# BIOSIMILAR MULTI-DISCIPLINARY EVALUATION AND REVIEW

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| **Application Type** | 351(k) |
| **Application Number** | BLA 761140 |
| **Submit Date** | December 19, 2019 |
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| **BsUFA Goal Date** | December 19, 2020 |
| **Division/Office** | Division of Hematologic Malignancies II (DHM II) / Office of Oncologic Diseases (OOD)<br>Division of Rheumatology and Transplant Medicine (DRTM) / Office of Immunology and Inflammation (OII) |
| **Review Completion Date** | December 15, 2020 |
| **Product Code Name** | ABP 798 |
| **Proposed Non-Proprietary Name**[1] | rituximab-arrx |
| **Proposed Proprietary Name**[1] | Riabni |
| **Pharmacologic Class** | CD20-directed cytolytic antibody |
| **Applicant** | Amgen, Inc. |
| **Applicant Proposed Indication(s)** | For the following:<br>• Adult patients with non-Hodgkin's Lymphoma (NHL).<br>o Relapsed or refractory, low grade or follicular, CD20-positive B-cell NHL as a single agent.<br>o Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single-agent maintenance therapy.<br>o Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy.<br>o Previously untreated diffuse large B-cell, CD20-positive NHL in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other anthracycline-based chemotherapy regimens.<br>• Adult patients with Chronic Lymphocytic Leukemia (CLL).<br>o Previously untreated and previously treated CD20-positive CLL in combination with fludarabine and cyclophosphamide (FC). |

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| | • Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA) in adult patients in combination with glucocorticoids. |
| **Recommendation on Regulatory Action** | *Approval* |

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## Reviewers of Biosimilar Multi-Disciplinary Evaluation and Review

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## Additional Reviewers of Application

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| **OSE/DEPI** | N/A |
| **OSE/DMEPA** | N/A |
| **OSE/DRISK** | N/A |
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CMC=Chemistry, Manufacturing, and Controls
OBP=Office of Biotechnology Products
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error and Prevention Analysis
DRISK=Division of Risk Management
DPMH=Division of Pediatric and Maternal Health

## Glossary

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|---|---|
| AC | Advisory Committee |
| ADA | Anti-drug Antibodies |
| ADME | Absorption, Distribution, Metabolism, and Excretion |
| AE | Adverse Event |
| BLA | Biologics License Application |
| BMER | Biosimilar Multi-Disciplinary Evaluation and Review |
| BMI | Body Mass Index |
| BPD | Biosimilar Biological Product Development |
| BsUFA | Biosimilar User Fee Agreements |
| CDER | Center for Drug Evaluation and Research |
| CDRH | Center for Devices and Radiological Health |
| CDTL | Cross-Discipline Team Leader |
| CFR | Code of Federal Regulations |
| CI | Confidence Interval |
| CMC | Chemistry, Manufacturing, and Controls |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| CRP | C-reactive Protein |
| CSC | Computational Science Center |
| CTD | Common Technical Document |
| CV | Coefficient of Variation |
| DEPI | Division of Epidemiology |
| DMC | Data Monitoring Committee |
| DMEPA | Division of Medication Error Prevention and Analysis |
| DPMH | Division of Pediatric and Maternal Health |
| DRISK | Division of Risk Management |
| eCTD | Electronic Common Technical Document |
| EU-MabThera | EU-approved MabThera (also referred to as EU-Rituxan) |
| FDA | Food and Drug Administration |
| FISH | Fluorescence In Situ Hybridization |
| GCP | Good Clinical Practice |
| GMR | Geometric Mean Ratio |
| ICH | International Conference on Harmonization |
| IND | Investigational New Drug |
| ITT | Intention to Treat |
| LLOQ | Lower Limit of Quantitation |
| MAPP | Manual of Policy and Procedure |
| mITT | Modified Intention to Treat |
| MOA | Mechanism of Action |

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|---|---|
| NAb | Neutralizing Antibody |
| NCI-CTCAE | National Cancer Institute – Common Terminology Criteria for Adverse Events |
| NCT | National Clinical Trial |
| OBP | Office of Biotechnology Products |
| OCP | Office of Clinical Pharmacology |
| OPDP | Office of Prescription Drug Promotion |
| OSE | Office of Surveillance and Epidemiology |
| OSI | Office of Scientific Investigations |
| OSIS | Office of Study Integrity and Surveillance |
| PD | Pharmacodynamics |
| PeRC | Pediatric Review Committee |
| PK | Pharmacokinetics |
| PMC | Postmarketing Commitments |
| PMR | Postmarketing Requirements |
| PREA | Pediatric Research Equity Act |
| PHS | Public Health Service |
| REMS | Risk Evaluation and Mitigation Strategies |
| ROA | Route of Administration |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SGE | Special Government Employee |
| SOC | System Organ Class |
| SOP | Standard Operating Procedures |
| TEAE | Treatment-Emergent Adverse Events |
| ULOQ | Upper Limit of Quantitation |
| US-Rituxan | US-licensed Rituxan |

# 1. Executive Summary

## 1.1. Product Introduction

ABP 798 (rituximab-arrx; Riabni) is a chimeric murine/human immunoglobulin G1 (IgG1), CD20-directed monoclonal antibody (mAb) that has been developed as a proposed biosimilar to US-licensed Rituxan (US-Rituxan, rituximab).

The Applicant is seeking licensure of ABP 798 (Riabni, rituximab-arrx) as biosimilar to US-licensed Rituxan for the adult Non-Hodgkin lymphoma (NHL), adult chronic lymphocytic leukemia (CLL), and adult Granulomatosis with Polyangiitis (GPA) and Microscopic Polyangiitis (MPA) indications that are the same as those previously approved for US-licensed Rituxan. The indications sought for licensure are:[2]

- Adult patients with non-Hodgkin's Lymphoma (NHL).
  - Relapsed or refractory, low grade or follicular, CD20-positive B-cell NHL as a single agent.
  - Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single-agent maintenance therapy.
  - Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy.
  - Previously untreated diffuse large B-cell, CD20-positive NHL in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other anthracycline-based chemotherapy regimens.
- Adult patients with Chronic Lymphocytic Leukemia (CLL).
  - Previously untreated and previously treated CD20-positive CLL in combination with fludarabine and cyclophosphamide (FC).
- Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA) in adult patients in combination with glucocorticoids.

## 1.2. Determination under section 351(k)(2)(A)(ii) of the Public Health Service (PHS) Act

Not applicable.

## 1.3. Mechanism of Action, Route of Administration, Dosage Form and Strength Assessment

ABP 798 (rituximab-arrx) binds to CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes, and malignant B cells. Upon binding to CD20, ABP 798 mediates B-cell lysis. Possible mechanisms of cell lysis include complement dependent cytotoxicity (CDC), antibody dependent cell mediated cytotoxicity (ADCC), signaling induced cell death (apoptosis), and antibody dependent cellular phagocytosis (ADCP), which are applicable to known and potential mechanisms of action of rituximab in B cell malignancies and in autoimmune diseases. Therefore, ABP 798 and US-Rituxan utilize the same mechanisms of action to the extent known.

ABP 798 is produced in genetically engineered Chinese Hamster Ovary (CHO) cells. ABP 798 drug product is manufactured to the same strengths, dosage form, and route of administration as US-licensed Rituxan. ABP 798 drug product also has the same formulation and presentation as US-licensed Rituxan. Riabni is a sterile, preservative-free colorless to pale yellow, clear to opalescent solution for intravenous (IV) infusion and supplied in single-dose vials containing ABP 798 at 100 mg/10 mL or 500 mg/50 mL.

Strength, presentation, and dosage forms:

- 100 mg/10 mL (10 mg/mL), single-dose vial, injection
- 500 mg/50 mL (10 mg/mL), single-dose vial, injection

Dating period:

- Drug Product: 36 months at 5°C
- Drug Substance: (b) (4) months at (b) (4) °C

## 1.4. Inspection of Manufacturing Facilities

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for Immunex Rhode Island Corporation (FEI 3003359885) and (b) (4) proposed for ABP 798 drug substance (DS) and drug product (DP) manufacture, respectively. All proposed manufacturing and testing facilities are acceptable based on their currently acceptable Current Good Manufacturing Practice (CGMP) compliance status and recent relevant inspectional coverage as described in the table below.

**Table 1: Summary of Establishment Information for ABP 798 Drug Substance and Drug Product**

| DRUG SUBSTANCE | | | | | |
|---|---|---|---|---|---|
| Function | Site Information | FEI Number | Preliminary Assessment | Inspectional Observations | Final Recommendation |

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|---|---|---|---|---|---|
| Drug substance manufacture; in-process, lot release, and stability testing; Working cell bank storage; Unprocessed bulk testing: mycoplasma | Immunex Rhode Island Corporation (Referred to as Amgen Rhode Island or ARI) 40 Technology Way, West Greenwich, Rhode Island, United States of America, 2817 | 3003359885 | Approve based Section 704(a)(4) records review | N/A | Approve |
| Drug substance in-process testing: glycan map; Master cell bank and working cell bank storage; Working cell bank manufacture; Drug product lot release and stability testing | Amgen Inc. (Referred to as Amgen Thousand Oaks or ATO) One Amgen Center Drive, Thousand Oaks, California, United States of America, 91320 | 2026154 | Approve - Based on Previous History | N/A | Approve |
| Drug substance in-process, lot release, and stability testing; Drug product in-process, lot release, and stability testing | Amgen Technology Ireland UC (Referred to as Amgen Dun Laoghaire or ADL) Pottery Road, Dun Laoghaire, Ireland | 3002808497 | Approve - Based on Previous History | N/A | Approve |
| Mycoplasma testing (unprocessed bulk) Adventitious viral testing (unprocessed bulk) | (b) (4) | | Approve - Based on Previous History | N/A | Approve |
| Master cell bank and working cell bank storage | Amgen Inc. (Referred to as Louisville Distribution Center or LDC) 12000 Plantside Drive, Louisville, KY, United States of America, 40299 | 3003750095 | No evaluation necessary | N/A | N/A |
| DRUG PRODUCT | | | | | |
| Function | Site Information | FEI Number | Preliminary Assessment | Inspectional Observations | Final Recommendation |

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| Drug product manufacture, Drug product in-process and lot release testing | [redacted] (b) (4) | | Approve based on facility profile | Pre-license inspection Waived | Approve |
| Drug product packaging and labeling | Amgen Manufacturing Ltd (Referred to as AML) Carr 31, KM 24.6 Juncos, Puerto Rico 00777 USA | 1000110364 | Approve based on facility profile | N/A | Approve |
| Drug product packaging and labeling | Amgen Europe B.V. (Referred to as ABR) | 3005889661 | Approve based on facility profile | N/A | Approve |

The commercial manufacture of ABP 798 DS at Immunex Rhode Island (ARI) is recommended for approval by Office of Pharmaceutical Manufacturing Assessment (OPMA) through the review of requested manufacturing site records in lieu of an on-site inspection under Section 704(a)(4) (FDASIA Sec. 706). The commercial manufacture of ABP 798 DP at [redacted] (b) (4) [redacted] (b) (4) was recommended for approval by OPMA based on the firm's compliance history, current acceptable CGMP status, and the [redacted] (b) (4) manufacture of other licensed products on the same vial-filling line.

## 1.5. Scientific Justification for Use of a Non-U.S.-Licensed Comparator Product

To support a demonstration that ABP-798 is highly similar to US-licensed Rituxan, and to establish the analytical portion of the scientific bridge to justify the relevance of data generated with studies using EU-approved MabThera as the comparator to the assessment of biosimilarity, the Applicant performed a comparative analytical assessment using 37 lots of US-licensed Rituxan, 30 lots of EU-approved MabThera, and 14 independent lots of ABP 798 drug product.

The analytical assessment included:

- Extensive comparative physiochemical and functional assessments of quality attributes.
- Comparative assessments of the degradation profiles under forced degradation conditions.

The Applicant used a risk-based approach for statistical evaluation of the analytical results:

- High risk-ranked attributes tested using quantitative assays were evaluated by equivalence testing.

- Moderate risk-ranked attributes tested using quantitative assays were evaluated by quality ranges (QR) (non-adjusted, age-adjusted or initial time point quality ranges) or using an expectation approach in which individual values were compared to a pre-defined limit or interval based on method capability and product knowledge. Age-adjusted quality ranges were considered as supportive data as part of the comparative analytical assessment.
- Low risk-ranked attributes or attributes tested using qualitative assays were evaluated using side-by-side visual comparisons.

Results from method validation, qualification, verification and transfer studies were provided to support the suitability of the methods used in the comparative analytical assessment.

Three pairwise comparisons of ABP 798, US-licensed Rituxan, and EU-approved MabThera were used to establish the analytical component of the scientific bridge to support the relevance of the data generated from studies using EU-approved MabThera as the comparator to the assessment of biosimilarity. The Applicant supported the establishment of the analytical portion of the scientific bridge using the same methods and statistical approaches used to support a demonstration that ABP 798 is highly similar to US-licensed Rituxan. The data support the conclusion that the analytical portion of the scientific bridge was established.

The PK similarity study (Study 20130108) in patients with rheumatoid arthritis met its primary PK endpoints and demonstrated PK similarity between ABP 798, US-Rituxan, and EU-MabThera, establishing the PK component of the scientific bridge.

Taken together, the comparative analytical results and the results of Study 20130108 establish the scientific bridge to justify the relevance of data generated from studies using EU-approved MabThera as the comparator product to the assessment of biosimilarity.

## 1.6. Biosimilarity Assessment

**Table 2: Summary and Assessment of Biosimilarity**

| **Comparative Analytical Studies** | |
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| Summary of Evidence | • A comparative analytical assessment using 37 lots of US-licensed Rituxan, 30 lots of EU-approved MabThera, and 14 independent lots of ABP 798 drug product was performed.<br>• The analytical assessment included extensive comparative physiochemical and functional assessments of quality attributes and comparative assessments of the degradation profiles under forced degradation conditions. |

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| | • Molecular attributes of the product were assigned to risk categories based on potential impact to activity, safety, efficacy, PK, PD, and immunogenicity and a risk-based approach for statistical evaluation of the analytical results was performed.<br>• Results from method validation, qualification, verification and transfer studies were provided to support the suitability of the methods used in the comparative analytical assessment.<br>• The analytical data submitted support a demonstration that ABP 798 is highly similar to US-licensed Rituxan, notwithstanding minor differences in clinically inactive components.<br>• Three pairwise comparisons of ABP 798, US-licensed Rituxan, and EU-approved MabThera were used to establish the analytical component of the scientific bridge to support the relevance of the data generated from studies using EU-approved MabThera as the comparator to the assessment of biosimilarity. The data support the conclusion that the analytical portion of the scientific bridge was established.<br>• ABP 798 has the same strengths, dosage form, and route of administration and US-licensed Rituxan. |
| Residual Uncertainties and Outcomes | • There are no residual uncertainties from a product quality perspective. |
| **Nonclinical Studies** | |
| Summary of Evidence | • A 4-week toxicity study in cynomolgus monkeys comparing ABP 798 and US-Rituxan found no toxicological differences and supports the demonstration of biosimilarity.<br>• The ABP 798 nonclinical development program was considered adequate to support clinical development. |
| Residual Uncertainties and Outcomes | • There are no residual uncertainties from a pharmacology/toxicology perspective. |
| **Clinical Pharmacology** | |
| Summary of Evidence | • Comparative PK between ABP 798, US-licensed Rituxan, and EU-approved MabThera was evaluated in a randomized, double-blind, active-controlled, 3-arm study in adult patients with moderate to severe |

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| | rheumatoid arthritis with an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs (N = 311, Study 20130108).<br>• Pharmacokinetic similarity was demonstrated; the 90% confidence interval for the geometric mean ratios for area under the serum concentration-time curve (AUC) of ABP 798 to US-licensed Rituxan, ABP 798 to EU-approved MabThera, and EU-approved MabThera to US-licensed Rituxan for $AUC_{0\text{-}inf}$, $AUC_{0\text{-}12wk}$, and $AUC_{0\text{-}2wk}$ were all within the PK similarity acceptance criteria of 80 to 125%. The data establishes PK similarity between ABP 798 and US-licensed Rituxan, establishes the PK component of the scientific bridge, and supports a demonstration of no clinically meaningful differences between ABP 798 and US-licensed Rituxan.<br>• Immunogenicity of ABP 798, US-licensed Rituxan and EU-approved MabThera was evaluated in Study 20130108 in patients with rheumatoid arthritis and of ABP 798 and US-licensed Rituxan in Study 20130109 in patients with Non-Hodgkin lymphoma. The scientific bridge was established, which justifies the relevance of comparative data generated using EU-approved MabThera to the assessment of biosimilarity. In Study 20130108, the overall incidence of anti-drug antibody (ADA) formation at Week 24 (before undergoing a single transition) was 13.4%, 10.6%, and 18.6 % in the ABP 798, EU-approved MabThera, and US-licensed Rituxan treatment arms, respectively, and at end of study at Week 48 was 14.4%, 13.8%, and 20.6% in the ABP 798/ABP 798, EU-approved MabThera/EU-approved MabThera, and US-licensed Rituxan/ABP 798 treatment arms, respectively. As such, the immunogenicity was overall comparable between the treatment arms prior to the single transition in the US-licensed Rituxan arm, as well as after a single transition from US-licensed Rituxan to ABP 798 as compared to not transitioning. In Study 2013019, following repeat IV dosing, the incidence of ADA formation was 2.4% and 0.8% in the ABP 798 and US-licensed Rituxan treatment arms, respectively. The incidence of anti-drug antibody and neutralizing |

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| | antibody formation of ABP 798 and that of US-licensed Rituxan was comparable in each study.<br>• The PK and immunogenicity data support a demonstration of no clinically meaningful differences between ABP 798 and US-licensed Rituxan. |
| Residual Uncertainties and Outcomes | • There are no clinical pharmacology residual uncertainties from a clinical pharmacology perspective. |
| **Clinical Studies – Rheumatoid Arthritis** | |
| Summary of Evidence | • Study 20130108 was a randomized, double-blind, active-controlled 3-arm PK similarity study evaluating PK, pharmacodynamics, comparative efficacy and safety of ABP 798, US-licensed Rituxan, and EU-approved MabThera in 311 adult patients with moderate to severe rheumatoid arthritis with an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs.<br>• The primary objective of the study was PK similarity. Comparative clinical efficacy was assessed as a secondary objective, where a key efficacy endpoint was the change from baseline in disease activity score (DAS) based on 28 joint counts and C-reactive protein (DAS28-CRP) at Week 24.<br>• Study 20130108 was not designed, nor powered, to provide a formal, statistical, comparative evaluation of efficacy. The clinical outcomes were analyzed using descriptive statistics and were found to be supportive of the totality of the data in the application.<br>• The scientific bridge was established, which justifies the relevance of comparative data generated using EU-MabThera to the assessment of biosimilarity.<br>• The estimated adjusted mean change from baseline in DAS28-CRP at Week 24 was similar across the treatment arms and the 90% confidence interval comparing ABP-798 with EU-approved MabThera or US-licensed Rituxan or pooled EU-approved MabThera + US-licensed Rituxan arms were within a margin of ±0.5.<br>• There were inconsistencies in the differences observed using some clinical response outcomes, |

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| | despite similar concepts being captured by the outcome measures. For instance, the DAS28-CRP at Week 24 were similar between arms, however, the American College of Rheumatology Response (ACR) 20 response rates or the proportion of patients with DAS28-CRP < 2.1, the results were similar between EU-approved MabThera and ABP-798 but numerically lower for US-licensed Rituxan. This suggests that any observed differences are likely due to the difference in the precision and accuracy of various outcome measures used in the study and the reviewers do not consider this as evidence of a meaningful difference in efficacy. These differences do not preclude a demonstration of no clinically meaningful differences between ABP-798 and US-licensed Rituxan.<br>• The safety profile of ABP 798 was similar to that of US-licensed Rituxan and EU-approved MabThera, with no notable difference between treatment arms.<br>• In patients who underwent a single transition from US-licensed Rituxan to ABP 798, safety and immunogenicity were comparable between treatment arms, with no meaningful differences.<br>• The data from Study 20130108 supports a demonstration of no clinically meaningful differences between ABP-798 and US-licensed Rituxan. |
| Residual Uncertainties and Outcomes | • There are no residual uncertainties from a clinical and clinical statistics perspective. |
| **Clinical Studies – Non-Hodgkin Lymphoma** | |

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| Summary of Evidence | • Study 20130109 was a randomized, double-blind, active-controlled study evaluating efficacy, safety, PK, PD, and immunogenicity of ABP 798 to US-licensed Rituxan in 256 patients with previously untreated, low tumor burden follicular lymphoma.<br>• The primary endpoint was risk difference (RD) of overall response rate (ORR) by Week 28 per independent review committee (IRC), with a prespecified noninferiority margin of -15% and a nonsuperiority margin of +35.5%. A second prespecified similarity margin of -15%, +15% was also evaluated.<br>• In the ABP 798 arm, ORR was 75% (95% CI: 67, 82) and in the US-licensed Rituxan arm, ORR was 68% (95% CI: 59, 76), per IRC. The risk difference of ORR at Week 28 was 7.07% (90% CI: -2.17, 16.29).<br>• The risk difference was within the prespecified noninferiority margin of -15% and nonsuperiority margin of +35.5%.<br>• Although the upper bound of the 90% confidence interval of the RD of ORR at 16.29% exceeded the upper limit of +15% of the prespecified symmetric similarity margin, it fell within a symmetric similarity margin of -17%, +17%, which the Agency determined was acceptable for this study. Therefore, although the upper bound of the pre-specified similarity margin of +15% was exceeded, it does not preclude a demonstration of no clinically meaningful differences between ABP 798 and US-licensed Rituxan. Furthermore, the results from the secondary clinical endpoints were similar between the ABP 798 and US-licensed Rituxan treatment arms and there were no meaningful differences between the treatment arms.<br>• The safety profile of ABP 798 was similar to that of US-licensed Rituxan, with no notable difference between treatment arms.<br>• The data from Study 20130109 supports a demonstration of no clinically meaningful differences between ABP 798 and US-licensed Rituxan. |

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| Residual Uncertainties and Outcomes | • There are no residual uncertainties from a clinical and clinical statistics perspective. |
| **Extrapolation of Data to Support Licensure as a Biosimilar** | |
| Summary of Evidence | • The Applicant submitted scientific justification for extrapolation of data and information to support licensure of ABP 798 for the following indications: adult Non-Hodgkin Lymphoma (NHL), adult Chronic Lymphocytic Leukemia (CLL), and adult Granulomatosis with Polyangiitis and Microscopic Polyangiitis (GPA/MPA). The justification is based on the mechanism of action, PK similarity, immunogenicity, and safety profile of ABP 798 compared to US-licensed Rituxan.<br>• The known and potential mechanisms of action of rituximab include antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, apoptosis, and antibody-dependent cellular phagocytosis. Based on information in published literature, the relevant target molecule, CD20, for each of these mechanisms of action is the same across all indications for which US-licensed Rituxan is approved and for which the applicant is seeking licensure (adult NHL, adult CLL, adult and GPA/MPA). Comparative analytical data provided by the Applicant support that ABP 798 has the same mechanism(s) of action as US-licensed Rituxan to the extent known.<br>• Pharmacokinetic similarity was demonstrated between ABP 798 and US-licensed Rituxan in Study 20130108 in patients with rheumatoid arthritis. There are no product-related attributes that would increase the uncertainty that the PK may differ between ABP 798 and US-Rituxan across the indications for which US-licensed Rituxan is approved. Therefore, a similar PK profile would be expected between ABP 798 and US-licensed Rituxan in indications for which US-licensed Rituxan has been previously approved and the Applicant is seeking licensure.<br>• Patients with rheumatoid arthritis (Study 20130108) and low tumor burden follicular lymphoma (Study |

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| | 20130109) are considered sensitive populations for detecting potential differences in immunogenicity following treatment. Because an adequate scientific bridge was established, the clinical immunogenicity results from studies 20130108 and 20130109 support a demonstration that there are no clinically meaningful differences in terms of immunogenicity between ABP 798 and US-licensed Rituxan. There are no product-related attributes that would increase the uncertainty that the ADA formation differs between ABP 798 and US-licensed Rituxan across indications for which US-licensed Rituxan has been previously licensed and for which Applicant is seeking licensure. Therefore, the incidence of immunogenicity for ABP 798 would be expected to be similar to that of US-licensed Rituxan in each of the indications for which the Applicant is seeking licensure.<br>• The results from studies 20130108 and 20130109 showed similar safety profiles between ABP 798, US-Rituxan, and EU-MabThera. The available safety data of US-licensed Rituxan (see USPI) does not indicate that there are any notable differences in expected toxicities for the indications for which US-licensed Rituxan was previously licensed and for which the Applicant is seeking licensure.<br>• The Applicant's proposed scientific justifications noted above are sufficient to support extrapolation of data and information in the application to support licensure of ABP 798 under section 351(k) of the PHS Act for the indications for which US-licensed Rituxan has been previously approved and for which the Applicant is seeking licensure. |
| Residual Uncertainties and Outcomes | • There are no residual uncertainties regarding the scientific justification for extrapolation. |

## 1.7. Conclusions on Licensure

In considering the totality of evidence submitted, the data and information submitted by the Applicant support that ABP 798 is highly similar to US-licensed Rituxan, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences in terms of safety, purity, and potency between ABP 798 and US-licensed Rituxan. The Applicant also provided adequate scientific justification for extrapolation of data and information to support licensure of ABP 798 for each indication for which licensure is sought. The information submitted by the Applicant demonstrates that ABP 798 is biosimilar to US-licensed Rituxan for each of the following indications for which US-licensed Rituxan has been previously licensed and Applicant is seeking licensure of:

- Adult patients with non-Hodgkin's Lymphoma (NHL).
  - Relapsed or refractory, low grade or follicular, CD20-positive B-cell NHL as a single agent.
  - Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single-agent maintenance therapy.
  - Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy.
  - Previously untreated diffuse large B-cell, CD20-positive NHL in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other anthracycline-based chemotherapy regimens.
- Adult patients with Chronic Lymphocytic Leukemia (CLL).
  - Previously untreated and previously treated CD20-positive CLL in combination with fludarabine and cyclophosphamide (FC).
- Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA) in adult patients in combination with glucocorticoids.

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# 2. Introduction and Regulatory Background

## 2.1. Important Safety Issues with Consideration to US-Licensed Rituxan

US-licensed Rituxan is a CD20-directed cytolytic antibody indicated for the treatment of

- Adult patients with non-Hodgkin's Lymphoma (NHL).

  - Relapsed or refractory, low grade or follicular, CD20-positive B-cell NHL as a single agent.
  - Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single-agent maintenance therapy.
  - Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy.
  - Previously untreated diffuse large B-cell, CD20-positive NHL in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other anthracycline-based chemotherapy regimens.
- Adult patients with Chronic Lymphocytic Leukemia (CLL).
  - Previously untreated and previously treated CD20-positive CLL in combination with fludarabine and cyclophosphamide (FC).
- Rheumatoid Arthritis (RA) in combination with methotrexate in adult patients with moderately-to severely-active RA who have inadequate response to one or more TNF antagonist therapies.
- Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA) in adult and pediatric patients 2 years of age and older in combination with glucocorticoids.
- Moderate to severe Pemphigus Vulgaris (PV) in adult patients.

The US prescribing information for Rituxan contains Warnings and Precautions for tumor lysis syndrome, infections, cardiac adverse reactions, renal toxicity, bowel obstruction and perforation, immunizations, and embryo-fetal toxicity. In addition, rituximab is associated with infusion-related reactions.

## 2.2. Summary of Presubmission Regulatory Activity Related to Submission

The table below summarizes the key regulatory interactions.

**Table 3: Key Regulatory Interactions**

| Date | Type/Topics |
|---|---|
| 10 July 2013 | BPD Type 2<br>• Comparative analytical assessment plan to characterize ABP 798 in comparison to US-licensed Rituxan and EU-approved MabThera<br>• Planned functional assays, regarding in vitro pharmacology, to comparatively assess ABP 798, US-licensed Rituxan and EU-approved MabThera<br>• Planned toxicology studies<br>• PK similarity study in patients with rheumatoid arthritis<br>• Comparative clinical study in patients with non-Hodgkin lymphoma |

| Date | Type/Topics |
|---|---|
| 05 April 2017 | BPD Type 2<br>• Aspects of the comparative analytical assessment plan and establishment of the analytical component of the scientific bridge between ABP 798, US-licensed Rituxan and EU-approved MabThera<br>• Design and analysis of the PK similarity study to establish PK similarity in patients with rheumatoid arthritis |
| 20 November 2019 | BPD Type 4<br>• Structure and content of the ABP 798 BLA |

## 2.3. Studies and Publicly Available Information Submitted by the Applicant

The nonclinical studies submitted by the Applicant to demonstrate that ABP 798 is biosimilar to US-Rituxan are summarized in Table 4 below.

**Table 4: Summary of Nonclinical Studies**

| Study Title | Study Number | Duration/Dose | Regimen/Route | Number of Subjects | Species |
|---|---|---|---|---|---|
| **Nonclinical Studies** | | | | | |
| A 1-month Intravenous Toxicology Study in the Cynomolgus Monkey | 116362 | 1 month | 20 mg/kg weekly/ Intravenous | 3/sex/group | Cynomolgus Monkey |
| Similarity Assessment using the Rituximab ADCP (PBMC) Assay | FR20-18 | 1.5-3 hours/0.09-100 ng/mL | ADCP in vitro assay | PBMCs from healthy donors | Ramos cell line |
| Evaluation of Target Internalization by ABP 798, Rituximab (US) and Rituximab (EU) in Raji cells | R20150177 | 2 hours/10 µg/mL | In vitro target internalization | n/a | Raji cells |
| Similarity Assessment using the | FR20-3C | 30-120 minutes/0.3-300 mg/µL | In vitro trogocytosis assay | n/a | Ramos cell line |

| Study Title | Study Number | Duration/Dose | Regimen/Route | Number of Subjects | Species |
|---|---|---|---|---|---|
| Rituximab Trogocytosis (PBMC} Assay | | | | | |
| Comparative Assessment of ABP 798 and Rituximab Binding to Fcγ Receptors on Primary Natural Killer Cells | R2018007 | 1 hour/0.78-480 μg/mL | In vitro FCγR assay | Healthy donors | PMBCs |
| In Vivo Evaluation of Efficacy and Safety of Test Articles in the Treatment of Subcutaneous RL Subcutaneous Human Non-Hodgkin's Lymphoma Xenograft Model | E0520-U1738 | 3 or 30 mg/kg | In vivo xenograft model assessment of antitumor activity | Mouse xenograft lymphoma tumor model | RL lymphoma cell line |

The clinical studies submitted by the Applicant to support a demonstration that ABP 798 is biosimilar to US-Rituxan are summarized in Table 5 below.

