Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Rituximab

Proprietary Product Name: MabThera

Sponsor: Roche Products Pty Ltd

Second round evaluation: 10 October 2015

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 Decemberision-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 the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words (Information redacted), where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of 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

Abbreviation	Meaning
FDA	Food and Drug Administration
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

Abbreviation	Meaning
QTc	Interval from beginning of QRS complex to end of the T wave; QT corrected
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

1. Introduction

This is a Category 1 Application for

1. *New Strength: 1600 mg/13.4 mL* Solution for subcutaneous Injection, Vial for Chronic Lymphocytic Leukaemia
2. *Change in Dosage Frequency* for Maintenance Therapy in Previously Untreated NHL Patients: 100 mg/10 mL and 500 mg/50 mL Vials, Concentrate Solution for Infusion, 1400 mg/11.7mL Solution for Injection, Vial (AUST R 60318, 60319, 207334) applies to currently registered SC and IV formulations
3. *Changes to PI* Requiring Data Evaluation (AUST R 207334).

MabThera Drug Class: CD20-directed cytolytic monoclonal antibody.

Currently approved oncology indications for IV rituximab:

> *Non-Hodgkin's Lymphoma (NHL)*
>
> *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.*
>
> *Chronic Lymphocytic Leukaemia (CLL)*
>
> *MabThera is indicated for the treatment of patients with CD20 positive CLL in combination with chemotherapy.*

Comment: Evidence to show the efficacy benefit without increase in adverse events is required to support this indication.

Proposed Indications:

1. *MabThera SC 1600mg for treatment of patients with CD20 positive Chronic Lymphocytic Leukaemia (CLL) in combination with chemotherapy.*
2. *To increase the dosing frequency (in both IV and SC formulations) for maintenance therapy in previously untreated non- Hodgkin's lymphoma (NHL) patients who have responded to induction treatment from once every 3 months to once every 2 months (100 mg/10 mL and 500 mg/50 mL Vials, Concentrate Solution for Infusion, 1400 mg/11.7mL Solution for Injection, Vial (AUST R 60318, 60319, 207334).*

2. Clinical rationale

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

Comment: The evidence to show the relationship of SC to IV in terms of convenience was unable to be located[1]. Further 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

[1] This was addressed in the sponsor's response to TGA's request for further information (Question 14) as well as in Study BO25341/SAWYER.

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.

3. Contents of the clinical dossier

3.1. Scope 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/13.4 mL) for use in CLL:

One new clinical trial, BO25341 (SAWYER) that builds on the earlier approval of MabThera SC 1400 mg in NHL. Study 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.

In addition, 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 the established safety and efficacy of Mabthera IV in CLL in Study ML17102. 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: 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.

3.2. 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. Hypogammaglobulinaemia 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.

Comment: This is appropriate.

3.3. Good clinical practice

The new PK study (BO 25341/SAWYER) was conducted in compliance with Good Clinical Practice.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

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

1. Study BO25341 – 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 1058161 (BP22333SparkThera). 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, no PK drug interaction studies.

4.1.1. Study BO25341

This was a Phase Ib study. It was published as an abstract at ASH 2012:

'Assouline S, Buccheri V, Delmer A, et al. Subcutaneous rituximab in combination with fludarabine and cyclophosphamide for patients with CLL: Initial results of a Phase 1b study (SAWYER [BO25341] show non-inferior pharmacokinetics and comparable safety to that of intravenous rituximab. 54th ASH annual meeting; Atlanta, Georgia, December 8-11, 2012. Abstract 1637.'

4.1.1.1. *Dates*

First patient enrolled: April 13, 2011. Data snapshot May 07, 2014.

Comment: Version BO25341D of the protocol included the possibility of performing snapshots during the study to address potential health authority or regulatory questions (it also clarified that a split in the dose over two days was allowed only in Cycle 1). The relationship between planned end date, data analysis and data snapshot in the results section was difficult to follow in the Study report.

4.1.1.2. *Design*

A two-part, randomised, open-label, parallel-group, multi-centre, Phase Ib study. All patients received treatment with rituximab (IV or SC) in combination with chemotherapy (fludarabine and cyclophosphamide). Rituximab IV doses were calculated on a BSA-adjusted basis, as per standard clinical practice. Rituximab SC was administered as a fixed dose.

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

Comment: The 1600 mg dose is the dose proposed in the indication.

4.1.1.3. *Summary of trial design*

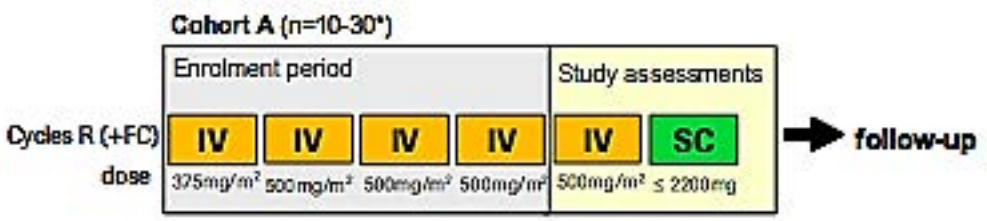
Part 1 Pilot dose selection In Part 1, a single cycle of rituximab SC was administered to select a dose of rituximab SC that would result in rituximab C_{trough} values comparable to those achieved with the IV regimen.

Part 2 C_{trough} non-inferiority In Part 2, patients were randomised 1:1 to receive rituximab IV 500 mg/m^2 or rituximab SC at the dose selected in Part 1 (1600 mg) to demonstrate non-inferiority of the rituximab C_{trough} levels with the SC dose compared with the IV dose.

4.1.1.4. *Trial design in detail*

All patients received treatment with rituximab (IV or SC) in combination with chemotherapy (fludarabine and cyclophosphamide).

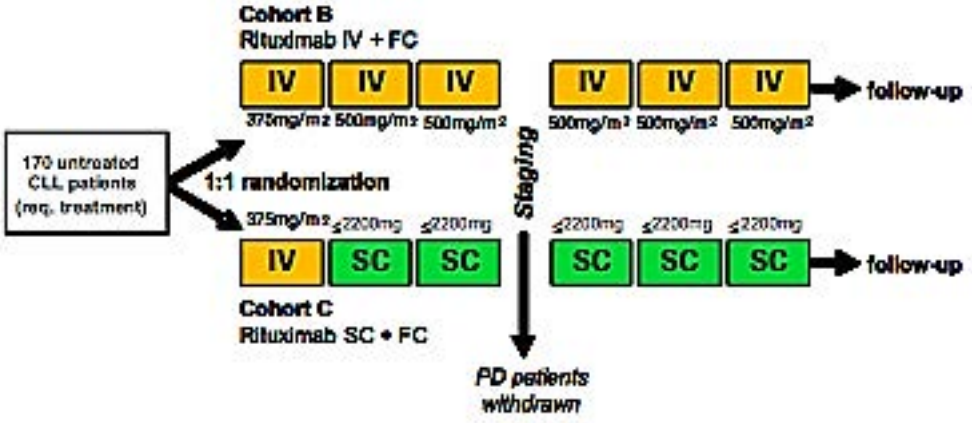
Figure 1: Part 1. Pilot dose confirmation



Initially 10 previously untreated CLL patients were to be enrolled into Cohort A. Following preliminary analysis of rituximab PK data from the first 10 patients, approximately 20 additional patients were able to be enrolled into Cohort A. Dependent on further analysis, and considering the theoretical possibility of observing increased variability in rituximab PK parameters due to allowing patients to receive either oral or IV FC, a further 30 patients were able to be enrolled – *thus* Cohort A was able to include up to approximately 60 patients.

Patients could be enrolled at any point during their treatment with rituximab IV in combination with FC, prior to commencement of treatment Cycle 5. If applicable, treatment prior to enrolment must have followed the dosing schedule outlined in Figure 2 below. In Cycle 5 (and previous cycles), patients received rituximab IV and subsequently in Cycle 6, IV rituximab was replaced by a single SC rituximab dose. Pharmacokinetic parameters for rituximab were assessed during Cycles 5 (IV rituximab) and 6 (SC rituximab).

Figure 2: Part 2. C_{trough} non-inferiority between SC and IV.



Approximately 170 previously untreated CLL patients were to be randomised 1:1 either to Cohort B (IV rituximab) or to Cohort C (SC rituximab) (see Figure 2). Rituximab was administered as an intravenous infusion in the first cycle for all patients.

- **Cohort B**: 375 mg/m^2 IV rituximab + FC, followed by 500 mg/m^2 IV rituximab + FC for up to 5 further cycles. All patients randomised to Cohort B were to receive chemotherapy (FC) in combination with IV rituximab at a dose of 375 mg/m^2 in cycle 1, and then 500 mg/m^2 on day 1 of each subsequent cycle (cycles 2-6).
- **Cohort C**: 375 mg/m^2 IV rituximab + FC, followed by SC rituximab at the dose determined from Part 1 of the study (≤2200 mg) + FC for up to 5 further cycles. In actuality, the dose was 1600 mg, not 2200 mg.

All patients randomised to Cohort C will receive chemotherapy (FC) in combination with IV rituximab at a dose of 375 mg/m^2 in cycle 1. In all subsequent cycles (2-6), patients will receive FC in combination with SC rituximab at the selected dose.

Number/type of subjects

- Part 1
  - 64 patients enrolled sequentially to Cohort A; 56 patients treated:
    - 16 patients in rituximab 1400 mg SC sub-cohort
    - 17 patients in rituximab 1600 mg SC sub-cohort
    - 23 patients in rituximab 1870 mg SC sub-cohort
- Part 2
  - 176 patients randomised to Cohort B and C: 174 patients treated: 87 patients in Cohort B (rituximab IV 500 mg/m^2)) and 87 patients in Cohort C (rituximab SC 1600 mg).

All patients were adults with previously untreated chronic lymphocytic leukaemia (CLL; documented CD20+ B-CLL confirmed according to International Workshop on Chronic Lymphocytic Leukaemia (iwCLL) criteria).These patients are representative of the current CLL population receiving IV rituximab.

Objectives

- Primary (Pilot dose confirmation, Part 1)

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

- Primary (C_{trough} non-inferiority, Part 2)

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

- Secondary (Part 1)
  - To describe the rate of incidence of injection-related reactions during the SC rituximab cycle
  - To describe patient and nurse preference regarding SC or IV administration.
- Secondary (Part 2)
  - To evaluate safety parameters among patients, who received SC rituximab, compared to patients who received IV rituximab
  - To assess site experience, specifically:
    - physician/nurse opinions on time savings with rituximab SC compared with rituximab IV
    - physician/nurse opinions on the convenience of rituximab SC compared with rituximab IV

The patient/nurse preference questionnaire was 2 questions regarding time savings and convenience of rituximab SC compared with usual practices. Specifically, in Part 1 of the trial, upon completion of dosing in Cycle 6, patients in Cohort A and their treating nurses were asked whether they have a preference of dosing route. During Part 2 it was assessed after Cycles 1 and 6 of treatment or after the last cycle of therapy if treatment was discontinued earlier. At these two time points for each patient enrolled, physicians/nurses taking part in this study were asked to answer the questions considering their experience across all patients. Descriptive statistics were used for the two questions assessing physicians' and nurses' opinions on a patient level regarding potential time savings and convenience with rituximab SC as compared to rituximab IV. Specifically, frequencies and percentages were presented for each response option, both separately by respondent type (physician or nurse) and for the total and by country.

Comment: The population group receiving one not two treatments so the safety comparisons are between the two groups. This is appropriate. The two questions on patient and nurse preference appeared exploratory. Can the sponsor provide information on the validation (internal and external) of the survey (there were two references supplied but neither was able to provide the necessary validation)?

- Secondary (both Part 1 and Part 2)
  - To assess additional PK parameters (including AUC) of both SC and IV rituximab
  - To compare the immunogenicity of SC rituximab with that of IV rituximab
  - To examine peripheral blood B-cell levels and B-cell depletion and repletion with SC rituximab compared to IV rituximab
  - Exploratory assessment of the efficacy of SC rituximab compared to IV rituximab, including Response rate, Complete Response (CR), Complete Response with incomplete bone marrow recovery (CRi), Partial Response (PR), Progression-free survival, Event free survival, Overall survival.

Endpoints:

The primary endpoint was PK. Efficacy endpoints were exploratory and are covered in Section 7. Safety is covered in Section 8.

Comment: A primary endpoint of a PK concentration is common for a Phase I or a pharmacology study. 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) or evidence of a study with appropriate efficacy or safety endpoints and sample size.

PK

The primary endpoint for Part 1 and Part 2 was to demonstrate non-inferiority in rituximab C_{trough} levels after rituximab IV or after rituximab SC. Secondary PK endpoints for Part 1 and Part 2 were AUC0-τ, C_{max}, T_{max}, and t1/2 of rituximab. All PK analyses were based on patients for whom PK assessments were available for both formulations. Patients were analysed according to treatment received.

Efficacy

Exploratory assessments of tumour response rate and minimal residual disease

PD

Pharmacodynamics endpoints included B-cell levels, as measured by peripheral blood CD19+ lymphocyte counts, and B-cell depletion and repletion.

Safety endpoints

Included adverse events (AEs), serious AEs (SAEs), and administration-related reactions (ARRs); human anti-chimeric/anti-human antibody levels; as well as haematology and clinical chemistry parameters. All patients who received at least one dose of study treatment were included in the safety analysis population (SAP) – covered in Section 8.

Population PK

Rituximab PK data from Part 1 were integrated into a population PK model using parametric, nonlinear, mixed- effects modelling (NONMEM version 7.2.0). Model-based simulations were performed to predict serum C_{trough} and AUC for incremental rituximab SC doses to define a dose to be taken into Part 2 of the trial.

