability and to allow data collection at different time points in the course of the treatment. Therefore Roche designed and executed the PrefMab study for which a dedicated questionnaire to assess Rituximab (MabThera) Administration Satisfaction (RASQ) was developed and validated.
- The required cross-over design to assess the patients' preference was incompatible with the designs of the SABRINA and SAWYER registration studies. It was also deemed unnecessary to postpone the conduct of the registration studies until the availability of the validated questionnaire.

Preliminary data from the PrefMab study were included in the sponsor's appeal documents, in support of the claims of improved comfort, convenience and compliance as a benefit of this formulation in the original application.

PrefMab is a multicentre, prospective, randomised, cross-over, open-label Phase IIIb study to evaluate patient preference of SC versus IV administered MabThera in combination with

chemotherapy in previously untreated adult patients with DLBCL or FL, summarised in the appeal document in Figure 6, reproduced below:

Figure 6. PrefMab Study Design



Interim data from the PrefMab study have been published by Rummel et al in 2014[32]. It is noted that this includes data from an Australian centre.

The primary endpoint was the patients' preference based on the Patient Preference Questionnaire (PPQ) which asked patients about their preference for one of the administration routes at Cycles 6 and 8 and the two main reasons for this preference.

Patients in both arms expressed a preference for MabThera SC. The treatment sequence of MabThera IV and SC in the trial (Arm A versus Arm B) did not appear to have an effect on patient preference for SC treatment. At Cycle 6, 495/620 patients (79.8%, 95% CI [76.5%-82.9%]) recorded a preference for SC administration with 36.1% expressing a very strong preference and another 34.4% expressing a fairly strong preference for SC administration. After Cycle 8, overall 477/591 patients (80.7%, 95% CI [77.3%-83.8%]) expressed a preference for SC administration: 77.1% in Arm A and 84.2% in Arm B. A very strong preference for SC administration was expressed by 39.3% of patients, whilst a fairly strong preference was recorded for 34.3% of patients. A total of 471 patients (83.2%) retained their preference between Cycle 6 and Cycle 8.

The most common reasons given at Cycle 8 for preferring SC administration were:

- Requires less time in the clinic (410 patients [69.4%])
- Feels more comfortable during administration (218 patients [36.9%])
- Feels less emotionally distressing (173 patients [29.3%])
- Lower level of injection site pain (92 patients [15.6%])

Patient satisfaction with administration of cancer therapy was evaluated using the Cancer Treatment Satisfaction Questionnaire (CTSQ) and the Rituximab (MabThera) Administration Satisfaction Questionnaire (RASQ) at Cycle 4 (when patients in Arm A received MabThera SC and Arm B received MabThera IV) and Cycle 8 (when patients in Arm A received MabThera IV and Arm B received MabThera SC). The CTSQ is a 16-item validated questionnaire measuring 3 domains related to patients' satisfaction with cancer therapy: expectations of therapy, feelings about side effects, and satisfaction with therapy (Trask et al. 2008)[33].

[32] This paper was provided as a prepublication. It was subsequently published as Rummel et al. Prefmab: Final Analysis of Patient Preference for Subcutaneous Versus Intravenous Rituximab in Previously Untreated CD20+ Diffuse Large B-Cell Lymphoma and Follicular Lymphoma. *Blood*. 2015;126:3972.
[33] Trask et al. Psychometric Validation of the Cancer Therapy Satisfaction Questionnaire. *Value in Health*. 2008;11(4):669-679.

For each of the three CTSQ domains, the treatment sequence (Arm A or Arm B) as well as the treatment immediately preceding the questionnaire (IV or SC) had no effect on the results of the CTSQ. The mean domain scores for all patients (any treatment sequence) were summarised in the appeal document as reproduced below (Table 6).

Table 6. PrefMab Summary of CTSQ Mean Scores - Any Treatment Sequence (ITT Population) PrefMab Summary of CTSQ Mean Scores - Any Treatment Sequence (ITT Population)

Domain		After IV treatment N=740	After SC treatment N=687
Expectations of therapy	Mean (SD)	80.84 (18.365)	81.96 (17.856)
	n	631	627
Feelings about side effects	Mean (SD)	60.69 (22.266)	61.62 (22.323)
	n	630	624
Satisfaction with therapy	Mean (SD)	84.58 (12.207)	85.38 (11.284)
	n	619	623

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

Roche decided to develop and validate the RASQ because CTSQ is a validated questionnaire and answers could not be changed to better reflect the nature of the administration route change, that is, SC vs IV as opposed to oral versus IV. The RASQ is a 20-item questionnaire measuring the impact of the mode of treatment administration on 5 domains: physical impact, psychological impact, impact on activities of daily living, convenience, and satisfaction.