**Table 5: Summary of Clinical Studies**

| Study Identity | Study Objective | Study Design | Study Population | Treatment Groups |
|---|---|---|---|---|
| **PK Similarity Study** | | | | |
| Study 20130108 | Comparative assessment of PK, efficacy, safety, and immunogenicity of ABP 798, US-licensed Rituxan, and EU-approved MabThera | Randomized, double-blind, active-controlled, 3-arm, multiple-dose | Moderate to severe, active RA on MTX | ABP 798: 104<br>US-Rituxan: 103<br>EU-MabThera: 104 |
| **Comparative Clinical Study** | | | | |
| Study 20130109 | Comparative assessment of efficacy, safety, PK, and | Randomized, double-blind, | Low tumor burden | ABP 798: 128<br>US-Rituxan: 128 |

| Study Identity | Study Objective | Study Design | Study Population | Treatment Groups |
|---|---|---|---|---|
| | immunogenicity of ABP 798 and US-licensed Rituxan | active-controlled, 2-arm trial | follicular lymphoma | |
| Abbreviations: MTX, methotrexate; PK, pharmacokinetic; RA, Rheumatoid arthritis | | | | |

# 3. Clinical Studies: Ethics and Good Clinical Practice

## 3.1. Submission Quality and Integrity

The data quality and integrity of the studies were acceptable. The BLA submission was in electronic common technical document (eCTD) format and was adequately organized.

## 3.2. Statistical Analysis of Clinical Data

The quality of the original data submission and the additional submissions in response to information requests were adequate to support evaluation and review of the submission.

## 3.3. Compliance with Good Clinical Practices

All studies were conducted according to Good Clinical Practice (GCP) as described in International Conference on Harmonisation (ICH) Guideline E6 and in accordance with the ethical principles outlined in the Declaration of Helsinki. The studies were conducted in compliance with the protocols. Informed consent, protocol, amendments, and administrative letters for the studies received Institutional Review Board/Independent Ethics Committee approval prior to implementation. Subjects signed informed consent documents. Written informed consent was obtained prior to subjects entering the studies (before initiation of protocol-specified procedures). The investigators explained the nature, purpose, and risks of the study to each subject. Each subject was informed that he/she could withdraw from the study at any time and for any reason. Each subject was given sufficient time to consider the implications of the study before deciding whether to participate. The investigators conducted all aspects of these studies in accordance with applicable national, state, and local laws of the pertinent regulatory authority.

## 3.4. Financial Disclosures

The Applicant submitted financial disclosure information from 980 investigators from studies 20130108 (rheumatoid arthritis) and 20130109 (low tumor burden follicular lymphoma). In Study 20130108, there were 335 investigators with financial disclosure information and no investigators had disclosable financial interest or arrangements. In Study 20130109, there were 645 investigators with financial disclosure information and no investigators had disclosable

financial interest or arrangements. For details, refer to the Clinical Investigator Financial Disclosure Review Template in Section 13.1.

# 4. Summary of Conclusions of Other Review Disciplines

## 4.1. Chemistry, Manufacturing and Controls (CMC)

ABP 798 (rituximab-arrx) binds to CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes, and malignant B cells. Upon binding to CD20, ABP 798 mediates B-cell lysis. Possible mechanisms of cell lysis include complement dependent cytotoxicity (CDC), antibody dependent cell mediated cytotoxicity (ADCC), signaling induced cell death (apoptosis), and antibody dependent cellular phagocytosis (ADCP), which are applicable to known and potential mechanisms of action of rituximab in B cell malignancies and in autoimmune diseases.

ABP 798 is produced in genetically engineered Chinese Hamster Ovary (CHO) cells. ABP 798 drug product has the same strengths, dosage form, and route of administration as US-licensed Rituxan. ABP 798 also has the same formulation and presentation as US-licensed Rituxan. Riabni is a sterile, preservative-free colorless to pale yellow, clear to opalescent solution for intravenous (IV) infusion and supplied in single-dose vials containing ABP 798 at 100 mg/10 mL or 500 mg/50 mL. The manufacture of ABP 798 is well-controlled and leads to a product that is safe, pure, and potent.

Strengths,presentation, and dosage forms:

- 100 mg/10 mL (10 mg/mL), single-dose vial, injection
- 500 mg/50 mL (10 mg/mL), single-dose vial, injection

Dating period:

- Drug Product: 36 months at 5°C
- Drug Substance: (b) (4) months at (b) (4) °C

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for Immunex Rhode Island Corporation (FEI 3003359885) and (b) (4) proposed for ABP 798 drug substance and drug product manufacture, respectively. All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspectional coverage as described in Table 1.

The commercial manufacture of ABP 798 drug substance at Immunex Rhode Island (ARI) is recommended for approval by Office of Pharmaceutical Manufacturing Assessment (OPMA) through the review of requested manufacturing site records in lieu of an on-site inspection

under Section 704(a)(4) (FDASIA Sec. 706). The commercial manufacture of ABP 798 drug product at (b) (4) was recommended for approval by OPMA based on the firm's compliance history, current acceptable CGMP status, and the (b) (4) manufacture of other licensed products on the same vial-filling line.

To support a demonstration that ABP-798 is highly similar to US-licensed Rituxan, and to establish the analytical portion of the scientific bridge, the Applicant performed a comparative analytical assessment using 37 lots of US-licensed Rituxan, 30 lots of EU-approved MabThera, and 14 independent lots of ABP 798 drug product.

The analytical assessment included:

- Extensive comparative physiochemical and functional assessments of quality attributes.
- Comparative assessments of the degradation profiles under forced degradation conditions.

The Applicant used a risk-based approach for statistical evaluation of the analytical results:

- High risk-ranked attributes tested using quantitative assays were evaluated by equivalence testing.
- Moderate risk-ranked attributes tested using quantitative assays were evaluated by quality ranges (QR) (non-adjusted, age-adjusted or initial time point quality ranges) or using an expectation approach in which individual values were compared to a pre-defined limit or interval based on method capability and product knowledge. Age-adjusted quality ranges were considered as supportive data as part of the comparative analytical assessment.
- Low risk-ranked attributes or attributes tested using qualitative assays were evaluated using side-by-side visual comparisons.

Results from method validation, qualification, verification and transfer studies were provided to support the suitability of the methods used in the comparative analytical assessment.

The analytical data support a demonstration that ABP 798 is highly similar to US-licensed Rituxan, notwithstanding minor differences in clinically inactive components. ABP 798 has the same strengths, dosage form, and route of administration as US-licensed Rituxan. ABP 798 has the same formulation and presentation as US-licensed Rituxan. The Applicant used a comprehensive array of analytical methods that were suitable to evaluate the critical quality attributes of ABP 798 and US-licensed Rituxan to support the demonstration that the products are highly similar. The numbers and types (strengths, expiry range, purpose of material) of lots tested and statistical analyses were appropriate to allow for a meaningful evaluation of the results of the analytical studies. The observed differences do not preclude a demonstration that ABP 798 and US-licensed Rituxan are highly similar. Refer to the Comparative Analytical Assessment chapter of the Integrated Quality Assessment for more details.

Three pairwise comparisons of ABP 798, US-licensed Rituxan, and EU-approved MabThera were used to establish the analytical component of the scientific bridge to support the relevance of the data generated from studies using EU-approved MabThera as the comparator to the assessment of biosimilarity. The Applicant supported the establishment of the analytical portion of the scientific bridge using the same methods and statistical approaches used to support a demonstration that ABP 798 is highly similar to US-licensed Rituxan. The data support the conclusion that the analytical portion of the scientific bridge was established.

## 4.2. Microbiology

Drug Substance (DS): Microbial quality of the DS manufacturing process is controlled (b) (4) Bioburden and endotoxin samples are monitored (b) (4) Microbial control (b) (4) was demonstrated (b) (4) Adequate controls are in place to maintain microbiological product quality during maximum hold periods and throughout the manufacturing process.

Drug Product (DP): (b) (4) Bioburden and endotoxin are tested during manufacture. Sterility and endotoxin are tested at release. Container closure integrity test using a validated vacuum decay method is included in the stability program.

## 4.3. Devices

Not applicable

### 4.3.1 Center for Devices and Radiological Health (CDRH)

Not applicable

### 4.3.2 Division of Medication Error Prevention and Analysis (DMEPA)

Not applicable

## 4.4. Office of Study Integrity and Surveillance (OSIS)

The Office of Study Integrity and Surveillance conducted a remote record review of the analytical portion of Study 20130108 conducted at (b) (4) (b) (4) For the analytical portion of Study 20130108, it was recommended that the PK, ADA, and nAb data be accepted with a few considerations and exceptions.

PK Data: OSIS recommended that the review division consider the potential impact of ADAs on the quantitation of ABP 798, EU-approved MabThera, and US-licensed Rituxan for 117 study samples confirmed as ADA positive. It was recommended that the remaining PK data from Study 20130108 was acceptable for Agency review.

ADA Data: OSIS recommended that the ADA data be accepted for Agency review. However, OSIS recommended that the review division consider the potential impact of drug intolerance on ADA results from 258 samples, which had drug concentrations above the the drug tolerance limit of the ADA assay and were reported as ADA negative.

nAb Data: OSIS recommended that the nAb data be accepted for Agency review with the following conisderations.

- Thirty-three samples that were screened as nAb negative had drug concentration above the quantitation limit were not reliable due to the issue of drug intolerance.
- For 35 other samples that were screened as nAb negative and had drug concentration below the quantitation limit, OSIS recommended the review division consider the potential impact from drug intolerance.
- For 29 samples reported as nAb positive, OSIS recommended the review division accept the results with consideration that the titer results from 4 samples, reported as nAb titer of 12,500, were likely underestimated.

The Office of Clinical Pharmacology acknowledged OSIS's recommendations. However, none of the samples identified by OSIS were included as part of the PK similarity assessment, and as such those samples did not alter the results or conclusions of the PK similarity analysis. Furthermore, as it relates to the drug tolerance levels for the ADA and nAb assays, the data were found to be acceptable considering 1) nAbs were detected in clinical samples with higher serum study drug levels (over 0.4 µg/mL, for example at weeks 24, 30 and 48), 2) the impact of ADA on PK and efficacy was comparable, and 3) the incidence of ADA is comparable. Refer to Section 6.3.4 and 6.4 and OBP Immunogenicity reviews for further details on PK and immunogenicity, respectively.

## 4.5. Office of Scientific Investigations (OSI)

Clinical site inspections were requested for two foreign clinical sites (France and Italy) and for the contract research organization (CRO) (b) (4) The Office of Scientific Investigations conducted an inspection at (b) (4) however the two foreign clinical

site inspections were cancelled due to the COVID-19 pandemic.

The CRO (b) (4) was inspected to evaluate the CRO's practices and procedures to determine compliance with applicable regulations for Study 20130109 in support of the BLA. The inspection of (b) (4) did not identify regulatory deficiencies with oversight and monitoring of the trial. Data from Study 20130109, based on the inspection, appear reliable in support of the proposed indications being sought.

A review of the Study 20130109 clinical site characteristics (i.e., number screened, number enrolled, overall response rate by treatment arm, serious adverse events, and protocol violations) demonstrated no meaningful differences between the clinical sites and the overall study outcomes, including the two foreign clinical sites selected for inspection and subsequently cancelled. Further, evaluation of the safety data submitted by the Applicant from Study 20130108 and 20130109 were determined to be of of adequate quality and there were no concerns regarding data integrity. Therefore, based on the inspection of the CRO (b) (4) and the safety data quality review, the clinical site inspections for Study 20130109 were determined to be not necessary to support the BLA.

# 5. Nonclinical Pharmacology and Toxicology Evaluation and Recommendations

## 5.1. Nonclinical Executive Summary and Recommendation

ABP 798 was developed as a biosimilar to US-Rituxan. Binding of US-Rituxan to CD20-positive tumor cells targets them for immunologically-mediated cell death.

A 4-week repeat-dose toxicology study in Cynomolgus monkeys with sacrifice on day 29 was conducted to compare US-Rituxan with ABP 798 for on-target and off-target toxicities. Once-weekly IV injections of vehicle control, US-Rituxan (20 mg/kg), or ABP 798 (20 mg/kg) resulted in no toxicological differences between the US-Rituxan and ABP 798 treatment groups with minimal toxicity related to the on-target activity in B cells. The results from this study support a demonstration of that ABP 798 is biosimilar to US-Rituxan.

In vitro studies summarized in section 2.3 were also conducted. Refer to Section 13.2 for detailed information. The results of these studies support a demonstration that ABP 798 is biosimilar to US-Rituxan.

### 5.1.1 Nonclinical Residual Uncertainties Assessment

There are no residual uncertainties identified in the nonclinical studies.

## 5.2. Product Information

**Product Formulation**

ABP 798 and US-licensed Rituxan are chimeric IgG1κ monoclonal antibodies against CD20, composed of human constant and murine variable regions. ABP 798 is manufactured using the Chinese hamster ovary (CHO) cell line. The antibody contains a single N-glycosylation site at Asn301 on each heavy chain. ABP 798 drug product is supplied as a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution intended for intravenous administration, containing 100 mg or 500 mg deliverable drug product. The vial contains a 10 mL or 50 mL deliverable volume of 10 mg/mL ABP 798 and compendial excipients, including 154 mM sodium chloride (9 mg/mL), 25 mM sodium citrate dihydrate (7.35 mg/mL), 0.07% (w/v) polysorbate 80 (0.7 mg/mL), and water for injection, at pH 6.5. ABP 798 is intended for intravenous administration. ABP 798 has the same formulation as US-licensed Rituxan.

**Comments on Novel Excipients**

There are no novel excipients.

**Comments on Impurities/Degradants of Concern**

Impurities and degradants are within appropriate specifications (refer to the Integrated Quality Assessment review). There are no impurities or degradants of concern.

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# 6. Clinical Pharmacology Evaluation and Recommendations

## 6.1. Clinical Pharmacology Executive Summary and Recommendation

| Review Issue | Recommendations and Comments |
|---|---|
| **Pharmacokinetics Similarity** | • Pharmacokinetic similarity between ABP 798 and US-Rituxan was demonstrated in patients with rheumatoid arthritis (RA) (Study 20130108) and supports a demonstration of no clinically meaningful difference between ABP 798 and US-Rituxan.<br>• These data also establish the PK component of the scientific bridge to support the relevance of |

| | |
|---|---|
| | comparative data generated using EU-MabThera in Study 20130108 to the assessment of biosimilarity. |
| **Pharmacodynamics Similarity** | • Not applicable |
| **Immunogenicity** | • The incidence of ADA and nAb formation for ABP 798 was comparable to that of US-Rituxan in patients with RA (Study 20130108) and in patients with Non-Hodgkin lymphoma (NHL) (Study 20130109). The comparable incidence of immunogenicity between ABP 798 and US-Rituxan in both studies supports a demonstration of no clinically meaningful differences between ABP 798 and US- Rituxan. |
| **Other (specify)** | • Not applicable. |

The clinical development for ABP 798 included 2 clinical studies:

1. Study 20130108, a PK similarity study (with an extension) to compare the PK, efficacy, safety, and immunogenicity of ABP 798, US-Rituxan, and EU-MabThera in adult patients with moderate to severe, active RA (n=104/ABP 798 arm, n=103/US-Rituxan arm, n=104/EU-MabThera arm);
2. Study 20130109, a comparative clinical study in adult patients with grade 1, 2, or 3a follicular B-cell NHL and low tumor burden evaluating ABP 798 (n=128) and US-Rituxan (n=128).

The results of the PK similarity study (Study 20130108) demonstrated PK similarity between ABP 798 and US-Rituxan. These data also establish the PK component of the scientific bridge to support the relevance of comparative data generated using EU-MabThera to the assessment of biosimilarity. In this study, the 90% confidence interval (CI) for the least square (LS) geometric means ratios (GMRs) for area under the serum concentration-time curve (AUC) from time 0 to infinity ($AUC_{inf}$), AUC from time 0 to week 12 ($AUC_{0\text{-}12wk}$), and AUC from time 0 to 14 days ($AUC_{0\text{-}14day}$) were contained within the pre-defined criteria of 80 to 125% (Table 6).

**Table 6: Study 20130108 PK Similarity Summary**

| PK Parameter | LS Geometric Mean (n) | | | LS GMR* (90% CI) | | |
|---|---|---|---|---|---|---|
| | ABP 798 | US-Rituxan | EU-MabThera | ABP 798 vs. US-Rituxan | ABP 798 vs. EU-MabThera | EU-MabThera vs. US-Rituxan |
| $AUC_{inf}$ (µg·hr/mL) | 152371.4 (94) | 159236.0 (94) | 172213.2 (96) | 95.69 (88.70, 103.23) | 88.48 (82.04, 95.42) | 108.15 (100.30, 116.62) |
| $AUC_{0\text{-}12wk}$ (µg·hr/mL) | 149590.5 (99) | 155778.7 (96) | 166811.0 (100) | 96.03 (89.50, 103.03) | 89.68 (83.63, 96.16) | 107.08 (99.84, 114.85) |
| $AUC_{0\text{-}14day}$ (µg·hr/mL) | 42203.8 (98) | 43378.8 (93) | 44925.3 (97) | 97.29 (91.74, 103.18) | 93.94 (88.63, 99.58) | 103.56 (97.66, 109.84) |
| $C_{max}$ following $1^{st}$ infusion of first dose (µg/mL) | 304.04 (103) | 305.80 (99) | 320.87 (103) | 99.42 (94.61, 104.48) | 94.75 (90.21, 99.53) | 104.92 (99.85, 110.25) |
| $C_{max}$ following $2^{nd}$ infusion of first dose (µg/mL) | 368.43 (96) | 374.44 (93) | 393.29 (97) | 98.40 (93.56, 103.48) | 93.68 (89.12, 98.48) | 105.03 (99.90, 110.44) |

*Presented as percent
Results based on ANCOVA model with treatment as fixed effect, and body weight and geographic region as covariates
**Source:** Table 10-1 and 10-2 of Clinical Study Report 20130108; LS GMR (90%CI) for EU-MabThera vs. US-Rituxan comparison represents the reciprocal values for the US-Rituxan vs. EU- MabThera comparison provided by the Applicant.

The immunogenicity of ABP 798 was comparable to that of US-Rituxan and EU-MabThera after repeat dosing in patients with RA and comparable to that of US-Rituxan after repeat dosing in patients with NHL. Also, in RA patients, the immunogenicity after a single transition from US-Rituxan to ABP 798 was overall comparable to those patients who did not undergo a single transition .

The overall incidence of anti-drug antibody (ADA) formation over the course of the study in patients with RA at Week 24 (before undergoing a single transition) was 13.4%, 10.6%, and 18.6 % in the ABP 798, EU-MabThera, and US-Rituxan treatment arms, respectively, and at end of study at Week 48 was 14.4%, 13.8%, and 20.6% in the ABP 798/ABP 798, EU-MabThera/EU-MabThera, and US-Rituxan/ABP 798 treatment arms, respectively (Study 20130108). The overall incidence of neutralizing antibody (nAb) formation over the course of the study in patients with RA at Week 24 (before undergoing a single transition) was 8.2%, 2.1%, 8.2% in the ABP 798, EU-MabThera, and US-Rituxan arms, respectively, and at the end of study at Week 48 was 8.2%, 4.3%, and 10.3% in the ABP 798/ABP 798, EU-MabThera/EU-MabThera, and US-Rituxan/ABP 798 treatment arms, respectively (Study 20130108). In RA patients, the overall ADA and nAb

incidence was not impacted by the single transition from US-Rituxan to ABP 798 as compared to patients who did not undergo a single transition, with the data showing that no patients who were previously ADA negative at all time points developed ADA positive status after transitioning to ABP 798 (Study 20130108).

Following repeat IV dosing in patients with NHL, the incidence of ADA formation over the course of the study was 2.4% and 0.8% in the ABP 798 and US-Rituxan treatment arms, respectively (Study 20130109). Following repeat IV dosing in patients with NHL, the incidence of nAb formation was 0.8% in both the ABP 798 and US-Rituxan treatment arms (Study 20130109).

### 6.1.1 Clinical Pharmacology Residual Uncertainties Assessment

PK similarity was demonstrated between ABP 798 and US-Rituxan in the 3-way PK similarity study (Study 20130108). Comparable incidence of immunogenicity for ABP 798 and US-Rituxan was observed in Studies 20130108 and 20130109. There were no clinical pharmacology residual uncertainties regarding the PK or immunogenicity assessment to support a demonstration of biosimilarity.

## 6.2. Clinical Pharmacology Studies to Support the Use of a Non-U.S.-Licensed Comparator Product

Study 20130108 adequately demonstrated PK similarity between ABP 798, US-Rituxan, and EU-MabThera, establishing the PK component of the scientific bridge.

## 6.3. Human Pharmacokinetics and Pharmacodynamics

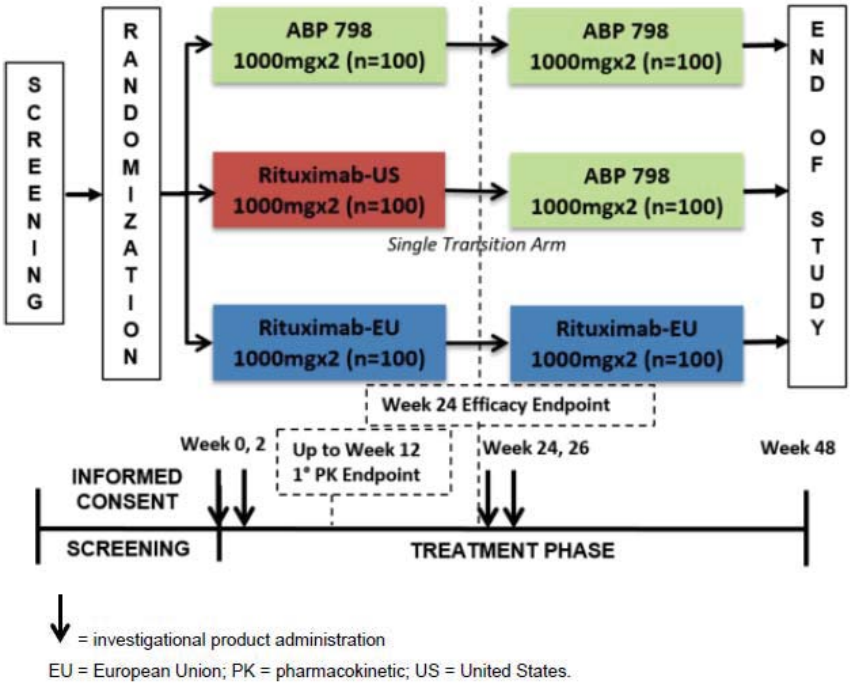
### 6.3.1 Clinical Pharmacology Study Design Features

The PK similarity study comparing ABP 798, US-Rituxan, and EU-MabThera was conducted in adult patients with moderate to severe, active RA who were on methotrexate (MTX) (≥ 7.5 mg/week) at a stable dose for ≥8 weeks prior to screening (Study 20130108, Figure 1). Approximately 300 patients were planned for dosing as shown in the schematic below. Patients received either ABP 798 (single-use vial), US-Rituxan (single-use vial), or EU-MabThera (single-use vial) at a dose of 1000 mg × 2 IV infusions administered 2 weeks apart on Day 1 and 15. At Week 24, patients initially randomized to receive ABP 798 or EU-MabThera were administered a second dose of the same treatment, while patients initially randomized to receive US-Rituxan were transitioned to receive ABP 798 (second dose). Patients received either ABP-798 or EU-MabThera at a dose of 1000 mg × 2 IV infusions administered 2 weeks apart on Week 24 and 26.

PK comparison between ABP 798 and US-Rituxan was also assessed in the comparative clinical study in adult patients with grade 1, 2, or 3a follicular B-cell NHL (Study 20130109, see Section 6.4 for study design).

Refer to Table 5 for a summary of the studies mentioned above.

**Figure 1: Study 20130108 Schema**




**Source:** Figure 8-1 of Clinical Study Report 20130108

### 6.3.2 Clinical Pharmacology Study Endpoints

In Study 20130108, the following PK endpoints, $AUC_{inf}$, $AUC_{0\text{-}14day}$, $AUC_{0\text{-}12wk}$, and $C_{max}$ of the first dose, were evaluated to compare the PK profiles of ABP 798, US-Rituxan, and EU-MabThera. Pharmacodynamics, efficacy (DAS28-CRP change from baseline at Week 24; primary efficacy endpoint), safety, and immunogenicity were the secondary endpoints of the study. The PK sampling schedule was as follows, Day 1 pre-dose, at end-of-infusion (EOI), and 3, 6 hours post-dose, 24 hours post-dose (Day 2), and 48 hours post-dose (Day 3), Day 15 pre-dose, at EOI, and 3, 6 hours post-dose, 24 hours post-dose (Day 16), and 48 hours post-dose (Day 17), and at Week 4, 8, 12, 24 (pre-dose), 26 (pre-dose), 30, and 48/end of study (EOS). Refer to Section 7 for detailed information on the efficacy and safety endpoints for Study 20130108.

In the comparative clinical study in patients grade 1, 2, or 3a follicular B-cell NHL (Study 20130109, Figure 8), the primary efficacy endpoint was the risk difference (RD) of overall response rate (ORR) by Week 28, whereas PK, PD, safety, immunogenicity and other efficacy endpoints (RD of ORR at Week 12) were secondary endpoints. Blood samples for PK comparison of ABP 798 and US-Rituxan were collected at baseline on Day 1, pre-dose at Weeks 2, 3, 4, 12, 20, immediately after EOI at Week 12, and a single PK sample at Week 28/EOS. Optional PK samples were collected at 2 hours post-dose at Week 1 and 4, and at Week 5. Refer to Section 7 for detailed information on the efficacy and safety endpoints for Study 20130109.

### 6.3.3 Bioanalytical PK Method and Performance

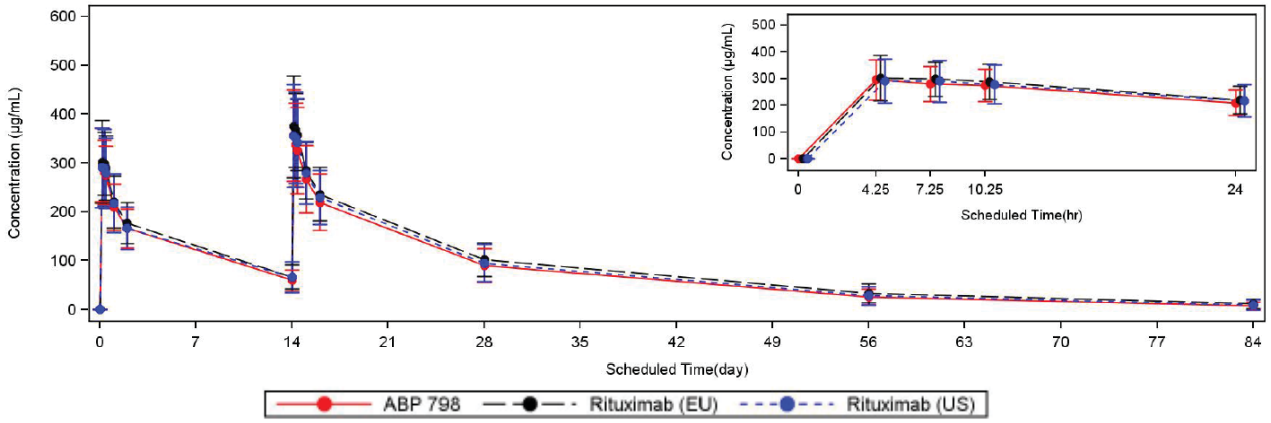
The methodologies used in the analysis of biological samples were sensitive, robust, and fully validated.

Serum concentrations of ABP 798, US-Rituxan, and EU-MabThera were quantified using a validated electrochemiluminescent (ECL) method. The ECL method was developed at Amgen, Inc. and validated at (b) (4). Method validation (method qualification report number: 120191; method validation report number: 120192, 120192 addendum #1) and sample analysis supporting studies 20130108 and 20130109 (bioanalytical clinical report, Amgen PKDM No. 120368 and 120490, respectively) were in-line with the Agency's recommendations outlined in the guidance for industry *Bioanalytical Method Validation* (May 2018), and all acceptance criteria as specified in the guidance were met. During method validation, ABP 798 was used to establish the calibration curves, and the accuracy and precision was evaluated using ABP 798, US-Rituxan, and EU-MaThera as quality control (QC) samples. See detailed information about the method validation in Appendix 13.4.

### 6.3.4 PK Similarity Assessment

The data from the PK similarity study (Study 20130108) establish the PK similarity between ABP 798 and US-Rituxan. These data also establish the PK component of the scientific bridge to support the relevance of the comparative data generated using EU-MabThera to the assessment of biosimilarity. Mean serum concentration-time profiles for ABP 798 (N = 104), US-Rituxan (N = 103), and EU-MabThera (N = 104) through Week 12 following IV infusion of 1000 mg on Day 1 and 15 are shown in Figure 2 and were similar between the 3 treatment arms. The 90% CIs for the LS GMRs of $AUC_{inf}$, $AUC_{0\text{-}12wk}$, and $AUC_{0\text{-}14day}$ were all within the pre-defined criteria of 80 to 125% (Table 6). Independent analyses conducted by the reviewer showed results that are comparable to that reported by the Applicant.