Observed PK data from Part 2 were analysed according to standard non-compartmental analysis (NCA) methods using WinNonlin. Hypothesis testing for C_{trough} was *based on the lower bound of 0.8 of the two-sided 90% confidence interval of the ratio* C_{trough}*(SC)/*C_{trough}*(IV) estimated on the log-transformed concentrations.* All NCA PK parameters were summarised using descriptive statistics, including arithmetic means, standard deviations, geometric means, coefficient of variations (CVs), medians and ranges.

There was no formal statistical testing. Non–inferiority was assessed comparing the relationship of the C_{trough} concentrations (log transformed).

Comment: Population PK was used to choose the dose of the study for Phase II. This has limitations in comparison to actual data.

Statistical analysis plan

Reporting tools; some analysis populations were described. As it was a PK study, some of the usual statistical planning to guide analysis of the Clinical Efficacy and Safety sections (for example, in the handling of Adverse Events and some population analysis) was not provided.

4.1.1.5. ***Results***

PK

Part 1

To determine a dose of rituximab SC that would yield comparable C_{trough} to that observed with rituximab IV 500 mg/m^2, three different fixed doses of rituximab SC were investigated: 1400 mg, 1600 mg and 1870 mg. The null hypotheses was that C_{trough}(SC)/C_{trough}(IV) ≤ 0.8 using the

log-transformed values. Non-inferior rituximab C_{trough} values and comparable AUC levels compared with the established rituximab IV dose of 500 mg/m^2 were seen with a q4w regimen in CLL. The selected 1600 mg dose of rituximab SC was then evaluated in Part 2.

Part 2

The primary endpoint of the study, to demonstrate non-inferior C_{trough} of the selected rituximab SC dose compared with rituximab IV 500 mg/m^2 in CLL was met. Based on the geometric mean for C_{trough} with a q4w regimen, 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 for the q4w regimen was 20% higher than the predicted value 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 greater than the pre-specified non-inferiority margin of 0.8.

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 $AUC_{\tau(SC)}AUC_\tau/AUC_{\tau(IV)}$ AUC_τ ratio of 1.10 with 90% CI 0.98 to 1.25.

Comment: The difference between predicted and actual C_{trough} was noted. The clinical significance of log transformed difference in ratio of 1.1 was not provided.

HuPH20 Pharmacokinetics

Plasma rHuPH20 concentrations were measured at pre-dose, and at 30 minutes, 1 h, and 24 h post-dose for patients dosed with their first dose of rituximab SC; in Part 1 this was Cycle 6 and in Part 2, Cohort C it was Cycle 2 (total patients 149). Plasma rHuPH20 concentrations were below the limit of quantification for all sampling time-points (one sample needed re-testing).

Comment: This result is consistent with previously evaluated rHuPH20 PK data for the rituximab subcutaneous formulation in the NHL indication. The evaluation and interpretation of this was not clear with short-term data in a small number of patients, the sponsor is requested to provide this.

4.1.2. Preference study

More patients and nurses preferred treatment with rituximab SC to IV (preference questionnaire) in Part 1. In Part 2, 71% of physicians and nurses who administered rituximab SC during the study indicated that at least 2 h could be saved when using rituximab SC in routine clinical practice (resource saving questionnaire). In response to the question on convenience (which formulation of rituximab (SC or IV) do you think is more convenient?), 87% of nurses and 94% of physicians at Cycle 6 chose rituximab SC as more or a little more convenient than rituximab IV.

Comment: The simplicity and small numbers of the preference study, with descriptive statistics only suggest that the findings are difficult to interpret and clinical relevance is unknown.

Table 1: Example of the results for patient/nurse preference by role/country in two countries Stage 1 (all patients)

	Rituximab SC 1400 mg N=16	Rituximab SC 1600 mg N=17	Rituximab SC 1870 mg N=23	No SC Dose Received N=8	Total N=64
Country: Mexico					
Patient's Preference					
SC	0	1 (100%)	0	0	1 (100%)
IV	0	0	0	0	0
Nurse's Preference					
SC	0	1 (100%)	0	0	1 (100%)
IV	0	0	0	0	0
Country: Poland					
Patient's Preference					
SC	3 (100%)	0	2 (100%)	1 (100%)	6 (100%)
IV	0	0	0	0	0
Nurse's Preference					
SC	3 (100%)	0	2 (100%)	1 (100%)	6 (100%)
IV	0	0	0	0	0
Country: Slovakia					
Patient's Preference					
SC	2 (100%)	1 (100%)	1 (100%)	0	4 (100%)
IV	0	0	0	0	0
Nurse's Preference					
SC	2 (100%)	1 (100%)	1 (100%)	0	4 (100%)
IV	0	0	0	0	0

- Percentages are based on the number of patients/nurses with a response.

Table 2: Nurse's opinion on convenience by role and country Stage 2 (All Patients)

	Rituximab IV 500 mg/m2 N=88	Rituximab SC 1600 mg N=88	Total N=176
Nurse's opinion: all roles and countries			
Cycle 1			
Rituximab SC is much more convenient	58 (81%)	48 (69%)	106 (75%)
Rituximab SC is a little more convenient	7 (10%)	8 (11%)	15 (11%)
Both formulations are equally convenient	4 (6%)	4 (6%)	8 (6%)
Rituximab IV is a little more convenient	2 (3%)	6 (9%)	8 (6%)
Rituximab IV is much more convenient	1 (1%)	4 (6%)	5 (4%)
Number of responses	72	70	142
Cycle 6/Early Termination			
Rituximab SC is much more convenient	57 (81%)	54 (77%)	111 (79%)
Rituximab SC is a little more convenient	5 (7%)	6 (9%)	11 (8%)
Both formulations are equally convenient	6 (9%)	3 (4%)	9 (6%)
Rituximab IV is a little more convenient	2 (3%)	7 (10%)	9 (6%)
Rituximab IV is much more convenient	0	0	0
Number of responses	70	70	140

- Percentages are based on the number of responses.

Comment: This survey appears to have small numbers completing and maybe prone to bias due to context lack of blinding. Further the estimates of time needs be supported by actual evidence on convenience or time taken for each infusion.

4.1.3. Study 1058161 (Protocol BP22333)

4.1.3.1. *Title*

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.

4.1.3.2. *Design*

This was a two-stage randomised, open-label, multicentre adaptive Phase Ib study.

- Stage 1: 42 centres in 20 countries: France (3 centres), Czech Republic (3), Israel (4), Spain (4), Canada (5), Russia (1), Australia (4), Slovakia (1), Denmark (1), Sweden (3), Brazil (3), Mexico (2), Poland (1), Finland (1), Italy (1), Peru (1), Ecuador (1), Great Britain (1), Norway (1), Switzerland (1).

- Stage 2: 53 centres in 21 countries: Czech Republic (3 centres), Israel (3), Great Britain (3), Brazil (3), Canada (4), Peru (2), France (3), Poland (2), Mexico (3), Sweden (4), Argentina (4), Russia (1), Australia (4), Italy (3), Spain (4), Slovakia (1), Finland (2), Switzerland (1), Denmark (1), Norway (1), Republic of Korea (1).

4.1.3.3. *Dates*

First patient entered: September 08, 2009. Data cut-off: July 15, 2013.

4.1.3.4. *Objectives:*

Primary objectives

- Stage 1 (Dose Finding)
  - To determine a rituximab SC dose that gives comparable (lower bound of 0.8 of the two-sided 90% confidence interval of the ratio C_{trough}(SC)/C_{trough}(IV) estimated on the log-transformed (base e) trough concentrations to those obtained with comparable rituximab IV dosing.
- Stage 2 (Dose Confirmation)
  - To demonstrate comparable C_{trough} of rituximab SC and rituximab IV with the SC dose determined from Stage 1, as assessed by a non-inferiority test with a lower boundary above 0.8 for the two-sided 90% confidence interval.

Secondary Objectives

- Stage 1 (Dose Finding)
  - To compare the safety profile of different doses of rituximab SC with the safety profile of rituximab IV (in particular, the incidence and severity of infusion-/injection-related reactions).
  - To evaluate area under the serum concentration– time curve of rituximab SC compared to that of rituximab IV.
  - To examine peripheral blood B-cell depletion and repletion with rituximab SC and rituximab IV.
- Stage 2 (Dose Confirmation)
  - To examine peripheral blood B-cell depletion and repletion with rituximab SC and IV.
  - To compare the safety profile of rituximab SC with the safety profile of rituximab IV (in particular, the incidence and severity of infusion/injection-related reactions).

4.1.3.5. *Methods*

In Stage 1 one 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.

Patients in the dose-finding part of Stage 1 received a single cycle of rituximab SC at one of three different BSA-adjusted test doses: 375, 625, and 800 mg/m^2. Patients participating in the SC extension phase in Stage 1 received between 1 and 5 cycles of rituximab SC (1400 mg).

In Stage 2, patients were randomised 1:1 to receive rituximab IV 375 mg/m^2 (same dose throughout study) or rituximab SC at the dose selected in Stage 1 (1400 mg) to demonstrate non- inferiority of the rituximab C_{trough} levels with the SC dose compared with the IV dose. Patients in Stage 2 received between 1 and 11 cycles of rituximab SC 1400 mg.

Patients randomised to an SC cohort in Stage 1 who had received at least 1 year of rituximab IV maintenance were given the option to switch to the final selected rituximab SC dose for the remaining cycles of their maintenance treatment (SC extension phase).

Rituximab was given on Day 1 of each cycle. The dosing regimen was once every three months (q3m) or once every two months (q2m) for a total of 8 or 12 cycles, respectively, of rituximab maintenance (24 months).

After completing maintenance treatment, patients in both Stage 1 and Stage 2 had three scheduled follow-up visits at 3, 6, and 9 months after their last cycle of rituximab.

4.1.3.6. *Number of patients*

- Stage 1:
  - 124 patients randomised 1:2:2:2 to Cohorts A – D:
    - 16 patients in Cohort A (rituximab IV 375 mg/m^2)
    - 34 patients in Cohort B (rituximab SC 375 mg/m^2)
    - 34 patients in Cohort C (rituximab SC 625 mg/m^2)
    - 40 patients in Cohort D (rituximab SC 800 mg/m^2)
- Stage 2

  157 patients randomised to Cohorts E and F:
    - 79 patients in Cohort E (rituximab IV 375 mg/m^2)
    - 78 patients in Cohort F (rituximab SC 1400 mg)

Inclusion Criteria: Adult patients with follicular lymphoma who had achieved at least a partial response after induction treatment with rituximab IV (as monotherapy or in combination with chemotherapy) and received at least one cycle of rituximab IV 375 mg/m^2 in the maintenance phase.

4.1.3.7. *Results*

Efficacy

N/A (tumour response data not collected).

Pharmacokinetics

- Stage 1 (Dose Finding)
  - PK data from Stage 1 were analysed using a PK reference model developed in the NHL population, and model-based simulations were then used to predict C_{trough} and AUC_{τ} values for various rituximab doses. It was assumed that patients in the SC arm received SC drug in the induction setting followed by SC drug in the maintenance setting.

Comment: It appears the PK reference model was developed in the IV 375 mg/m^2 population. If so the limitations of the assumptions of this model in its applicability to the CLL population and the SC population with follicular lymphoma need discussion. The trial states that '*Patients randomised to an SC cohort in Stage 1 who had received at least 1 year of rituximab IV maintenance were given the option to switch to the final selected rituximab SC dose for the remaining cycles of their maintenance treatment (SC extension phase)*.' It is thus presumed that the assumption for the simulation is correct and that the 1 year of prior rituximab IV therapy was in a period before the Stage 1 dose finding study.

- Stage 2 (Dose Confirmation)
  - The primary endpoint of Stage 2 was to demonstrate non- inferiority in C_{trough} levels of rituximab after the first cycle of rituximab IV for patients in Cohort E or rituximab SC for patients in Cohort F post-randomisation. PK data from Stage 2 were analysed with a population PK approach, and predicted data were generated.

- C_{trough} was estimated for the maintenance Cycle 2 time point (that is, after an induction phase and one maintenance cycle of rituximab SC). Two C_{trough} values were estimated for each patient, one *assuming* the two monthly (q2m) dosing regimen and one assuming the q3m dosing regimen.
- PK data from 118 patients were integrated into a population PK model, and model-based simulations predicted that a fixed dose of 1400 mg rituximab SC would yield a non-inferior C_{trough} over rituximab IV given either as a q2m or q3m regimen during maintenance.

Comment: It is noted that this is simulated data.

PK data from 153 patients were integrated into the population PK model, and model-based simulations were used to predict the PK parameters each patient would have at Cycle 2 of maintenance treatment. The geometric mean C_{trough}(SC)/C_{trough}(IV) ratios and corresponding 90% confidence intervals were 1.24 [1.02;1.51] for the q2m regimen, and 1.12 [0.86;1.45] for the q3m regimen. As the lower bounds of the 90% confidence intervals were above the pre-specified non-inferiority boundary of 0.8, non-inferiority of C_{trough} with rituximab SC 1400 mg was demonstrated, and the primary endpoint of Stage 2 was met.

The geometric mean $AUC_{\tau\ (SC)}$ AUCτ/$AUC_{\tau(IV)}$ AUC_{τ} ratio was 1.35 for both q2m and q3m regimens, each with corresponding lower limit of 1.23 for the two-sided 90% confidence intervals. Thus the exposure is 35% higher in the SC dosing, irrespective of the Q2 or Q3 m regimen.