Within each of the five RASQ domains, the treatment sequence (Arms A or B) as well as the treatment immediately preceding the questionnaire (IV or SC) had no effect on the results of the RASQ. The mean domain scores for all patients (any treatment sequence) were summarised in the appeal document as reproduced below (Table 7):

Table 7. PrefMab Summary of RASQ Mean Scores – Any Treatment Sequence (ITT Population)

Domain		After IV treatment N=740	After SC treatment N=687
Physical impact	Mean (SD)	82.26 (15.584)	82.07 (15.850)
	n	622	619
Psychological impact	Mean (SD)	77.70 (16.377)	84.01 (14.356)

Domain		After IV treatment N=740	After SC treatment N=687
	n	614	612
Impact on activities of daily living	Mean (SD)	57.66 (25.148)	83.95 (16.537)
	n	433	461
Convenience	Mean (SD)	59.03 (20.750)	81.02 (13.119)
	n	619	599
Satisfaction	Mean (SD)	74.86 (19.368)	87.28 (14.964)
	n	617	624

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

The sponsor also included pharmacoeconomics and outcomes results for the SAWYER study with the appeal documents:

- Although not a formal study objective, administration time for MabThera SC injections was collected in Part 2 of the study and summarised over all cycles. The median duration of MabThera SC administration at Cycles 2-6 was 7.0 minutes, with the majority of SC injections (90%; 330/369 injections) taking less than 9 minutes to administer. In contrast, the median duration for MabThera IV infusions, excluding infusions requiring dose modifications/interruptions, were 210 minutes (3.5 hours), with the majority of infusions lasting between 180 and 300 minutes.
- When asked about their preferred dosing route (IV or SC) after the Cycle 6 SC injection, 91% each of patients and their treating nurses in Part 1 indicated a preference for MabThera SC compared to treatment with MabThera IV.
- Physician and Nurse's opinion on convenience and time saving was also collected in Part 2 of the study. In response to the question on convenience, 79% each of nurses and physicians indicated that rituximab SC was much more convenient than rituximab IV. In response to the question on time saving, the majority of physicians/nurses (71%) indicated that at least 2 hours could be saved when using MabThera SC in routine clinical practice.

Roche acknowledges that patients'preference for MabThera SC versus IV has not been studied in CLL patients using validated outcome questionnaires. However, in the dedicated patient preference study PrefMab, conducted during combined immunochemotherapy of patients with FL and DLBCL, patient-assessed satisfaction and convenience data consistently favoured SC dosing compared with the IV formulation. The data are supported by patient satisfaction/preference data in favour of SC dosing in SAWYER study Part 1 in CLL, and data from site personnel opinions on convenience and resource-savings from SAWYER study Part 2 in CLL.

Consistent with the findings in the SAYWER study it was not expected that the slightly higher volume of MabThera SC 1600 mg would have any negative effect on CLL patients' preference for MabThera SC. Safety of volumes in excess of the proposed 13.4 mL volume

of administration of MabThera SC 1600 mg has been shown in SAWYER Part 1 (22 patients received MabThera SC 1870 mg at a volume of 15.6 mL).

In addition, investigation of rHuPH20 (vorhyaluronidase) as a permeation enhancer to establish IV-like access of a large volume of immunoglobulins via SC injection has demonstrated safe administration of volumes up to 716 mL per injection site at comparable injection rates used to administer MabThera SC (Wasserman et al. 2012) [34].

In conclusion, Roche considers that the incremental benefit of the availability of MabThera SC has been demonstrated in carefully designed studies and that the results are applicable to MabThera SC 1600 mg for the treatment of patients with CLL.

Delegate of the Minister's comment

Delegate of the Minister accepts that the published results of the PrefMab study summarised above, in conjunction with supportive data from the SAWER study, are sufficient to establish an incremental benefit of MabThera SC for the treatment of patients with CLL in terms of patient and health professional preference and convenience. As no health economics data were presented, no conclusions can be drawn regarding potential resource savings attributable to the more rapid infusion times.