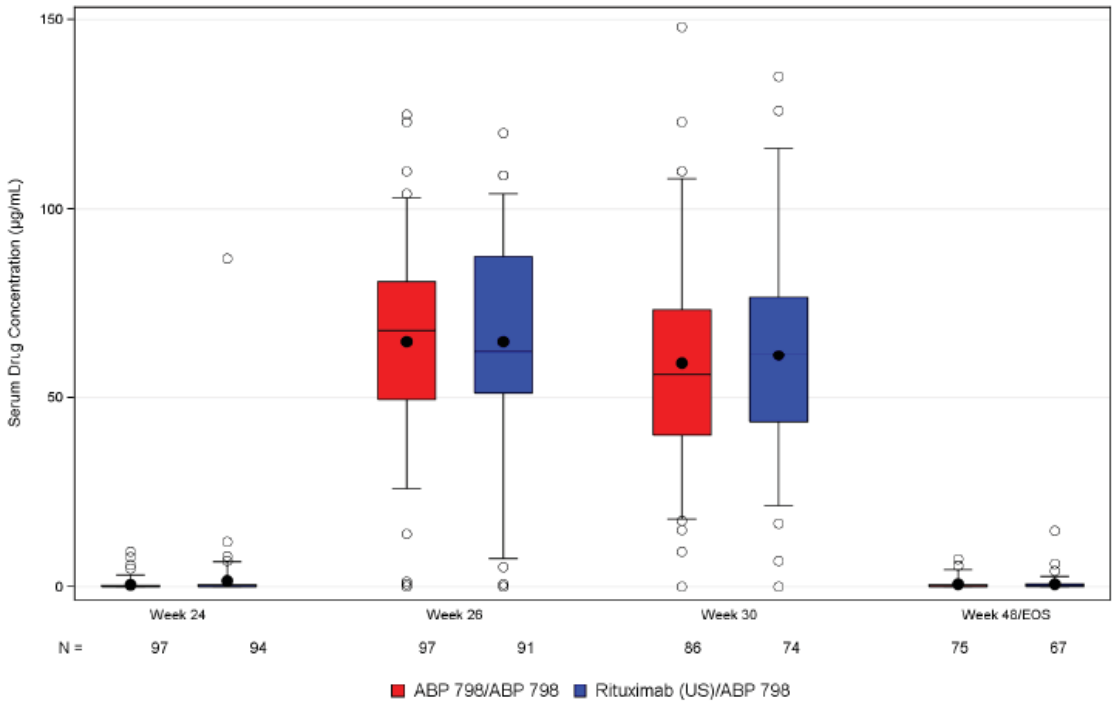
**Figure 2: Mean (±SD) Serum Concentration-Time Profiles Through Week 12 Following IV Infusion of 1000 mg on Day 1 and 15 of ABP 798, US-Rituxan, EU-MabThera in Patients with RA (Study 20130108)**




**Source:** Figure 10-1 of Clinical Study Report 20130108

The serum trough concentrations over time from Week 24 through Week 48 (EOS) in the ABP 798 treatment arm (ABP 798/ABP 798) and US-Rituxan transitioned to ABP 798 treatment arm (US-Rituxan/ABP 798) following the second dose of 1000 mg IV infusion administered on Week 24 and 26 were generally in the same range in RA patients (Figure 3).

**Figure 3: Boxplot of Serum Trough Concentrations Over Time from Week 24 Through Week 48 Following IV Infusion of 1000 mg on Week 24 and 26 in the ABP 798/ABP 798 Treatment Arm and US-Rituxan/ABP 798 Treatment Arm in Patients with RA (Study 20130108)**

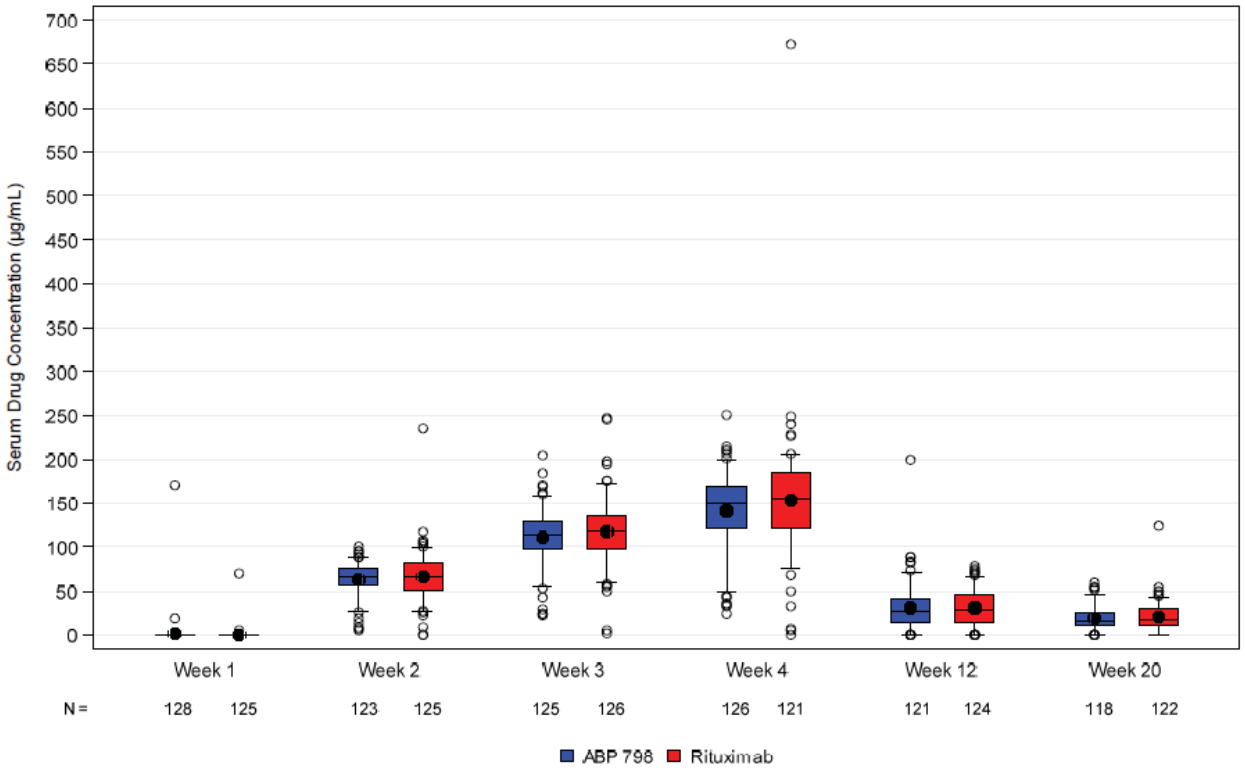



The solid black circle represents the mean and the horizontal line inside the box represents the median
**Source:** Figure 14-9.4.5. of Clinical Study Report 20130108

Biopharmaceutical inspection was requested for the bioanalytical site for Study 20130108. Refer to Section 4.4 for detailed information relating to the OSIS recommendations. The Office of Clinical Pharmacology acknowledged OSIS's recommendations. However, none of the samples identified by OSIS were included as part of the PK similarity assessment, and as such those samples did not alter the results or conclusions of the PK similarity analysis.

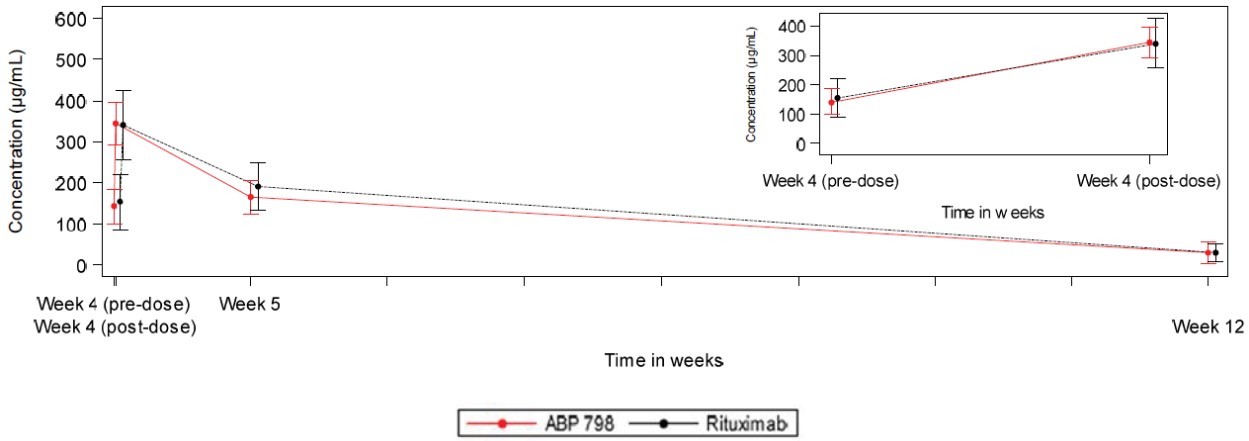
In the comparative clinical study in patients with grade 1, 2, or 3a follicular B-cell NHL (Study 20130109), following multiple IV infusion doses of either ABP 798 or US-Rituxan, the serum concentrations over time profiles (Figure 4 and Figure 5) were generally in the same range across the treatment arms.

**Figure 4: Boxplot of Serum Trough Concentrations Over Time Through Week 20 Following Multiple IV Infusion Doses of Either ABP 798 or US-Rituxan in Patients with NHL (Study 20130109)**




Rituximab refers to US-Rituxan
**Source:** Figure 11-1 of Clinical Study Report 20130109

**Figure 5: Mean (±SD) Serum Concentration-Time Profiles From Week 4 Through Week 12 Following Multiple IV Infusion Doses of Either ABP 798 or US-Rituxan in Patients with NHL (Study 20130109)**




Rituximab refers to US-Rituxan
**Source:** Figure 11-2 of Clinical Study Report 20130109

### 6.3.5 PD Similarity Assessment

B-cell kinetic data was not used to support PD similarity assessment for ABP 798 and US-Rituxan, and it was not necessary to support a demonstration of biosimilarity.

**Exploratory PD assessment**
Circulating CD19+ B-cell counts, a surrogate marker for CD20+ B-cells, were measured in both the PK similarity study and comparative clinical study. In Study 20130108, the percent of patients with complete depletion in the CD19+ cell count at Day 3 was comparable between the treatment arms (94.8%, 96.9%, 92.8% in the ABP 798, EU-MabThera, and US-Rituxan arms, respectively). In Study 20130109, the percent of patients with complete depletion of CD19+ cell count at Day 8 was comparable between the treatment arms (98.3% for both the ABP-798 and US-Rituxan arms).

## 6.4. Clinical Immunogenicity Studies

**Design features of the clinical immunogenicity assessment**

Immunogenicity assessment upon repeat dosing of ABP 798, US-Rituxan, and EU-MabThera has been evaluated in patients with moderate to severe, active RA in Study 20130108. In one treatment arm, patients initially randomized to US-Rituxan underwent a single transition to ABP 798 treatment at Week 24. Refer to Table 5 and Figure 1 for more details on the study design.

Immunogenicity assessment upon repeat dosing of ABP 798 and US-Rituxan has been evaluated in patients with grade 1, 2, or 3a follicular B-cell NHL in the comparative clinical study, Study 20130109 (Figure 8). Approximately 250 patients were planned to be randomized (1:1) to receive a 375 mg/m$^2$ IV infusion of either ABP 798 (single-dose vial; n=128) or US-Rituxan (single-dose vial; n=128) once-weekly for 4 weeks followed by dosing at Weeks 12 and 20. Patients remained in the study until Week 28.

Refer to Table 5 for a summary of the studies mentioned above.

**Immunogenicity endpoints**

In Studies 20130108 and 20130109, the formation of ADA and the neutralizing activity of ADA were evaluated for immunogenicity assessment.

**Immunogenicity assay's capability of detecting the antidrug antibodies (ADA) in the presence of proposed product, reference product, and any other comparator product (as applicable) in the study samples**

(b) (4) developed the binding antibody assay for detecting ADA in the presence of concentrations of ABP 798, US-Rituxan, and EU-MabThera. The drug tolerance for this assay is 72.1 µg/mL ABP

798, 65 µg/mL US-Rituxan, and 170 µg/mL EU-MabThera tolerated in the presence of 10 ng/mL of ADA and up to 200 µg/mL ABP 798, US-Rituxan, and EU-MabThera tolerated in the presence of 500 ng/mL and 1000 ng/mL of ADA. Amgen Inc. developed the neutralizing antibody assay for detecting nAb in the presence of ABP 798 concentrations. The Office of Clinical Pharmacology and the Office of Biotechnology Products (OBP) acknowledged OSIS's recommendations (refer to Section 4.4). The drug tolerance for this assay is up to 200 ng/mL excess ABP 798 and up to 400 ng/mL excess ABP 798 tolerated in the presence of 400 ng/mL and 800 ng/mL, respectively, positive control ADA. The 0.4 µg/mL study drug concentration is slightly below the lowest mean serum concentration of ABP 798 detected in Study 20130108 of 0.54 µg/mL. This is acceptable considering 1) nAbs were detected in clinical samples with higher serum study drug levels (over 0.4 µg/mL, for example at weeks 24, 30 and 48), 2) the impact of ADA on PK and efficacy was comparable, and 3) the incidence of ADA is comparable. Refer to the OBP Immunogenicity review for further details.

**Adequacy of the sampling plan to capture baseline, early onset, and dynamic profile (transient or persistent) of ADA formation**

The sampling plan is adequate to capture the baseline, early onset, and dynamic profile of ADA formation:

- Study 20130108: Blood samples were collected at baseline, and at Week 2, 24, 30 and 48/EOS for assessment of the ADA formation of ABP 798, US-Rituxan, and EU-MabThera

- Study 20130109: Blood samples were collected at baseline, and at Week 12, 20, and 28/EOS for assessment of the ADA formation of ABP 798 and US-Rituxan

**Incidence of ADA (Provide the incidence of pre-existing antibodies at baseline and the incidence of ADA throughout the study)**

In Study 20130108, immunogenicity at baseline were comparable between each treatment arm. Following 2 doses of 1000 mg × 2 IV infusions administered 2 weeks apart, 14/97 (14.4%), 13/94 (13.8%), and 20/97 (20.6%) patients developed ADA (ADA+) in the ABP 798/ABP 798, EU-MabThera/EU-MabThera, and US-Rituxan/ABP 798 treatment arms, respectively, by Week 48 (Table 7). Following the first dose of 1000 mg × 2 IV infusions administered 2 weeks apart, 13/97 (13.4%), 10/94 (10.6%), and 18/97 (18.6%) patients in the ABP 798, EU-MabThera, and US-Rituxan arms, respectively, had developed ADA by Week 24. Although there were some minor numerical differences, these differences were not considered meaningful and overall, the immunogenicity profile was comparable between the treatment arms prior to the single transition in the US-licensed Rituxan arm, as well as after a single transition from US-licensed Rituxan to ABP 798 as compared to not transitioning.

Study 20130108 also assessed the development of ADA and nAb and the potential for an increase in magnitude of immune response following a single transition from US-Rituxan to ABP 798 (US-Rituxan/ABP 798 arm). The first blood sample collected following transition to ABP 798 was at Week 30. In this treatment arm, the number of patients who developed ADA by Week

24 was 18/97 (18.6%) and by Week 30 was 20/97 (20.6%). No patients who were previously ADA negative at all time points developed ADA after receiving the second dose of ABP 798. The Applicant reports that 2 patients in the US-Rituxan/ABP 798 arm had a robust binding (ADA+) and neutralizing (nAb+) ADA response following the first dose and persisted after the second dose. Both patients developed nAb response prior to receiving the second dose of ABP 798, therefore, the response was not due to the single transition from US-Rituxan to ABP 798. In Study 20130108, the ADA incidence was overall similar between ABP 798, US-Rituxan, and EU-MabThera treatment arms and was not impacted by the single transition from US-Rituxan to ABP 798 in RA patients.

In Study 20130109, following administration of 375 mg/m$^2$ IV infusion once weekly for 4 weeks followed by dosing at Weeks 12 and 20, 3/126 (2.4%) and 1/123 (0.8%) patients developed ADA (ADA+) in the ABP 798 and US-Rituxan treatment arms, respectively, by Week 28 (Table 8). Overall, the ADA incidence was similar between the treatment arms following repeat dosing in patients with grade 1, 2, 3a follicular B-cell NHL.

## Table 7: Immunogenicity Results for Binding ADA and nAb in Study 20130108

| Variable | ABP 798/ ABP 798 (N = 104) | Rituximab (EU)/ Rituximab (EU) (N = 104) | Rituximab (US)/ ABP 798 (N =103) |
|---|---|---|---|
| Subjects with an on-study result[a] | 104 | 104 | 103 |
| Total antibody incidence, n (%) | | | |
| Binding antibody positive anytime | 21 (20.2) | 23 (22.1) | 26 (25.2) |
| Neutralizing antibody positive anytime | 11 (10.6) | 7 (6.7) | 14 (13.6) |
| Subjects with a result at baseline | 104 | 104 | 103 |
| Pre-existing antibody incidence, n (%) | | | |
| Binding antibody positive at baseline | 7 (6.7) | 10 (9.6) | 6 (5.8) |
| Neutralizing antibody positive at baseline | 2 (1.9) | 2 (1.9) | 3 (2.9) |
| Subjects with a binding negative or no result at baseline and a postbaseline result by week 2 | 93 | 87 | 91 |
| Developing antibody incidence, n (%) | | | |
| Binding antibody positive postbaseline | 5 (5.4) | 3 (3.4) | 5 (5.5) |
| Neutralizing antibody positive postbaseline | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Subjects with a binding negative or no result at baseline and a postbaseline result by week 24 | 97 | 94 | 97 |
| Developing antibody incidence, n (%) | | | |
| Binding antibody positive postbaseline | 13 (13.4) | 10 (10.6) | 18 (18.6) |
| Neutralizing antibody positive postbaseline | 8 (8.2) | 2 (2.1) | 8 (8.2) |
| Subjects with a binding negative or no result at baseline and a postbaseline result by week 30 | 97 | 94 | 97 |
| Developing antibody incidence, n (%) | | | |
| Binding antibody positive postbaseline | 14 (14.4) | 11 (11.7) | 20 (20.6) |
| Neutralizing antibody positive postbaseline | 8 (8.2) | 2 (2.1) | 10 (10.3) |
| Subjects with a binding negative or no result at baseline and a postbaseline result by week 48 | 97 | 94 | 97 |
| Developing antibody incidence, n (%) | | | |
| Binding antibody positive postbaseline | 14 (14.4) | 13 (13.8) | 20 (20.6) |
| Neutralizing antibody positive postbaseline | 8 (8.2) | 4 (4.3) | 10 (10.3) |
| Subjects with a binding negative or no result at baseline and a postbaseline result | 97 | 94 | 97 |
| Developing antibody incidence, n (%) | | | |
| Binding antibody positive postbaseline | 14 (14.4) | 13 (13.8) | 20 (20.6) |
| Transient[b] | 8 (8.2) | 8 (8.5) | 11 (11.3) |
| Neutralizing antibody positive postbaseline | 8 (8.2) | 4 (4.3) | 10 (10.3) |
| Transient[b] | 7 (7.2) | 2 (2.1) | 5 (5.2) |

IP = investigational product.
Note: Baseline was defined as the last non-missing assessment taken prior to the first dose of study IP. Percentages were calculated using the corresponding category count as the denominator.
[a] Subjects considered on-study after signing informed consent.
[b] A positive postbaseline result with a negative result at the subject's last time point tested within the study period.

Rituximab (US)/ABP 798 is the treatment arm in which patients transition from US-Rituxan to ABP 798 at Week 24

**Source:** Table 11-17 of Clinical Study Report 20130108

**Table 8: Immunogenicity Results for Binding ADA and nAb in Study 20130109**

| Variable | ABP 798 (N = 128) | Rituximab (N = 126) |
|---|---|---|
| Subjects with an on-study result[a] | 128 | 126 |
| Total antibody incidence, n (%) | | |
| Binding antibody positive anytime | 4 (3.1) | 4 (3.2) |
| Neutralizing antibody positive anytime | 1 (0.8) | 1 (0.8) |
| Subjects with a result at baseline | 127 | 126 |
| Pre-existing antibody incidence, n (%) | | |
| Binding antibody positive at or before baseline | 1 (0.8) | 3 (2.4) |
| Neutralizing antibody positive at or before baseline | 0 (0.0) | 0 (0.0) |
| Subjects with a binding antibody negative or no result at baseline and a postbaseline result by week 12 | 122 | 121 |
| Developing antibody incidence, n (%) | | |
| Binding antibody positive postbaseline | 3 (2.5) | 1 (0.8) |
| Neutralizing antibody positive postbaseline | 1 (0.8) | 1 (0.8) |
| Subjects with a binding antibody negative or no result at baseline and a postbaseline result by week 20 | 126 | 123 |
| Developing antibody incidence, n (%) | | |
| Binding antibody positive postbaseline | 3 (2.4) | 1 (0.8) |
| Neutralizing antibody positive postbaseline | 1 (0.8) | 1 (0.8) |
| Subjects with a binding antibody negative or no result at baseline and a postbaseline result by week 28 | 126 | 123 |
| Developing antibody incidence, n (%) | | |
| Binding antibody positive postbaseline | 3 (2.4) | 1 (0.8) |
| Neutralizing antibody positive postbaseline | 1 (0.8) | 1 (0.8) |
| Subjects with a binding antibody negative or no result at baseline and a postbaseline result | 126 | 123 |
| Developing antibody incidence, n (%) | | |
| Binding antibody positive postbaseline | 3 (2.4) | 1 (0.8) |
| Transient[b] | 2 (1.6) | 0 (0.0) |
| Neutralizing antibody positive postbaseline | 1 (0.8) | 1 (0.8) |
| Transient[b] | 1 (0.8) | 0 (0.0) |

Note: Baseline was defined as the last non-missing assessment taken prior to the first dose of investigational product. Percentages were calculated using the corresponding category count as the denominator.

[a] Subjects considered on-study after signing informed consent.

[b] Negative result at the subject's last time point tested within the study period.

**Source:** Table 11-4 of Clinical Study Report 20130109

## Neutralizing antibodies

In Study 20130108, following 2 doses of 1000 mg × 2 IV infusions administered 2 weeks apart, 8/97 (8.2%), 4/94 (4.3%), and 10/97 (10.3%) patients in the ABP 798/ABP 798, EU-MabThera/EU-MabThera, and US-Rituxan/ABP 798 treatment arms, respectively, developed nAb (nAb+) by Week 48 (Table 7). In the US-Rituxan/ABP 798 arm, the number of patients who

were nAb+ by Week 24 was 8/97 (8.2%) and at Week 30, after the transition to ABP 798, was 10/97 (10.3%). Refer to the 'incidence of ADA' section above for further details.

In Study 20130109, following administration of 375 mg/m$^2$ IV infusion once weekly for 4 weeks followed by dosing at Weeks 12 and 20, by Week 28, 1/126 (0.8%) and 1/123 (0.8%) patients in the ABP 798 and US-Rituxan, respectively, were nAb+ (Table 8).

The results of the nAb analyses support that nAb incidence was comparable between the products and was comparable between those who transitioned and those who did not.

**Impact of ADA on the PK, PD, safety, and clinical outcomes of the proposed biosimilar product**

Impact of ADA and nAb on PK

For Study 20130108, the impact of ADA and nAb status on the PK of ABP 798, US-Rituxan, and EU-MabThera before the single transition at Week 24 in patients with RA is shown in Table 9. In all treatment arms, clearance (CL) increased and half-life ($t_{1/2}$) decreased leading to lower systemic exposure in ADA+ patients compared to ADA- patients. A similar trend for CL and $t_{1/2}$ was observed in nAb+ patients compared to nAb- patients in the 3 treatment arms. Overall, the impact of ADA and nAb on the PK was comparable between the ABP 798 and US-Rituxan arms.

The impact of ADA and nAb status on the PK, efficacy, and safety following a single transition from US-Rituxan to ABP 798 was not assessed since it was considered not to be clinically meaningful given that no new patients developed ADA, the magnitude of the immune response was similar and generally low across the treatment arms following the transition, and comparable $C_{trough}$ between arms.

**Table 9: Clearance and Half-life of ABP 798, US-Rituxan, and EU-MabThera by ADA Status and nAb Status in Patients with RA (Study 2013108)**

| Parameter | | N | ABP 798 Mean (SD) | n | EU-MabThera Mean (SD) | n | US-Rituxan Mean (SD) |
|---|---|---|---|---|---|---|---|
| | **ADA Status** | | | | | | |
| CL (L/hr) | ADA+ | 13 | 0.02187 (0.01642) | 7 | 0.01577 (0.00480) | 17 | 0.01731 (0.00664) |
| | ADA- | 75 | 0.01292 (0.00380) | 80 | 0.01170 (0.00358) | 71 | 0.01242 (0.00428) |
| $t_{1/2}$ (hr) | ADA+ | 13 | 238.84 (88.06) | 8 | 291.42 (90.28) | 18 | 226.82 (74.62) |
| | ADA- | 77 | 381.44 (98.07) | 81 | 412.71 (118.29) | 72 | 390.84 (93.91) |
| | **nAb Status** | | | | | | |
| CL (L/hr) | nAb+ | 8 | 0.02511 (0.02006) | 2 | 0.01713 (0.00402) | 7 | 0.01680 (0.00344) |
| | nAb- | 80 | 0.01316 (0.00411) | 85 | 0.01190 (0.00376) | 81 | 0.01306 (0.00519) |
| $t_{1/2}$ (hr) | nAb+ | 8 | 219.32 (93.22) | 2 | 229.07 (89.59) | 8 | 196.90 (68.83) |
| | nAb- | 82 | 374.65 (100.22) | 87 | 405.78 (118.84) | 82 | 373.76 (102.26) |

**Source:** Appendix Table 1 and 2 of Summary of Clinical Pharmacology Studies

In Study 20130109, given that only a small number of patients developed ADA+ and nAb+ status, an assessment of the impact of ADA and nAb status on the PK, efficacy, and safety of ABP 798 and US-Rituxan in patients with NHL was not considered meaningful and therefore was not conducted.

Impact of ADA and nAb on efficacy

For Study 20130108 in patients with RA, the impact of ADA and nAb status on the primary efficacy endpoint of DAS28-CRP change from baseline at Week 24 in the ABP 798, US-Rituxan, and EU-MabThera treatment arms is shown in Table 10. Numerically, the DAS28-CRP change from baseline at Week 24 seem comparable between the ABP 798 and US-Rituxan treatment arms, for both ADA+ and ADA- patients, as well as nAb+ and nAb- patients. Although caution should be exercised given the small sample sizes in the ADA+ and nAb+ groups, the results as shown in numerical changes in DAS28-CRP from baseline at Week 24 are comparable between the ABP 798 and US-Rituxan treatment arms.

**Table 10: Repeated Measures Analysis of DAS28-CRP Change From Baseline at Week 24 by ADA and nAb Status in Patients with RA (Study 20130108)**

| | ABP 798 | EU-MabThera | US-Rituxan |
|---|---|---|---|
| **ADA** | | | |
| **ADA+** | | | |
| N | 13 | 10 | 19 |
| Week 24 Change from Baseline | | | |
| Adjusted Mean (SE)[a] | -2.464 (0.4944) | -2.233 (0.5128) | -2.240 (0.4166) |
| 95% CI[a] | -3.458, -1.469 | -3.271, -1.195 | -3.081, -1.398 |
| Difference between Means[a] | | -0.230 | -0.224 |
| 90% CI[a] | | -1.239, 0.778 | -1.095, 0.647 |
| 95% CI[a] | | -1.442, 0.981 | -1.271, 0.823 |
| **ADA-** | | | |
| N | 84 | 84 | 78 |
| Week 24 Change from Baseline | | | |
| Adjusted Mean (SE)[a] | -1.952 (0.1417) | -2.098 (0.1450) | -1.769 (0.1497) |
| 95% CI[a] | -2.231, -1.673 | -2.383, -1.812 | -2.064, -1.474 |
| Difference between Means[a] | | 0.146 | -0.183 |
| 90% CI[a] | | -0.166, 0.457 | -0.500, 0.134 |
| 95% CI[a] | | -0.226, 0.518 | -0.561, 0.195 |
| **nAb** | | | |
| **nAb+** | | | |
| N | 8 | 2 | 8 |
| Week 24 Change from Baseline | | | |
| Adjusted Mean (SE)[a] | -2.718 (0.8460) | -0.820 (1.3910) | -2.333 (0.6591) |
| 95% CI[a] | -4.562, -0.874 | -3.847, 2.207 | -3.782, -0.884 |
| Difference between Means[a] | | -1.898 | -0.385 |
| 90% CI[a] | | -4.233, 0.437 | -1.818, 1.047 |
| 95% CI[a] | | -4.763, 0.967 | -2.151, 1.381 |
| **nAb-** | | | |

| | | | |
|---|---|---|---|
| n | 89 | 92 | 89 |
| Week 24 Change from Baseline | | | |
| Adjusted Mean (SE)[a] | -1.964 (0.1372) | -2.106 (0.1380) | -1.811 (0.1421) |
| 95% CI[a] | -2.234, -1.694 | -2.378, -1.834 | -2.091, -1.531 |
| Difference between Means[a] | | 0.142 | -0.153 |
| 90% CI[a] | | -0.156, 0.439 | -0.455, 0.149 |
| 95% CI[a] | | -0.213, 0.497 | -0.513, 0.207 |

[a] Adjusted mean, SE, 95% CI of adjusted mean, difference between means (ABP 798 - Rituximab), 90% and 95% CIs for difference between means is based on repeated measures analysis with the DAS28-CRP change from baseline as the response and the stratification variables (for region strata levels are EU vs. NA), visit, treatment, treatment-by-visit interaction and the baseline DAS28-CRP measurement as predictors, and unstructured covariance structure in the model
**Source:** Table 14-4.2.5. and Table 14-4.2.6. of Clinical Study Report 20130108

Impact of ADA and nAb on safety

For Study 20130108, the incidence of any infusion reactions including hypersensitivity adverse event by ADA and nAb status for ABP 798, US-Rituxan, and EU-MabThera before the single transition at Week 24 in patients with RA is shown in Table 11. The incidence of infusion reactions including hypersensitivity were similar between patients with ADA+ and ADA- status in the ABP 798 and US-Rituxantreatment arms, and comparable in patients with ADA+ status between the ABP 798 and US-Rituxan arms. In the ABP 798 and US-Rituxan arms, no nAb+ patients reported any infusion reactions including hypersensitivity.

**Table 11: Incidence of Any Infusion Reactions Including Hypersensitivity Adverse Events for ABP 798, US-Rituxan, and EU-MabThera by ADA Status and nAb Status in Patients with RA (Study 2013108)**

| | **ABP 798** | | **EU-MabThera** | | **US-Rituxan** | |
|---|---|---|---|---|---|---|
| | ADA-<br>N=84<br>n(%) | ADA+<br>N=13<br>n(%) | ADA-<br>N=84<br>n(%) | ADA+<br>N=10<br>n(%) | ADA-<br>N=78<br>n(%) | ADA+<br>N=19<br>N(%) |
| **Any infusion reactions including hypersensitivity adverse event** | 10 (11.9) | 1 (7.7) | 5 (6.0) | 1 (10.0) | 9 (11.5) | 2 (10.5) |
| | nAb-<br>N=89<br>n(%) | nAb+<br>N=8<br>n(%) | nAb-<br>N=92<br>n(%) | nAb+<br>N=2<br>n(%) | nAb-<br>N=89<br>n(%) | nAb+<br>N=8<br>n(%) |
| **Any infusion reactions including hypersensitivity adverse event** | 11 (12.4) | 0 (0) | 6 (6.5) | 0 (0) | 11 (12.4) | 0 (0) |

**Source:** Table 1 and 2 of RTQ 2020-08-05 - Clinical Pharmacology

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# 7. Statistical and Clinical Evaluation and Recommendations

## 7.1. Statistical and Clinical Executive Summary and Recommendation

The clinical and clinical statistical review evaluated ABP 798 as a potential biosimilar to US-licensed Rituxan, supported by two clinical studies, Study 20130108 and Study 20130109. Study 20130108 was a randomized, double-blind, active-controlled 3-arm PK similarity study evaluating PK, pharmacodynamics, comparative efficacy and safety of ABP 798, US-licensed Rituxan, and EU-approved MabThera in 311 adult patients with moderate to severe rheumatoid arthritis with an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs. Study 20130108 also established the PK component of the scientific bridge between ABP 798, US-licensed Rituxan, and EU-approved MabThera, which, in addition to the established analytical portion of the scientific bridge between the products, justified the relevance of the data generated using EU-approved MabThera in Study 20130108 to the assessment of biosimilarity. The Applicant also conducted Study 20130109, a randomized, double-blind, active-controlled study evaluating the comparative efficacy, safety, PK, PD, and immunogenicity of ABP 798 to US-licensed Rituxan in 256 patients with previously untreated, low tumor burden follicular lymphoma.