The median C_{max} for rituximab SC and rituximab IV were slightly higher for the q2m regimen (209 and 201 µg/mL, respectively) and for the q3m regimen (189 and 184 µg/mL, respectively). The median T_{max} in the rituximab SC arm was approximately 3 days as compared to the T_{max} for the rituximab IV arm which occurs at or close to the end of the infusion.

HuPH20 Pharmacokinetics

One of the 185 patients with available data had plasma rHuPH20 concentrations above the limit of quantification

Pharmacodynamics results

Repletion was defined as CD19+ cell counts of 80 cells/mm3 (0.08×10^9 cells/L) or greater.

Available data from 124 patients in Stage 1 and 154 patients in Stage 2 showed that all patients were effectively depleted of CD19+ cells (B cells) at baseline and throughout maintenance treatment.

In Stage 1, median B-cell levels across all cohorts remained at 0.00×10^9 cells/L until the 9-month follow-up visit, at which time point an increase in B-cell counts was observed. Median counts at the 9-month follow-up visit were 0.05 × 109 cells/L in the IV cohort (Cohort A, n = 13), and 0.02 × 109 cells/L in the three SC cohorts (Cohort B, n = 22; Cohort C, n = 23; and Cohort D, n = 25).

In Stage 2, median B-cell counts remained at 0.00×10^9 cells/L during maintenance treatment and up to the 9-month follow-up visit. At the 9-month follow-up visit, an increase in B-cell counts could be seen in both treatment groups, with median counts of 0.02×10^9 cells/L in both cohorts (Cohort E, n = 52; Cohort F, n = 51).

In Stage 2, at the 9-month follow-up visit however, 7/52 patients (13.5%) in the IV cohort had repleted B-cell counts compared with 13/51 patients (25.5%) in the SC cohort. At the 6-month follow-up visit, already 3/51 patients (5.9%) in the SC cohort were repleted compared with none in the IV cohort.

Comment: This shows significantly worse time to repletion data in the SC arm. Can the sponsor provide correlative PKPD data – as it is possible the small but different C_{max} and AUC between the IV and SC doses in Part 2 explain the worse PD parameters.

Conclusions

Conclusions are presented in the following section 4.2 Summary of pharmacokinetics.

4.2. Summary of pharmacokinetics

The primary endpoint of the BO25341 study, to demonstrate non-inferiority of C_{trough} of rituximab SC dose compared with rituximab IV 500 mg/m^2 in CLL was met.

The secondary endpoint in Part 2 of that study 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 $AUC_{\tau(SC)}AUC_\tau/AUC_{\tau(IV)}$ AUC_τ ratio of 1.10 with 90% CI 0.98 to 1.25.

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

In Stage 1 of this study, a dose of 1400 mg rituximab SC was *predicted* to yield comparable C_{trough} to rituximab IV 375 mg/m^2 in NHL maintenance. Validation data for these predictions (that is, actual data) are required, especially when the concerns over the applicability of the model are taken into account. The incidence of ARRs was different across treatment cohorts during the dose-finding cycle and much higher in the SC cohorts than the IV cohort.

In Stage 2, comparable C_{trough} of rituximab SC 1400 mg and rituximab IV 375 mg/m^2 in NHL maintenance was seen on Cycle 1 and simulated for Cycle 2. ARRs were more commonly reported in patients treated via the SC route. It is noted that study was in follicular lymphoma yet the indication is for NHL. The sponsor is requested to justify the likely translatability of this data to the NHL population in terms of efficacy, safety and dose. Although pre-specified the clinical rationale for trough ratio of 0.8 being comparable is not given.

Was the PK reference model developed in the IV 375 mg/m^2 population? If so the limitations of the assumptions of this model in its applicability to the CLL population and the SC population with follicular lymphoma need discussion. The trial states that '*Patients randomised to an SC cohort in Stage 1 who had received at least 1 year of rituximab IV maintenance were given the option to switch to the final selected rituximab SC dose for the remaining cycles of their maintenance treatment (SC extension phase)*'. It is thus presumed that the assumption for the simulation is correct – and that the 1 year of prior rituximab IV therapy was before the Stage 1 dose finding study.

There are significant issues with the assumptions and translatability of the work in this Phase Ib study. For example, for the maintenance study the predictions are for Cycle 2 and not for the remaining cycles. What evidence does the sponsor have to show us that there is not accumulation if given after 2 months – both simulated and actual? What evidence does the sponsor have to show the safety is non inferior when moving from a 3 month to a 2 month regimen (especially with higher simulated concentrations noted in Cycle 2)? It is noted that the C_{max} for both SC and IV is higher for the first simulated cycle – (Cycle 2). What is the clinical relevance for this (that is, what is the link with the B-cell depletion and repletion. What happens to the C_{max} for the remainder of the cycles?

A significantly shorter time to B cell repletion was noted in the SC arm. Can the sponsor provide correlative PK/PD data – as it is possible the small but different C_{max} and AUC between the IV and SC doses in Part 2 explain the worse PD parameters?

4.3. Evaluator's overall conclusions on pharmacokinetics

The 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.[2]

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

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

5.1.1. B-cell Depletion and Repletion

B cell repletion has been discussed in the PK section above for the BP22333 study – and noted that repletion is quicker in the SC arm. For the BO 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 2 years after last treatment. B-cell depletion was defined as < 80 cells/mm^3. In part 1, baseline B-cell counts before treatment 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.

5.1.2. 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.

[2] See also *Final outcome* in AusPAR.

5.2. Evaluator's overall conclusions on pharmacodynamics

For the BO study, effect on B-cell depletion is stated to be similar across the two groups (IV and SC).

6. Dosage selection for the pivotal studies

The dosage selected for the Part 2 of the Phase I study was based on PK modelling of Phase I data in that study.

Comment: 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.

However the choice of the 1600 mg dose, using efficacy and safety data was not made clear – 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 on C_{max} (safety and efficacy) was not clear.

7. Clinical efficacy

7.1. Indication 1: Treatment of CLL with subcutaneous rituximab 1600 mg.

7.1.1. Pivotal efficacy studies

There was no pivotal study. Efficacy endpoints for the subcutaneous formulation of 1600 mg of rituximab in CLL were measured in the Phase Ib Study BO25341.

7.1.1.1. *Study BO25341*

This study has been described in Section 4.

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 (PFS, EFS and OS) were not analysed because these data are not yet mature.

Part 1

At 3 months of follow-up there was no progression in any rituximab SC dose group, however these patients had all had 5 cycles of IV rituximab. Complete responses (CR) were recorded in 5/16 (31%) patients in the rituximab 1400 mg SC treatment sub-cohort, 9/17 (53%) patients in the 1600 mg SC treatment sub-cohort and 9/23 (39%) patients in the 1870 mg SC treatment sub-cohort. Partial responses (PR) were recorded in 10/16 (63%) patients in the 1400 mg SC sub-cohort, 7/17 (41%) patients in the 1600 mg SC sub-cohort, and 13/23 (57%) patients in the 1870 mg SC sub-cohort.

Note: Repletion after 5 cycles of treatment at 3 months is not common, so it is unclear what this data offers to guide efficacy.

Part 2

Using the ITT analysis, the proportion of patients with a tumour response (CR/CRi/PR) at 3 months of follow up as reported by the investigator was similar in the rituximab IV (80.7%) and rituximab SC (85.2%) treatment arms. The difference in response rates was 4.55% (95% CI -7.2 to 16.3).

The CR/CRi rates were comparable in the two treatment groups at 3 months of follow up (33.0% in the rituximab IV arm versus 26.1% in the rituximab SC arm; difference: -6.82 [95% CI: -20.9; 7.3]).

At 3 months of follow up, 2.3% of patients in both the rituximab IV and rituximab SC treatment arms had progressed.

The results were similar in the per protocol dataset to the ITT dataset. The proportion of patients with a tumour response (CR/CRi/PR) at 3 months of follow up as reported by the investigator was similar in the rituximab IV (95.5%) and rituximab SC (96.7%) treatment arms. Complete responses (CR/CRi) were recorded in 24/67 (35.8%) patients in the rituximab IV arm and 19/60 (31.7%) patients in the rituximab SC arm.

Comment: The relationship of CR to patient relevant outcomes was not provided.

Table 3: Part 2: Summary of Tumor Response at 3 Months of Follow Up (ITT Population)

	Rituximab IV 500 mg/m2 (N=88)		Rituximab SC 1600 mg (N=88)
Responders$	71 (80.7 %)		75 (85.2 %)
Non-Responders	17 (19.3 %)		13 (14.8 %)
95% CI for Response Rates*	[70.9; 88.3]		[76.1; 91.9]
Difference in Response Rates		4.55	
95% CI for Difference in Response Rates#		[-7.2; 16.3]	
p-Value (Chi-squared Test)		0.4227	
Odds Ratio		1.38	
95% CI for Odds Ratio		[0.63;3.05]	
Complete Response (CR and CRi)	29 (33.0 %)		23 (26.1 %)
95% CI for CR and CRi Rates*	[23.3; 43.8]		[17.3; 36.6]
Difference in CR and CRi Rates		-6.82	
95% CI for Difference in CR and CRi Rates#		[-20.9; 7.3]	
p-Value (Chi-squared Test)		0.3216	
Odds Ratio		0.72	
95% CI for Odds Ratio		[0.38;1.38]	
Partial Response (PR)	42 (47.7 %)		52 (59.1 %)
95% CI for PR Rates*	[37.0; 58.6]		[48.1; 69.5]
Difference in PR Rates		11.36	
95% CI for Difference in PR Rates#		[-3.9; 26.7]	
p-Value (Chi-squared Test)		0.1308	
Odds Ratio		1.58	
95% CI for Odds Ratio		[0.87;2.87]	
Stable Disease (SD)	1 (1.1 %)		0 (0.0 %)
95% CI for SD Rates*	[0.0; 6.2]		[0.0; 4.1]
Progressive Disease (PD)	2 (2.3 %)		2 (2.3 %)
95% CI for PD Rates*	[0.3; 8.0]		[0.3; 8.0]
Not Evaluated/Missing (NE) &	14 (15.9 %)		11 (12.5 %)

Subgroup analyses of response rate at 3 months of follow-up

Response rate at 3 months of follow-up was analysed by the following BSA categories: low (≤1.81m^2), medium (1.81m2<BSA≤2.00m^2) and high (>2.00m^2), by gender and by C_{trough} on the ITT population.

Overall, subgroup analyses supported the analysis on the total ITT population and ORR was comparable between rituximab IV and rituximab SC in the subgroups explored. Numerical differences were observed in the low, medium and high BSA sub-groups (upper and lower 33rd percentiles) between the IV and the SC arms. A 5.71% difference in ORR was observed in the low BSA subgroup in favour of rituximab IV; the ORR for the medium and high BSA subgroup was higher (11.01% and 5.71%) in the rituximab SC arm. However, the ORR CIs were overlapping for all subgroups, and there were no apparent differences despite the variable point estimates.

A further exploratory analysis of response rates at the extremes of BSA based on the upper and lower 20th percentiles of BSA were limited by small numbers. Although numerical differences between both arms in each gender and between genders in each arm were observed, there were no apparent differences when taking into consideration the small patient numbers and slight imbalance between the arms with respect to gender. With respect to C_{trough}, the ORR was

numerically higher in the low C_{trough} subgroup (5.14% difference [95% CI: -8.9%; 19.2%]), in favour of the SC arm.

Comment: Caution should be applied in interpreting these results given the possibility of bias introduced by other baseline prognostic variables that could be associated with low BSA (for example,, comorbidities, patient's history, environment), the risk of false-positive findings resulting from multiple comparisons and small sample sizes within subgroups.

Table 4: Part 2: Subgroup Analyses of Response Rate at 3 Months of Follow-up (ITT Population)

	Response Rate (CR, CRi, PR) at 3 Months of Follow up [95% CI]		
Subgroup	**Rituximab IV N=88**	**Rituximab SC N=88**	**Difference [95% CI]**
***BSA** (low: BSA ≤1.81 m^2; medium: 1.81 m^2 <BSA ≤2.00 m^2; high: BSA >2.00 m^2)*			
Low	n=33 78.8% [61.1%; 91.0%]	n=26 73.1% [52.2%; 88.4%]	-5.71% [-30.1%; 18.6%]
Medium	n=29 79.3% [60.3%; 92.0%]	n=31 90.3% [74.2%; 98.0%]	11.01% [-9.1%; 31.1%]
High	n=26 84.6% [65.1%; 95.6%]	n=31 90.3% [74.2%; 98.0%]	5.71% [-13.9%; 25.3%]
***Gender** (male vs.female)*			
Male	n=53 81.1% [68.0%; 90.6%]	n=62 90.3% [80.1%; 96.4%]	9.19% [-4.7%; 23.1%]
Female	n=35 80.0% [63.1%; 91.6%]	n=26 73.1% [52.2%; 88.4%]	-6.92% [-30.8%; 17.0%]
***C_{Trough}** (low: C_{Trough} ≤ 88.75 µg/mL; high: C_{Trough} > 88.75 µg/mL)*			
Low	n = 43 90.7% [77.9%; 97.4%]	n = 24 95.8% [78.9%; 99.9%]	5.14% [-8.9%; 19.2%]
High	n = 26 96.2% [80.4%; 99.9%]	n = 41 95.1% [83.5%; 99.4%]	-1.03% [-13.0%; 11.0%]

Table 5: Part 2: Minimal Residual Disease at 3 Months of Follow-Up (ITT Population)

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

7.2. Indication 2: Reducing the dosing interval from 3 to 2 months in NHL

Efficacy data was not provided in BP22333.[3]

7.3. Analyses performed across trials

There were no efficacy pooled analyses or meta-analyses.