Grouped concerns regarding quality of proposed formulation MabThera SC 1600 mg/13.4ml for CLL:

[Initial decision] Delegate's points 49, 50 and 51 of the decision letter:

- The Delegate is not satisfied that the quality of the proposed new formulation for MabThera SC 1600 mg/13.4mL has been satisfactorily established for the reasons provided below.
- The sponsor did not provide any data (as requested) to allow the [initial] Delegate, the quality evaluator or the ACPM to make an independent assessment [information redacted].In the absence of the data, the TGA cannot make an independent assessment and cannot otherwise be satisfied that there is sufficient evidence to counter concerns regarding quality.
- As this was not the only deficiency leading to the decision not to approve the application to register MabThera SC 1600 mg/13.4mL, and the other matters have not been resolved by the sponsor's pre-ACPM response, the [initial] Delegate did not consider that it would change the outcome of the application to have these data submitted after the ACPM. Any future applications or appeal processes to register MabThera SC 1600 mg/ 13.4mL would need to provide these data for the TGA to be able to make a full assessment of the concerns raised by the EMA. The sponsor would also be required to state whether this has been a concern raised by any other regulatory authority with whom the proposed usage has been discussed.

Sponsor's response

The TGA Milestone 5 Quality Evaluation Report (November 2015) recommended that MabTheraSC 1600 mg should be approved. The evaluator noted that the formulation of MabThera SC1600 mg is identical to that of the currently registered 1400 mg. The formulation of MabThera SC consists of 120 mg/mL rituximab in histidine/histidine hydrochloride monohydrate, trehalose dihydrate, methionine, rHuPH20, and polysorbate80.

[34] Wasserman et al. Recombinant human hyaluronidase-facilitated subcutaneous infusion of human immunoglobulins for primary immunodeficiency. *J Allergy Clin Immunol.* 2012;130(4):951-957.

The TGA [initial] decision letter (point 50) refers to the TGA request in the [initial] Delegate's Overview for additional data to be provided. This resulted from information provided by Roche in December 2015 that noted additional data were requested by the EMA in the course of their review of the same application. In the pre-ACPM response of 18 January2016, Roche provided the following response to TGA:[35]

[information redacted]

Roche's evaluation and conclusions provided to the EMA were accepted and MabThera SC1600 mg was approved in the EU on 25 May 2016.

The Committee for Human Medicinal Products (CHMP) added the following recommendation for future quality development to the positive opinion:

[information redacted]

Delegate of the Minister's comment

The Delegate of the Minister accepts the sponsor explanation for the concerns raised by the EMA, and the results of the root cause analysis.[information redacted]

Grouped concerns regarding changing the dosing frequency of MabThera SC 1400 mg/11.7ml in the follicular lymphoma maintenance setting:

[Initial decision] Delegate's points 44, 47 and 52 of the decision letter

The TGA decision to reject the proposed 2-monthly dosing frequency for MabThera SC 1400 mg in maintenance NHL was because no direct long term data on safety and efficacy for the increased MabThera SC dosing frequency were presented in support of this change and there was a concern about potential accumulation.

Sponsor's response

With the recent approval of the 2-monthly maintenance treatment for MabThera IV together with the accepted PK-based clinical bridging development of MabThera SC, Roche considers the required data has been provided to support a 2-monthly maintenance dosing interval for the SC formulation as well as the IV formulation in first line FL patients without requiring additional safety and efficacy data.

The 2-monthly dosing interval for FL maintenance therapy with MabThera SC was studied in the SparkThera and SABRINA studies and the data were included in the approved application PM-2012-04453-1-4 and current application PM-2014-04709-1-4. A short summary of the PK and safety data related to 2-monthly maintenance dosing is provided below for reference.

SparkThera

Patients in Stage 2 of the SparkThera study (previously untreated and relapsed FL patients) received either 2-monthly or 3-monthly maintenance dosing with MabThera IV or SC for 2 years or until disease progression. At final analysis, the results showed that MabThera SC 1400 mg was non-inferior in terms of C_{trough} to MabThera IV 375 mg/m^2 for both dosing intervals with the lower limit of the 90% CI above the pre-specified non-inferiority boundary of 0.8). The MabThera IV and SC regimen administered every 2 or every 3 months were investigated in the study. Overall, no notable difference was found between SC and IV arms.