In Study 20130108, the primary objective of the study was PK similarity, with comparative clinical efficacy assessed as a secondary objective using descriptive statistics. A key efficacy endpoint was the change from baseline in disease activity score (DAS) based on 28 joint counts and C-reactive protein (DAS28-CRP) at Week 24. The estimated adjusted mean change from baseline in DAS28-CRP at Week 24 was similar across the treatment arms and the 90% confidence interval comparing ABP-798 with EU-approved MabThera or US-licensed Rituxan or pooled EU-approved MabThera + US-licensed Rituxan arms were within a margin of ±0.5. In additional clinical outcome measures, such as ACR responses or the proportion of patients with DAS28-CRP < 2.1, the results were similar between EU-approved MabThera and ABP-798 but numerically lower for US-licensed Rituxan. As Study 20130108 was not designed, nor powered, to provide a formal, statistical, comparative evaluation of comparative efficacy, the results suggest that any observed differences are likely due to the difference in the precision and accuracy of various outcome measures used in the study and are not considered as an evidence of a meaningful difference in efficacy or losses in efficacy. These differences do not preclude a demonstration of no clinically meaningful differences between ABP-798 and US-licensed Rituxan. The safety profile of ABP 798 was similar to that of US-licensed Rituxan and EU-approved MabThera, with no notable difference between treatment arms. In patients who underwent a single transition from US-licensed Rituxan to ABP 798, safety and immunogenicity were comparable between treatment arms, with no meaningful differences.

In Study 20130109, the primary endpoint was risk difference (RD) of overall response rate (ORR) by Week 28 per independent review committee (IRC), with a prespecified noninferiority margin of -15% and a nonsuperiority margin of +35.5%. A second prespecified similarity margin of -15%, +15% was also evaluated. In the ABP 798 arm, ORR was 75% (95% CI: 67, 82) and in the

US-licensed Rituxan arm, ORR was 68% (95% CI: 59, 76), per IRC. The risk difference of ORR at Week 28 was 7.07% (90% CI: -2.17, 16.29). The risk difference was within the prespecified noninferiority margin of -15% and nonsuperiority margin of +35.5%. Although, the upper bound of the 90% confidence interval of the RD of ORR at 16.29% exceeded the upper limit of +15% of the prespecified symmetric similarity margin, it fell within a symmetric similarity margin of -17%, +17%, which the Agency determined was acceptable for this study, and it does not preclude a demonstration of no clinically meaningful differences between ABP 798 and US-licensed Rituxan. The results from the secondary clinical endpoints were similar between the ABP 798 and US-licensed Rituxan treatment arms and there were no meaningful differences between the treatment arms. The safety profile of ABP 798 was similar to that of US-licensed Rituxan, with no notable difference between treatment arms. The incidence of anti-drug antibody and neutralizing antibody formation of ABP 798 and that of US-licensed Rituxan was comparable.

The collective evidence from the clinical studies support a demonstration of no clinically meaningful differences between ABP-798 and US-licensed Rituxan.

### 7.1.1. Statistical and Clinical Residual Uncertainties Assessment

There are no residual uncertainties from a clinical and clinical statistical perspective.

## 7.2. Review of Clinical Studies with Statistical Endpoints

### 7.2.1. Study 20130108 – Rheumatoid Arthritis

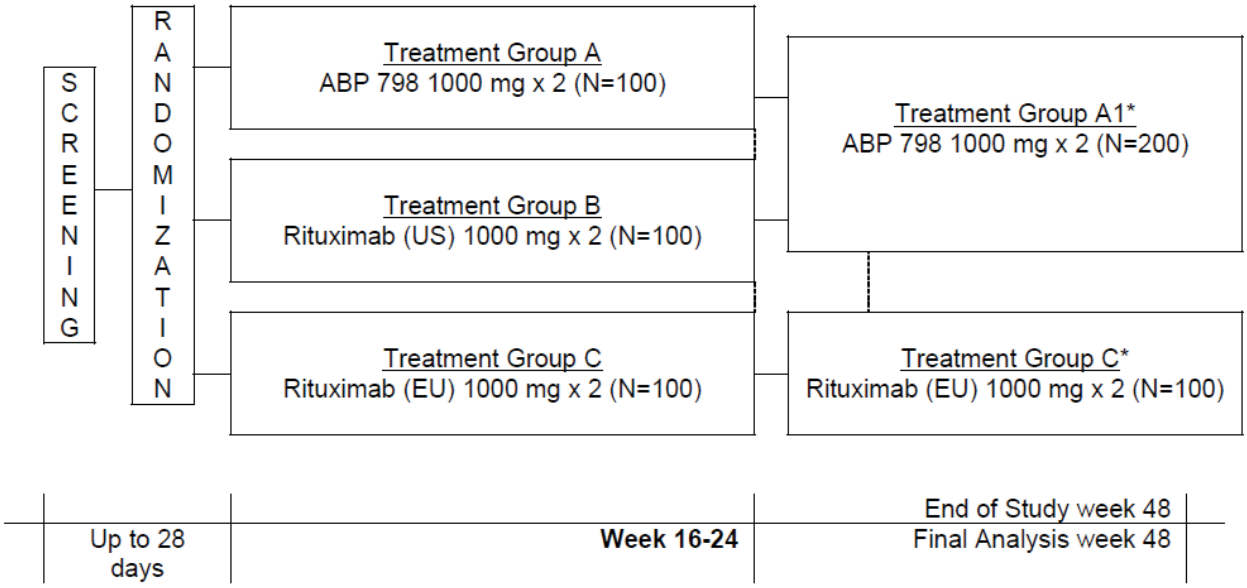
Study 20130108 was a randomized, double-blind, active-controlled, three-arm, multiple dose, pharmacokinetic similarity clinical study. The primary objective was to determine the PK, pharmacodynamics, efficacy, safety, and immunogenicity of ABP 798 compared with United States (US)-licensed rituximab (US-Rituxan) and European Union (EU)-authorized rituximab (EU-MabThera) in patients with moderate to severe RA.

**Study Design and Endpoints**

Patients were randomized in a 1:1:1 ratio to receive ABP 798 (Group A), US-Rituxan (Group B), or EU-MabThera (Group C). Randomization was stratified by geographic region (North America, Eastern Europe, and Western Europe), seropositivity (rheumatoid factor (RF)-positive and/or anti-cyclic citrullinated peptide (CCP)-positive vs. RF-negative and CCPnegative), and number of prior biologic therapies used for RA (1 vs. >1).

The ABP 798, US-Rituxan, or EU-MabThera dose was two 1000 mg dose intravenous (IV) infusions administered two weeks apart (Figure 6). At Week 24, patients on Group A and C continue to receive the second dose of the same treatment. Patients on Group B will transition to receive two 1000 mg of ABP 798 dose intraveneous (IV) infusions administered two weeks apart as their second dose.

**Figure 6: Study Design, 20130108**




* Retreatment will begin at week 24 or earlier, ie, anytime from week 16 to week 24 in individual subjects if necessary in the opinion of the Investigator.

[Source: Protocol Version 4.0]

Although the primary objective for the study was to determine PK similarity (See Section 6 Clinical Pharmacology Evaluation and Recommendations), the study also specified clinical efficacy endpoints. The SAP specified the primary efficacy endpoint to evaluate clinical efficacy as the change from baseline in disease activity score (DAS) based on 28 joint counts and C-reactive protein (DAS28(CRP)) at Week 24. DAS28(CRP) is a continuous outcome derived by combining tender joints counts out of 28 joints (TJC28), swollen joints out of 28 joints (SJC28), CRP (mg/L), and patient's global assessment of disease activity [GH].[3]

Other secondary endpoints included DAS 28-CRP change from baseline, proportion of patients with American College of Rheumatology Response 20/50/70 (ACR20/ACR50/ACR70), hybrid ACR evaluated at weeks 8, 12, 40 and 48.

The efficacy endpoint, DAS28 was calculated using a weighted sum of number of tender joints (0-28), number of swollen joints (0-28), C-Reactive Protein (CRP) measurement (mg/L), and Patient Global Assessment of Disease Activity measured on VAS (0 – 100 mm).

DAS28(CRP) was calculated as:

$DAS28(CRP) = (0.56 * TJC28) + (0.28 * sqrtSJC28) + (0.36 * \ln(CRP + 1)) + (0.014 * GH) + 0.96$

where,

TJC28 = number of tender joints (0-28): tender joint count (TJC)

SJC28 = number of swollen joints (0-28): swollen joint count (SJC)

CRP = C-Reactive Protein (CRP) measurement (mg/L)

GH = Patient Global Assessment of Disease Activity measured on VAS (0–100mm)

ACRX response was calculated as: at least X% improvement from baseline in swollen and tender joint counts and at least a X% improvement from baseline in at least 3 of the following 5 remaining ACR core set measures: subject and physician global assessment using a 100 mm visual analogue scale (VAS), pain assessment using a 100 mm VAS, disability assessment using the health assessment questionnaire disability index (HAQ-DI), and acute phase reactant level (CRP).

Hybrid ACR response is a continuous score of the mean improvement in the core set measures combining the ACR20, ACR50, and ACR70 response rates. The hybrid ACR can be calculated when all 7 components are available using Table 12.

**Table 12: Study 20130108 Derivation of Hybrid ACR**

| | Mean % change in all 7 core measures | | | |
|---|---|---|---|---|
| ACR Status | <20 | 20 ≤ACR < 50 | 20 ≤ACR < 50 | ≥70 |
| Not ACR20 | Mean % change | 19.99 | 19.99 | 19.99 |
| ACR20 but not ACR50 | 20 | Mean % change | 49.99 | 49.99 |
| ACR50 but not ACR70 | 50 | 50 | Mean % change | 69.99 |
| ACR70 | 70 | 70 | 70 | Mean % change |

[Source: SAP for Study 20130108]

If a core set measure worsens by > 100% , the percentage change will be limited to 100%.

***Study Location:*** A total of 311 screened patients with RA were randomized from 57 sites across six countries with approximately 37.6% from North America (US only), 37.0% from Poland, 9.6% from Bulgaria, 7.4% from Hungary, 5.8% from Germany, and 2.6% from Estonia.

**Statistical Methodologies**

The protocol-defined statistical analyses were detailed in an initial version of the SAP (version 1.0, dated 17 October 2014). The SAP was finalized prior to unblinding of data for final analysis (version 2.0, dated 10 December 2018). The SAP for this study was not previously submitted to the Agency for review.

The protocol-defined primary endpoint was PK. The statistical reviewer refers the reader to section [6.3.1] for details on the planned statistical analysis for PK parameters. In this section, the statistical reviewer reviewed the statistical analysis methods for the clinical efficacy endpoints.

The protocol defined several datasets for analysis.

- The full analysis set consisted of all patients randomized in the study, regardless of actual treatment received.
- The safety analysis set consisted of all randomized patients who received at least one dose of study infusion, according to the actual treatment received.
- The per protocol set consisted of all randomized patients who have had two full infusions for the 1st dose (drug compliance of 90%-110%), have completed the week 24 disease assessment (complete DAS28(CRP) assessment in the week 24 window of day 106-210 and before the 1st infusion of the 2nd dose), and did not experience a protocol deviation up to week 24 that affects their evaluation for the secondary objectives of the study to assess clinical efficacy.

Efficacy analyses were conducted based on the full analysis set. Because patients on US-rituximab were switched to ABP-798, the statistical reviewer focused on the treatment period prior to the switching. Therefore, for all key analyses and analysis at individual timepoints, data collected up to Week 24, prior to the second infusion were used.

The pre-specified baseline stratification factors used for the statistical analysis are included as geographic region (North America, Eastern Europe, and Western Europe), seropositivity (RF-positive and/or CCP-positive vs. RF-negative and CCPnegative), and number of prior biologic therapies used for RA (1 vs. >1).

In general, study 20130108 was not formally designed to provide comparison between groups for efficacy endpoints. The SAP specified that if the PK endpoints met the similarity margin, the EU-MabThera and US-Rituxan arms will be pooled for the clinical efficacy outcomes. The SAP specified a similarity margin of +/- 0.6 using the specified key clinical endpoint based on the change from baseline in DAS28(CRP) at Week 24. Neither the SAP nor protocol provided the justification for this margin based on clinical and statistical considerations.

Descriptive analyses were conducted for the above specified clinical efficacy endpoints. For responder endpoints, counts, number of subjects, frequency and percentages are reported with denominator based on the total number of randomized patients in the arm unless otherwise stated. For continuous data, means, standard deviation, minimum, median, maximum are summarized and reported when possible.

The primary efficacy endpoint, DAS28(CRP) through Week 24 prior to the second infusion, was analyzed using a repeated measures analysis fit to the change from baseline in DAS28(CRP) adjusting for stratification variables, baseline DAS28(CRP) value, visit week as categorical variable, treatment, visit and treatment interaction. Within-subject variation across visits was accounted using a spatial covariance structure due to unequal spacing of visit. The SAP specified however that the unstructured covariance will be evaluated to determine which covariance matrix will produce a lower Akaike's information criterion. The applicant reported the differences in the adjusted mean change from baseline in DAS28(CRP) at each visit comparing ABP-798 vs EU-MabThera and ABP-798 vs US-Rituxan, respective 95% CIs and 90%

CIs from the model. Missing data was not imputed for the primary analysis of DAS28(CRP). During the review of the application, it was noted that the unstructured covariance structure was used for reporting all the key results.

The SAP specified several sensitivity analysis to evaluate potential model mis-specification. These analysis were not considered relevant for review purposes. The statistical reviewer considered the following of use for review. They included

1. Repeating the MMRM analysis model on the per protocol dataset.
2. A linear regression model, assuming homoskedasticity, fit to the change from baseline in DAS28(CRP) adjusting for baseline DAS28(CRP), baseline stratification factors, and treatment at each study visit.

In the second analysis, the statistical used only data through Week 24 prior to the second infusion.

To address the missing data assumptions, the applicant included a tipping point analysis. The applicant imputed the missing data based on the history of the DAS28(CRP). After which, the applicant varied the range of the missing data between -0.9 to 0.9 for ABP-798 arm and pooled EU and US rituximab arm to evaluate when the conclusions of similarity was tipping.

Subgroup analysis were specified and conducted for the following subgroups. They included

- Age Group (<65 years vs ≥65 years)
- Sex
- Race (Caucasian vs Non-Caucasian)
- Duration of Disease
- Screen Seropositivity
- Oral Corticosteroid use at baseline (Yes vs No)
- Prior biologic use
- Binding ADA status during first dose period (negative vs positive)
- Neutralizing ADA status during first dose period (negative vs positive)

For subgroup analyses where the subgroup factor is a stratification variable, the MMRM analysis was conducted within each subgroup categories excluding the subgroup variable. In this review, subgroup results based on anti-drug antibody and neutralizing antibody, which were determined after randomization, were not presented.

For the analyses of ACR20/50/70, descriptives at each visit week was reported. The applicant specified several regression approaches, such as GEE, GLM with different link function using a binomial family, to compare ACR responses between ABP-798, EU-MabThera, and US-Rituxan arms. The statistical reviewer reported results based on risk differences, i.e., the difference in probability of a response between arms. At each visit week through Week 24, the ACR response rate will be fit using a generalized linear model, using binomial family and log link (identity link respective), adjusting for treatment factor, stratification variables. Using this model, the adjusted RD, associated 90% CI are reported.

**Additional Statistical Analysis**

As supportive analyses, the statistical reviewer presented cumulative distribution curves at Week 24 were computed for observed DAS28(CRP) to descriptively assess for potential departures of similarity based on the entire observed distribution. The cumulative distribution curve was also reported for ACR endpoints at all study visit weeks for descriptive purposes by treatment arm.

The statistical reviewer carried out all key analyses in all randomized patients to evaluate mean differences between treatment groups at key time points in all randomized patients regardless of adherence to the treatment or to the protocol (i.e., the intention-to-treat or de facto estimand). The statistical reviewer also reported analyses in the PP population to evaluate mean differences between treatment groups at key time points in the subset of patients who tolerate and adhere, corresponding to a different estmand. The FDA guidance[4] and ICH guidelines[5] indicate that the evaluation of both estimands is important in the context of a study designed to compare treatments. The de facto evaluation is critical because, unlike the per-protocol evaluation, it preserves the integrity of randomization and therefore guarantees reliable inference regarding possible differences in effects of the treatment strategies (if there are no missing data). There is also value in the per-protocol analysis. Because this analysis is restricted to the subset of patients who adhere, differences in the per-protocol effect may be larger and easier to detect in the presence of true differences between treatments.

The tipping point analysis results presented by the Applicant evaluated a specific missing not at random assumption depending on the history of the DAS28(CRP). The statistical reviewer included a tipping point analysis that relaxes the dependence on the history of DAS28(CRP) collected post baseline. In this tipping point analyses, the statistical reviewer computed confidence intervals based on a normal approximation for the difference in means at Week 24. Then, the statistical reviewer varied the potential outcomes of the dropouts on both arms independently to completely explore the tipping point space. This allows for a follow-up discussion of the plausibility of those assumptions under which the conclusions change.

**Margin Selection**

The similarity margin for this study was not agreed upon with the Agency in pre-submission communications. Neither the protocol nor SAP included any justification for the proposed margin selected. Based on the BPD Type 2 meeting minutes dated May 02, 2017, the Agency further recommended that the similarity margin for Week 24 mean change in DAS28 in a comparative clinical study in RA be no greater in magnitude than +/- 0.5. This margin was based on meta-analyses of historical effects of DAS28(CRP) and discussions with clinicians weighing

the clinical importance of different losses in effect against the feasibility of different study sizes (Table 13**Error! Reference source not found.**). The Agency was amenable to a proposal for a relaxed lower margin such as an asymmetric margin of (-0.6 , 0.5), provided sufficient justification was included in the SAP and protocol. The Agency also noted that the efficacy comparison should be prespecified as a co-primary objective with the recommended margin by the Agency.

**Table 13: Historical Effect of "Rituximab"[6] on Mean Change in DAS28 at Week 24 in Randomized Clinical Trials of Patients with Active RA who were Receiving Background Methotrexate (MTX)**

| Study | MTX + "Rituximab" | | MTX + Placebo | | Difference in Mean Change |
|---|---|---|---|---|---|
| | N | Mean Change | N | Mean Change | |
| Cohen et al.[1] | 298 | -1.9 | 201 | -0.4 | -1.5 |
| Emery et al.[2] | 122 | -2.1 | 122 | -0.7 | -1.4 |
| Emery et al.3 | 170 | -1.7 | 172 | -0.8 | -0.9 |
| Edwards et al.4 | 40 | -2.6 | 40 | -1.3 | -1.3 |
| Meta-Analysis (fixed effects): Difference (95% CI) [5] | | | | | -1.3 (-1.4, -1.1) |
| Meta-Analysis (fixed effects): Difference (95% CI) [6] | | | | | -1.3 (-1.6, -1.0) |
| Heterogeneity p-value | | | | | 0.03 |

Note: standard deviations used in meta-analysis found in the following systematic review in literature: Volkmann, Elizabeth R., et al. "Rituximab for rheumatoid arthritis: A meta-analysis and systematic review." Clinical Medicine Insights. Therapeutics 2 (2010): 749.

1 Cohen, Stanley B., et al. "Rituximab for rheumatoid arthritis refractory to anti–tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks." Arthritis & Rheumatism 54.9 (2006): 2793-2806.

2 Emery, Paul, et al. "The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial."Arthritis & Rheumatism 54.5 (2006): 1390-1400.

3 Emery, P., et al. "Efficacy and safety of different doses and retreatment of rituximab: a randomised, placebo-controlled trial in patients who are biological naive with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab's Efficacy in MTX iNadequate rEsponders (SERENE))." Annals of the rheumatic diseases (2010): annrheumdis119933.

4 Edwards, Jonathan CW, et al. "Efficacy of B-cell–targeted therapy with rituximab in patients with rheumatoid arthritis." New England Journal of Medicine 350.25 (2004): 2572-2581.

5 Based on inverse variance weights

6 Based on DerSimonian-Laird approach

[Source: Agency Reponse to April 5, 2017 Meeting]

Based on the review of the previous BPD meeting minutes, there was no subsequent agreement on the margin. The SAP and protocol lacked justification of such a margin and did not include DAS28(CRP) as a co-primary objective in addition to the PK endpoints. Therefore, based on these considerations, the statistical reviewer considered the results collected from the clinical efficacy endpoints as a descriptive assessment and found them to be supportive of the study objective, and thus the totality of the data in the application.

**Subject Disposition**

Overall, approximately 91% of the randomized patients completed the study (Table 14**Error! Reference source not found.**) by the end of Week 26. The study discontinuation rates were numerically similar across treatment arms. Overall, 93% of the patients completed two doses of randomized treatment (Table 15), i.e., based on completing the second dose of IP. More patients randomized to US-Rituxan discontinued randomized treatment for reasons of adverse events relative to EU-MabThera arm. The reasons for discontinuation from treatment (Table 15) or discontinuation from study (Table 14) for both treatment groups were numerically similar.

**Table 14: Study 20130108 Disposition of Patients who Completed the Study By Week 26**

| | ABP-798 (N=104) | EU-MabThera (N=104) | US-Rituxan/ABP-798 (N=103) | Total (N=311) |
|---|---|---|---|---|
| Completed Study | 95 (91%) | 94 (90%) | 93 (90%) | 282 (91%) |
| Reasons for Discontinuing Study | 9 (9%) | 10 (10%) | 10 (10%) | 29 (9%) |
| Adverse Event | 1 (1%) | 2 (2%) | 4 (4%) | 7 (2%) |
| Lack Of Efficacy | 1 (1%) | 3 (3%) | 1 (1%) | 5 (2%) |
| Lost To Follow-Up | - | 1 (1%) | 2 (2%) | 3 (1%) |
| Other | 1 (1%) | - | - | 1 (<1%) |
| Physician Decision | 2 (2%) | - | - | 2 (1%) |
| Withdrawal By Subject | 4 (4%) | 4 (4%) | 3 (3%) | 11 (4%) |

[Source: Statistiscal Reviewer]

**Table 15: Study 20130108 Disposition of Patients who Completed Randomized Treatement based on Second Infusion of Second Dose**

| | ABP-798 (N=104) | EU-MabThera (N=104) | US-Rituxan/ABP-798 (N=103) | Total (N=311) |
|---|---|---|---|---|
| Completed Treatment | 97 (93%) | 99 (95%) | 93 (90%) | 289 (93%) |
| Reasons for Discontinuing Treatment | 7 (7%) | 5 (5%) | 10 (10%) | 22 (7%) |
| Adverse Event | 3 (3%) | 1 (1%) | 6 (6%) | 10 (3%) |
| Lack Of Efficacy | 1 (1%) | 1 (1%) | 1 (1%) | 3 (1%) |

| | | | | |
|---|---|---|---|---|
| Lost To Follow-Up | - | - | 1 (1%) | 1 (<1%) |
| Physician Decision | 1 (1%) | - | - | 1 (<1%) |
| Protocol Deviation | - | 1 (1%) | - | 1 (<1%) |
| Withdrawal By Subject | 2 (2%) | 2 (2%) | 2 (2%) | 6 (2%) |

[Source: Statistiscal Reviewer]

**Demographics and Baseline Characteristics**

Patient demographics and baseline characteristics were generally comparable across the treatment arms (Table 16). Patients were on average 56 years of age, more frequently female (85%), more frequently white (92%), and neither Hispanic nor Latino (91%). The randomized patients were mainly from Eastern Europe and 38% of the randomized patients were from North America.

**Table 16: Study 20130108 Baseline Characteristics for all Randomized Patients in Study**

| | ABP-798 (N=104) | EU-MabThera (N=104) | US-Rituxan (N=103) | Total (N=311) |
|---|---|---|---|---|
| **Age (years)** | 54.6 (10.7) | 56.8 (11.3) | 56.4 (10.7) | 55.9 (10.9) |
| **Age > 65** | 17 (16%) | 30 (29%) | 25 (24%) | 72 (23%) |
| **Female** | 90 (87%) | 91 (88%) | 83 (81%) | 264 (85%) |
| **Race** | | | | |
| ***White*** | 97 (93%) | 99 (95%) | 91 (88%) | 287 (92%) |
| ***Black*** | 5 ( 5%) | 3 ( 3%) | 10 (10%) | 18 ( 6%) |
| ***Asian*** | 0 ( 0%) | 2 ( 2%) | 1 ( 1%) | 3 ( 1%) |
| ***Other*** | 2 ( 2%) | 0 ( 0%) | 1 ( 1%) | 3 ( 1%) |
| **Geographical Location** | | | | |
| ***Eastern Europe*** | 59 (57%) | 58 (56%) | 59 (57%) | 176 (57%) |
| ***North America*** | 38 (37%) | 40 (38%) | 39 (38%) | 117 (38%) |
| ***Western Europe*** | 7 ( 7%) | 6 ( 6%) | 5 ( 5%) | 18 ( 6%) |
| **Ethnicity** | | | | |
| ***Hispanic/Latino*** | 8 ( 8%) | 10 (10%) | 11 (11%) | 29 ( 9%) |
| ***Not (Hispanic/Latino)*** | 96 (92%) | 94 (90%) | 92 (89%) | 282 (91%) |
| **Height (cm)** | 164.4 (9.4) | 163.5 (7.9) | 165.2 (9.0) | 164.4 (8.8) |
| **Weight (kg)** | 79.1 (17.0) | 75.9 (18.0) | 77.5 (17.9) | 77.5 (17.7) |
| **Body Mass Index (kg/m$^2$)** | 29.4 (6.4) | 28.5 (7.1) | 28.4 (6.3) | 28.8 (6.6) |

Counts (percentages relative to N) or means (standard deviation) are presented.
[Source: Statistical Reviewer]

Baseline RA disease characteristics were generally comparable across the treatment arms (Table 17) except for some numerical differences. The average RA disease duration was 11.8

years with patients randomized to US-Rituxan arm averaging a higher RA disease duration. A similar proportion of patients in each treatment group were seropositive (ABP 798: 82%, US-Rituxan: 85%, EU-MabThera: 88%). Patients had an average of 18 swollen joints, 25 tender joints, and HAQ-DI of 1.6. The average weekly MTX dose was approximately 16 mg/week in each treatment group with the EU-MabThera and US-Rituxan averaging higher baseline dose of MTX.

**Table 17: Study 20130108 Baseline Disease Characteristics for all Randomized Patients in Study**

| | ABP-798 (N=104) | EU-MabThera (N=104) | US-Rituxan (N=103) | Total (N=311) |
|---|---|---|---|---|
| **RA disease duration (years)** | 11.4 (7.4) | 11.7 (7.9) | 12.5 (9.2) | 11.8 (8.2) |
| ***< 5 years*** | 22 (21%) | 21 (20%) | 22 (21%) | 65 (21%) |
| ***≥ 5 years*** | 82 (79%) | 83 (80%) | 81 (79%) | 246 (79%) |
| **CRP (mg/L)** | 20.4 (25.6) | 17.6 (22.8) | 18.2 (22.9) | 18.7 (23.8) |
| **Patient global assessment** | 65.8 (21.3) | 63.9 (19.0) | 66.4 (20.1) | 65.4 (20.1) |
| **Physician global assessment** | 66.2 (14.2) | 63.3 (14.0) | 63.7 (17.4) | 64.4 (15.3) |
| **Patient pain assessment** | 63.0 (22.2) | 62.5 (19.6) | 63.6 (21.6) | 63.0 (21.1) |
| **Swollen joint counts (out of 28)** | 12.8 (6.2) | 12.8 (6.2) | 13.7 (6.3) | 13.1 (6.2) |
| **Swollen joint counts (out of 66)** | 19.3 (12.0) | 18.4 (10.3) | 19.0 (11.3) | 18.9 (11.2) |
| **Tender joint counts (out of 28)** | 18.1 (6.8) | 16.0 (6.9) | 17.3 (7.0) | 17.1 (6.9) |
| **Tender joint counts (out of 68)** | 31.7 (16.0) | 26.6 (14.4) | 29.0 (14.7) | 29.1 (15.1) |
| **HAQ-DI (0 – 3 scale)** | 1.7 (0.6) | 1.6 (0.6) | 1.6 (0.6) | 1.6 (0.6) |
| **DAS28CRP** | 6.1 (1.0) | 5.8 (1.0) | 6.0 (1.0) | 6.0 (1.0) |
| **Seropositivity** | | | | |
| ***RF + and/or CCP +*** | 85 (82%) | 91 (88%) | 88 (85%) | 264 (85%) |
| ***RF + and CCP +*** | 71 (68%) | 79 (76%) | 75 (73%) | 225 (72%) |
| ***RF + and CCP -*** | 3 ( 3%) | 4 ( 4%) | 2 ( 2%) | 9 ( 3%) |
| ***RF - and CCP +*** | 11 (11%) | 7 ( 7%) | 11 (11%) | 29 ( 9%) |
| ***RF - and CCP -*** | 19 (18%) | 13 (12%) | 15 (15%) | 47 (15%) |
| **Baseline MTX dose (mg/week)** | 15.8 (5.3) | 16.6 (5.1) | 16.8 (4.7) | 16.4 (5.0) |
| **Use of MTX** | 104 (100%) | 104 (100%) | 103 (100%) | 311 (100%) |
| **Use of Oral Corticosteroids** | 58 (56%) | 52 (50%) | 51 (50%) | 161 (52%) |
| **Use of NSAIDs** | 68 (65%) | 59 (57%) | 67 (65%) | 194 (62%) |

Counts (percentages relative to N) or means (standard deviation) are presented.
Abbreviations: CRP=C-reactive protein; NSAIDS=non steroidal anti-inflammatory drugs; HAQ-DI=health assessment questionnaire-disability index; MTX=methrotrexate; RA=rheumatoid arthritis; RF=rheumatoid factor; HAQ-DI=health assessment questionnaire-disability index; CCP=cyclic citrullinated peptide
[Source: Statistical Reviewer]

**Analysis of Primary Clinical Endpoint(s)**

At Week 24, the estimated adjusted mean change from baseline in DAS28(CRP) was numerically larger for patients on the ABP-798 arm compared to patients on EU-MabThera and numerically smaller compared to patients on US-rituximab arm. Overall, the 90% confidence limits comparing ABP-798 with EU-MabThera or US-Rituxan or pooled EU-MabThera and US-Rituxan arms were within the Applicant's preferred margin of ±0.6 at Week 24. These CIs were within the Agency's preferred margin of ±0.5.