7.4. Evaluator's conclusions on treatment of CLL with 1600 mg

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 no consistent difference between the subcutaneous and the intravenous administration route.

The sponsor is requested to provide data to show the relationship of the efficacy surrogates to overall survival and progression free survival, in CLL.

7.5. Evaluator's conclusions on reducing the dosing interval in NHL

The simulations of PK for Cycle 2 in BP22333 showed accumulation of 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. Therefore even disregarding the concern regarding accumulation, efficacy has not been shown.

What was shown in Part 2 however and 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.[4]

8. Clinical safety

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data: BO 25341 and BP22333.[5]

[3] The PRIMA study (MO18264) evaluated the benefit of maintenance therapy with rituximab on progression-free survival as compared to no maintenance therapy (observation), after induction of response with chemotherapy plus rituximab in previously untreated patients with high-tumour-burden follicular lymphoma.
[4] The sponsor stated that Study BP22333 was not intended to support the change in dosing frequency. The final report from this study was provided to fulfil a post-approval commitment related to rituximab SC 1400 mg registration and together with the updated report form Study BO22334 (SABRINA), make minor changes to the PI.
[5]The sponsor stated that Study BP22333 was not intended to provide evaluable safety data for the submission related to treatment of CLL with subcutaneous rituximab 1600 mg, which was based primarily on Study BO25341. Studies BP22333 (SparkThera) and BO22334(SABRINA) provided data in NHL and were provided to support PI updates and to fulfil a TGA commitment.

8.1.1. BO 25341

Recording of Adverse Events (AE)

AEs were summarised using descriptive statistics in three ways:

- AEs recorded during all cycles.
- AEs recorded during Cycle 5 only, which included all events reported between the time of administration of the Cycle 5 infusion and the Cycle 6 injection, or administration of Cycle 5 + 28 days if Cycle 6 was not administered
- AEs recorded during Cycle 6 only, which included all new events from the administration of the Cycle 6 SC injection + 28 days

During Part 1, AEs (all-grades) were reported in 59/64 patients (92%) patients across the rituximab dosing sub-cohorts. Grade ≥ 3 AEs were reported in 40 patients (63%) and SAEs in 20 patients (31%). Four patients who did not receive an SC dose were withdrawn from treatment prior to Cycle 5. There were no treatment-related deaths. During Cycle 5 of Part 1, where the safety data were restricted to a single cycle of rituximab IV treatment, 30 patients (47%) across the rituximab dosing sub-cohorts experienced at least one AE. Grade ≥3 AEs were experienced by 18 patients (28%) and two patients experienced a serious adverse event. During Cycle 6, between the SC dose sub-cohorts the number of patients who experienced at least one AE (of any grade) increased with increasing doses.

Comment: Although this has implications for safety, the dose chosen for the requested indication is 1600 mg, and proportionate AE increase with increased doses is not uncommon.

8.1.1.1. *Adverse events of special interest*

Administration-related reactions (ARR) overall

Part 1

By preferred term, the most frequently reported ARRs were chills, experienced by 1, 4 and 1 patient in the 1400, 1600 mg and 1870 mg sub-cohort respectively, pyrexia (0, 5, 0 patients, respectively), nausea (2, 2, 0 patients, respectively), injection site erythema (0, 2, 2 patients, respectively), injection site pain (0, 2, 2 patients, respectively), and vomiting (1, 2, 0 patients, respectively).

ARRs during Cycle 5: nausea in 12% and abdominal pain in 1 patient (6%). One patient had nausea and abdominal pain, both assessed with a severity of CTC Grade 3. The other event of nausea was of Grade 1 severity.

ARRs during Cycle 6 were experienced by 2 patients (13%), 5 patients (29%) and 5 patients (23%) in the rituximab SC 1400 mg, 1600 mg and 1870 mg sub-cohorts, respectively. The majority of events (10/14 events) were related to the injection site (that is, injection site pain, erythema, discoloration and oedema – all seen in 1600 mg and 1870 mg sub-cohorts). Other ARRs included erythema (1 patient in each of the rituximab 1400 mg [6%] and 1870 mg [5%] SC sub-cohorts), abdominal pain (1 patient [6%] in the rituximab SC 1400 mg sub-cohort) and nausea (1 patient [6%] in the rituximab SC 1600 mg sub-cohort). All of these events were assessed with a CTC Grade of 1.

Part 2

The most frequently occurring ARR events were in the SOCs of general disorders and administration site conditions (15% in the rituximab IV arm versus 31% in the rituximab SC arm). This was followed by gastrointestinal disorders (16 patients [18%] and 7 patients [8%], respectively), and vascular disorders (14 patients [16%] and 4 patients [5%], respectively).

The incidence of individual ARRs was similar between the arms except for injection site erythema which was only reported in the rituximab SC arm (0% IV versus 12% SC) and nausea, which was only reported in the rituximab IV arm (5% IV versus 0% SC). During Cycle 2-6, four patients (5%) in the rituximab SC arm reported 4 ARR events of Grade ≥ 3 intensity: injection site erythema, anxiety, thrombocytopenia, and urticaria-these latter two events of thrombocytopenia and urticaria led to withdrawal of the patients from study treatment.

Local cutaneous reactions

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%]). Most common AEs in the administration site reactions were local cutaneous reactions in the rituximab SC arm: injection site erythema (26% [22 patients]), injection site pain (16% [14 patients]), injection site swelling (5% [4 patients]) and injection site bruising (4% [3 patients]) Other local cutaneous reactions in the rituximab SC arm were reported with ≤ 2% incidence. In the rituximab IV arm, reported events were local to the site of administration and were coded as follows: injection site swelling and infusion site swelling.

In terms of intensity, Grade 1 was reported in (25% [21 patients]), Grade 2 (15% [13 patients]). Two patients (2%) reported local cutaneous reactions of Grade 3 intensity following first rituximab SC administration: 1 patient experienced injection site erythema, injection site pain, and injection site swelling at Cycle 2 while the other patient experienced injection site erythema during Cycle 2 and Cycle 3. Two patients (2%) in the rituximab IV arm reported AE of Grade 2 intensity (injection site swelling and infusion site swelling).

Infections and infestations

These were similar between the IV and SC groups.

Neutropenia

Neutropenia was reported by 52/89 patients (58%) in the rituximab IV arm and 55/85 patients (65%) in the rituximab SC arm.

Febrile neutropenia

This was reported in 8% (7/89) of patients in the IV arm and 11% (9/85) of patients in the rituximab SC arm. During Cycles 2 to 6, the incidence of febrile neutropenia was 2% (2/84 patients) in the rituximab IV arm and 6% (5/85 patients) in the rituximab SC arm.

Age and gender

No clear difference in AEs between the two groups in age. Grade ≥ 3 AEs were experienced by a higher percentage of female patients than male patients: 42% of females versus 26% of males in the rituximab IV arm and 36% of females versus 27% of males in the rituximab SC arm, respectively.

AEs by BSA and AUC

No clear pattern was observed although in both in Cycle 1 and Cycles 2-6, there was a trend towards a higher incidence of Grade ≥ 3 AEs with lower BSA in both IV and SC treatment arms.

Comment: A higher incidence of AEs in females and a trend towards a higher incidence of Grade ≥ 3 AEs in patients with lower BSA were reported. Whether this may be due to an exposure issue was not discussed.

Table 6: Part 1: Overview of Adverse Events (Safety Analysis Population)

No. of Pts (%) experiencing:	Rituximab SC 1400 mg N=16	Rituximab SC 1600 mg N=17	Rituximab SC 1870 mg N=22	Rituximab SC 1000 mg N=1	No Rituximab SC received N=8
All cycles (all events up until the clinical data cutoff date)					
AEs (all grades)	13 (81)	16 (94)	21 (95)	1	8
Grade ≥3 AEs	11 (69)	12 (71)	10 (45)	1	6
SAEs	5 (31)	7 (41)	4 (18)	1	3
AEs leading to withdrawal	-	-	-	-	4
Cycle 5 (during single cycle administration of rituximab IV)					
AEs (all grades)	7 (44)	7 (41)	13 (59)	1	2
Grade ≥3 AEs	5 (31)	5 (29)	5 (23)	1	2
SAEs	-	1 (6)	1 (5)	-	-
AEs leading to withdrawal	-	-	-	-	-
Cycle 6 (during single cycle administration of rituximab SC)					
AEs (all grades)	7 (44)	10 (59)	19 (86)	1	N/A
Grade ≥3 AEs	3 (19)	4 (24)	3 (14)	1	N/A
SAEs	-	2 (12)	-	-	N/A
AEs leading to withdrawal	-	-	-	-	N/A

8.1.2. Study BP22333

The PK of study has been discussed in Section 4, Pharmacokinetics.

8.1.2.1. *Safety*

Stage 1 (dose finding)

Stage 1, AEs were experienced by 14/16 patients (88%) in the rituximab IV 375 mg/mg^2 group (Cohort A), 23/34 patients (68%) in the rituximab SC 375 mg/m^2 group (Cohort B), 26/34 patients (76%) in the rituximab SC 625 mg/m^2 group (Cohort C), and 30/40 patients (75%) in the rituximab SC 800 mg/m^2 group (Cohort D). Serious AEs were experienced by 3/16 patients (19%), 5/34 patients (15%), 5/34 patients (15%), and 4/40 patients (10%) in Cohorts A to D, respectively.

AEs leading to withdrawal from treatment were experienced by 1 patient (3%) in each of the three rituximab SC cohorts (B – D). Each of these events was considered serious, but not assessed as related to study treatment.

AEs leading to dose modification or interruption were experienced by 3/16 patients (19%), 6/34 patients (18%), 3/34 patients (9%), and 4/40 patients (10%) in Cohorts A to D, respectively.

Three patients experienced SAEs leading to dose modification/interruption, of which one was assessed to be related to study drug.

Table 7: Summary of reported AEs in Cohorts A to D

	Cohort A RITUXIMAB IV 375 MG/M2 N = 16 No. (%)	Cohort B RITUXIMAB SC 375 MG/M2 N = 34 No. (%)	Cohort C RITUXIMAB SC 625 MG/M2 N = 34 No. (%)	Cohort D RITUXIMAB SC 800 MG/M2 N = 40 No. (%)
Total Pts with at Least one AE	14 (88)	23 (68)	26 (76)	30 (75)
Total Number of AEs	85	116	107	113
Patients with at least one				
AE leading to Death	0 (0)	0 (0)	0 (0)	0 (0)
Serious AE	3 (19)	5 (15)	5 (15)	4 (10)
Serious AE leading to withdrawal from treatment	0 (0)	1 (3)	1 (3)	1 (3)
Serious AE leading to dose modification/interruption	0 (0)	2 (6)	0 (0)	1 (3)
Related serious AE	0 (0)	1 (3)	1 (3)	1 (3)
AE leading to withdrawal from treatment	0 (0)	1 (3)	1 (3)	1 (3)
AE leading to dose modification/interruption	3 (19)	6 (18)	3 (9)	4 (10)
Related AE	6 (38)	14 (41)	14 (41)	17 (43)
Related AE leading to withdrawal from treatment	0 (0)	0 (0)	0 (0)	0 (0)
Related AE leading to dose modification/interruption	2 (13)	4 (12)	2 (6)	0 (0)
Severe AE	4 (25)	9 (26)	5 (15)	8 (20)

Comment: Can the sponsor elucidate how the dose of those patients relates to AEs?

Stage 2 (dose confirmation)

Administration reactions (ARRs) were reported more frequently among patients in the rituximab SC than the IV group.

Table 8: Administration Reactions

Body System/ Adverse Event	RITUXIMAB IV 375 MG/M2 N = 77 No. (%)	RITUXIMAB SC 1400 MG N = 77 No. (%)	Total N = 154 No. (%)
ALL BODY SYSTEMS			
Total Pts with at Least one AE	4 (5)	26 (34)	30 (19)
Total Number of AEs	7	49	56
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Total Pts With at Least one AE	2 (3)	14 (18)	16 (10)
INJECTION SITE ERYTHEMA	-	4 (5)	4 (3)
PAIN	-	3 (4)	3 (2)
SWELLING	-	3 (4)	3 (2)
CHILLS	1 (1)	1 (1)	2 (1)
FATIGUE	1 (1)	-	1 (<1)
INFLUENZA LIKE ILLNESS	1 (1)	-	1 (<1)
INJECTION SITE OEDEMA	-	1 (1)	1 (<1)
INJECTION SITE PAIN	-	1 (1)	1 (<1)
INJECTION SITE REACTION	-	1 (1)	1 (<1)
LOCALISED OEDEMA	-	1 (1)	1 (<1)
OEDEMA	-	1 (1)	1 (<1)
Total Number of AEs	3	16	19
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Total Pts With at Least one AE	-	14 (18)	14 (9)
ERYTHEMA	-	10 (13)	10 (6)
RASH	-	3 (4)	3 (2)
URTICARIA	-	1 (1)	1 (<1)
Total Number of AEs	-	14	14
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
Total Pts With at Least one AE	-	6 (8)	6 (4)
MYALGIA	-	5 (6)	5 (3)
PAIN IN EXTREMITY	-	1 (1)	1 (<1)
Total Number of AEs	-	6	6
VASCULAR DISORDERS			
Total Pts With at Least one AE	1 (1)	4 (5)	5 (3)
HYPERAEMIA	-	2 (3)	2 (1)
HAEMATOMA	-	1 (1)	1 (<1)
HOT FLUSH	-	1 (1)	1 (<1)
HYPERTENSION	1 (1)	-	1 (<1)
Total Number of AEs	1	4	5
NERVOUS SYSTEM DISORDERS			
Total Pts With at Least one AE	-	4 (5)	4 (3)
DIZZINESS	-	2 (3)	2 (1)
LETHARGY	-	2 (3)	2 (1)
Total Number of AEs	-	4	4
IMMUNE SYSTEM DISORDERS			
Total Pts With at Least one AE	1 (1)	2 (3)	3 (2)
HYPERSENSITIVITY	1 (1)	2 (3)	3 (2)
Total Number of AEs	1	2	3
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Total Pts With at Least one AE	-	1 (1)	1 (<1)
LYMPHADENOPATHY	-	1 (1)	1 (<1)
Total Number of AEs	-	1	1
EYE DISORDERS			
Total Pts With at Least one AE	1 (1)	-	1 (<1)
EYE IRRITATION	1 (1)	-	1 (<1)
Total Number of AEs	1	-	1
GASTROINTESTINAL DISORDERS			
Total Pts With at Least one AE	-	1 (1)	1 (<1)
ABDOMINAL PAIN	-	1 (1)	1 (<1)
Total Number of AEs	-	1	1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
Total Pts With at Least one AE	-	1 (1)	1 (<1)
CONTUSION	-	1 (1)	1 (<1)
Total Number of AEs	-	1	1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Total Pts With at Least one AE	1 (1)	-	1 (<1)
DYSPNOEA	1 (1)	-	1 (<1)
Total Number of AEs	1	-	1

AEs were experienced by 83% of patients in the rituximab IV 375 mg/mg^2 group (Cohort E) and 88% of patients in the rituximab SC 1400 mg group (Cohort F). Serious AEs were experienced by 19% and 16% of patients in the IV and SC cohorts, respectively.