[35] The sponsor addressed this point and summarised information that had been submitted to EMA.

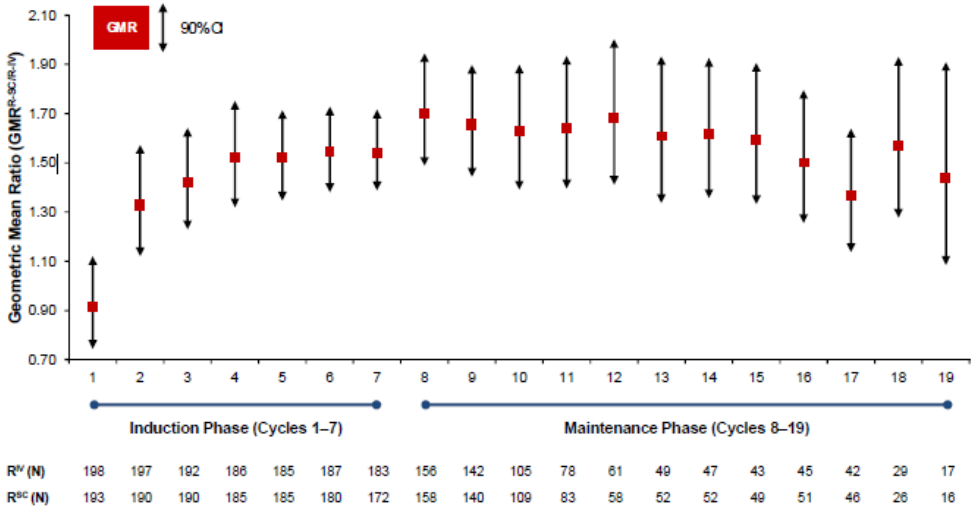
SABRINA

In the Phase III SABRINA study, patients (previously untreated FL patients) received maintenance therapy every 2 months with MabThera IV or SC for 2 years or until disease progression. Serum C_{trough} was analysed at induction Cycles 1 - 8 and maintenance Cycles 9 - 19 during the study.

Except following the first cycle where all patients received MabThera IV at a BSA-adjusted dose, geometric mean ratios for $C_{trough(SC)}/C_{trough(IV)}$ were greater than 1 during the entire treatment course (induction and maintenance cycles). Geometric mean C_{trough} values decreased following the first cycle of maintenance treatment as expected due to the longer dosing interval in moving from induction (q3w) to maintenance (q2m) (Figure 6). Values for MabThera IV and SC, respectively, were 77.6 and 131.5 mg/mL at predose Cycle 8, the last induction cycle, decreasing to 37.7 and 61.3 µg/mL at predose Cycle 9, the first maintenance cycle. Steady state appeared to be reached around the third cycle of maintenance treatment (Cycle 11) for both IV and SC dosing regimens and was maintained until the end of the maintenance phase. The geometric mean ratio for $C_{trough(SC)}/C_{trough(IV)}$ at Cycle 19 (predose Cycle 20) was 1.58 (90% CI [1.38, 1.80]). In conclusion, MabThera serum C_{trough} levels over time (induction and maintenance) did not reveal any signs of accumulation during the every 2 –months maintenance therapy as compared to levels achieved after 8 cycles of induction.

The incidence and the profile of the reported AEs in the SABRINA study were comparable between the SC and IV arms, including the 2-monthly maintenance dosing. The only difference observed was in the incidence of local cutaneous reactions, which was higher in the SC arm as anticipated due to a change in the route of administration. A graph summarising this data was included in the appeal document as Figure 6, and has been reproduced below:

Figure 7. Geometric Mean Ratio (Ctrough, SC/Ctrough, IV) of Ctrough During the Treatment Period (Cycles 1-19) (ITT Population)



Based on the data from the phase III PRIMA study with MabThera IV, the approval of the PK- based clinical bridging approach for MabThera SC 1400 mg and the updated maintenance data (efficacy and safety) from the Phase III SABRINA study, Roche considers that sufficient long term safety and efficacy has been provided to allow approval of 2-monthly maintenance for the MabThera SC 1400 mg formulation.