**Table 18: Study 20130108 Difference (90% CI) in the LS Mean Change from Baseline in DAS28(CRP) by Treatment Group, Primary Analysis**

| Week | ABP-798 | EU-MabThera | US-Rituxan | ABP-798 vs EU-MabThera | ABP-798 vs US-Rituxan | ABP-798 vs Pooled "Rituximab" |
|---|---|---|---|---|---|---|
| 8 | -1.62 | -1.74 | -1.48 | 0.12 (-0.15, 0.38) | -0.14 (-0.40, 0.12) | -0.01 (-0.24, 0.21) |
| 12 | -1.65 | -2.15 | -1.91 | 0.51 (0.24, 0.77) | 0.26 (-0.01, 0.53) | 0.38 (0.15, 0.62) |
| 24 | -2.01 | -2.12 | -1.94 | 0.11 (-0.17, 0.39) | -0.07 (-0.35, 0.21) | 0.02 (-0.23, 0.26) |

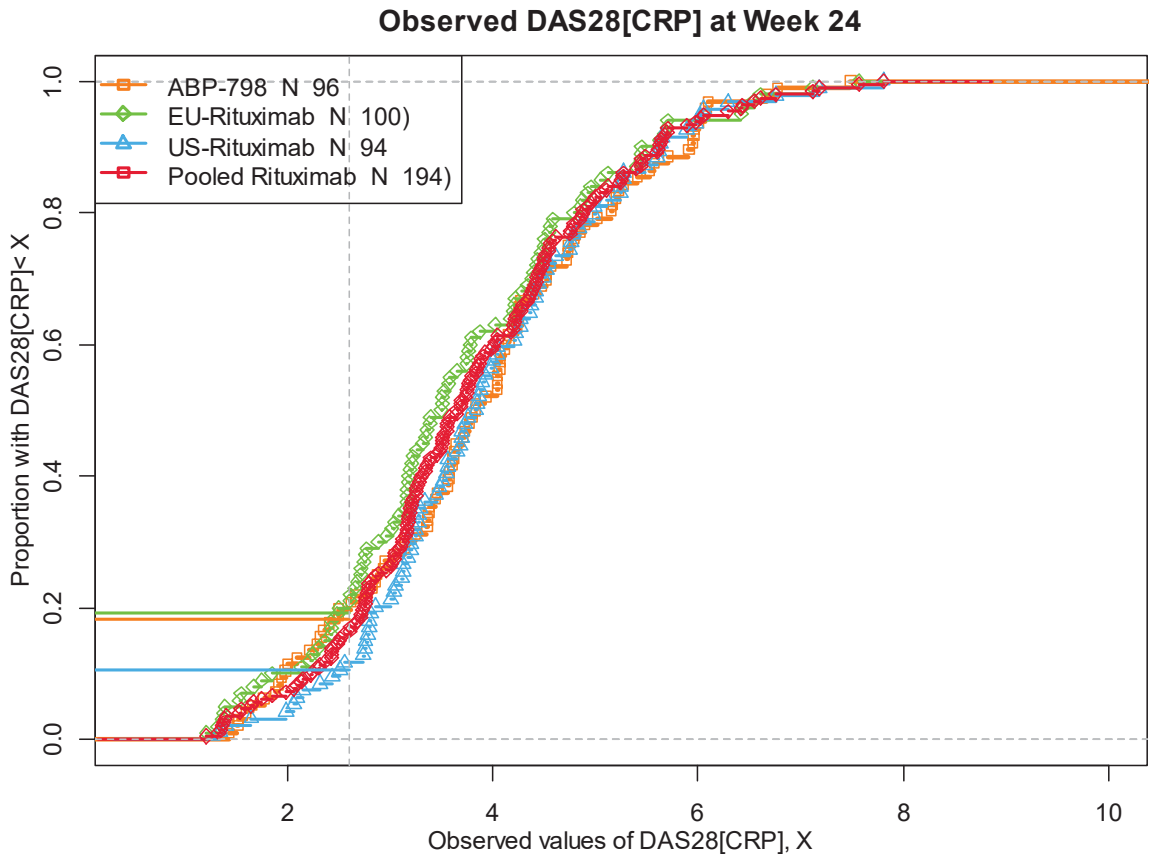
The mixed model repeated measures regression was fit to the change from baseline in DAS28(CRP) adjusting for baseline, stratification factors, visit, treatment, interaction of categorical visit and treatment, with unstructured covariance matrix, and Kenward-Roger degrees of freedom was used to estimate the denominator degrees of freedom. Data through Week 24 prior to the second infusion was used in the model.
Pooled "rituximab" included both EU-MabThera and US-Rituxan.
Abbreviations: LS=least squares; DAS28(CRP)=Disease Activity Score-28–C-reactive protein
[Source: Statistical Reviewer]

Additional supportive analysis based on the per protocol analysis and by visit analysis using ANCOVA were consistent with the above findings (Table 18).

The components of the change from baseline in DAS28(CRP) endpoint include tender/painful joint count (28), swollen joint count (28), C-reactive protein (CRP) and patient's global assessment of arthritis (PGA) are presented in Table 55. At Week 24, the mean change from baseline in CRP in the US-Rituxan arm was numerically higher compared to either ABP-798 or EU-MabThera, with differences observed in the spread of the distribution. At Week 12, there were numerical differences in the distribution in patient global and SJC28 in the ABP-798 arm relative to EU-MabThera or US-Rituxan.

At Week 24, there were numerical differences for lower values of the DAS28(CRP) < 4 based on the cumulative distribution curves for ABP-798, EU-MabThera, and US-Rituxan (Figure 7). In particular, the proportion of patients with DAS28(CRP) < 2.6 was lower in the US-Rituxan arm compared to the other groups for values of DAS28(CRP) < 2.6, a criteria used to indicate low disease activity. These differences were consistent with the results based on the primary analysis.

**Figure 7: Cumulative Responder Curve for Observed DAS28(CRP) at Week 24**




Abbreviations: LS=least squares; DAS28(CRP)=disease activity score in 28 joints–C-reactive protein
Pooled "rituximab" included both EU-MabThera and US-Rituxan.
[Source: Statistical Reviewer]

**Potential Effects of Missing Data**

At Week 24, 9, 6, and 8 patients from ABP-798, Eu-MabThera, US-Rituxan arm respectively did not have complete DAS28(CRP) data. The Applicant included tipping point analysis to explore the sensitivity of results to violations in assumptions about the missing data (i.e., to various missing not- at-random assumptions). The statistical reviewer also performed his own tipping point analyses. The findings from the tippoing point analysis were consistent with the observed results from the primary analysis,i.e., the missing DAS28(CRP) on any of the arms has to be

sufficiently extreme to tip the results towards loss of efficacy or gains in efficacy relative to either EU-MabThera or US-Rituxan. Therefore, the tipping point results were supportive of the finding of no meaningful differences in efficacy or loss of efficacy between products.

**Analysis of Other Clinical Endpoint(s)**

The estimated proportions of ACR20 responders were 71%, 67%, 64% at week 24 for subjects receiving ABP-798, EU-MabThera, and US-Rituxan respectively. There was a numerically higher probability of ACR20 response comparing ABP-798 vs US-Rituxan at Week 24. The probability of ACR 50/70 responses at week 24 were consistent across arms.

At Week 12, the probability of ACR20/50/70 response rates were numerically lower comparing ABP-798 with EU-MabThera, despite the response rate being consistent with US-Rituxan. At Week 8, the probability of ACR20/50/70 responses were consistent across arms. These findings were consistent with the results observed for DAS28CRP.

**Table 19: Study 20130108 Probability of ACR20/50/70 Response at Visit Weeks by Treatment Arm**

| Prob | ABP-798 (N=104) | EU-MabThera (N=104) | US-Rituxan (N=103) | Pooled-"Rituximab" (N=207) | ABP-798 vs EU-MabThera Diff (90% CI) | ABP-798 vs US-Rituxan Diff (90% CI) | ABP-798 vs Pooled "Rituximab" Diff (90% CI) |
|---|---|---|---|---|---|---|---|
| Week 8 | | | | | | | |
| ACR20 | 57/101 (56.4%) | 60/100 (60.0%) | 52/96 (54.2%) | 112/196 (57.1%) | -3.6% (-15.0%, 7.8%) | 2.5% (-9.1%, 14.1%) | -0.6% (-10.6%, 9.3%) |
| ACR50 | 27/101 (26.7%) | 29/99 (29.3%) | 24/96 (25.0%) | 53/195 (27.2%) | -1.8% (-12.1%, 8.4%) | 2.0% (-8.0%, 12.0%) | 0.1% (-8.7%, 8.8%) |
| ACR70 | 7/101 (6.9%) | 12/100 (12.0%) | 9/96 (9.4%) | 21/196 (10.7%) | -5.7% (-11.8%, 0.3%) | -3.3% (-8.7%, 2.2%) | -4.4% (-9.1%, 0.4%) |
| Week 12 | | | | | | | |
| ACR20 | 69/102 (67.6%) | 74/101 (73.3%) | 61/97 (62.9%) | 135/198 (68.2%) | -7.9% (-18.3%, 2.4%) | 3.5% (-7.5%, 14.5%) | -2.3% (-11.6%, 7.0%) |
| ACR50 | 37/102 (36.3%) | 48/101 (47.5%) | 31/97 (32.0%) | 79/198 (39.9%) | -11.1% (-22.3%, 0.1%) | 4.4% (-6.4%, 15.3%) | -3.2% (-12.8%, 6.4%) |
| ACR70 | 13/101 (12.9%) | 20/101 (19.8%) | 16/97 (16.5%) | 36/198 (18.2%) | -5.7% (-14.0%, 2.7%) | -4.2% (-12.4%, 4.1%) | -4.9% (-11.9%, 2.1%) |
| Week 24 | | | | | | | |
| ACR20 | 70/99 (70.7%) | 68/102 (66.7%) | 60/94 (63.8%) | 128/196 (65.3%) | 2.0% (-8.3%, 12.3%) | 5.6% (-5.1%, 16.3%) | 3.8% (-5.2%, 12.8%) |
| ACR50 | 39/98 (39.8%) | 40/102 (39.2%) | 37/95 (38.9%) | 77/197 (39.1%) | 0.2% (-10.7%, 11.1%) | 0.4% (-10.7%, 11.5%) | 0.3% (-9.2%, 9.8%) |
| ACR70 | 19/99 (19.2%) | 20/102 (19.6%) | 16/95 (16.8%) | 36/197 (18.3%) | 1.6% (-7.3%, 10.5%) | 2.4% (-6.5%, 11.4%) | 2.1% (-5.7%, 9.8%) |

A binomial regression using an identity link was fit to the responder endpoint adjusting for stratification factors, treatment based on data collected up to Week 24 prior to the next infusion.
Pooled "rituximab" included both EU-MabThera and US-Rituxan.
[Source: Statistical Reviewer]

The estimated mean change from baseline in the remaining components ACR, not presented in components of DAS28CRP were numerically similar across arms at Week 24 (Table 19). At Week 12, we note numerical differences in the distribution between ABP-798 with US-Rituxan in components of SJC66.

**Other Clinical Endpoints**

The difference in LS means for Hybrid ACR responses comparing ABP-798 with EU-MabThera, US-Rituxan, and pooled EU-MabThera and US-Rituxan were numerically similar at Week 24 (Table 20). At Week 12, there was a significant loss of efficacy (90% upper CI is lower than 0) in Hybrid ACR comparing ABP-798 vs EU-MabThera, despite a lack of trend observed in the comparison with US-Rituxan.

**Table 20: Study 20130108 Difference in LS Means (90% CI) for Hybrid ACR Comparing ABP-798 with EU-MabThera, US-Rituxan, and pooled EU-MabThera and US-Rituxan Arms**

| Week | ABP-798 vs EU-MabThera | ABP-798 vs US-Rituxan | ABP-798 vs Pooled-EU-MabThera and US-Rituxan |
|---|---|---|---|
| 8 | -2.52 (-8.1, 3.1) | 0.25 (-5.4, 5.9) | -1.15 (-6.0, 3.7) |
| 12 | -8.12 (-14.0, -2.3) | -1.79 (-7.7, 4.1) | -5.06 (-10.2, 0.0) |
| 24 | -1.24 (-7.5, 5.0) | 0.77 (-5.6, 7.2) | -0.25 (-5.7, 5.2) |

The Hybrid ACR was fit using a mixed model repeated measures regression adjusting for stratification factors, visit, treatment, interaction of categorical visit and treatment, with unstructured covariance matrix, and Kenward-Roger degrees of freedom was used to estimate the denominator degrees of freedom. Data through Week 24 prior to the second infusion were used in the regression.
Abbreviations: LS=least squares; ACR=American College of Rheumatology; CI=confidence intervals
[Source: Statistical Reviewer]

**Additional Analyses**

There were no notable efficacy trends or loss of efficacy towards ABP 798 or US-rituximab based on subgroup analyses by sex, race, age, geographical region, as well as protocol-defined key RA baseline characteristics as summarized in the table below.

In general, there were lack of precision for the subgroups specified in the study, and are presented to be comprehensive.

**Table 21: Study 20130108 Subgroup Analysis of Change from Baseline in DAS28(CRP)**

| | n (%) | ABP-798 vs EU-MabThera | ABP-798 vs US-Rituxan | ABP-798 vs Pooled EU-MabThera and US-Rituxan |
|---|---|---|---|---|
| Overall | | 0.11 (-0.2, 0.4) | -0.07 (-0.4, 0.2) | 0.02 (-0.2, 0.3) |
| Age Group | | | | |
| Age <65 years | 234 (75%) | 0.28 (-0.0, 0.6) | 0.06 (-0.3, 0.4) | 0.17 (-0.1, 0.4) |
| Age ≥65 years | 70 (23%) | -0.77 (-1.4, -0.1) | -0.90 (-1.6, -0.2) | -0.83 (-1.4, -0.2) |
| Race | | | | |
| Non-White | 24 (8%) | -1.04 (-2.5, 0.4) | -0.73 (-1.9, 0.5) | -0.84 (-1.9, 0.2) |
| White | 280 (90%) | 0.19 (-0.1, 0.5) | -0.05 (-0.3, 0.2) | 0.07 (-0.2, 0.3) |
| Gender | | | | |
| F | 258 (83%) | 0.12 (-0.2, 0.4) | -0.02 (-0.3, 0.3) | 0.05 (-0.2, 0.3) |
| M | 46 (15%) | 0.48 (-0.5, 1.5) | -0.11 (-1.0, 0.7) | 0.05 (-0.7, 0.9) |
| Geographical Region | | | | |
| Europe | 189 (61%) | 0.47 (0.2, 0.8) | 0.06 (-0.3, 0.4) | 0.26 (-0.0, 0.5) |
| North America | 115 (37%) | -0.55 (-1.1, -0.0) | -0.34 (-0.9, 0.2) | -0.44 (-0.9, 0.0) |
| Duration of RA Disease | | | | |
| <5 years | 62 (20%) | 0.46 (-0.2, 1.2) | -0.05 (-0.8, 0.7) | 0.22 (-0.4, 0.8) |
| >=5 years | 242 (78%) | 0.06 (-0.2, 0.4) | -0.08 (-0.4, 0.2) | -0.01 (-0.3, 0.3) |
| Seropositiivity | | | | |
| RF-negative and CCP-negative | 44 (14%) | 0.14 (-0.7, 1.0) | 0.18 (-0.7, 1.0) | 0.16 (-0.6, 0.9) |
| RF-positive and/or CCP-positive | 260 (84%) | 0.06 (-0.2, 0.4) | -0.14 (-0.4, 0.2) | -0.04 (-0.3, 0.2) |
| Use of Corticosteroids | | | | |
| N | 145 (47%) | -0.06 (-0.5, 0.3) | -0.42 (-0.8, -0.0) | -0.25 (-0.6, 0.1) |
| Y | 159 (51%) | 0.22 (-0.2, 0.6) | 0.23 (-0.2, 0.6) | 0.23 (-0.1, 0.6) |
| Number of biologics used | | | | |
| 1 | 162 (52%) | 0.27 (-0.1, 0.7) | 0.03 (-0.4, 0.4) | 0.15 (-0.2, 0.5) |
| >1 | 142 (46%) | -0.08 (-0.5, 0.3) | -0.20 (-0.6, 0.2) | -0.14 (-0.5, 0.2) |

The counts and percentage within each subgroup was computed relative to N=311
[Source: Statistical Reviewer]

**Statistical Considerations**

Study 20130108 design: The study was designed and conducted as a PK similarity study with the primary objective to demonstrate PK similarity between ABP-798, US-Rituxan, and EU-MabThera and to establish the PK component of the scientific bridge between the three products. The study was not designed with the intention of using DAS28(CRP) as a co-primary endpoint, i.e., to further evaluate similarity based on clinical endpoints. The data on DAS28(CRP), ACR, hybrid ACR were collected as secondary endpoints. Even though a specified margin was included in the SAP and protocol, there were no justification on the use of a relaxed margin. In addition, we have the following observations.

- Sample size: Related to the bullet above, the sample size of the study, while sufficient for the assessment of PK similarity, was small (approximately 100 patients per arm). This is smaller than the sample size needed to adequately assess efficacy endpoints using a pre-specified similarity margin in studies in RA (range of 200 to 300 patients per arm), after establishing PK similarity between the three products in a separate clinical study.
- Baseline Differences: We did not identify differences in baseline disease characteristics were between the treatment arms.
- Inconsistent results depending on outcome measures of clinical response: There is inconsistency in the differences observed using some clinical response outcomes versus others, despite similar concepts captured by these outcome meaures. For example, using DAS28(CRP) as an outcome, the mean changes were very similar between the arms. However, when using ACR20 response rates or the proportion of patients with DAS28(CRP) < 2.1, the results were similar between EU-MabThera and ABP-798 but rates for US-Rituxan were lower.

Taken into consideration of the above listed, the study had met the PK primary objective, i.e., 3-way PK similarity between ABP-798, EU-MabThera, US-Rituxan.

Study 20130108 was not adequately designed or powered to provide a formal, statistical comparative evaluation of efficacy. A descriptive assessment of the results showed that there were differences in ACR responses compared to DAS28(CRP). However, as described above, the results suggest that any observed differences are likely due to the difference in the precision and accuracy of various outcome measures used in the study and are not considered as an evidence of a meaningful difference in efficacy or losses in efficacy. Moreover, other, minor numerical differences between the treatment arms were considered to be small and without any consistent trends. Therefore, these differences do not preclude a demonstration of no clinically meaningful differences, and the descriptive assessment of the results are supportive of the totality of the data in the application.

Overall, as a scientific bridge was established to justify the relevance of data generated with EU-MabThera as the comparator to the assessment of biosimilarity, the data from Study 20130108 provide supportive data for no clinically meaningful differences between ABP 798 and US-Rituxan.

### 7.2.2. Study 20130109 – Follicular Lymphoma

**Title: A Randomized, Double-blind, Study Evaluating the Efficacy, Safety, and Immunogenicity of ABP 798 Compared with Rituximab in Subjects with CD20 Positive B-cell Non-Hodgkin Lymphoma**

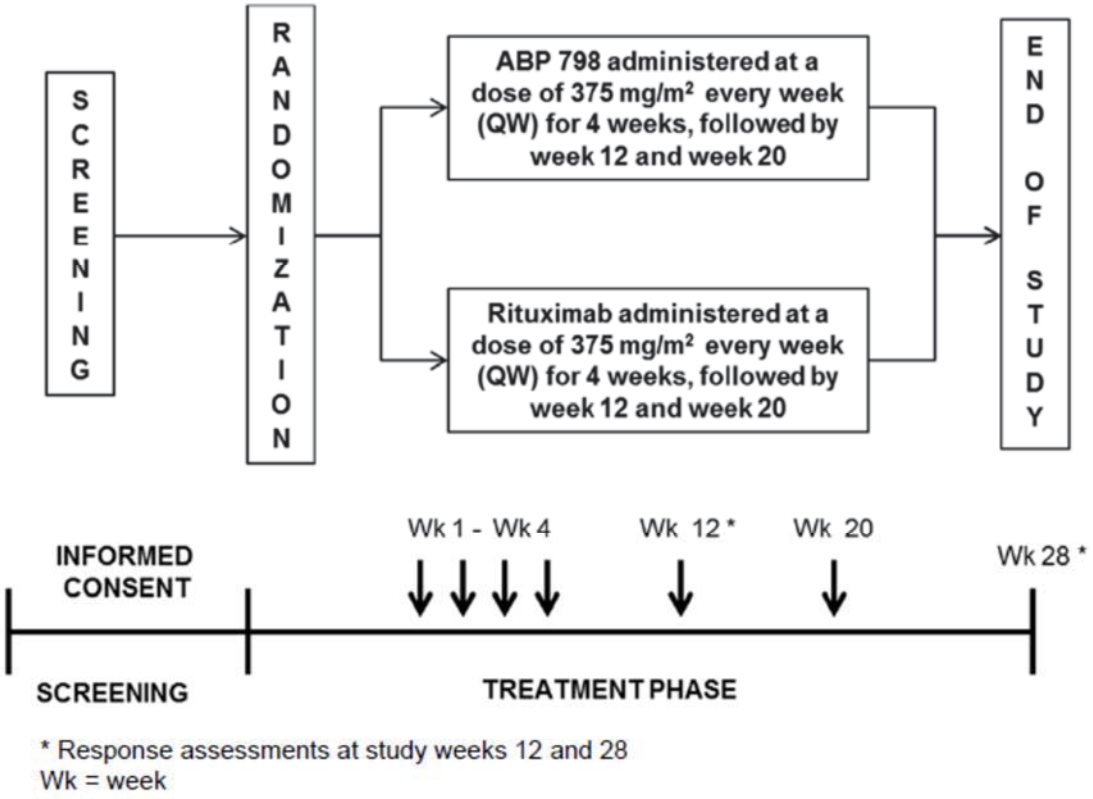
**Study Initiation: 25 May 2016**
**Study Completion: 28 June 2019**

**Database lock: 07 August 2019**

**Overview and objectives**

Study 20130109 was designed as a randomized, double-blind, active-controlled, 2 arm study evaluating the efficacy, pharmacokinetics, pharmacodynamics, safety, tolerability and immunogenicity of ABP 798 versus US-Rituximab in adult subjects with Grade 1, 2 or 3a follicular B-cell NHL and low tumor burden. A total of 256 patients were randomized in a 1:1 ratio to receive a 375 mg/m$^2$ IV infusion of either ABP 798 or US-Rituximab once weekly for 4 weeks followed by dosing at weeks 12 and 20. Tumor assessments were performed at screening and Weeks 12 and 28. Randomization was stratified by geographic region (Europe, Americas, Japan, Asia Pacific – Other) and age group (> 60 years of age, ≤ 60 years of age). Subjects remained on study until Week 28. The study design schema is as shown in Figure 8 below.

**Figure 8: Study 20130109 Schema**




*Source: Study Protocol Version 5*

The schedule of activities for Study 20130109 is shown in the Applicant's table below.

**Table 1. Schedule of Assessments and Procedures**

| | | Treatment Phase | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Screen ≤ 28 days | Visit 1 Baseline Day 1, Week 1 | Visit 2 Week 2 (± 3 days) | Visit 3 Week 3 (± 3 days) | Visit 4 Week 4 (± 3 days) | OPTIONAL Visit 4a Week 5 (± 3 days) | Visit 5 Week 12 (± 7 days) | Visit 6 Week 20 (± 7 days) | End of Study /Week 28 (± 7 days) |
| **General Assessments** | | | | | | | | | |
| Informed consent form | X | | | | | | | | |
| Post-infusion observation (4 hour) | | X [a] | | | | | | | |
| Medical and medication history | X | | | | | | | | |
| Physical examination | X | X [b] | X | X | X | | X | X | X |
| Vital signs [c] | X | X [d] | X [d] | X | X | | X | X | X |
| Electrocardiogram [e] | X | | | | | | | | X |
| ECOG performance status | X | | | | | | | | X |
| Clinical disease assessment | | X | X | X | X | | X | X | X |
| Concomitant medication | X | X | X | X | X | | X | X | X [f] |
| Adverse event recording | X [g] | X | X | X | X | | X | X | X |
| **Treatments** | | | | | | | | | |
| Dosing of ABP 798 / rituximab [h] | | X | X | X | X | | X | X | |
| **Disease Assessments** | | | | | | | | | |
| CT Scan | X [i] | | | | | | X | | X [j] |
| Bone marrow biopsy [k] | X | | | | | | | | X [k] |
| **Laboratory Assessments** | | | | | | | | | |
| Serology (HBsAg, HBcAb, HCV) | X | | | | | | | | |
| Serum chemistry [l,m] | X | X [m] | X | X | X | | X | X | X |
| Hematology [m] | X | X [m] | X | X | X | | X | X | X |
| Pregnancy [n] | X | | | | | | | | |
| PK sampling [o,p,q] | | X [p] | X | X | X [p] | X [p] | X | X | X |
| Pharmacodynamic (CD19+ cell count) [q,r] | | X | X | X | X | | | | X |
| Antidrug antibodies [q,s] | | X | | | | | X | X | X |
| IgG and IgM [q] | | X | X | X | X | | | | X |

CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus antibody; Ig = Immunoglobulin.
(See footnotes below)

[a] The first 12 randomized subjects will be observed for safety for 4 hours after the first administration of IP.
[b] Includes weight and height **within 8 days of visit 1**.
[c] Systolic blood pressure and diastolic blood pressure will be measured on the same arm (preferentially on the left arm) after the subject has been in a supine/sitting position for 5 minutes.
[d] All subjects will be monitored for hypersensitivity reactions to IP by assessment of vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature) on visit 1 and visit 2 at the following time points: before IP infusion; approximately every 60 minutes during IP infusion; at the end of IP infusion; at approximately 60 minutes after the end of IP infusion. Subjects with signs and symptoms of a hypersensitivity reaction to IP will have vital signs assessed and oxygen saturation monitored by pulse oximetry.
[e] 12-lead electrocardiogram recordings will be obtained after the subject has been supine for 5 minutes.
[f] Includes any additional treatment for NHL.
[g] Only serious adverse events will be reported from signing of the informed consent until day 1.
[h] The ABP 798/rituximab dose will be calculated based on the height and weight obtained within 8 days of visit 1. ABP 798/rituximab dose to be administered after all assessments are completed for each visit. If any scheduled dose of IP in the first 4 visits (ie, visit 1, visit 2, visit 3, and visit 4) is delayed from the scheduled visit date (by more than 3 days), then the dose will be administered as soon as possible and subsequent doses will be adjusted accordingly to remain once per week from the adjusted dose date. See Section 8.5.6 for more details regarding dose adjustments, dose escalation, and stopping rules.
[i] Subjects must have a baseline scan (CT of the neck [if palpable lymph node >1.0 cm]), chest, abdomen, and pelvis to assess disease burden within **6 weeks** before randomization. For subjects with contraindications to the contrast agent, the decision as to whether a non-contrast CT is used should be based on anatomic location of the disease and comparability with images previously taken in the course of the study.
[j] **End-of-study CT scan can be taken within 28 days prior to EOS visit. Subjects who discontinue from the study due to disease progression should have a CT scan (as described in Section 9.6) prior to initiation of new anti-cancer treatment, if deemed clinically acceptable.**
[k] Subjects must have a bone marrow biopsy within 12 months before randomization. Previously confirmed positive bone marrow involvement does not need to be repeated for purposes of screening. An end-of-study biopsy is required if bone marrow involvement is identified at baseline **for complete response (CR) confirmation. If a confirmatory bone marrow assessment is not obtained, these subjects should be considered as only having a partial response (PR).**
[l] Clinical laboratory tests will be performed at local laboratories. Additional and repeat laboratory safety testing may be performed at the discretion of the Investigator.
[m] Serum chemistry and hematology for baseline (day 1) can be performed up to 3 days before baseline (day 1).
[n] Serum or urine pregnancy tests for females of childbearing potential only at a local laboratory.
[o] Pharmacokinetics samples will be collected at baseline on day 1/visit 1/week 1, predose at weeks 2, 3, 4, 12, and 20, and immediately after the end of infusion at week 12, and a single PK sample at week 28/EOS.
[p] **Subjects who agree to optional additional PK sampling will also be required to have PK samples collected at 2 hours (± 1 hour) postdose at week 1 and week 4 and at visit 4a (week 5)**
[q] Pharmacokinetics, pharmacodynamic, antidrug antibody and IgG and IgM samples will be sent to a central laboratory. Details will be provided in a laboratory manual.
[r] Pharmacodynamic CD19+ cell count will be analyzed at baseline on day 1/week 1 and at weeks 2 (day 8), 3, 4 and 28.
[s] Antidrug antibodies will be analyzed by Amgen or a designee. Sampling will be at baseline on day 1/week 1, prior to fifth dose at week 12, prior to the sixth dose at week 20 and at week 28/EOS. Subjects with positive antidrug antibody results will be assessed for neutralizing antibodies. Additional blood samples may be obtained to rule out antidrug antibodies.

*Source: Study Protocol Version 5.*

**Reviewer comment: The schedule of study events is appropriate. Echocardiogram was performed at baseline and at end of treatment. Laboratory, AE, and PK assessments are also appropriate.**

**Study Objectives**

Primary objective:

The primary objective for this study is to evaluate the efficacy of ABP 798 compared with US-Rituximab.

Secondary Objectives:

The secondary objective is to assess the pharmacokinetics, pharmacodynamics, safety, tolerability,and immunogenicity of ABP 798 compared with US-Rituximab.