AEs leading to withdrawal from treatment were experienced by 5 patients (6%) and 4 patients (5%) in the IV and SC cohorts, respectively. For four of these patients (2 patients in each group), the AE leading to withdrawal was considered serious.

AEs leading to dose modification or interruption were experienced by 9% and 12% of patients in the IV and SC cohorts, respectively. For three of these patients, all in the SC cohort, the AE

leading to dose modification/interruption was considered serious and in two cases were assessed to be related to study drug.

There was markedly increased incidence between treatment groups in terms of related AEs (29% IV versus 52% SC), primarily due to a higher incidence of ARRs in the rituximab SC group.

8.1.2.2. *Immunogenicity*

No patients in Stage 1 had positive responses for anti-rituximab antibodies. In Stage 2, the overall prevalence of anti-rituximab antibodies at baseline was < 1% based on 153 evaluable patients (0% in the IV cohort and 1/77 patients [1%] in the SC cohort). Following study drug administration, 3/77 patients in the rituximab IV group and 1/77 patients in the rituximab SC group were considered to be positive for anti-rituximab antibodies, giving a post-baseline incidence of anti-rituximab antibodies of 4% and 1%, respectively.

All of the confirmed-positive samples (anti- rHuPH20 antibodies) across both stages were negative for the presence of neutralizing antibodies.

8.2. Pivotal studies that assessed safety as a primary outcome

There were no studies that assessed safety as a primary outcome.

8.3. Dose-response and non-pivotal efficacy studies

The two dose-response studies were the BO25341 study which used three SC cohorts in the first part of the Phase Ib study, and the Phase Ib BP22333 study which had 4 cohorts in the first phase.

8.4. Pivotal studies that assessed safety as a primary outcome

Not applicable.

8.5. Patient exposure

8.5.1. Part 1

Median treatment duration 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.

8.5.2. 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 9: 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)

8.6. Adverse events

8.6.1. All adverse events (irrespective of relationship to study treatment)

8.6.1.1. *Pivotal studies*

Not applicable.

8.6.1.2. *BO25341*

Part 1: Dose modifications and interruptions (including for AEs)

AEs caused delays during Cycle 5, 4 patients in the 1400 mg SC sub-cohort and 7 patients in the 1600 mg SC sub-cohort, all due to AEs. In addition, the infusion was interrupted (stopped and re-started) in 1 patient in the 1600 mg SC sub-cohort. During Cycle 6, administration of the rituximab SC dose was delayed for 5 patients in each of the 1400 mg, 1600 mg and 1870 mg SC sub-cohorts. In addition, the SC injection was interrupted (stopped and re-started) for 2 patients in the 1870 mg SC sub-cohort. The most common reason for dose delay/interruption was AEs - reported for 5 patients in the 1400 mg SC sub-cohort, 4 patients in the 1600 mg SC sub-cohort and 7 patients in the 1870 mg SC sub-cohort.

Part 1: Adverse events

AEs were reported by 10 patients [63%], 12 patients [71%], and 16 patients [73%] for the 1400 mg, 1600 mg and 1870 mg rituximab SC sub-cohorts, respectively.

The most common AEs occurred in the SOC of blood and lymphatic disorders - 10 patients (63%), 12 patients (71%), and 12 patients (55%) in the 1400 mg, 1600 mg and 1870 mg SC sub-cohorts, respectively. Other SOCs for which AEs were commonly reported, in the 1400 mg, 1600 mg and 1870 mg SC sub-cohorts, respectively, included:

- Gastrointestinal disorders (5 patients [31%], 10 patients [59%], and 10 patients [45%])
- Infections and infestations (8 patients [50%], 8 patients [47%], and 9 patients [41%]), and general disorders
- Administration site conditions (3 patients [19%], 9 patients [53%], and 8 patients [36%])

Using preferred term, the AEs most commonly considered related to study drug included neutropenia (6 patients versus 4 patients versus 5 patients in the 1400 mg, 1600 mg and 1870 mg sub-cohorts, respectively), chills (1, 4 and 1 patient), leukopenia (2, 4 and 0 patients), pyrexia (1, 5 and 0 patients), injection site erythema (0, 2 and 4 patients), and injection site pain (0, 3, 3 patients).

Part 2: Adverse events

In Phase II, the incidence of adverse events in the two treatment arms was similar (91% IV versus 96% SC) and the common events (adverse events with an incidence of at least 20% in any treatment arm) by SOC were (IV versus SC):

- Blood and lymphatic system disorders (70% versus 75%)
- General disorders and administration site conditions (48% versus 71%)
- Gastrointestinal disorders (56% versus 56%)
- Infections and infestations (49% versus 56%)
- Skin and subcutaneous tissue disorders (30% versus 44%)
- Musculoskeletal and connective tissue disorder (22% versus 32%)
- Respiratory, thoracic and mediastinal disorders (22% versus 27%)

There was higher incidence of general disorders and administration site conditions, skin and subcutaneous tissue disorders and musculoskeletal and connective tissue disorders in the rituximab SC arm compared with the rituximab IV arm.

By preferred term, the higher incidence of AE reporting in the SC arm versus the IV arm in the SOC of general disorders and administration site conditions was driven by injection site erythema (0% IV versus 26% SC) and injection site pain (0% IV versus 16% SC), in the SOC skin and subcutaneous tissue disorders by AEs such as erythema (7% IV versus 15% SC), and in the SOC of musculoskeletal and connective tissue disorders by AEs such as arthralgia (1% IV versus 9% SC), pain in extremity (2% IV versus 7% SC) and bone pain (2% IV versus 6% SC).

8.6.2. Treatment-related adverse events (adverse drug reactions)

8.6.2.1. *Pivotal studies*

Not applicable.

8.6.2.2. *Other studies*

In Part II, treatment-related AEs were reported more in the SC (79%) than in the IV (58%) arms. Overall, 190 versus 234 events in the rituximab IV vs SC arm were considered related to study drug.

AEs most commonly considered related to study drug included (IV versus SC) general disorders and administration site conditions (20 [22%] versus 46 patients [54%], respectively), blood and lymphatic system disorders (27 [30%] versus 25 patients [29%]), gastrointestinal disorders (23 [26%] versus 13 patients [15%]) and skin and subcutaneous tissue disorders (8 [9%] versus 22 patients [26%]). There were sizeable increases in the rate AEs in the rituximab SC arm: injection site erythema/pain, and erythema, compared to the IV arm.

8.6.3. Adverse events by intensity

Adverse events were graded on a five-point intensity scale (Grade 1 to 5) according to NCI CTCAE version 4. Grade 3 - 5 AEs were defined as severe adverse events.

In Part 1, three Grade 5 events were reported, two in the 1400 mg SC sub-cohort (gastric adenocarcinoma, cardiac failure) and one in the 1870 mg SC sub-cohort (metastases to peritoneum) . Overall 64%, 75% and 83% of events in the 1400 mg, 1600 mg and 1870 mg rituximab SC sub-cohort were CTC Grade 1 or 2 events.

In terms of gender, Grade ≥ 3 AEs were experienced by 6 females and 5 males in the 1400 mg SC sub-cohort, 2 females and 10 males in the 1600 mg SC sub-cohort and 1 female and 9 males in the 1870 mg SC sub-cohort. Neutropenia was the only Grade ≥ 3 AE reported in more than one female patient in any SC sub-cohort (reported in 2 female patients in the 1400 mg SC sub-

cohort, 1 female patient in the 1600 mg SC sub-cohort and 1 female patient who received 1000 mg SC rituximab). In male patients, Grade ≥ 3 neutropenia was reported by 5, 6 and 7 male patients in the 1400, 1600 and 1870 mg SC sub-cohorts, respectively and Grade ≥ 3 leukopenia was reported in 2 patients in the 1400 mg SC sub-cohort and 4 patients in the 1600 mg SC sub-cohort.

Comment: More men than women reported SAEs.

Table 10: Part 2: Adverse Events with an Incidence ≥ 5% during Cycle 1 versus Cycles 2 – 6 (Safety Analysis Population)

	Cycle 1		Cycles 2–6	
Preferred Term	Rituximab IV N=84	Rituximab SC N=85	Rituximab IV N=84	Rituximab SC N=85
Nausea	23 (26%)	20 (24%)	18 (21%)	21 (25%)
Neutropenia	21 (24%)	16 (19%)	43 (51%)	51 (60%)
Pyrexia	11 (12%)	8 (9%)	13 (15%)	21 (25%)
Vomiting	11 (12%)	8 (9%)	11 (13%)	12 (14%)
Thrombocytopenia	8 (9%)	4 (5%)	16 (19%)	19 (22%)
Headache	6 (7%)	2 (2%)	3 (4%)	5 (6%)
Chills	5 (6%)	9 (11%)	4 (5%)	6 (7%)
Constipation	5 (6%)	3 (4%)	2 (2%)	5 (6%)
Leukopenia	5 (6%)	7 (8%)	8 (10%)	14 (16%)
Anaemia	5 (6%)	5 (6%)	12 (14%)	7 (8%)
Asthenia	5 (6%)	1 (1%)	11 (13%)	4 (5%)
Abdominal pain	4 (4%)	-	1 (1%)	8 (9%)
Erythema	4 (4%)	4 (5%)	3 (4%)	12 (14%)
Diarrhoea	4 (4%)	3 (4%)	5 (6%)	6 (7%)
Cough	3 (3%)	1 (1%)	6 (7%)	8 (9%)
Fatigue	3 (3%)	3 (4%)	6 (7%)	5 (6%)
Pruritus	2 (2%)	2 (2%)	3 (4%)	5 (6%)
Rash	2 (2%)	2 (2%)	7 (8%)	8 (9%)
Febrile neutropenia	1 (1%)	3 (4%)	2 (2%)	5 (6%)
Insomnia	1 (1%)	1 (1%)	4 (5%)	-
Nasopharyngitis	1 (1%)	1 (1%)	3 (4%)	4 (5%)
Upper respiratory tract infection	1 (1%)	1 (1%)	6 (7%)	7 (8%)
Arthralgia	-	2 (2%)	1 (1%)	6 (7%)
Bone pain	-	1 (1%)	2 (2%)	5 (6%)
Dizziness	-	1 (1%)	3 (4%)	4 (5%)
Hyperuricaemia	-	-	2 (2%)	4 (5%)
Injection site erythema	-	-	-	22 (26%)
Injection site pain	-	-	-	14 (16%)
Injection site swelling	-	-	1 (1%)	4 (5%)
Respiratory tract infection	-	-	3 (4%)	6 (7%)
Urinary tract infection	-	-	5 (6%)	2 (2%)

In Part II it can be seen that there were increased incidence of neutropenia, injection site pain and swelling and general erythema, abdominal pain, general erythema, pyrexia, febrile neutropenia, arthralgia, bone pain, respiratory tract infection in the SC group compared to IV.

8.6.4. Deaths and other serious adverse events

8.6.4.1. *Study BO25341*

Part 1: Deaths

At study snapshot (May 7, 2014), 2 patients in the 1400 mg SC sub-cohort (adenocarcinoma gastric and cardiac failure) and 2 patients in the 1870 mg sub-cohort had died (metastases to the peritoneum and one patient died due to disease progression). An additional patient who received 1000 mg SC rituximab in error (205910/1271) during Cycle 6 died as a result of bone marrow failure.

Part 1: Serious adverse events

All SC treatment sub-cohorts had patients experiencing at least one SAE (5 patients [31%], 7 patients [41%] and 4 patients [18%] for the 1400 mg, 1600 mg and 1870 mg rituximab SC sub-cohorts, respectively). By SOC, the most frequently reported AEs were:

- Blood and lymphatic system disorders (1 patient [6%], 2 patients [12%] and 2 patients [9%], respectively).
- Infections and infestations (2 patients [13%], 3 patients [18%] and 1 patient [5%], respectively).

Comment: The numbers and percentages do not appear to be consistent for example, 2 patients is [12%] and 2 patients is then [9%].[6]

By preferred term, febrile neutropenia was experienced by 0 patients in the 1400 mg, 1 patient in the 1600 mg and 2 patients in the 1870 mg SC sub-cohort. Pneumonia was reported for 1 patient in each of the three rituximab SC sub-cohorts, all remaining SAEs were each reported for single patients.