In conclusion, Roche is concerned that a rejection of the 2-monthly dosing frequency for MabThera SC 1400 mg in follicular lymphoma maintenance settings is inconsistent with previous TGA decisions.

Delegate of the Minister's comment

The Delegate of the Minister has considered and has accepted the updated efficacy and safety data from the Phase III SABRINA study. In conjunction with this Delegate's review of all of the other [initial] Delegate's points of concerns detailed above, the Delegate of the Minister is on balance of the opinion that this change should be approved. The Delegate of the Minister accepts the sponsor's arguments that there is unlikely to be unacceptable excess risk associated with the use of MabThera SC in follicular lymphoma maintenance settings at the increased frequency of 2 monthly based on PK data and the efficacy results of the PRIMA trial. The Delegate of the Minister acknowledges that this decision is consistent with the previous TGA decision to approve a 3 monthly maintenance interval for MabThera SC.

Final outcome

The final decision letter was issued on 25 November 2016. The following is an extract from the letter:

The Delegate of the Minister has decided to revoke the initial decision and substitute with a decision to include in the Australian Register of Therapeutic Goods (Submission No PM-2014-04709-1-4):

> A new strength of MabThera SC (rituximab injection 1600 mg/13.4mL) for use in chronic lymphocytic leukaemia; and
>
> A new dosage frequency for the approved MabThera SC (rituximab injection 1400 mg/11.7mL) strength for maintenance therapy in patients with previously untreated follicular lymphoma who have responded to induction treatment.

Taking the decision in that letter into account, MabThera SC now has the following indications:

> ***Chronic Lymphocytic Leukaemia***
>
> *MabThera SC 1600 mg is indicated for the treatment of patients with CD20 positive chronic lymphocytic leukaemia (CLL) in combination with chemotherapy.*
>
> **Non-Hodgkin's Lymphoma**
>
> MabThera SC 1400 mg is indicated for treatment of patients with:
>
> - *CD20 positive, previously untreated, Stage III/IV follicular, B-cell non-Hodgkin's lymphoma,*
> - *CD20 positive, relapsed or refractory low grade or follicular, B-cell non-Hodgkin's lymphoma,*
> - *CD20 positive, diffuse large B-cell non-Hodgkin's lymphoma, in combination with chemotherapy*

A new dosage frequency for MabThera SC containing rituximab injection 1400 mg/11.7 mL causes this product to be taken as separate and distinct good from that currently included in the ARTG under the provisions of section 16(1) of the Act. However, by virtue of Therapeutic Goods (Groups) Order No. 1 of 2001, MabThera SC with this new dosing frequency is for the purpose of registration in relation to your company, grouped with MabThera SC injection containing rituximab injection 1400 mg/11.7 mL with the old dosing frequency; that is with Aust R No. 207334.

Specific conditions of registration for this product

- Updated data from the SAWYER (BO25341) and SABRINA (BO22334) studies (including MRD data that must be analysed in relation to the outcomes in the SAWYER trial) must be submitted to TGA for evaluation within 6 months of completion of the final analyses, or by the last working day of 2018, whichever is sooner. In the event that there is an unavoidable delay, the sponsor may apply to TGA for this condition to be varied.

  (Note: Following completion of this evaluation, the TGA may impose new conditions on the registration or listing or vary or remove conditions imposed under subsection (2B).)

- The sponsor must submit to TGA for approval a revised assay [information redacted].
- The Risk Management Plan (RMP) must reflect the possibility of unknown new toxicity (especially infective complications) arising from the increase exposure to and different route of administration of MabThera SC in comparision to MabThera IV, with timely notification of any new or emerging safety signal to TGA for review and possible action. In particular, the sponsor has previously acknowledged in the response to the Clinical Evaluation that '*Immunogenicity associated with the subcutaneous formulation (NHL/CLL SC formulations) is currently included in the RMP list of safety concerns as Missing Information*'. The Pharmacovigilance Plan must therefore further assess the incidence and clinical relevance of the development of HAHAs (antibodies to rituximab) and HACAs (antibodies to vorhyaluronidase) through routine pharmacovigilance and additional pharmacovigilance activities (BP22333/SparkThera and BO22334/SABRINA studies).

Attachment 1. Product Information

The PI approved for MabThera at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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