**Eligibility Criteria**

Inclusion criteria:

Patients eligible for inclusion have to meet all of the following criteria:

1. Males and females ≥ 18 years of age
2. Histologically confirmed (by lymph node or extranodal region biopsy), Grade 1, 2, or 3a follicular B-cell NHL expressing CD20 within 12 months before randomization
3. Stage 2-4 with measurable disease (per International Working Group)
    a) Subjects must have a baseline CT c/a/p (computed tomography [CT]) of the neck (if palpable lymph node > 1.0 cm), to assess disease burden within 6 weeks before randomization
    b) Subjects must have had a baseline bone marrow biopsy within 12 months before randomization. Previously confirmed positive bone marrow involvement does not need to be repeated for purposes of screening.
4. Low tumor burden based on the Groupe d'Etudes des Lymphomes Folliculaires(GELF) criteria
5. Largest nodal or extranodal mass ≤ 7 cm
    a) No more than 3 nodal sites with diameter > 3 cm
    b) No splenomegaly > 16 cm by CT scan and no symptomatic splenomegaly
    c) No significant pleural or peritoneal serous effusions by CT
    d) Lactate dehydrogenase ≤ upper limit of normal (ULN)
    e) No B symptoms (night sweats, fever [temperature > 38°C], weight loss > 10% in the previous 6 months)
6. Eastern Cooperative Oncology Group (ECOG) performance status score 0 or 1
7. The following laboratory values obtained during screening:
    a) Absolute neutrophil count (ANC) ≥ 1.5 x 109/L (1,500/µL)
    b) Lymphocytes < 1.5 x the ULN
    c) Platelets ≥ 100 x 109/L (100,000/µL)
    d) Hemoglobin ≥ 10.0 g/dL
    e) Total bilirubin < 1.5 x the ULN

f) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 2 x ULN subjects with an elevated unconjugated bilirubin (Gilbert's syndrome) will be eligible if hepatic enzymes and function are otherwise within normal limits (ie, AST, ALT, and alkaline phosphatase are within normal limits) and there is no evidence of hemolysis
g) adequate renal function as defined by creatinine < 1.5 x ULN or estimated creatinine
clearance ≥ 50 mL/min calculated by the Cockcroft-Gault method

Exclusion Criteria:

Patients eligible must not meet any of the following criteria:

1. Diffuse large cell component and/or Grade 3b follicular NHL
2. History or known presence of central nervous system metastases
3. Palliative radiotherapy within 3 months before randomization
4. Malignancy other than NHL within 5 years (except treated in-situ cervical cancer, or squamous or basal cell carcinoma of the skin)
5. Major surgical procedure within 4 weeks before randomization or planned major surgical procedure during the treatment phase
6. Any of the following in the 6 months before randomization:
    a) Clinically significant cardiovascular disease (including MI, unstable angina, symptomatic CHF- NYHA ≥Class 3), serious uncontrolled cardiac arrhythmia)
    b) Peripheral vascular disease
    c) Cerebrovascular accident
    d) Transient ischemic attack
7. Medically uncontrolled hypertension or SBP > 160 mmHg or DBP > 100 mmHg
8. Known active or history of active tuberculosis (TB)
9. Positive for hepatitis B surface antigen (HbsAg), hepatitis B core antibody (HBcAb), or hepatitis C virus (HCV) antibody at screening
10. Known to be human immunodeficiency virus positive
11. Recent infection requiring a course of systemic anti-infective agents that was completed ≤ 7 days before randomization (with the exception of uncomplicated urinary tract infection)
12. Other investigational procedures that can impact the study data, results, or patient safety while participating in this study are excluded; participation in observational studies is allowed.
13. Subject is currently enrolled in or has not yet completed at least 30 days or 5 half-lives (whichever is longer) since ending other investigational device or drug study(s), including vaccines, or subject is receiving other investigational agent(s)
14. Previous use of either commercially available or investigational chemotherapy, biological, or immunological therapy for NHL (including rituximab or biosimilar rituximab, or other anti-CD20 treatments)
15. Systemic corticosteroid use within 3 months before randomization (inhaled are allowable)

16. Live vaccines within 28 days prior to the first dose of IP
17. History of neurologic symptoms suggestive of central nervous system demyelinating disease
18. Woman of childbearing potential who is pregnant or is breastfeeding
19. Woman of childbearing potential who does not consent to use highly effective methods of birth control (eg, true abstinence, sterilization, birth control pills, Depo Provera injections, or contraceptive implants) during treatment and for an additional 12 months after the last administration of the protocol-specified treatment
20. Man with a partner of childbearing potential who does not consent to use highly effective methods of birth control (eg, true abstinence, vasectomy, or a condom in combination with hormonal birth control or barrier methods used by the woman) during treatment and for an additional 12 months after the last administration of the protocol specified treatment
21. Subject has known sensitivity to any of the products to be administered during the study, including mammalian cell derived drug products
22. Subject previously has been randomized in this study
23. Subject likely to not be available to complete all protocol-required study visits or procedures
24. History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the Investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion

***Reviewer comments: The inclusion and exclusion criteria are appropriate***

**Drug Administration**
1. ABP 798 at a dose of 375 mg/$m^2$ administered as an IV infusion once weekly for 4 weeks followed by dosing at Weeks 12 and 20.
2. US-Rituxan at a dose of 375 mg/$m^2$ administered as an IV infusion once weekly for 4 weeks followed by dosing at Weeks 12 and 20.

**Dose Modifications**
There were no recommended dose adjustments or escalations for ABP 798 or US-Rituxan.

**Analysis Populations**
The full analysis set (FAS) includes all randomized subjects and is based on the randomized treatment assignment.

The modified full analysis set includes all randomized subjects with evidence of disease at baseline per the tumor assessment from the central, independent, blinded assessments. Nine patients from the FAS were excluded in the mFAS set for not having evidence of disease at baseline.

The per-protocol (PP) analysis set was a subset of the modified full analysis set and

included subjects who completed all 4 weekly doses of investigational product or who permanently discontinued investigational product prior to completing 4 weekly doses due to reasons allowed per protocol (ie, disease progression, adverse events and death); who had at least 1 postbaseline tumor assessment prior to the EOS from the central, independent, blinded assessments; and who did not experience a protocol deviation that would affect their evaluation for the primary objective of the study. Analyses for the PP analysis set was based on actual treatment received. The PP analysis set was used for sensitivity analyses of the primary efficacy endpoint.

The safety analysis set included all randomized subjects who received at least 1 dose of investigational product and was based on actual treatment received. Analyses of safety, immunogenicity, and PK endpoints were based on the safety analysis set.

**Statistical Methodologies**

The primary efficacy endpoint of this study was risk difference (RD) of overall response rate (ORR) by Week 28 per the independent review committee (IRC). The risk difference of overall response rate was calculated as overall response rate in the ABP 798 arm minus overall response rate in the US-Rituxan arm. Overall response rate was defined as the percentage of subjects with a complete response (CR), complete response unconfirmed (CRu), or partial response (PR) as defined by the 1999 IWG-NHL criteria (Cheson et al, 1999). The overall response rate was calculated separately based on the IRC, and the local investigator's assessment. Tumor assessment were performed at baseline and Weeks 12 and 28. The primary analysis of overall response rate was based on the modified Full Analysis Set.

The modified full analysis set (mFAS) included all patients randomized in the study who have evidence of disease at baseline per the IRC tumor assessments. The Full Analysis Set (FAS) included all patients randomized in the study and was used for supportive purposes.

The safety analysis set includes all randomized subjects who received at least 1 dose of study treatment. All safety analyses were conducted on this analysis set according to actual treatment received. The analysis of pharmacokinetic and pharmacodynamic endpoints was also conducted on the patients in the safety analysis set.

The study was deemed successful if the 90% confidence interval for the risk difference was entirely contained with the interval (-15%, 35.5%). To obtain this interval, the applicant estimated the ORR to be 85% on both the treatment arms based on the Ardeshna et al [2010] reference. The Applicant found that 125 patients per arm (N=250) would provide approximately 95% power at a 0.05 significance level to demonstrate equivalence between ABP 798 and US-Rituxan with a noninferiority margin of -15% and a nonsuperiority margin of 35.5%.

The Applicant found that the sample size of 250 patients can provide approximately 83% power for an analysis with 0.025 significance level assuming that the ORR is 85% and a symmetrical margin of 15% for noninferiority and nonsuperiority.

Secondary endpoints included RD of ORR at Week 12, PK, PD and safety. The PK endpoints were serum concentrations at predose at each of the planned PK visits and immediately after the end of infusion at Week 12. The PD endpoints included the percentage of patients with complete depletion of CD19+ cell count from baseline to study Day 8 and total IgG and IgM antibody levels; and serum concentrations at predose and immediately after the end of infusion at Week 12. The safety endpoints included treatment-emergent AEs and serious adverse events (SAEs), clinically significant changes in laboratory values and vital signs, incidence of antidrug antibodies, progression-free survival (PFS) and overall survival (OS).

The point estimate and confidence limits of the RD of ORR by Week 28 were estimated using a generalized linear model adjusted for the stratification factors (geographic region and age group) as covariates. In addition, a 2-sided 95% confidence interval was calculated and evaluated against a symmetrical margin of 15% for noninferiority and nonsuperiority.

To assess the robustness of the primary ORR analysis results, additional sensitivity analyses were performed using the central, independent, blinded assessments on the per protocol analysis set according to actual treatment received and using the investigator's assessment of disease on the full analysis set.

There were no multiplicity adjustments for any of the secondary endpoints.

The statistical analysis plan had two versions to reflect the changes in the protocol ammendments.

***Reviewer comments: The asymmetrical margins for the clincal study were set without prior aggreement with the FDA. The Agency recommends the use of symmetrical margins and conveyed this recommendation to the Applicant in the BPD Type 2 meeting on 7/10/2013. The Applicant subsequently submitted the protocol and the Agency reiterated its recommendation for a symmetrical margin on 8/29/2016 by conveying the following comment:***

***"It is not clear whether or not your proposal to use non-symmetric margins (15% for non-inferiority, 35.5% for non-superiority) as the primary basis for demonstration of equivalence between ABP 798 and rituximab is justified from a medical perspective. From a statistical perspective, the proposed 35.5% margin for demonstration of non-superiority is not acceptable, because it is highly unlikely that the upper bound for the difference in ORR can be greater than 35.5% with the ORR for rituximab assumed to be 85%. The use of symmetric margins is recommended for demonstration of equivalence between ABP 798 and rituximab."***

***During the review of this application, an information request was sent to the Applicant for the justification using the asymmetrical margins.***

***A summary of the justification in Applicant's response to the information request follows:***

***This guidance (Food and Drug Administration (FDA) Guidance for Industry, Non-inferiority Clinical Trials to Establish Effectiveness) states that in some cases, it would be appropriate to use an asymmetric interval with a larger upper bound to rule out superiority than lower bound to rule out inferiority. An asymmetric interval could be reasonable, for example, if the dose used in the clinical study is near the plateau of the dose-response curve and there is little likelihood of dose-related effects (eg, toxicity). The proposed asymmetric margins are further supported by Ardeshna et al (2010), Lowry and Ardeshna (2012), and Rueda et al (2012); based on the expected ORR as described in these publications, the dose and regimen used in Study 20130109 is near the plateau of the dose-response curve. The 375 mg/m2 dose is near the plateau of the dose-response curve. Similar exposure and safety profiles, including dose interruptions, reductions, or discontinuation, were confirmed between ABP 798 and US-Rituxan.***

***A similarity margin of 17%, 17% is acceptable (refer to related discussion in the review in the discussion of the results below).***

***Of note, PFS and OS are considered safety endpoints in this protocol/SAP, which are typically considered to be part of the efficacy endpoints (refer to related discussion in the Other Clinical Endpoints section below).***

***The duration of response (DoR) is also considered in the efficacy evaluation and was not included in the SAP as an endpoint. An information request was sent to the Applicant for the evaluation of this endpoint (refer to the discussion of this endpoint in the Other Clinical Endpoints section below).***

***As per the 2016 version of the protocol, the primary analysis of ORR was to be conducted based on central, independent, blinded radiologists' assessments on the FAS according to randomized treatment. Subjects without measurable disease at baseline and those without post-baseline disease assessments will be counted as non-responders in the primary analysis. The Applicant modified the primary analysis population to be the mFAS. FDA's primary analysis will be based on the FAS population and the mFAS will be considered to be part of the sensitivity analysis; this comment was also conveyed to the Applicant as part of the protocol review on 8/29/2016.***

**Protocol Amendments**

The original protocol (Version 1.0) was dated February 26, 2014 and was amended four times during the course of the study. Notable amendments and protocol changes pertinent to the United States are briefly summarized below:

- Amendment 1, 12/22/2015: Added language for Inclusion of patients with Grade 3a disease and for exclusion of patients with Grade 3b disease
- Amendment 2, 1/7/2016 (v.3): Changes introduced in version 2 were restated
- Amendment 3, 6/24/2016 (v.4): Specified the dose of ABP 798/US-Rituxan will be calculated at baseline and remain the same throughout the study. Added stopping criteria for infusion related reactions.
- Amendment 4, 7/17/2017 (v.5): Added optional PK sampling visit (week 1, 4, and 5). Redefined criteria for defining low tumor burden and added language to require bone marrow biopsy at end of study to confirm CR.

The following were the changes in the statistical analysis plan (SAP) based on the protocol:

• The SAP defined a modified full analysis set, which will be used for all efficacy analyses based on the central, independent, and blinded tumor assessments.
• The SAP states that the per protocol analysis set will be a subset of the modified full analysis set instead of the full analysis set.

***Reviewer comments: The protocol amendments and changes appear reasonable with no concerning changes. The full analysis set will be used for the the primary analysis by the Agency.***

**Analysis Populations**
The patients in the different analysis populations are summarized in the table below.

**Table 22: Analysis Populations for Study 20130109**

| | **ABP 798 N=128 (%) n (%)** | **US-Rituxan N=128 (%) n (%)** |
|---|---|---|
| All randomized patients/ Full analysis Set (FAS) | 128 (100) | 128 (100) |
| Modified Full Analysis Set (mFAS) | 123 (96) | 124 (97) |
| PP population | 120 (94) | 120 (94) |
| Safety population | 128 (100) | 126 (98) |

*Source: ADSL.xpt dataset and CSR*
*PP = per protocol*

**Subject Disposition**
An overview of patient disposition by full analysis set is shown in the Table 23 below. The primary analysis was planned with the intention of demonstrating the risk difference of overall response rate by Week 28. Of the 256 randomized subjects in the full analysis set, 119 (93%) subjects completed treatment with ABP 798 whereas 123 (96.1%) completed treatment with US-Rituxan. The majority of the reasons for discontinuation in the ABP 798 group were disease

progression in 4 patients (3.1%) and adverse events in 3 patients (2.3%). Reasons for discontinuing US-Rituxan included adverse event, subject request, subject dissatisfaction with treatment efficacy, physician decision, and protocol violation in 1 (0.8%) subject each. In the modified Full Analysis Set which provides the basis for the primary analysis, there were 123 patients (96.1%) in the ABP 798 arm and 124 patients (96.9%) in the US-Rituxan arm. Five (3.9%) patients in the ABP 798 arm and 4 (3.1%) patients in the US-Rituxan arm did not have evidence of disease at baseline per central assessment. The majority of the reasons for discontinuation in the ABP 798 group were again disease progression in 4 patients (3.3%) and adverse events in 3 patients (2.4%).

**Table 23 Study 20130109 Patient Disposition**

| **Analysis** | **Disposition** | **Treatment** | |
|---|---|---|---|
| | | **ABP 798 N = 128 n (%)** | **US-Rituxan N = 128 n (%)** |
| **Full Analysis Set** | Treatment complete | 119 (93) | 123 (96.1) |
| | Discontinued Treatment | 9 (7) | 5 (3.9) |
| | Disease progression | 4 (3.1) | 0 (0) |
| | Adverse event | 3 (2.3) | 1 (0.8) |
| | Physician decision | 1 (0.8) | 1 (0.8) |
| | Subject request | 0 (0) | 1 (0.8) |
| | Subject dissatisfaction | 0 (0) | 1 (0.8) |
| | Protocol violation | 0 (0) | 1 (0.8) |
| | Other | 1 (0.8) | 0 (0) |
| **Modified Full Analysis Set** | | **Treatment** | |
| | | **ABP 798 N= 123 n (%)** | **US-Rituxan N= 124 n (%)** |
| | Treatment complete | 114 (92.7) | 119 (96) |
| | Discontinued Treatment | 9 (7.3) | 5 (4) |
| | Disease progression | 4 (3.3) | 0 (0) |
| | Adverse event | 3 (2.4) | 1 (0.8) |
| | Physician decision | 1 (0.8) | 1 (0.8) |
| | Subject request | 0 (0) | 1 (0.8) |
| | Subject dissatisfaction | 0 (0) | 1 (0.8) |
| | Protocol violation | 0 (0) | 1 (0.8) |
| | Other | 1 (0.8) | 0 (0) |

**Protocol deviations:**
In the full analysis set, 6 (4.7%) subjects in the ABP 798 treatment group and 16 (12.5%) subjects in the US-Rituxan treatment group experienced at least 1 important protocol deviation. The most common important protocol deviation was in the category of Assessment – Safety and occurred in 4 (3.1%) subjects in the ABP 798 treatment group and 10 (7.8%) subjects in the US-Rituxan treatment group. Within the Assessment – Safety category, the most common deviation was related to hypersensitivity reactions monitoring and occurred in 2 (1.6%) patients in the ABP 798 treatment group and 4 (3.1%) in the US-Rituxan treatment group. Other important protocol deviations were attributed to an end of study biopsy not being done in 3 (2.3%) US-Rituxan patients and 1 (0.8%) ABP 798 patient, to a failure to report a serious adverse event within 24 hours in 4 (3.1%) US-Rituxan treatment patients versus 0 ) ABP 798 patients and to an end of study visit not performed in 1 (0.8%) ABP 798 patient versus 0 US-Rituxan patients.

**Demographics and Baseline Characteristics**
Demographic characteristics and disease characteristics based on the full analysis set are summarized in **Table 24** below. Demographic characteristics were generally similar across treatment arms. Overall, the majority of patients were Caucasian (79%) and less than 60 years of age (55%). The median age was 59 years (range 24 to 84 years). All patients had an ECOG performance status of 0 or 1.

**Table 24: Study 20130109 Baseline Demographic Characteristics in the FAS Patient Population.**

| Characteristic | ABP 798<br>n=128<br>n (%) | US-Rituxan<br>n=128<br>n (%) |
|---|---|---|
| **Age (years)** | | |
| **Median** | 58.5 | 58.5 |
| **Min, Max** | 24, 79 | 25, 84 |
| **Age group, n (%)** | | |
| **≤ 60 years** | 71 (56) | 70 (55) |
| **> 60years** | 57 (45) | 58 (45) |
| **Gender, n (%)** | | |
| **Female** | 68 (53) | 62 (48) |
| **Male** | 60 (47) | 66 (52) |
| **Race, n (%)** | | |
| **Caucasian** | 102 (80) | 101 (79) |
| **Asian** | 24 (19) | 22 (17) |
| **Other** | 2 (2) | 5 (4) |
| **ECOG PS** | | |
| **0** | 107 (84) | 108 (86) |
| **1** | 21 (16) | 18 (14) |

Source: CSR, Full Analysis Set

A summary of disease characteristics based on the full analysis set is presented in Table 25 below. The disease characteristics were generally similar between the treatment arms. Twenty percent of patients had Grade 3a follicular lymphoma, 73% of patients had stage 3 or 4 disease, 27% had bone marrow involvement, and the median number of nodal sites was 2. Fifteen percent of patients were considered high risk based on the presence of 3 or more risk factors in Follicular Lymphoma International Prognostic Index. No patients had B symptoms.

**Table 25: Study 20130109 Baseline Patient Disease Characteristics**

| Characteristic | ABP 798<br>N = 128<br>n (%) | Rituxan<br>N = 128<br>n (%) |
|---|---|---|
| **Histologic grade** | | |
| **Grade 1** | 30 (23) | 28 (22) |
| **Grade 2** | 73 (57) | 74 (58) |
| **Grade 3a** | 25 (20) | 26 (20) |
| **Ann Arbor Stage At Screening** | | |
| **Stage 3** | 57 (44.5) | 55 (43) |
| **Stage 4** | 34 (27) | 40 (31) |
| **FLIPI Risk Group** | | |
| **Low** | 55 (43) | 58 (45) |
| **Intermediate** | 56 (44) | 48 (38) |
| **High** | 17 (13) | 22 (17) |
| **Presence of B symptoms** | | |
| **No** | 128 (100) | 128 (100) |
| **Bone Marrow Involvement** | | |
| **Yes** | 30 (23.4) | 39 (30.5) |
| **Indeterminate** | 3 (2.3) | 2 (1.6) |
| **No** | 95 (74.2) | 86 (67.2) |
| **Unknown** | 0 (0) | 1 (0.8) |
| **Number of Nodal Sites** | | |
| **Median** | 2 | 3 |
| **Min, Max** | 1, 6 | 1, 6 |

Abbreviations: FLIPI, Follicular lymphoma international prognostic index
Source: CSR, Full Analysis Set

Treatment Compliance

Each dose of investigational product was administered intravenously by study personnel. The amount of investigational product administered per dose as well as the cumulative dose administered were comparable for both arms of the study. The duration of exposure for the

two treatment arms was also similar.

Concomitant Medications

All of the patients (100%) received concomitant medications. The use of concomitant medication was balanced between treatment arms. The most common concomitant medications used were anti-histamines, steroids, antibiotics, a histamine-2 blocker, and a urate lowering medication.

**Analysis of Primary Clinical Endpoint(s)**

The primary efficacy endpoint of ORR by Week 28 per IRC was analyzed in the FAS population. The risk difference between the treatment arms was 7.07% and the upper bound of the 90% exact confidence interval was 16.29%, below the prespecified margin of 35.5% but above the pre-specified secondary margin of 15%. The results in the FAS population are summarized in **Error! Reference source not found. Error! Reference source not found.**below.

**Table 26: Study 20130109 Primary Efficacy Endpoint, Risk Difference of Overall Response Rate by Week 28 in the FAS per IRC**

| | **ABP 798 (N = 128)** | **US-Rituxan (N = 128)** |
|---|---|---|
| **Best overall response [n (%)]** | | |
| CR | 29 (23.6) | 32 (25.8) |
| Cru | 0 (0.0) | 3 (2.4) |
| PR | 67 (54.5) | 52 (41.9) |
| ORR [n (%)] | 96 (75.0) | 87 (68) |
| 95% CI of ORR (%) | (66.6,82.2) | (59.1,75.9) |
| Risk difference[1] [90% CI] (%) 2-sided | **7.07 [-2.17; 16.29]** | |
| Risk difference[1] [95% CI] (%) 2-sided | **7.07 [-3.9; 18.06]** | |

Source: ADRS.xpt dataset, reviewer generated; Abbreviations: CI: confidence interval, ORR: objective response rate, CRu: unconfirmed CR
N: number of patients
[1] Risk difference adjusted for strata as covariates
[1] The non-inferiority margin was set to -15% points: lower bound of the 95 % CI was above -15%

Nine patients were excluded from the modified FAS for not having disease at baseline per IRC. The difference in ORR by Week 28 between the study drug and the reference drug was 7.7%. The 90% confidence interval estimated by adjusting for the strata as covariates was -1.4% and 16.8%. The lower bound of the 90% confidence interval of the risk difference is -1.4%, which is above the pre-specified non-inferiority margin of -15%. The upper bound of the 90% CI is 16.8%

and is below the 35.5% non-inferiority margin. A 2-sided 95% CI was also calculated; the 2-sided 95% CI of RD of ORR by Week 28 was (-3.2%, 18.6%). The results in the mFAS population are summarized in Table 27 below.

**Table 27: Study 20130109 Primary Efficacy Endpoint, Risk Difference of Overall Response Rate by Week 28 in the mFAS per IRC**

| | **ABP 798 (N = 123)** | **US-Rituxan (N = 124)** |
|---|---|---|
| **Best overall response [n (%)]** | | |
| CR | 29 (23.6) | 32 (25.8) |
| Cru | 0 (0.0) | 3 (2.4) |
| PR | 67 (54.5) | 52 (41.9) |
| ORR [n (%)] | 96 (78.0) | 87 (70.2) |
| 95% CI of ORR (%) | (69.7, 85.0) | (61.3, 78.0) |
| Risk difference[1] [90% CI] (%) 2-sided | **7.7 [-1.4; 16.8]** | |
| Risk difference[1] [95% CI] (%) 2-sided | **7.7 [-3.2; 18.6]** | |

Source: ADRS.xpt dataset, reviewer generated; Abbreviations: CI: confidence interval, ORR: objective response rate, CRu: unconfirmed CR
N: number of patients
[1] Risk difference adjusted for strata as covariates
[1] The non-inferiority margin was set to -15% points: lower bound of the 95 % CI was above -15%

**Reviewer's Comments:**
**For this comparative clinical study, the Agency recommends use of a symmetric similarity margin. Following evaluation of the prespecified asymmetric similarity margin (-15%, +35.5%), with which the Agency did not agree, the Applicant used a symmetric similarity margin of -15%, +15%. The 90% confidence interval of the risk difference of ORR [RD 7.07% (90% CI: -2.17, 16.29)] at Week 28 crossed the upper bound of the +15% symmetric similarity margin.**

**Although the applicant's justification for the asymmetric margin is not adequate, the Agency has determined that a symmetric similarity margin of -17%, +17% is acceptable for this study. This margin is informed by the randomized, controlled study of rituximab vs. watch-and-wait strategy by Ardeshna et al. 2014, which demonstrated that the response rate at 7 months is 88% in the rituximab maintenance arm vs. 6% of spontaneous remission in the control arm. The treatment effect size is 82% with 95% CI of (75%, 87%). It is also consistent with the 2018 Oncologic Drugs Advisory Committee (ODAC), which found that -17%/+17% margin enables the preservation of 77 percent of treatment effect (see 2018 Oncologic Drugs Advisory Committee (ODAC), available from: https://www.fda.gov/advisory-committees/advisory-committee-calendar/meeting-oncologic-drugs-advisory-committee-10102018-10102018). The**

**90% confidence interval of the risk difference of ORR [RD 7.07% (90% CI: -2.17, 16.29)] at Week 28 is within the acceptable symmetric similarity margin of -17%, +17%. Therefore, although the upper bound of the pre-specified symmetric similarity margin of +15% was exceeded, it does not preclude a demonstration of no clinically meaningful differences between ABP 798 and US-licensed Rituxan.**

**Potential Effects of Missing Data and Sensitivity Analyses**

The results based on the investigator's assessment of disease in the full analysis set are presented in **Table 28** and the PP analysis set according to actual treatment received are presented in **Table 29**.

The observed ORR per the investigator's assessment by Week 28 are 80.47 (95% CI: 72.53, 86.94) in the ABP 798 arm and 79.69 (95% CI: 71.67, 86.28) in the US-Rituxan arm. The RD of the point estimates of ORR is 0.52% (90% CI: -7.76, 8.88) contained with the (-15%, 35.5%) margins.

**Table 28: Study 20130109 Risk Difference of Overall Response Rate by Week 28 in the FAS per the Investigator Assessment**

| | ABP 798 (N = 128) | US-Rituxan (N = 128) |
|---|---|---|
| **Best overall response [n (%)]** | | |
| CR | 36 (28.13) | 41 (32.03) |
| Cru | 4 (3.13) | 2 (1.56) |
| PR | 63 (49.22) | 59 (46.09) |
| ORR [n (%)] | 103 (80.47) | 102 (79.69) |
| 95% CI of ORR (%) | (72.53, 86.94) | (71.67, 86.28) |
| Risk difference[1] [90% CI] (%) 2-sided | **0.52 [-7.76, 8.88]** | |
| Risk difference[1] [95% CI] (%) 2-sided | **0.52 [-9.35, 10.39]** | |

Source: ADRS.xpt dataset, reviewer generated; Abbreviations: CI: confidence interval, ORR: objective response rate, CRu: unconfirmed CR
N: number of patients
[1] Risk difference adjusted for strata as covariates
[1] The non-inferiority margin was set to -15% points: lower bound of the 95 % CI was above -15%

**Reviewer's Comments:**
**Although the observed rates of ORR by investigator are higher than those observed by the IRC assessment, the analysis of RD suggests no difference in the two treatment arms.**

In response to the information request request for justification of interpretation of the IRC and investigator assessments, the Applicant mentioned the following:

This sensitivity analysis of the primary endpoint based on the investigator's assessment is important to consider in the interpretation of clinical study results as it provides additional ORR data gathered in a blinded manner. Potential biases in image interpretation were controlled by blinding of the treatment and use of computed tomography as a preferred method for radiographic tumor assessment on the study, a quantitative measure which is widely performed and reported in clinical medicine. The ORR by investigators assessment are well balanced between the ABP 798 and US-Rituxan treatment arms and are consistent with what is expected based on historical rituximab results from other studies (Ardeshna et al, 2014) and the RD of ORR is within the ±15% symmetrical margins.

**Reviewer's Comments:**
**We acknowledge the Applicant's justification. However, the response assessed by investigator is likely subject to biases. Analysis results by investigator is considered as supportive evidence. The efficacy evaluation is primarily based on the ORR by IRC assessment.**

The observed ORR per the IRC assessment of ORR by Week 28 in the PP patient population is 79.17 (95% CI: 70.80, 86.04) in the ABP 798 arm and 70.83 (95% CI: 61.84, 78.77) in the US-Rituxan arm. The RD of the point estimates of ORR is 8.01% (90% CI: -1.11, 17.13) contained with the (-15%, 35.5%) margins.

**Table 29: Study 20130109 Risk Difference of Overall Response Rate by Week 28 in the Per Protocol Patient Population**

| | ABP 798 (N = 120) | US-Rituxan (N = 120) |
|---|---|---|
| **Best overall response [n (%)]** | | |
| CR | 29 (24.17) | 32 (26.67) |
| CRu | 0 | 3 (2.50) |
| PR | 66 (55.00) | 50 (41.67) |
| ORR [n (%)] | 95 (79.17) | 85 (70.83) |
| 95% CI of ORR (%) | (70.80, 86.04) | (61.84,78.77) |
| Risk difference[1] [90% CI] (%) | **8.01 [-1.11, 17.13]** | |
| Risk difference[1] [95% CI] (%) | **8.01 [-2.86, 18.88]** | |

Source: ADRS.xpt dataset, reviewer generated; Abbreviations: CI: confidence interval, ORR: objective response rate, CRu: unconfirmed CR
N: number of patients
[1] Risk difference adjusted for strata as covariates
[1] The non-inferiority margin was set to -15% points: lower bound of the 95 % CI was above -15%

**Reviewer's Comments:**

**The analysis of RD in the PP population is consistent with the results in the FAS population, and suggests no difference in the two treatment arms.**

**Analysis of Secondary Clinical Endpoint(s)**

The difference in ORR by Week 12 between the study drug and the reference drug was 0.7%. The 90% confidence interval estimated by adjusting for the strata as covariates was -9.45% and 10.85%. The results in the FAS population are summarized in Table 30 below.