In Cycle 5, one patient in the rituximab SC 1600 mg sub-cohort experienced an SAE of upper respiratory tract infection (CTC Grade 2) and 1 patient (5%) in the rituximab SC 1870 mg sub-cohort experienced an SAE of febrile neutropenia (CTC Grade 3). Both events were considered related to study treatment by the investigator.

In Cycle 6, two patients (12%), both in the rituximab SC 1600 mg sub-cohort experienced an SAE - serious diarrhoea (CTC Grade 3, unrelated) and 1 serious cholecystitis (CTC Grade 3, unrelated).

Table 11: Part 2: Deaths

Treatment Group CRTN/Pt. No.	Age yr	Sex	Weight kg	Race	Cause of Death	Last Trt Cycle	Day of Death	Date of Death	Relation to Trial Treatment	Autopsy
Rituximab IV 500 mg/m2										
[redacted]	61	F	92	WHITE	DIARRHOEA	CYCLE 6	292	07FEB2014	UNRELATED	NO
	69	M	64	WHITE	***DISEASE PROGRESSION	CYCLE 6	354	04APR2014		UNK
	59	M	68	WHITE	LISTERIOSIS	CYCLE 4	137	18MAY2013	UNRELATED	NO
	55	M	88	WHITE	***DISEASE PROGRESSION	CYCLE 6	335	08MAR2014		NO
Rituximab SC 1600 mg										
[redacted]	48	M	80	WHITE	***DISEASE PROGRESSION	CYCLE 6	526	09APR2014		NO
	50	M	69	WHITE	PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY	CYCLE 2	443	22JAN2014	RELATED	UNK
	74	F	107	WHITE	HERPES ZOSTER	CYCLE 5	533	15APR2014	RELATED	NO
	58	M	75	WHITE	***DISEASE PROGRESSION	CYCLE 6	371	13JAN2014		NO
	60	M	70	WHITE	***DISEASE PROGRESSION	CYCLE 6	318	12FEB2014		NO

Part 2: SAE

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 anaemia (3 patients [3%] and 0 patients).

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). There is a numerical increase in SAEs in the SC arm in the febrile neutropenia category.

8.6.5. Discontinuation due to adverse events

8.6.5.1. *Pivotal studies*

N/A

[6] See Question 15 Sponsor response below for clarification.

8.6.5.2. ***Other studies***

Part 1

Four patients who never received rituximab SC were withdrawn from the study prior to Cycle 5 due to AEs (3 patients due to neutropenia, and 1 patient due to Guillain–Barre Syndrome). Narratives for patients withdrawing from study treatment due to AEs were provided.

Part 2

Table 12: Part 2: Adverse Events Leading to Treatment Discontinuation (Safety Analysis Population)

Body System/ Adverse Event	Rituximab IV 500 mg/m2 N = 89 No. (%)	Rituximab SC 1600 mg N = 85 No. (%)	Total N = 174 No. (%)
ALL BODY SYSTEMS			
Total Pts with at Least one AE	7 (8)	9 (11)	16 (9)
Total Number of AEs	7	9	16
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Total Pts With at Least one AE	6 (7)	6 (7)	12 (7)
NEUTROPENIA	3 (3)	1 (1)	4 (2)
THROMBOCYTOPENIA	1 (1)	2 (2)	3 (2)
ANAEMIA	-	1 (1)	1 (<1)
FEBRILE NEUTROPENIA	1 (1)	-	1 (<1)
HAEMATOTOXICITY	-	1 (1)	1 (<1)
HAEMOLYTIC ANAEMIA	-	1 (1)	1 (<1)
PANCYTOPENIA	1 (1)	-	1 (<1)
Total Number of AEs	6	6	12
INFECTIONS AND INFESTATIONS			
Total Pts With at Least one AE	-	2 (2)	2 (1)
CYTOMEGALOVIRUS INFECTION	-	1 (1)	1 (<1)
MENINGITIS	-	1 (1)	1 (<1)
Total Number of AEs	-	2	2
RENAL AND URINARY DISORDERS			
Total Pts With at Least one AE	1 (1)	-	1 (<1)
RENAL FAILURE ACUTE	1 (1)	-	1 (<1)
Total Number of AEs	1	-	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Total Pts With at Least one AE	-	1 (1)	1 (<1)
URTICARIA	-	1 (1)	1 (<1)
Total Number of AEs	-	1	1

8.7. Laboratory tests

8.7.1. Liver function

8.7.1.1. ***Pivotal studies***

N/A

8.7.1.2. ***Other studies***

Nil obvious differences in the two groups and nil events of clinical significance

8.7.2. Kidney function

8.7.2.1. ***Pivotal studies***

N/A

8.7.2.2. ***Other studies***

There were no obvious differences in the two groups; nil events of clinical significance.

8.7.3. Other clinical chemistry

8.7.3.1. *Pivotal studies*

N/A

8.7.3.2. *BO25341*

There were some changes in chemistry parameters in both rituximab treatment sub-cohorts however there were no new trends or patterns.

8.7.4. Haematology

8.7.4.1. *BO25341*

There were some changes in haematology parameters including mean and median coagulation parameters in both rituximab treatment sub-cohorts however there were no new trends or patterns.

8.7.5. Electrocardiograph

8.7.5.1. *Pivotal studies*

N/A

8.7.5.2. *BO25341*

Clinically significant ECG abnormalities were not observed in any rituximab SC sub-cohorts in Part I. Similarly, in Part II at the follow up 28 day assessment, 1 patient in the rituximab SC arm had a clinically significant ECG abnormality which was later judged to be not clinically significant.

8.7.6. Other

8.7.6.1. *Anti-rituximab antibodies (HACAs)*

The incidence of HACA was low; 3 of the 61 patients tested, one in each SC dose, who was negative for HACA at pre-dose Cycle 5 had a positive result for HACA post Cycle 5 (treatment-induced HACA). All 3 patients were responders at the 3-month follow-up visit and experienced similar AEs compared with the overall population. However, one of the patients died due to an AE (cardiac failure); this was considered unrelated to study treatment by the investigator. Given the limited number of patients with positive HACA results, no definitive conclusion on the incidence of HACA positivity, the comparative frequency in the SC versus the IV group and the clinical consequences of developing these from the two different administration routes can be made.

Comment: was the information on the relative frequency in incidence (using existing IV data) available.[7]

8.7.6.2. *Anti-rHuPH20 antibodies (HAHAs)*

At baseline (pre-SC dose Cycle 6), 5/56 (9%) patients had positive results for HAHAs and 4 had positive responses at subsequent time points. Post-SC dose Cycle 6, one of the 5 patients became HAHA-negative and was considered to have a treatment-unaffected response. A further 2 patients who were baseline-negative for HAHA became positive and were considered to have a treatment-induced response.

[7] The sponsor stated that sensitivities of the newer assay developed for the rituximab SC clinical development program and the older assay used in the earlier rituximab IV studies cannot be directly compared, as they are dependent on the method and the positive control.

None of the patients with positive HAHA samples had neutralizing antibodies. All patients with positive HAHAs samples were responders at the 3-month follow-up visit, with the exception of one patient who had stable disease. The AE profile of these patients was similar to that of the overall population. One patient died due to bone marrow failure, 336 days after their last study treatment (Cycle 6). The cause of death was considered unrelated to trial treatment by the investigator.

In Part 2 the incidence between the two groups (IV and SC) was similar although the numbers were small and the clinical outcomes of development across the two routes are unknown.

8.7.7. Vital signs

8.7.7.1. *Pivotal studies*

Not applicable.

8.7.7.2. *Other studies*

In Part 1, ECOG scores were low at screening, with all patients having an ECOG PS score of 0 or 1. ECOG PS scores remained low throughout Cycle 5 and Cycle 6 of the study and no patient had an ECOG PS score >1. There was no evidence of clinically relevant differences between the SC treatment sub- cohorts over time for any vital sign parameter.

In Part 2 the ECOG performance scores in both treatments remained low throughout the study. There was no evidence of clinically relevant differences between the rituximab IV and SC treatment groups over time for any vital sign parameter.

8.8. Post-marketing experience

This was summarised in the 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 global safety database cut-off date (28 July 2014) and clinical database cut-off date (31 July 2014). The data included is now from interventional clinical trials. Moved table for 'reports of medication error with the marketed product' to Section SV.4.4 (not track changed).

8.9. Evaluator's overall conclusions on clinical safety

In the BO study, the SC increasing dose sub-cohorts showed that the number of patients who experienced at least one 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 (PML and Herpes Zoster). There is a numerical increase in 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, respiratory tract infection in the SC group compared to IV.

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 ARR was seen.

9. First round benefit-risk assessment

9.1. 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.

There has been no benefit demonstrated in the request to move the therapy from 3 to 2 months.

9.2. 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%]).

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

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

9.3. First round assessment of benefit-risk balance

Overall, the subcutaneous route appears to have a similar effect on some of the surrogates of efficacy (such as tumour response) - however, whether or not this translates into as good as, better or worse PFS or OS is unknown.

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 (F and C) 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.

The evidence to support the request to shorten dosing from 3 to 2 months in NHL was noted based on on PRIMA trial and the PK bridging program for NHL as well as simulation data (which was not verified clinically). Further the simulations suggested accumulation may be an issue with 2 monthly dosing of this drug.

10. First round recommendation regarding authorisation

- Unfavourable in the 1600 mg dose for CLL.
- Lack of data to support shortening the course of therapy (the evaluator notes the TGA letter recommending the sponsor submit this data however).[8]

[8]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).

- Unfavourable for the reduction of dosing interval for NHL maintenance from 3 to 2 months.

11. Clinical questions

11.1. Additional expert input

Additional advice was provided regarding the relationship of patients in the PK study to the likely patient population receiving this drug if registered in Australia.

11.2. 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.
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.
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 this 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 on C_{max} and AUC (safety and efficacy) was not clear.
14. Evidence to show the relationship of SC to IV in term of convenience – please provide.
15. The numbers and percentages do not appear to be consistent for example, 2 patients is [12%] and 2 patients is then [9%] in the Safety data.

16. Can the sponsor please provide information on the relative frequency in incidence of HAHA and HACA 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 M117102 were not able to be located.
19. Can the sponsor please add incidence and clinical relevance of HAHA and HACA antibodies to the RMP?

12. Second round evaluation of clinical data submitted in response to questions

12.1. Responses to TGA's request for further information

Type F- New Strength: MabThera SC 1600mg/13.4mL, solution for injection, vial for use in patients with Chronic Lymphocytic Leukaemia (Provisional AUST R 235147).

This application to register an additional strength of rituximab (1600 mg) for subcutaneous injection for the treatment of CLL is based on clinical data from the two-part rituximab SC Study BO25341/SAWYER provided in the submission.

12.1.1. Evaluation of response

The sponsor states the development program for rituximab SC was based on the assumption that serum rituximab levels at least as high as those after IV infusion would result in at least the same degree of target-site saturation and would therefore result in at least the same degree of efficacy, regardless of the route of administration. This statement in itself has at least 3 assumptions which have not been tested, but clarifies the sponsor choice of primary endpoint in the study (Cmin). However, due to the relatively lower bioavailability from SC (70%) versus 100% IV, and slow rate of absorption into the vascular compartment compared to an IV infusion, it is expected that SC will have higher trough, lower peak, longer time to T_{max}, for example. If levels at least as high are needed from a SC injection, AUC may thus well be the most appropriate comparator. In addition, C_{max} of the SC version had previously been shown to be lower, expected from a SC preparation, which also suggests that a one off concentration is not the most appropriate endpoint. Of importance also is the fact that the degree of target-site saturation for a vascular disease from a drug given into the vascular space (that is, IV may be different to a drug given under the skin (that is, SC). The efficacy may also be related to C_{max} and $C_{over\ time}$ (that is, exposure). Thus it is important to know the PK parameter associated with target site saturation, assuming that this is the relevant surrogate for measuring outcomes.

The choice of C_{min} thus remains an unsubstantiated assumption, as there was no evidence provided to show that efficacy or toxicity of rituximab SC was related to maximal or minimal concentration (as opposed to time above a specific concentration, AUC, maximal concentration in first cycle, average concentration over a cycle, average concentration over a treatment period, all of which from a pharmacology perspective could be relevant, for example). This section still needs significant work and justification.

The sponsor also states the clinical development program was based on PK- bridging to the approved rituximab IV dose and dosing intervals for NHL and CLL. The studies were designed to demonstrate non-inferior PK in order to ensure a rituximab exposure at least as high with rituximab SC as with IV. By extrapolation of the PK results, it was expected that the efficacy would also be comparable. This assumption was previously accepted by the TGA for the submission to register rituximab 1400 mg SC formulation (NHL).

12.1.2. Evaluation of response

This is noted but this evaluator did not review that data; this evaluation is undertaken independently of that decision.

The evaluator notes that the paragraph above discusses 'serum rituximab levels as high as'…and then refers to 'non-inferior exposure'. These are two different PK parameters. Further, concentrations were used as a primary endpoint, AUC was a secondary endpoint. The justification of these, rather than the relationship of B-cell depletion to outcomes is not made, nor of the choice of C_{min} as opposed to AUC. The statement regarding extrapolation of the PK data to an expectation of efficacy is therefore flawed; it is noted that the data reporting in 2018 will help with the understanding of this PK-PD relationship. From a pharmacology perspective the evaluator has no expectation from this reasoning that SC efficacy would be non-inferior to IV.

The sponsor summarises by stating, '*there is no reason to expect that the treatment benefit as demonstrated through end of treatment response rates will not translate into PFS (and OS) benefit*'. This is another not well substantiated assumption that is, that response rates translate into something meaningful for patients in this disease. The evaluator suggests that although this is possible, the alternative is also possible and for a relatively easy endpoint to ascertain (PFS or OS), this data should have been easily able to capture, particularly from data that is already available in other haematology conditions.

These are actually the major problems with this application that is:

- Assumption that SC treatment has the same PK-PD relationship as IV,
- Choice of a PK parameter that is not clearly substantiated as an appropriate primary clinical endpoint in this route,
- Assumption that in this blood disease a rapid depot of drug SC as opposed to slow infusion directly into the site of effect (blood) can be measured by similar concentration or exposure parameters without ascertaining this prior to the study,
- The lack of a PD endpoint (B-cell depletion) known to be a relevant clinical endpoint in this disease was not the primary endpoint.

12.2. Question 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?

12.2.1. Sponsor's response

The sponsor states that rituximab SC offers a less burdensome and more efficient treatment option to deliver comparable efficacy and safety to patients eligible for rituximab therapy. In particular, the benefit would be greatest when rituximab SC is administered with orally available chemotherapy regimens. In the chronic lymphocytic leukaemia (CLL) study BO25341/SAWYER, 30% of patients were treated with oral fludarabine and cyclophosphamide (FC); therefore rituximab SC already provides CLL patients an option of IV-free immune chemotherapy with increased convenience.

12.2.2. Evaluation of response

The changing field of therapy for CLL (end of patent life for IV therapies, entry of biosimilars and new drug availability and administration routes) is noted however the numbers for oral FC in Australia are not reported. Thus it remains unknown to the evaluator whether non IV

rituximab therapy would result in an IV free treatment regimen in Australia. Even if that was so, SC rituximab does not provide an injection free solution – rather that the injection is altered from the IV route to SC route. The exploratory questionnaire results are noted however there was no evidence comparing IV and SC injections on QoL in the CLL group, notwithstanding a large bolus of fluid (13.4 mL) is placed subcutaneously in the abdomen on leaving the clinic. Even with a SC injection, the patients still cannot take the therapy at home as a nurse is required to perform the procedure.

The sponsor quotes the Sehn paper 2007 '*Increased usage of rituximab has also placed a strain on medical resources at many centres with respect to time and resources required to prepare and administer the infusion*'. This may be so however it is not clear how much time/resources is actually devoted to connecting an IV infusion[9] versus giving an SC injection. Cost is not an issue for registration so this discussion is relevant only in so far as this has an effect on patient outcomes. In any case the increase in amount of drug needed to be given in the SC formulation (1600 mg versus 375 mg/m^2) could well increase drug costs significantly.[10]

12.3. Question 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.

MabThera 1400 mg solution for subcutaneous injection for use in NHL indications received its initial approval on March 23, 2014, in the EU. As of September 16, 2015, 11 cases with fatal outcome (14 adverse events) reported likely or highly likely related to rituximab SC were noted in the Company Safety Database, all in NHL indications. Of these, only 1 case reporting 2 adverse events came from spontaneous reporting sources. The reported events are in line with the current knowledge about rituximab, with events most commonly reported in the system organ class Infections and infestations, mainly sepsis and pneumonia.

Comment: The evaluator is not reassured with this information. What was the cause of the 11 deaths *'likely or highly likely'* related to rituximab SC – anaphylaxis, sepsis due to skin contamination or apron cellulitis, for example?

12.4. Question 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.

12.4.1. Sponsor's response

The sponsor states that these were provided in a previous NHL submission, but based on this current request, the most recent report (update CSR MO18264 [Report 1057423]) is now provided in with the current response submission (Report 1057423).

12.4.2. Evaluation of response

M018264 was reviewed. This was a study of IV rituximab with a primary objective to evaluate the benefit of maintenance therapy with IV rituximab on progression-free survival as compared to no maintenance therapy (observation), after induction of response with chemotherapy plus rituximab in previously untreated patients with high-tumour-burden follicular lymphoma (not CLL). This study was in maintenance therapy, and provided information on time to relapse post stopping rituximab IV (12 months), useful in confirming information on B-cell repletion after IV

[9] IV administration is typically 2-4 hours.
[10] For CLL, the IV dose is 500 mg/m^2 (for second and subsequent doses) versus SC 1600 mg fixed dose.

therapy in the pivotal study in this application. The dosing frequency was 2 monthly and thus addresses an aspect of the requested indication (that is, increase frequency of IV dosing) in the application.

Study M17102 was also provided. This study was stopped at the pre-planned interim analysis, after two-thirds of the 357 progression-free survival (PFS) events required for the final analysis had occurred at the recommendation of the Data and Safety Monitoring Board. The study had met its primary endpoint: rituximab in combination with FC had better PFS efficacy compared to FC alone. This study was reviewed to enable consideration of increasing the dosing frequency, as in Part B) of the submission, as subjects received 375 mg/m2 on Cycle 1 and 500 mg/m2 for each subsequent cycle, every 28 days. However the requested indication is not for 28 days, therefore the Evaluator is not clear of the relevance of this study, especially as the dose used was 500 mg/m^2.

12.5. Question 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?

12.5.1. Evaluation of response

The sponsor confirms the lack of rigorousness of the preference analysis, which was as well as being a secondary endpoint was an exploratory analysis. The sponsor confirms the absence of internal or external validation of the survey. This is disappointing as Part 2 of the study was an opportunity to collect well validated survey and QoL data from both groups to examine difference in patient experiences of the two formulations. Lacking this, any discussion on improved QoL or patient benefit for SC formulation is without substantiation.

12.6. Question 5

Comparative figures between the two groups for the Part 2 data PD endpoint of B-cell depletion was not available – can this be provide? Further the relationship of B-cell depletion to PK parameters.

12.6.1. Sponsor's response

The sponsor confirms B-cell depletion is the desired pharmacodynamic effect of rituximab therapy in both non- Hodgkin's lymphoma (NHL) and chronic lymphocytic leukaemia (CLL). However comparison of peripheral blood B-cell depletion (defined as < 80 cells/mm^3) after rituximab SC and rituximab IV administration was defined as a secondary pharmacodynamic endpoint in study BO25341/SAWYER. The trial was not designed to formally test a specific hypothesis about B-cell depletion, and only descriptive analyses were planned without formal statistical testing. As noted in the CER, following the last cycle of treatment (that is, Cycle 6), 95% of patients were B-cell depleted (96% IV versus 95% SC).

12.6.2. Evaluation of response

The sponsor notes B cell depletion is the desired PD endpoint yet the trial was not designed to formally test a specific hypothesis about B-cell depletion, and only descriptive analyses were planned without formal statistical testing.

BP22333 aimed to determine and confirm a rituximab SC dose that is non-inferior to rituximab IV dose in NHL settings – this was a different indication to the CLL data in SAWYER. Although a secondary endpoint also, recovery of B-cell counts was different at 9 months after the last dose of rituximab, with 13.5% of patients in the IV cohort and 25.5% of patients in the SC cohort in Stage 2 considered to have B-cell counts recovered at that time point.

The sponsor confirms there is no dose-exposure-response data, however this recovery data is essentially such. It shows SC formulation is not as effective as IV formulation as twice as many patients have B-cells recovered at 9 months in the SC vs IV group. This is consistent with the MO18264 study which showed patients receiving IV rituximab took 12 months for B cell repletion.

12.7. Question 6

The relationship of CR to patient relevant outcomes such as PFS and OS was not provided, can the sponsor provide this please.

12.7.1. Sponsor's response

The sponsor states that this information has previously been provided in the IV setting in another indication.

12.7.2. Evaluation of response

The question still holds – is the relationship between CR and PFS/OS the same in SC administration which has PK consistent with depot injection – that is, absorption into vascular and lymph compartments. The different PK profiles could well alter the relationship between CR and PFS/OS either in time or quantity. Also CLL is not the same as NHL, and an assumption of the same relationship between response and survival needs to be justified.

Overall as previously discussed, the sponsor's assumptions of C_{trough} need to be justified. It is stated that 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. But what is this time? It will be different between SC and IV as the SC depot has to be absorbed into the vascular compartment. Why was the time point for measurement of C_{trough} the same for both modes of administration? Should we expect significantly higher C_{trough}s by the time the SC injection reaches steady state; the evidence suggests so. Overall the comparison on pharmacology between rapid SC deposit versus a slow IV infusion have not been made and therefore the evaluator is not convinced that the assumptions about the PK parameters chosen for the SC formulation hold.

The proof of the study would be measurement and relationship with B-cell depletion, toxicity, PFS and OS. Some of these were measured however these were not primary endpoints.

The sponsor goes on to state that '*By ensuring serum levels above a trough reached after SC administration, target receptor saturation is maintained relative to rituximab IV and therefore the same degree of anti-B-cell activity is expected*'. This evidence on target receptor saturation was not provided however. Expectations and assumptions need to be justified.

The sponsor also notes that in line with this argument, rituximab C_{trough} levels have been demonstrated to correlate with response rates in FL as well as DLBCL patients (Yin et al. 2010; Tobinai et al. 2004). This may be correct in the IV setting but as discussed evidence has not been presented to show if this holds in the SC setting.

The sponsor states AUC was therefore considered an important secondary endpoint, however the discussion regarding the fact that SC absorption has an extra PK phase (absorption from depot) compared to IV suggests AUC should have been considered an important primary endpoint.

In terms of C_{max} as a primary endpoint, the sponsor states that '*the time of rituximab reaching its target and with very little time for elimination of rituximab…(then) in this context, it is not unexpected that* C_{max} *does not correlate with efficacy (Tobinai et al. 2004) and was therefore selected as explorative PK endpoint only*'. Yet it is known from earlier rituximab work from this sponsor that C_{max} were not comparable between the two modes of administration, as expected from a SC formulation.

'*A potential impact of the SC route of administration on the anti-B-cell activity of rituximab was considered low and independent of the underlying B-cell malignancy. This is based on a comparison of response rates at the same time point in follicular lymphoma -Study BO22334. This study is ongoing and efficacy continues to be evaluated through secondary endpoints of complete response rate at the end of maintenance and time-to-event endpoints such as PFS.*' This study was in FL and not CLL.

This data is important as is the evidence that supports the assumptions made in this study. The Sargent work discussed in the sponsor response was in abstract form and discussed surrogate endpoints in follicular lymphoma. It is possible that the relationship between OR, CRR and PFS is different in different malignancies and with different administration routes. It would be preferable to have the data showing the relationship CRR and PFS in the CLL dataset, and in the SC and IV formulations.

12.8. Question 7

Noting the differences in AEs between men and women, can the sponsor link these events to AUC data?

The sponsor states '*Although there was generally a higher incidence of Grade ≥ 3 AEs and SAEs in female patients as compared to male patients in both IV and SC treatment arms, the overall incidence of these events was balanced across the treatment arms: 81% of females in the IV arm and 80% of females in the SC arm experienced Grade ≥3 AEs, while 42% of females in the IV arm and 36% of females in the SC arm reported SAEs. A similar trend was observed in male patients (64% in IV arm versus 65% in SC arm for Grade≥3 AEs, and 26% in IV arm versus 27% in SC arm for SAEs) ….. serious febrile neutropenia events were reported with a higher incidence in females than males in the SC arm (24% vs 5%, respectively) and in the IV arm (8% versus 2%, respectively). By comparison, SAEs of neutropenia and leukopenia were observed with very low incidence in the SC arm in female and male patients (0% female versus 2% male for neutropenia, and 4% female versus 0% male for leukopenia)*.'

12.8.1. Evaluation of response

The evaluator has assumed the word 'patients' was a typo and 'females' was intended, as per the Figure supplied. The increased Grade 3 or 4 SAEs was significantly higher in women in both IV and SC, mainly due to febrile neutropenia and also severe anaemia. This could be related to increased drug exposure in women; however it is noted that Cmin at Cycle 5 and AUC at Cycle 6 were similar between men and women.

12.9. Question 8

Please provide evidence to link the PK parameters (trough and AUC) to efficacy.

12.9.1. Sponsor's response

The sponsor states that because the active component is identical in both formulations, serum levels (C_{trough}) after rituximab SC at least as high as after rituximab IV were expected to produce at least the same degree of target saturation and at least the same level of efficacy, irrespective of the route of administration. The clinical development studies (BP22333/Sparkthera and BO22334/SABRINA in non-Hodgkin's lymphoma (NHL), and BO25341/SAWYER in chronic lymphocytic leukaemia [CLL]) were designed to demonstrate non-inferior pharmacokinetics per the established IV dose for the respective dosing intervals in order to ensure a rituximab exposure at least as high as after IV. By extrapolation of the pharmacokinetic results, there was no reason to believe that the efficacy would not be comparable also.

12.9.2. Evaluation of response

The fact that similar concentrations 'are expected' is noted, seemingly without regard to pharmacological principles on absorption, distribution and clearance from subcutaneous formulations versus intravenous. Further, the reliance on assumed extrapolation is noted.

The sponsor states that C_{trough} was selected as the primary PK endpoint in the rituximab SC studies as it reflects the degree of target site saturation after sufficient time is allowed for rituximab levels to reach equilibrium between the central and peripheral compartments. By ensuring serum levels above a trough reached after SC administration, target receptor saturation is maintained relative to rituximab IV and therefore the same degree of anti- B-cell activity is expected.