**Table 30: Study 20130109 Secondary Efficacy Endpoint, Risk Difference of Overall Response Rate by Week 12 in the FAS**

| | ABP 798 (N = 128) | US-Rituxan (N = 128) |
|---|---|---|
| **Best overall response [n (%)]** | | |
| CR | 14 (10.94) | 9 (7.03) |
| Cru | 1 (0.78) | 1 (0.78) |
| PR | 58 (45.3) | 62 (48.4) |
| ORR [n (%)] | 73 (57.0) | 72 (56.2) |
| 95% CI of ORR (%) | (47.99, 65.74) | (47.2,65.0) |
| Risk difference[1] [90% CI] (%) | **0.7 [-9.45, 10.85]** | |
| Risk difference[1] [95% CI] (%) | **0.7 [-11.40, 12.80]** | |

Source: ADRS.xpt dataset, reviewer generated; Abbreviations: CI: confidence interval, ORR: objective response rate, CRu: unconfirmed CR
N: number of patients
[1] Risk difference adjusted for strata as covariates
[1] The non-inferiority margin was set to -15% points: lower bound of the 95 % CI was above -15%

**Other Clinical Endpoints**

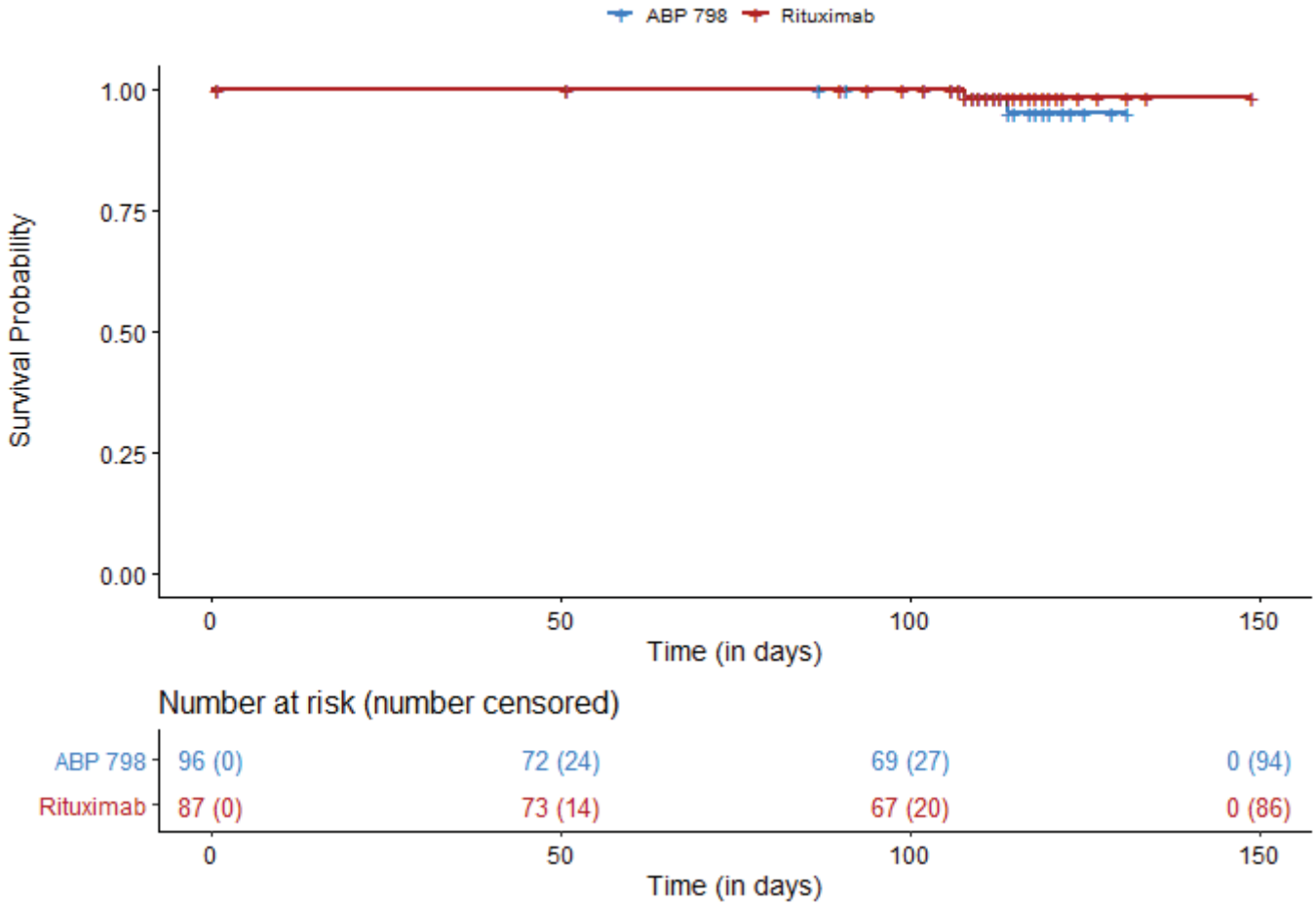
The duration of response as per the investigator and IRC assessments in the patients with a response was evaluated and is presented in the table below. The medians were not reached by both the IRC and investigator assessments with a majority of the patients being censored for having ongoing responses at data cut-off. There were two and one disease progressions on the ABP 798 and and US-Rituxan arm respectively per the IRC assessment. According to the investigator assessment, there were one and three disease progressions on the ABP 798 and US-Rituxan arms respectively. The Kaplan Meier (KM) curves for the duration of response per the IRC assessments and investigator assessment are presented in Figure 9 and Figure 10, respectively.

**Table 31: Study 20130109 Duration of Response per IRC and Investigator Assessments in the FAS Population**

| | ABP 798 | US-Rituxan |
|---|---|---|
| **Duration of Response per IRC** | | |
| Patients with CR/CRu/PR | 96 | 87 |
| Patients with disease progression, n (%) | 2 (2) | 1 (1) |
| Censored at data cutoff, n (%) | 94 (98) | 86 (99) |
| Median (95%CI) | NE | NE |
| **Duration of Response per Investigator** | | |
| Patients with CR/CRu/PR | 103 | 102 |
| Patients with disease progression, n (%) | 1 (1) | 3 (3) |
| Censored at data cutoff, n (%) | 102 (99) | 99 (97) |
| Median (95%CI) | NE | NE |

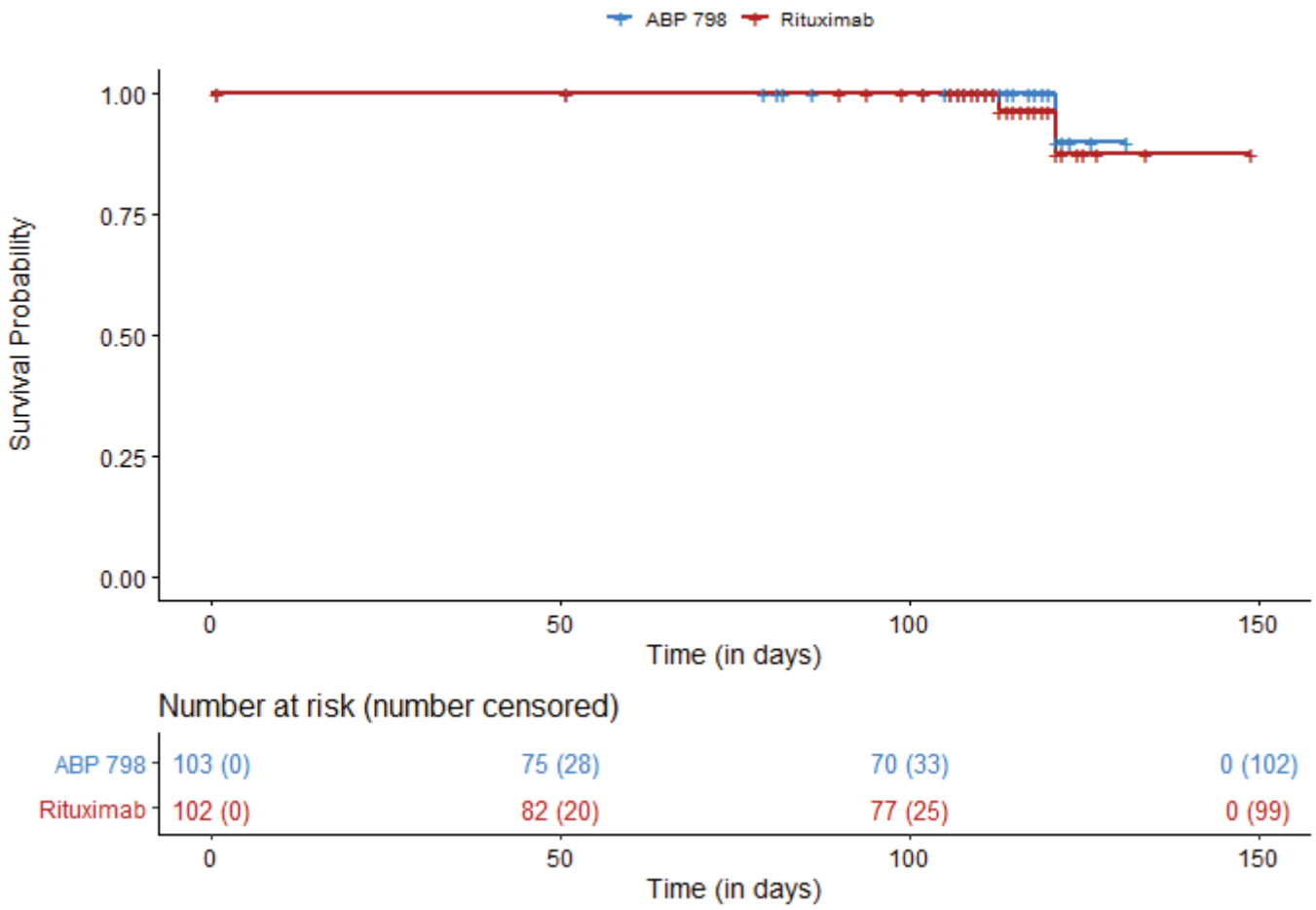
Source: ADDOR.xpt dataset, reviewer generated
Abbreviations: CI: confidence interval, CRu: unconfirmed CR N: number of patients, NE: not estimable

**Figure 9: Study 20130109 Duration of Response in Responders in FAS per IRC**




Source: ADDOR.xpt dataset, reviewer generated

**Figure 10: Study 20130109 Duration of Response in Responders in FAS per Investigator**




Source: ADDOR.xpt dataset, reviewer generated

Both the PFS and OS endpoints were pre-specified to be safety endpoints in the protocol/SAP and hence analyzed in the safety population.

As per the investigator's assessment of disease, 7 (5.4%) patients in the ABP 798 treatment group and 9 (7.1%) patients in the US-Rituxan treatment group had disease progression. As per IRC assessment of disease, 4 (3.1%) patients in the ABP 798 treatment group and 3 (2.4%) patients in the US-Rituxan treatment group had disease progression. Medians for the PFS endpoint were not reached on either of the treatment arms. The results are summarized in Table 32 along with the Kaplan Meier curves in Figure 11 and Figure 12 for the IRC and investigator assessments, respectively.

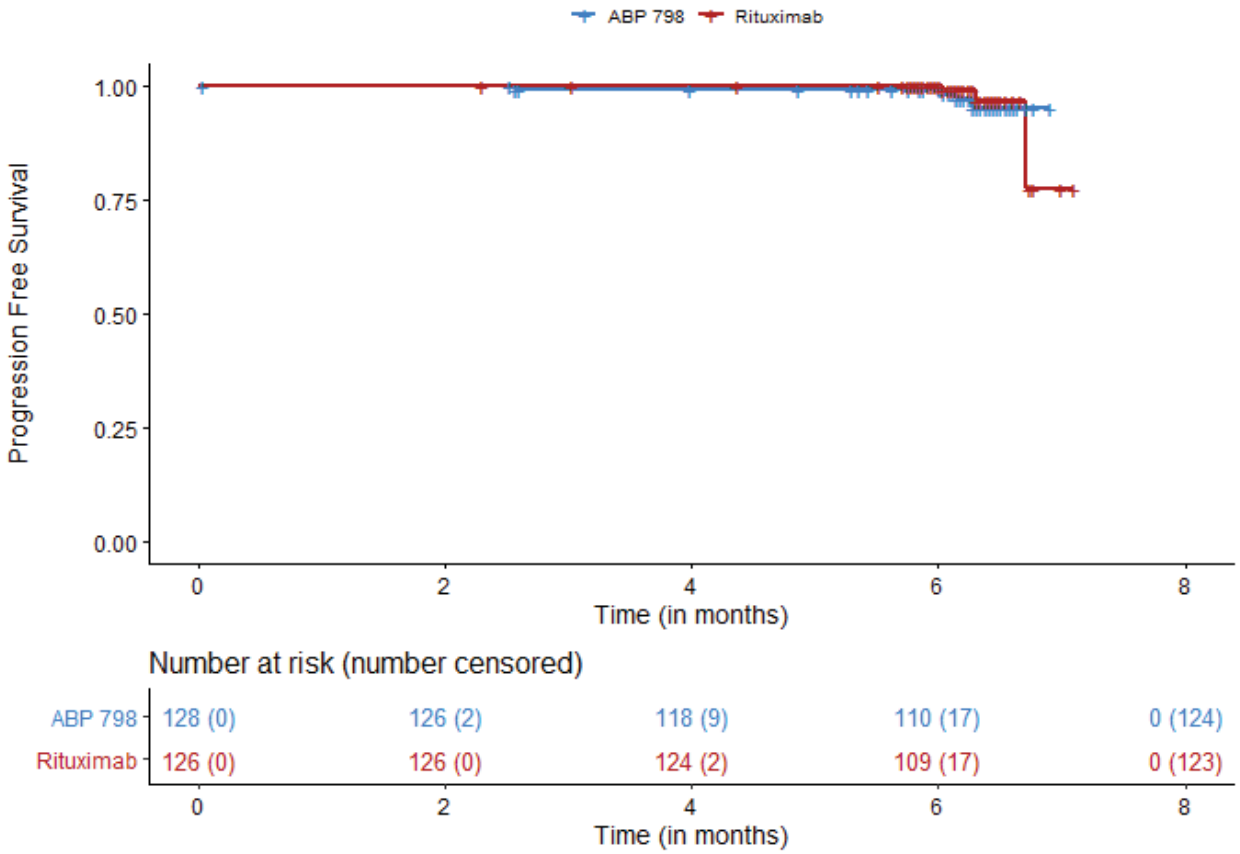
There were no deaths on both arms at the time of database cutoff and hence no events to provide any overall survival estimates.

**Table 32: Study 20130109 Progression-free Survival per IRC and Investigator Assessments in the Safety Analysis Population**

| | ABP 798 (N = 128) | US-Rituxan (N = 126) |
|---|---|---|
| **PFS per IRC** | | |
| Patients with disease progression, n (%) | 4 (3.1) | 3 (2.4) |
| Censored at data cutoff, n (%) | 124 (96.9) | 123 (97.6) |
| Median (95%CI) | NE | NE (6.7, NE) |
| HR (95% CI)[1] | Ref | 1.114 (0.1982, 4.066) |
| **PFS per Investigator** | | |
| Patients with disease progression, n (%) | 7 (5.4) | 9 (7.1) |
| Censored at data cutoff, n (%) | 121 (94.5) | 117 (92.9) |
| Median (95%CI) | NE | NE (6.7, NE) |
| HR (95% CI)[1] | Ref | 1.425 (0.4924, 4.123) |

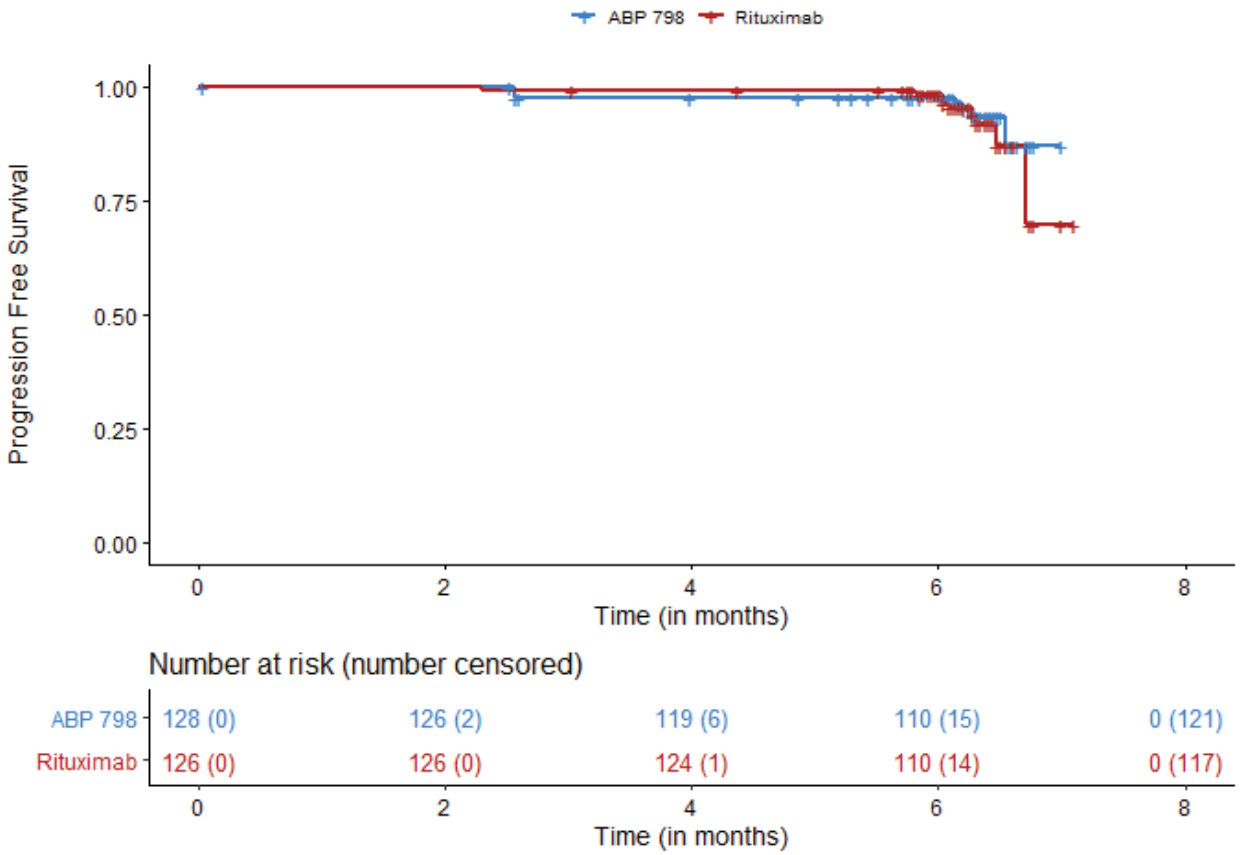
Source: ADTTE.xpt dataset, reviewer generated,
Abbreviations: CI: confidence interval, ORR: objective response rate, CRu: unconfirmed CR N: number of patients, NE: not estimable, Ref: reference arm
[1] Risk difference adjusted for strata as covariates

**Figure 11: Study 20130109 Progression-Free Survival per IRC in the Safety Population**




*Source: ADTTE.XPT dataset, reviewer generated.*

**Figure 12: Study 20130109 Progression-Free Survival per Investigator in the Safety Population**




*Source: ADTTE.XPT dataset, reviewer generated.*

**Additional Analyses**

Subgroup analyses were planned by the stratification variables and Follicular lymphoma international prognostic index (FLIPI). FLIPI is based on the following 5 prognostic factors (Solal-Celigny et al, 2004):

- Age (≥ 60 years)
- Ann Arbor disease stage (stage III-IV, stage III includes IIIE, IIIES, and IIIS)
- Hemoglobin level (< 120 g/L)
- Serum lactate dehydrogenase level (> upper limit of normal)
- Number of nodal sites (> 4)

Subjects with 0 to 1 prognostic factors are defined as low risk, subjects with 2 prognostic factors are defined as intermediate risk, and subjects with 3 or more prognostic factors are defined as high risk.

Subgroup analyses are not adjusted for the stratification factors. The RD of ORR by Week 28 was estimated in each of the subgroups by the baseline covariates in the full analysis set. In each case, the RDs and the 90% CIs were calculated using the methods used for the primary analysis.

The subgroup analysis in the prespecified subgroups of interest are presented in the table below. Some of the subgroups, like region, have very few patients to draw any conclusions. For subgroups with larger sample sizes, results were consistent with results from the primary analysis, presented in the topmost row.

**Table 33: Study 20130109 Risk Difference of Overall Response Rare by Week 28 per IRC in Subgroups of Interest in FAS**

| | ABP 798 (N = 128) n (%) | US-Rituxan (N = 128) n (%) | RD[1] (90% CI) |
|---|---|---|---|
| | | | |
| **Overall ORR (n=256)** | 96/128 (75.0) | 87/128 (67.97) | 7.07 (-2.17, 16.29) |
| **Geographic region** | | | |
| Europe (n=174) | 66/88 (75.00) | 59/86 (68.60) | 6.40 (-4.80, 17.59) |
| Asia Pacific – Other (n=46) | 19/23 (82.61) | 16/23 (69.57) | 13.04 (-7.40, 33.49) |
| Americas (n=21) | 7/10 (70.00) | 8/11 (72.73) | -2.73 (-35.22, 29.77) |
| Japan (n=15) | 4/7 (57.14) | 4/8 (50.00) | 7.14 (-35.19, 49.48) |
| **Age** | | | |
| <=60 years (n=141) | 51/71 (71.83) | 51/70 (72.86) | -1.03( -13.42, 11.36) |
| >60 years (n=115) | 45/57 (78.95) | 36/58 (62.07) | 16.88 (3.14, 30.62) |
| **FLIPI risk group** | | | |
| Low (n=113) | 41/55 (74.55) | 40/58 (68.97) | 5.58(-8.32, 19.48) |
| Intermediate (n=104) | 39/56 (69.64) | 35/48 (72.92) | -3.27(-17.88, 11.34) |
| High (n=39) | 16/17 (94.12) | 12/22 (54.55) | 39.57 (19.75, 59.40) |

Source: ADTTE.xpt dataset, reviewer generated,
Abbreviations: CI: confidence interval, ORR: objective response rate, N: number of patients
[1] Risk difference not adjusted for strata as covariates

Regarding the secondary clinical endpoints, other clinical endpoints, and other analyses described above, the results were similar between the ABP 798 and US-Rituxan treatment arms and there were no meaningful differences between the treatment arms.

**Overall Conclusions**

For Study 20130109, the risk difference of ORR met the prespecified asymmetric margin of -15%/+35%. Although the risk difference of ORR exceeded the upper bound of the -15/+15% prespecified similarity margin, it fell within the symmetric margin of -17/+17%, which the

Agency determined is acceptable for this study. Therefore, this difference does not preclude a demonstration that ABP 798 has no clinically meaningful differences from US-licensed Rituxan. Overall, the results from the secondary endpoints were similar across treatment arms, supportive of the totality of the data in the application. Therefore, the clinical data support a demonstration of no clinically meaningful differences between ABP 798 and US-Rituxan.

## 7.3.Review of Safety Data

### 7.3.1 Study 20130108 – Rheumatoid Arthritis

***ABP 798 Clinical Program in RA: Clinical Safety***

Study 20130108 provides the data to evaluate clinical safety in rheumatoid arthritis patients. A total of 311 RA patients were randomized 1:1:1 into three treatment arms: n=104/ABP 798 arm, n=103/US-Rituxan arm, n=104/EU-MabThera arm.

The primary objective of Study 20130108 was to demonstrate PK similarity of ABP 798 relative to that of US-Rituxan and EU-MabThera at Week 24. Secondary objectives included assessment of clinical efficacy, safety, and immunogenicity of ABP 798 compared with US-Rituxan and EU-MabThera. This study also provides an assessment of the impact of a single transition from US-Rituxan to ABP 798 on safety and immunogenicity.

At week 24, patients in the US-Rituxan treatment group underwent a single transition to ABP 798 treatment group. Subjects initially randomized to receive US-Rituxan transitioned to receive ABP 798 at a dose of 1000 mg × 2 IV infusions administered 2 weeks apart on week 24 and week 26 as the second dose (referred to as US-Rituxan/ABP 798 treatment group). Subjects initially randomized to receive ABP 798 or EU-MabThera received a second dose of the same treatment (i.e., either ABP 798 or EU-MabThera at a dose of 1000 mg × 2 IV infusions administered 2 weeks apart on week 24 and week 26; referred to as ABP 798/ABP 798 treatment group and EU-MabThera/EU-MabThera treatment group, respectively).

It is important to note that the second dose may have been administered prior to week 24 in individual subjects (i.e., any time from week 16 to week 24), per investigator discretion. The end-of-study (EOS) was defined as week 48 (or 24 weeks after the first infusion of the second dose for subjects retreated before week 24). Therefore, reference to 24-week or 48-week study period in the discussion below includes subjects who may have received the second dose as early as Week 16.

This section will focus on the safety results from study 20130108 from the 24-week safety data (defined as the study period from Day 1 until first infusion of second dose) and any relevant safety trends from the 48-week safety data (defined as the study period from Day 1 until end of study). A brief discussion of any change in safety after a single transition (particularly, infusion-related reactions) will also be presented.

*Categorization of Adverse Events*
Safety was evaluated by monitoring adverse events (AEs), serious adverse events (SAEs), adverse events of special interest (AESI), treatment-emergent adverse events (TEAEs), death, electrocardiograms (ECGs), physical examination, clinical laboratory tests, immunoglobulin (IgM, IgG, and IgA) testing, and immunogenicity.
Standard definitions of adverse event (AE) and serious adverse event (SAE) were utilized. Adverse events in the clinical studies were coded to the appropriate system organ class (SOC) and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0. Severity of adverse events and shifts from baseline in clinical laboratory values were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

The AESI identified for both the RA study and the NHL study were infusion reactions including hypersensitivity, cardiac disorders, serious infections, progressive multifocal leukoencephalopathy (PML), hematological reactions, hepatitis B reactivation, opportunistic infections, severe mucocutaneous reactions, and gastrointestinal perforation. The RA study also included the AESI of hypogammaglobulinemia.

*Adequacy of Safety Data*
Of the 311 subjects randomized, all (100%) received at least 1 infusion of investigational product and were included in the safety analysis set. The number of infusions and doses administered to subjects were similar between the treatment groups. For disposition of subjects, see section on Patient Disposition under Section 7.2.1 (RA).

## Major Safety Results

No new safety signals were identified in the ABP 798 group compared to the known adverse event profile of US-licensed Rituxan. Overall, there were no major differences in adverse events (AE), serious adverse events (SAE), or AEs leading to discontinuations between the treatment groups. The total number of treatment emergent adverse events was numerically higher in the ABP 798 arm (50%) than in the US-Rituxan (43%) or EU-MabThera (43%). Infections were the most common adverse event in all treatment groups. The most common TEAEs reported in >5% of subjects were upper respiratory infection, RA, nasopharyngitis, nausea and bronchitis. AESI were comparable between ABP 798 and US-Rituxan, including the incidence of infusion related reactions. The proportion of subjects with serious AEs, and discontinuations secondary to AEs were overall low in number and similar across treatment arms. No deaths were reported.

An overview of AEs for the 24-week study period (Day 1 until first infusion of second dose) is summarized in Table 34.

**Table 34: Study 20130108 Summary of Safety – Day 1 Until First Infusion of Second Dose (Safety Analysis Set)**

| Overview of AEs - Day 1 Until First Infusion of Second Dose | | | |
|---|---|---|---|
| | ABP 798<br>N=104<br>n(%) | US-Rituxan<br>N=103<br>n(%) | EU-MabThera<br>N=104<br>n(%) |
| Patients with ≥1 TEAE | 52(50) | 44(43) | 44(43) |
| Patients with ≥1 SAE | 4(4) | 5(5) | 5(5) |
| AE leading to Discontinuation | 3(3) | 4(4) | 1(1) |
| Infections | 29(28) | 23(22) | 25(24) |
| Infusion related reactions | 12(12) | 12(12) | 7(7) |
| Anaphylaxis | 0 | 0 | 0 |
| Death | 0 | 0 | 0 |
| Any AESI | 19(18) | 18(18) | 11(11) |

Source: FDA analysis of data from Amgen 351(k) BLA submission, SCS Table 9, CSR 20130108 Tables 12-2, 12-5; 12-16; AE: adverse event; SAE: serious adverse event, IRR: Infusion related reaction

Similar trends in safety were observed for the overall 48-week study period (Day 1 through end of study). Table 35 summarizes AEs through the overall study period.

**Table 35: Study 20130108 Summary of Safety – Day 1 through End of Study (Safety Analysis Set)**

| Overview of AEs – Day 1 through End of Study (RA Study 20130108 - Safety Analysis Set) | | | |
|---|---|---|---|
| | ABP 798/ABP 798<br>N=104<br>n(%) | US-Rituxan/ABP 798<br>N=103<br>n(%) | EU-MabThera/EU-MabThera<br>N=104<br>n(%) |
| Patients with ≥1 TEAE | 67(64) | 56(54) | 54(52) |
| Patients with ≥1 SAE | 8(8) | 8(8) | 8(8) |
| AEs leading to Discontinuation | 3(3) | 7(7) | 2(2) |
| Infections | 45(43) | 32(31) | 34(33) |
| Infusion related reactions | 16(15) | 16(16) | 9(9) |
| Anaphylaxis | 0 | 0 | 0 |
| Death | 0 | 0 | 0 |
| Any AESI | 25(24) | 23(22) | 15(14) |

Source: FDA analysis of data from Amgen 351(k) BLA submission, SCS Tables 11, 31; CSR 20130108 Tables 12-8, 12-17; AE: adverse event; SAE: serious adverse event, IRR: Infusion related reaction

### *Deaths*

No deaths were reported in Study 20130108.

### *Serious Adverse Events (SAEs)*

The incidence of SAEs was low across treatment arms, throughout the study. There were no notable differences in the incidence or severity of SAEs between the treatment groups.

SAEs reported in the 24-week study period (day 1 until first infusion of the second dose) are presented in Table 36. The most common SAEs were reported in the System Organ Class (SOC) of infections and infestations. One case each of the following infections were reported – biliary tract infection, diverticulitis in the ABP 798 treatment group; pneumonia, sepsis syndrome and urinary tract infection in the EU-MabThera group. No infections were reported for the US-Rituxan treatment group. Under the SOC of cardiac disorders, there was 1 case each of acute myocardial infarction (ABP 798), coronary artery disease (ABP 798), and chronic cardiac failure (US-Rituxan).