Target receptor saturation and relationship to trough after SC administration is unknown. In line with this argument, the sponsor states that rituximab C_{trough} levels have been demonstrated to correlate with response rates in follicular lymphoma, diffuse large B-cell lymphoma, as well as CLL patients (Yin et al. 2010; Tobinai et al. 2004; Li et al. 2012). In addition, correlation between response and serum rituximab level, from Cycle 2 C_{trough}, has been described (Berinstein et al. 1998; Igarashi et al. 2002; Tobinai 2002). C_{trough} was also correlated with remission quality and progression-free survival (Jäger 2012) further supporting the selection of the primary endpoint. The assumption that similar (C_{trough}) to establish a rituximab exposure at least as high SC as after IV remains flawed. AUC can vary significantly with similar C_{trough}. It is still not clear why C_{trough} was chosen as the primary endpoint when AUC is the measure of exposure the sponsor appears to be seeking, and that extrapolation was undertaken on C_{trough} to 'believe that efficacy would 'not' be comparable also. This also contradicts the statement in response to Question 5 that B cell deletion is the aim of therapy. It appears that to maintain consistency of argument that AUC should have been primary PK endpoint, with B-Cell depletion as primary endpoint. Further whilst C_{trough} might have been a reasonable surrogate after IV infusion, the relationship of C_{trough} to outcome may well not be the same after SC injection due to the fact that the drug is not injected directly into the site of sampling (that is, vascular compartment). Further, the geometric mean ratio SC/IV for C_{trough} was 1.53 (90% CI [1.27; 1.85]) that is, could be up to 85% more for SC injection at one time point. This brings into major question the choice of dose of 1600 mg – a point raised by the popPK expert report and TGA's Pharmaceutical Sub Committee (PSC). It is no surprise then that surrogate markers such as ORR are at least similar between IV and SC, however with more exposure one would expect the ORR to be significantly higher, based on assumptions made in this application regarding the relationship of concentrations to outcome.

12.10. Question 9

Please provide information on evaluation and interpretation of the antibody data

12.10.1. Sponsor's response

The presence of human anti-chimeric antibodies (HACAs) directed against rituximab and human anti-human antibodies (HAHAs) directed against rHuPH20 is being evaluated in all clinical studies with rituximab SC.

12.10.2. Evaluation of response

Information on interpretation was answered in Question 16 which also focused on incidence of antibody formation.

12.11. Question 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).

12.11.1. Sponsor's response

The GMR for AUC_{τ} was 1.10 (90% CI [0.98; 1.24]), that is, 10% higher.

12.11.2. Evaluation of response

The 90% CI mean it is possible that the AUC is between 2% lower up to 24% more.

12.12. Question 11

20. MO18264 was not submitted with this application. Can this be provided please?

12.12.1. Sponsor's response

This was provided and was summarised in answer to Question 3.

12.13. Question 12

The relationship between planned end date, data analysis and data snapshot in the results section was difficult to follow in the Study report.

12.13.1. Sponsor's Response

As of the database snapshot date of May 07, 2014, all patients in Study BO25341 (both parts) had completed or had withdrawn from the treatment period of the study. The study is still ongoing, and patients continue to be followed up. The last follow-up visit is scheduled to take place approximately 4 years after the last dose of study treatment. The last patient was randomised on June 17, 2013, so based on the last patient visit occurring 4.5 years thereafter, the study is expected to be completed by the end of 2017. The final analysis will be conducted in 2018, and the results will be presented in a final study report which is currently estimated to be available in Q4 2018. To fulfil a commitment made during the course of the submission to register rituximab SC 1400 mg for NHL indications (PM-2012-04453-1-4), the final CSR will be submitted to TGA.

12.13.2. Evaluation of response

This is reasonable. The data is keenly awaited. Essentially this is an increased dose but given by a route not related to the site of treatment (that is, vascular), resulting in a greater AUC; questions persist around the likelihood of improved response and/or increase toxicity. This would be important to know prior to registration, due to the large number of assumptions made in this study design.

12.14. Question 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_{trough} but the relative difference on C_{max} and AUC (safety and efficacy) was not clear.

12.14.1. Sponsor's response

The sponsor states that the most conservative PK parameter to ensure the prevention of under dosing is to demonstrate C_{trough} non-inferiority (primary endpoint) whilst showing that AUC levels after rituximab SC (secondary endpoint) are at least as high as after rituximab IV when given at the CLL dose of 500 mg/m^2 and the CLL dosing interval (q4w).

12.14.2. Evaluation of response

This is the same assumption raised earlier in responses and suffers from the same pharmacological rationale. The most conservative PK parameter in this setting (that is, SC route

of administration, with different times to C_{max}, clearance, etc.) in the view of the evaluator is likely to be the AUC.

The sponsor goes on to note the problems with blood concentrations in the SC setting, thus it is even more concerning that C_{trough} was chosen as the primary endpoint '*rituximab* C_{max} *after IV administration is measured prior to the distribution to the target sites located in the peripheral compartment (that is,, nodal sites, bone marrow, and extranodal site) and is therefore considered non-predictive for efficacy. Rituximab* C_{max} *in the blood after SC administration will only be reached after a significant delay, with a time to maximum drug concentration (*T_{max}*) of approximately 3-5 days. This means that* C_{max} *after SC administration will be influenced by the duration and the overlap of the absorption, distribution, and elimination until* C_{max} *is reached, which renders any comparison of* C_{max} *in the blood after IV and SC administration misleading'*. This is relevant because the issues around differential (and unknown) absorption, distribution and elimination apply to C_{min} (C_{trough}) as well as C_{max}. They are also likely to vary with age and with body composition, issues which were not addressed in the population PK, but were highlighted by the independent pharmacometrician report in response to this and the PSC report.

The 'predictions' are based on 100 simulated trials (again a low number, most simulations for a clinical study are around 10,000 or more).

12.15. Question 14

Evidence to show the relationship of SC to IV in term of convenience – please provide

12.15.1. Sponsor's response

Immuno chemotherapy with rituximab, fludarabine, and cyclophosphamide (R-FC) remains the standard of care in previously untreated patients with chronic lymphocytic leukemia (CLL) requiring treatment (Eichhorst et al. 2015) and a clinically established treatment option for patients with previously treated CLL (Robak et al. 2010).

Most patients already have an intravenous port for other therapies. However it is conceivable that oral fludarabine and cyclophosphamide may be used in the future instead of IV in a 5 day rather than 3 day protocol. In this case the absence of need for IV therapy may make alternate routes of infusion for rituximab of interest for patients who do not want an IV for the rituximab infusion every cycle.

12.15.2. Evaluation of response

As previously discussed, the surveys were not internally nor externally validated.

12.16. Question 15

The numbers and percentages do not appear to be consistent for example, 2 patients is [12%] and 2 patients is then [9%] in the Safety data.

12.16.1. Evaluation of response

The sponsor provided the denominators to explain this difference.

12.17. Question 16

Can the sponsor please provide information on the relative frequency in incidence of HAHA and HACA in IV and SC doses?

12.17.1. Sponsor's response

Given the small number of patients who developed HACAs in Part 2, no definitive conclusions on the impact of anti-rituximab antibodies on efficacy and/or safety can be made.

In terms of clinical consequences in patients with a positive HAHA response, 12/13 patients who had a positive HAHA response at any time during Part 2 of the study were responders at the 3- month follow-up visit.

The sponsor states that presence of HACAs and HAHAs continues to be evaluated in all clinical studies with rituximab SC and '*Immunogenicity associated with the subcutaneous formulation (NHL/CLL SC formulations)*' is categorised as Missing Information in the Risk Management Plan (RMP).

12.17.2. Evaluation of response

This pharmacovigilance aspect needs to be documented as a specific item in the RMP.

12.18. Question 17

Does the sponsor have time-to-event endpoint (PFS, EFS and OS) data for this study yet?

12.18.1. Sponsor's response

Study BO25341 is still ongoing, and patients continue to be followed up.

12.19. Question 18

Information on Study MO18264 to support the increased frequency of dosing, and results from the Study ml17102 were not able to be located.

12.19.1. Sponsor's response

Provided in response to Question 3.

12.20. Question 19

Can the sponsor please add incidence and clinical relevance of HAHA and HACA antibodies to the RMP?

12.20.1. Sponsor's response

In the Pharmacovigilance Plan of the RMP, Roche plans to continue to assess the incidence and clinical relevance of the development of HACAs and/or HAHAs through routine pharmacovigilance and additional pharmacovigilance activities (BO22334 and BO25341 studies).

b) Type F Change in Dosage Frequency. Maintenance therapy in previously untreated NHL Patients 100 mg/10 mL and 500 mg/50 mL injection, vial (AUST R 60318, 60319) 1400 mg/11.7mL solution for injection, vial (AUST R 207334).

Study M018264 was submitted for the response and was reviewed. This was a study of IV rituximab with a primary objective to evaluate the benefit of maintenance therapy with IV rituximab on progression-free survival as compared to no maintenance therapy (observation), after induction of response with chemotherapy plus rituximab in previously untreated patients with high-tumour-burden follicular lymphoma (not CLL). This study was in maintenance therapy, and provided information on time to relapse post stopping rituximab IV, useful in confirming information on B-cell repletion after IV therapy in the pivotal study in this Application (which was 12 months). The dosing frequency was 2 monthly and thus addresses an aspect of the requested indication as requested in the application.

Study M17102 was also provided. This study was stopped at the pre-planned interim analysis, after two-thirds of the 357 progression-free survival (PFS) events required for the final analysis had occurred at the recommendation of the Data and Safety Monitoring Board. This study was reviewed to enable consideration of increasing the dosing frequency as subjects received 375 mg/m^2 on Cycle 1 and 500 mg/m^2 for each subsequent cycle, every 28 days.

Overall, there is evidence showing benefit of 2 monthly maintenance therapy with IV rituximab, however outcomes with 2 months compared to 3 is not available. Further there is no data on SC every 2 months. Further the data in M17102 used IV rituximab every 28 days, and at a dose of 500 mg/m^2.

c) Type J Changes to PI Requiring Data Evaluation 1400 mg/11.7 mL solution for injection, vial (AUST R 207334).

12.20.2. Sponsor's response

This is discussed in Section 13 below.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

New clinical information was submitted in response to questions; specifically Studies M17102 M018264 were resubmitted as evidence for the requested change in indication to treat NHL patients every 2 rather than 3 months.

The potential benefits of rituximab SC are unchanged from those identified in the first round report but have not been justified. Further there is no evidence on the benefits provided – efficacy and toxicity data will be provided in 2018.

13.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of rituximab in the proposed usage are unchanged from those identified in the first round report.

The population PK expert report raises two potential risks - flat dosing, without taking into account BSA which was a covariate in the model, and the increased exposure as a risk for toxicity. The evaluator agrees with these potential risks.

The evaluator also agrees with the concern of the PSC regarding differential absorption and PK in people of different body size and composition having a SC injection.

13.3. Second round assessment of benefit-risk balance

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 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 (375 mg/m^2 to 1600 mg/m^2) per cycle of therapy[11].

In terms of Part B, there is evidence showing benefit of 2 monthly maintenance therapy with IV rituximab, however outcomes with 2 months compared to 3 is not available. Further there is no data on SC use every 2 months. Therefore this change in maintenance dose is not recommended due to absence of comparative safety and toxicity evidence.

14. Second round recommendation regarding authorisation

The requested indication is not supported. This is because of uncertainty in benefit in overall survival and progression free survival and absence of evidence of any benefit to patients.

Specifically:

- The changing drug armamentarium for therapy for CLL is noted however it remains unknown to the evaluator whether non IV rituximab therapy would yet result in an IV free treatment regimen in Australia.
- Even if a move to oral therapies occurs, SC rituximab does not provide an injection free solution
- Even with a SC injection, the patient still cannot take the therapy at home as a nurse is required to perform the procedure, reconstitute the drug and connect up the formulation.
- The sponsor confirms the lack of rigorousness of the preference analysis, an analysis for which there was an absence of internal or external validation.
- The sponsor confirms B-cell depletion is the desired pharmacodynamic effect of rituximab therapy in both non- Hodgkin's lymphoma, yet this was not the primary endpoint of the study.
- The pharmacological choice of the C_{trough} parameter as a comparative endpoint in SC to IV therapy is uncertain and not justified. The use of this parameter as the primary endpoint in the study is problematic for interpretation of expected efficacy.
- Recovery B cell data suggests SC formulation is not as effective as SC formulation as twice as many patients have B-cells recovered at 9 months in the SC versus IV group. This is consistent with the MO18264 study which showed patients receiving IV rituximab had 12 months prior to B cell repletion.
- The sponsor states that '*By ensuring serum levels above a trough reached after SC administration, target receptor saturation is maintained relative to rituximab IV and therefore the same degree of anti-B-cell activity is expected*'. This evidence on target receptor saturation was not provided however.
- There is a reliance on an assumption that similar concentrations 'are expected' from SC and IV formulations, without regard to pharmacological principles on absorption, distribution and clearance in subcutaneous depots versus after injection directly into the site of action (intravenous in this condition).

[11]For CLL, the IV dose is 500 mg/m^2 (for second and subsequent doses) versus SC 1600 mg fixed dose.

- The geometric mean ratio SC/IV for C_{trough} was 1.53 (90% CI [1.27; 1.85]) that is, could be up to 85% more for SC injection at one time point, which could be an incorrect sampling time in older patients or those with increased subcutaneous fat.
- The issues around differential (and unknown) absorption, distribution and elimination apply to comparative Cmin (C_{trough}) as well as C_{max}.

Study B025341 is still ongoing, and patients continue to be followed up. The last follow-up visit is scheduled to take place by the end of 2017. The final analysis will be conducted in 2018, and the results will be presented in a final study report which is currently estimated to be available in Q4 2018. This data is necessary for ensuring that SC rituximab is not less effective or more toxic, based on the uncertainty with the choice of the pharmacology endpoints discussed above.

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