**Table 36: Study 20130108 Serious Adverse Events by SOC – Day 1 Until First Infusion of Second Dose (Safety Analysis Set)**

| Serious Adverse Events - Day 1 Until First Infusion of Second Dose | | | |
|---|---|---|---|
| | ABP 798 N=104 n(%) | US-Rituxan N=103 n(%) | EU-MabThera N=104 n(%) |
| Patients with ≥1 SAE | 4(4) | 5(5) | 5(5) |
| Infections and Infestations | 2(2) | 0 | 2(2) |
| Cardiac Disorders | 1(1) | 1(1) | 1 (1) |
| Skin and subcutaneous tissue disorders | 0 | 2(2) | 0 |
| Hepatobiliary Disorders (PT: Cholecystitis) | 1(1) | 0 | 0 |
| Injury (PT: Forearm fracture) | 0 | 0 | 1(1) |
| Musculoskeletal & connective tissue disorders (PT: Bursitis) | 0 | 0 | 1 |
| Renal and urinary disorders (PT: Tubulointerstitial nephritis) | 0 | 1(1) | 0 |
| Vascular disorders (PT: Hypertension) | 0 | 1(1) | 0 |

Source: FDA analysis of data from Amgen 351(k) BLA submission, SCS Table 17, CSR 20130108 Tables 12-11, 14-6.4.2.1; AE: adverse event; SAE: serious adverse event, PT: preferred term

Similar trends in SAEs were noted for the 48-week study period (day 1 through End of Study). The incidence of SAEs was similar between treatment groups: ABP 798/ABP 798 – 8 subjects (8%), US-Rituxan/ABP 798 – 8 subjects (8%), and EU-MabThera/EU-MabThera – 8 subjects (8%). In addition to SAEs reported in the 24-week period (Table 36), the following SAEs were reported during this period: Erythema migrans, UTI, cerebrovascular accident (1 case each; ABP 798/ABP 798); pneumonia, abdominal pain, rectal hemorrhage, intraductal papilloma of the breast (1 case each; US-Rituxan/ABP 798); acute myocardial infarction, renal neoplasm, back pain (n=2), arthralgia (n=1; EU-MabThera/EU-MabThera). SAE's reported were consistent with the safety profile of US-licensed Rituxan (see USPI). No new safety signals were identified.

### *Adverse Events leading to Discontinuation*

In the 24-week study period (from day 1 until the first infusion of the second dose), 3 (3%) subjects in the ABP 798 treatment group, 4 (3.9%) subjects in the US-Rituxan group, and 1 (1.0%) subject in the EU-MabThera group, discontinued investigational product or discontinued the study due to an adverse event, see Table 34. None of the adverse events leading to discontinuation of investigational product or discontinuation from the study were serious adverse events and none were grade ≥ 3. Most adverse events leading to discontinuation of investigational product or study were infusion-related reactions (i.e., hypersensitivity, urticaria, blister, erythema, pruritus, rash, and rash pruritic), each with an n of 1 except for pruritus (n=2).

In the 48-week study period (Day 1 through end of study), AE's resulting in discontinuation were numerically higher in the US-Rituxan/ABP-798 group (7 subjects, 7%), compared to ABP 798/798 (3 subjects, 3%); and EU-MabThera/EU-MabThera (2 subjects, 2%). Two SAEs led to discontinuation which included one case of abdominal pain in the transition arm (US-Rituxan/ABP-798) and one case of pneumonia in the EU-MabThera/EU-MabThera maintenance group. Table 37 provides the summary of AEs leading to discontinuation in study 20130108.

Although numerical differences were observed in the AE's leading to discontinuation, these did not appear to be meaningful, the overall number of AE's leading to discontinuation were low, and no new safety signals were identified.

**Table 37: Study 20130108 Overview of Adverse Events leading to Discontinuation (Safety Analysis Set)**

| Overview of AEs leading to Discontinuation | | | |
|---|---|---|---|
| | ABP 798<br>N=104<br>n(%) | US-Rituxan<br>N=103<br>n(%) | EU-MabThera<br>N=104<br>n(%) |
| **AE leading to Discontinuation (Day 1 Until First Infusion of Second Dose)** | **3(3)** | **4(4)** | **1(1)** |
| | ABP 798/ ABP 798<br>N=97<br>n(%) | US-Rituxan/ABP 798<br>N=95<br>n(%) | EU-MabThera/EU-MabThera<br>N=99<br>n(%) |
| **AEs leading to Discontinuation (Single Transition Period (Day of First Infusion of Second Dose through End of Study))** | **0** | **3(3)** | **1(1)** |
| Abdominal pain | 0 | 1(1) | 0 |
| Extravasation | 0 | 1(1) | 0 |
| Oropharyngeal pain | 0 | 1(1) | 0 |
| Pancreatic disorder | 0 | 1(1) | 0 |
| Pneumonia | 0 | 0 | 1(1) |
| | ABP 798/ABP 798<br>N=104<br>n(%) | US-Rituxan/ABP 798<br>N=103<br>n(%) | EU-MabThera/EU-MabThera<br>N=104<br>n(%) |
| **AEs leading to Discontinuation (Day 1 through End of Study)** | **3(3)** | **7(7)** | **2(2)** |

Source: FDA analysis of data from Amgen 351(k) BLA submission, SCS Tables 21, 22, 23; CSR 20130108 Tables 12-9, 12-10; AE: adverse event

## *Adverse Events of Special Interest (AESI)*

Overall Summary of AESI

An overview of the AESI is outlined in Table 38 and Table 39 for the 24-week study period, and 48-week study period, respectively. Similar trends in AESI were noted between the 24-week and overall study period. Infusion-related reactions (IRR), followed by hematological reactions, were the most commonly reported AESI across the treatment groups. There were slight numerical imbalances in the AESI of hematological reactions, serious infections, and cardiac disorders, between ABP 798 and US-Rituxan, however, the type and severity of AEs did not raise a safety concern and were within the expected range of the safety profile of US-Rituxan (see USPI). Additionally, there was no impact on safety in patients who underwent a single transition from US-Rituxan to ABP 798 as compared to those who did not undergo a single transition.

**Table 38: Study 20130108 Summary of Adverse Events of Special Interest - Day 1 until First Infusion of Second Dose (Safety Analysis Set)**

| Overview of AESI - Day 1 Until First Infusion of Second Dose | | | |
|---|---|---|---|
| | ABP 798<br>N=104<br>n(%) | US-Rituxan<br>N=103<br>n(%) | EU-MabThera<br>N=104<br>n(%) |
| Any AESI | 19(18) | 18(18) | 11(11) |
| Infusion related reactions | 12(12) | 12(12) | 7(7) |
| Hematological reactions | 4(4) | 3(3) | 2(2) |
| Serious infections | 2(2) | 1(1) | 3(3) |
| Cardiac disorders | 2(2) | 2(2) | 2(2) |
| Opportunistic infection | 1(1) | 1(1) | 0 |
| Source: FDA analysis of data from Amgen 351(k) BLA submission, SCS Tables 9, 28, CSR 20130108 Tables 12-13; AESI: adverse event of special interest | | | |

**Table 39: Study 20130108 Summary of Adverse Events of Special Interest – Day 1 through End of Study (Safety Analysis Set)**

| Overview of AEs – Day 1 through End of Study (RA Study 20130108 - Safety Analysis Set) | | | |
|---|---|---|---|
| | ABP 798/ABP 798<br>N=104<br>n(%) | US-Rituxan/ABP 798<br>N=103<br>n(%) | EU-MabThera/EU-MabThera<br>N=104<br>n(%) |
| Any AESI | 25(24) | 23(22) | 15(14) |
| Infusion related reactions | 16(15) | 16(16) | 9(9) |
| Hematological reactions | 5(5) | 7(7) | 2(2) |
| Serious infections | 4(4) | 1(1) | 4(4) |
| Cardiac disorders | 4(4) | 2(2) | 3(3) |
| Opportunistic infection | 1(1) | 1(1) | 2(2) |
| Source: FDA analysis of data from Amgen 351(k) BLA submission, SCS Tables 11, 31; CSR 20130108 Tables 12-15; AESI: adverse event of special interest | | | |

*Infusion-related reactions including hypersensitivity*

IRR were comparable between ABP 798 (12%) and US-Rituxan (12%) groups. A lower incidence of IRR was reported in the EU-MabThera (7%) group. There was no increase in IRR in patients who transitioned from US-Rituxan to ABP 798. In the entire study period, all infusion reactions including hypersensitivity AESI were grade 1 or 2 in severity and none were serious adverse

events. The most common (≥ 2% of subjects in any treatment group) infusion reaction including hypersensitivity AESI were pruritus, erythema, headache, and rash. No cases of anaphylaxis were reported.

Across all treatment groups, the proportion of subjects experiencing infusion-related reactions including hypersensitivity was highest following the first infusion of the first dose, as seen in Table 40 below.

**Table 40: Study 20130108 Infusion-Related Reactions by Infusion - Day 1 through EOS (Safety Analysis Set)**

| | ABP 798/ABP 798 N = 104 n (%) | Rituximab (EU)/Rituximab (EU) N = 104 n (%) | Rituximab (US)/ABP 798 N = 103 n (%) |
|---|---|---|---|
| Any infusion reaction including hypersensitivity adverse event[a] | 16 (15.4) | 9 (8.7) | 16 (15.5) |
| Subjects dosed with first infusion of first dose (N1) | 104 | 104 | 103 |
| Any infusion reaction adverse event following first infusion of first dose | 10 (9.6) | 7 (6.7) | 10 (9.7) |
| Subjects dosed with second infusion of first dose (N1) | 102 | 103 | 99 |
| Any infusion reaction adverse event following second infusion of first dose | 5 (4.9) | 1 (1.0) | 2 (2.0) |
| Subjects dosed with first infusion of second dose (N1) | 97 | 99 | 95 |
| Any infusion reaction adverse event following first infusion of second dose | 4 (4.1) | 3 (3.0) | 4 (4.2) |
| Subjects dosed with second infusion of second dose (N1) | 97 | 99 | 93 |
| Any infusion reaction adverse event following second infusion of second dose | 4 (4.1) | 0 (0.0) | 1 (1.1) |

Source: FDA analysis of data from Amgen 351(k) BLA submission. CSR 20130108 Table 12-18; [a] Subject was included only once, even if they experienced multiple events of the same AE during the period.
Percentages were calculated as n/N1*100. Infusion reactions including hypersensitivity must have start date same as, or one day after, investigational product administration start date. Rituximab (EU) refers to EU-Rituxan. Rituximab (US) refers to US-Rituxan.

*Other AESI*

Hematological reactions (including anemia, lymphopenia, leukopenia, thrombocytopenia, monocytopenia) with the exception of 1 case of grade 3 severity lymphopenia in EU-MabThera group were of Grade 1 or 2 severity, and none were SAEs. The most common (≥ 2% of subjects in any treatment group) hematological reaction AESI was anemia (ABP 798 - 3 (3%), EU-MabThera - 0 (0%), and US-Rituxan 5 (5%) subjects.

A total of 10 serious infections were reported in the overall study period (day 1 through the EOS) across all treatment groups:

- ABP 798/ ABP 798: n=1 each (1%) of biliary tract infection, diverticulitis, erythema migrans, urinary tract infection
- EU-MabThera/EU-MabThera: n=2 (2%) of pneumonia, n=1 (1%) of urinary tract infection, sepsis syndrome, upper respiratory tract infection
- US-Rituxan: n=1 (1%) of erysipelas
- No serious infections were reported in the US-Rituxan/ABP 798 group.

Of the 10 serious infections, pneumonia (2 cases (2%) – EU rituximab) and urinary tract infection ( 1 case each (1%) - ABP 798 & EU-MabThera groups) were the only events by PT that were reported in more than 1 subject across all treatment groups.

A total of 9 cardiac disorder AEs were reported in the overall study period (day 1 through the EOS) across all treatment groups:

- ABP 798/ ABP 798: n=1 each (1%) acute coronary syndrome, acute myocardial infarction, cardiac failure chronic, coronary artery disease, sinus tachycardia, tachycardia
- EU-MabThera/EU-MabThera: n=1 each (1%) acute myocardial infarction, tachycardia, atrial fibrillation
- US-Rituxan: n=1 each (1%) cardiac failure chronic, palpitations
- No cardiac disorder AEs were reported in the US-Rituxan/ABP 798 group.

Two AE's of opportunistic infections (both grade 1 severity) were reported in the overall study period (day 1 through the EOS) across all treatment groups:

- ABP 798: n=1 (1%) urinary tract infection fungal
- US-Rituxan: n=1 (1%) herpes zoster

The event of herpes zoster involved the spine and inguinal region and was considered an opportunistic infection for this category of AESI (herpes zoster systemic or disseminated, involving 2 or more dermatomes was, by definition, considered an opportunistic infection).

There were no reported cases of PML, Hepatitis B reactivation, hypogammaglobulinemia, severe mucocutaneous reactions, gastrointestinal perforation in study 20130108.

### *Common AEs*

Across all 3 treatment groups, in both the 24-week and 48-week study periods, the SOC with the mostly commonly reported AEs were Infections and Infestations, see Table 34 and Table 35. The most common Preferred Terms (PTs) reported in all subjects were upper respiratory tract infection, rheumatoid arthritis, nasopharyngitis, nausea and bronchitis. AEs of RA (i.e. worsening of RA) were mild (grade 1 or 2) in nature. The small numerical differences between the treatment arms were not meaningful, were mostly driven by AEs of mild severity; and review of the type, nature, and severity of events did not raise any safety concerns. In summary, adverse events were consistent with the known safety profile of US-licensed Rituxan. No new safety signals were identified further supporting the demonstration that there are no meaningful differences across the treatment arms in the indications studied.

### *Laboratory Findings, Vital Signs and Electrocardiograms (ECGs)*

The distribution of laboratory findings and, vital signs findings was balanced between the ABP 798, US-Rituxan and EU-MabThera treatment groups. No new or unexpected laboratory

findings were reported in the ABP 798 clinical program. Electrocardiograms (ECGs) were collected at screening only for the RA study.

### Safety after a single transition

Similar trends in safety were noted for single transition phase of the study in which patients initially randomized to US-Rituxan were switched to receive ABP 798 at Week 24 compared to patients who did not undergo a single transition. Infusion-related reactions were similar across treatment arms in the single transition period of the study. There was no notable difference in the incidence of SAEs following a single transition of RA patients from US-Rituxan to ABP 798. In general,
there did not appear to be more TEAEs in subjects after a single transition.

### Immunogenicity

Refer to Section 6.4. The reviewer is in agreement with the Clinical Pharmacology team's assessment of immunogenicity and its impact on PK, safety and efficacy in study 20130108.

### Overall Summary of Safety and Immunogenicity

Given that an adequate scientific bridge was established to justify the relevance of data generated with EU-MabThera as the comparator to the assessment of biosimilarity, the submitted safety and immunogenicity data from Study 20130108 (ABP 798, US-Rituxan, and EU-MabThera dosed on the background of methotrexate in patients with RA) supports the demonstration of no clinically meaningful differences between ABP 798 and US-Rituxan.
The safety database submitted for ABP 798 is adequate to provide a reasonable descriptive comparison between the products. The analysis of the data indicates a safety profile of ABP 798, similar to that of US-Rituxan. While some minor numerical differences were identified there were no notable differences between ABP 798 and US-Rituxan in treatment-emergent adverse events, serious adverse events, adverse events leading to discontinuations, or deaths between the treatment groups. The safety risks identified are consistent with the known adverse event profile of US-licensed Rituxan[7]. The safety data in patients with RA support the demonstration that there are no clinically meaningful differences between ABP 798 and US-Rituxan. In addition, transitioning of non-treatment naïve patients, i.e., patients previously treated with US-Rituxan to ABP 798 does not appear to result in an increase of clinically significant adverse reactions. The FDA safety analyses are generally consistent with the Applicant's.

## 7.3.2 Study 20130109 – Follicular Lymphoma

## Methods

The clinical review of safety for this BLA is based on the following:

- Clinical study report for Study 20130109
- Protocol and statistical analysis plan for Study 20130109
- Datasets from Study 20130109
- Summary of clinical safety

The data and datasets submitted to this BLA were of adequate quality to perform the safety review. Overall, there were no concerns regarding the integrity of the BLA submission.

The safety population includes all randomized patients who have received at least one dose of study treatment. The safety analysis considers all-causality treatment-emergent adverse events, defined as new or worsening events occurring in the safety population at or after the first study treatment up to and including 30 days after last dose of study treatment. The safety population consisted of 254 patients, 128 in the ABP 798 arm and 126 in the US-Rituxan arm.

**Clinical Studies Used to Evaluate Safety**
Study 20130109 was used to evaluate the safety population for patients with NHL.

**Categorization of Adverse Events**
Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA). Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03. Per the Applicant, treatment-emergent adverse events were defined as those that begin or increase in severity or frequency at or after the time of first study treatment up to the end of study visit.

**Safety Analyses**

**Exposure**
Patients received a dose of 375 mg/m$^2$ for both ABP 798 and US-Rituxan. The table below provides a summary of exposure and number of cycles during treatment. The median duration of exposure was 27 weeks for each treatment arm. Patients received similar amounts of investigational product during those 27 weeks (4050 mg in the ABP 798 arm and 4140 in the US-Rituxan arm).

**Table 41: Study 20130109 Exposure Summary**

| Rx Exposure | ABP 798<br>N = 128 | US-Rituxan<br>N = 126 |
|---|---|---|
| Total number of doses administered (EOS)<br>Median<br>Min, Max | <br>6<br>1, 6 | <br>6<br>4, 6 |
| Duration of IP exposure (weeks)<br>Median<br>Min, Max | <br>27.3<br>0.1, 31.9 | <br>27.3<br>11.9, 30.9 |
| Amount (mg) per dose (EOS))<br>Median<br>Min, Max | <br>686<br>6, 1054 | <br>693<br>510, 978 |
| Total cumulative dose (EOS)<br>Median<br>Min, Max | <br>4050<br>6, 6324 | <br>4140<br>2991, 5868 |
| Cycle length in weeks (EOS)<br>Median<br>Min, Max | <br>4.5<br>0.1, 6.4 | <br>4.5<br>3, 5.1 |
| Abbreviations: EOS, end-of-study<br>Source: FDA analysis of ADAE dataset | | |

Relevant Characteristics of the Population Evaluated for Safety

The safety population consisted of 254 patients, 128 in the ABP 798 arm and 126 in the US-Rituxan arm. Demographic characteristics and disease characteristics are summarized in Table 24 and Table 25 in Section 7.2.2. Demographic characteristics were generally similar across treatment arms. Overall, the majority of patients were Caucasian (79%) and less than 60 years of age (55%). The median age was 59 years (range 24 to 84 years). All patients had an ECOG performance status of 0 or 1. The disease characteristics were also generally similar between the treatment arms. Twenty percent of patients had Grade 3a follicular lymphoma, 73% of patients had stage 3 or 4 disease, 27% had bone marrow involvement, and the median number of nodal sites was 2. Fifteen percent of patients were considered high risk based on the presence of 3 or more risk factors in Follicular Lymphoma International Prognostic Index. No patients had B symptoms.

***Reviewer Comment: The demographics and disease characteristics are well balanced between the two treatment arms. The majority of patients were Caucasian and Asian. African Americans are a minority in this study. The demographic make-up did not compromise the sensitivity of the study or impact the ability to draw conclusions about meaningful differences between the two treatment arms.***

**Deaths**

As of the end-of-study at Week 28, there were no treatment-related deaths in either treatment

arm.

Serious Adverse Events

The table below displays a summary of serious adverse events (SAE) that occurred during treatment. During treatment, 5% of patients in each arm experienced a serious adverse event. The SAEs were well balanced between treatment arms.

**Table 42: Study 20130109 Serious Adverse Events**

| Treatment | ABP 798 N= 128 | | US-Rituxan N= 126 | |
|---|---|---|---|---|
| **Serious Adverse Event** | **All grades n (%)** | **Grade 3/4 n (%)** | **All grades n (%)** | **Grade 3/4 n (%)** |
| **Total** | 5 (4) | 4 (3) | 5 (4) | 3 (2) |
| Sepsis | 1 (< 1) | 1 (< 1) | 0 | 0 |
| Lower respiratory infection | 1 (< 1) | 1 (< 1) | 0 | 0 |
| Viral infection | 1 (< 1) | 0 | 0 | 0 |
| Hip fracture | 1 (< 1) | 1 (< 1) | 0 | 0 |
| Limb traumatic fx | 1 (< 1) | 1 (< 1) | 0 | 0 |
| Stomatitis | 1 (< 1) | 1 (< 1) | 0 | 0 |
| Abdominal pain | 0 | 0 | 1 (< 1) | 1 (<1) |
| Colitis ulcerative | 0 | 0 | 1 (< 1) | 0 |
| Dysphagia | 0 | 0 | 1 (< 1) | 0 |
| Pyrexia | 1 (< 1) | 0 | 0 | 0 |
| Chills | 0 | 0 | 1 (< 1) | 0 |
| CAD | 0 | 0 | 1 (< 1) | 1 (<1) |
| Headache | 0 | 0 | 1 (<1) | 1 (<1) |
| ED | 0 | 0 | 1 (<1) | 0 |
| Rhinorrhea | 0 | 0 | 1 (<1) | 0 |

Abbreviations: CAD, coronary artery disease; ED, erectile dysfunction; Fx, fracture
Source: FDA analysis of ADAE dataset

**Dropouts and/or Discontinuations**

In the ABP 798 arm, 4 patients (3%) discontinued treatment due to an infusion-related reaction. One patient in the US-Rituxan arm discontinue treatment due to diarrhea.

**Treatment Emergent Adverse Events**

The table below provides a summary of treatment-emergent adverse events in > 10% of patients during treatment in decreasing order of incidence. During treatment, 84% of patients receiving ABP 798 and 75% of patients receiving US-Rituxan experienced a treatment-emergent adverse event. The most common adverse events in both treatment arms included fatigue, rash, pruritis, abdominal pain, nausea, headache, and musculoskeletal pain.

**Table 43: Study 20130109 Treatment-Emergent Adverse Events in >10% of Patients during Treatment**

| Treatment-Emergent Adverse Events | ABP 798 N= 128 | | US-Rituxan N= 126 | |
|---|---|---|---|---|
| | All grades n (%) | Grade 3/4 n (%) | All grades n (%) | Grade 3/4 n (%) |
| **Total** | 107 (84) | 14 (11) | 95 (75) | 13 (10) |
| Fatigue | 25 (20) | 0 | 18 (14) | 0 |
| Rash | 15 (12) | 0 | 11 (9) | 0 |
| Pruritis | 6 (4.7) | 0 | 14 (11) | 0 |
| Abdominal pain | 7 (5) | 1 (< 1) | 16 (13) | 1 (< 1) |
| Nausea | 6 (4.7) | 0 | 14 (11) | 0 |
| Headache | 16 (12) | 0 | 13 (10) | 1 (< 1) |
| MSK pain | 14 (11) | 0 | 16 (13) | 0 |

Source: FDA analysis of ADAE dataset

***Reviewer Comment: The treatment-emergent adverse events are generally well balanced between treatment arms. There was a greater incidence of fatigue and rash in the ABP 798 arm vs a greater incidence of pruritis, abdominal pain, and nausea in the US-Rituxan arm. The differences are unlikely to have a meaningful impact on safety.***

Adverse Events of Special Interest

Major events of interest, which are listed as Boxed Warnings in the prescribing information for US-Rituxan, include infusion reactions, severe mucocutaneous reactions, Hepatitis B virus reactivation, and progressive multifocal leukoencephalopathy. The table below provides a summary of adverse events of special interest. There was a low incidence of serious infections, specifically 1 episode of sepsis and lower respiratory tract infection in the ABP 798 arm. The incidence of infusion reactions was well matched in both arms. There were no fatal infusion reactions during the conduct of the study. The most common (> 5% of subjects in any treatment group) infusion reaction signs and symptoms were headache, fatigue, rash, urticaria,

nausea, and pruritus. There was 1 incident of grade 3 anaphylactic reaction in the ABP 798 arm. There were no reported cases of severe mucocutaneous reactions, Hepatitis B virus reactivation, or progressive multifocal leukoencephalopathy during the conduct of Study 20130109.

**Table 44: Study 20130109 Adverse Events of Special Interest**

| | ABP 798 N = 128 | | US-Rituxan N = 126 | |
|---|---|---|---|---|
| **Adverse Events of Special Interest** | **All grades n (%)** | **Grade 3/4 n (%)** | **All grades n (%)** | **Grade 3/4 n (%)** |
| Any serious infection | 2 (2) | 1 (<1) | 0 | 0 |
| Sepsis | 1 (< 1) | 1 (<1) | 0 | 0 |
| Lower respiratory infection | 1 (<1) | 1 (<1) | 0 | 0 |
| Viral infection | 1 (<1) | 0 | 0 | 0 |
| Infusion reaction | 55 (43) | 4 (3) | 54 (43) | 4 (3) |
| Headache | 10 (8) | 0 | 7 (6) | 1 (< 1) |
| Fatigue | 9 (7) | 0 | 8 (6) | 0 |
| Rash | 7 (6) | 0 | 5 (4) | 0 |
| Urticaria | 7 (6) | 1 (< 1) | 2 (2) | 1 (<1) |
| Nausea | 5 (4) | 0 | 9 (7) | 0 |
| Pruritis | 5 (4) | 0 | 12 (10) | 0 |
| Dyspnea | 4 (3) | 0 | 2 (2) | 0 |
| Anaphylactic Rx | 1 (<1) | 1 (< 1) | 0 | 0 |

Source: FDA analysis of ADAE dataset

**Laboratory Findings**

The treatment arms had similar laboratory findings, with most abnormalities being Grade 1-2. In the ABP 798 arm, common (≥10%), all-grade hematology abnormalities included leukopenia, anemia, and neutropenia, with 3-5% of patients experiencing Grade 3 neutropenia. For non-hamtologic laboratory findings, Grade 1-2 elevations of AST or ALT were common. The table below summarizes the laboratory abnormalities.

**Table 45: Study 20130109 Select Laboratory Abnormalities in >5% of Patients by Maximum Postbaseline Grade**

| Laboratory Parameter | ABP 798 N = 128 | | US-Rituxan N = 126 | |
|---|---|---|---|---|
| | All grades n (%) | Grade3/4 n (%) | All grades n (%) | Grade 3/4 n (%) |
| **Hematology** | | | | |
| Leukopenia | 35 (27) | 0 | 35 (28) | 0 |
| Anemia | 22 (17) | 1 (<1) | 15 (12) | 0 |
| Neutropenia | 14 (11) | 4 (3) | 12 (9) | 6 (5) |
| Thrombocytopenia | 5 (4) | 0 | 6 (5) | 0 |
| **Chemistry** | | | | |
| AST increase | 29 (23) | 0 | 17 (13) | 1 (<1) |
| ALT increase | 23 (18) | 1 (<1) | 12 (9) | 0 |
| Bilirubin | 11 (9) | 0 | 13 (10) | 0 |
| Alk Phos | 7 (5) | 0 | 7 (6) | 0 |
| Source: FDA analysis | | | | |

**Vital Signs**

Mean changes from baseline in vital sign values were comparable between treatment groups (Source: Section 12.8, CSR).

**Electrocardiograms/QT**

No clinically significant EKG abnormalities were reported in either treatment group (Source: Section 12.8, CSR).

**Overall Conclusions**

The submitted safety data from Study 20130109 supports the demonstration of no clinically meaningful differences between ABP 798 and US-Rituxan. The safety database submitted for ABP 798 is adequate to provide a reasonable descriptive comparison between the products. The analysis of the data indicates a safety profile of ABP 798 similar to that of US-Rituxan. While some minor numerical differences were identified there were no notable differences between ABP 798 and US-Rituxan in treatment-emergent adverse events, serious adverse events, adverse events leading to discontinuations, or deaths between the treatment groups. The safety risks identified are consistent with the known adverse event profile of US-licensed Rituxan (see USPI).

### 7.3.3 Clinical Conclusions on Immunogenicity

Refer to Section 6.4 for details on the clinical immunogenicity assessment and section 1.5 (scientific justification for use a non-U.S.-licensed comparator product). In general, immunogenicity of ABP 798 and US-licensed Rituxan and EU-approved MabThera was evaluated in Study 20130108 in patients with rheumatoid arthritis and the immunogenicity of ABP 798 and US-licensed Rituxan was evaluated in Study 20130109 in patients with non-Hodgkin lymphoma. In Study 20130108, the overall incidence of ADA formation after repeat intravenous dosing was 14.4%, 13.8%, and 20.6% in the ABP 798/ABP 798, EU-approved MabThera/EU-approved MabThera, and US-licensed Rituxan/ABP 798 treatment arms, respectively. Additionally, the immunogenicity was overall comparable after transition from US-licensed Rituxan to ABP 798 to those that did not transition. In Study 2013019, following repeat IV dosing, the incidence of ADA formation was 2.4% and 0.8% in the ABP 798 and US-licensed Rituxan treatment arms, respectively. The incidence of anti-drug antibody and neutralizing antibody formation of ABP 798 and that of US-licensed Rituxan in both studies was comparable. The immunogenicity data support a demonstration of no clinically meaningful differences between ABP 798 and US-licensed Rituxan.

## 7.4. Extrapolation to Support Licensure of Non-Studied Indications

The Applicant submitted scientific justification for extrapolation of data and information to support licensure of ABP 798 (rituximab-arrx; Riabni) as a biosimilar to US-licensed Rituxan for the following indications and for which US-Rituxan has been previously approved: Adult Non-Hodgkin Lymphoma (NHL), Adult Chronic Lymphocytic Leukemia (CLL), and Adult Granulomatosis with Polyangiitis and Microscopic Polyangiitis (GPA/MPA). The Applicant also submitted its pediatric assessment for pediatric GPA/MPA in pediatric patients 2 years of age and older, which contains a scientific justification for extrapolation of data and information to support the assessment;[8] the Applicant is not currently seeking licensure of this indication, and the Agency could not license ABP 798 for this indication until the expiration of orphan exclusivity. (For ease of reference, this review uses pediatric GPA/MPA to refer to pediatric GPA/MPA in pediatric patients 2 years of age and older.) The justification is based on the mechanism of action, PK, immunogenicity, and safety profile of ABP 798 compared to US-licensed Rituxan.

- MOA: The known and potential mechanisms of action of rituximab include antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, apoptosis, and antibody-dependent cellular phagocytosis. Based on information in published literature, the relevant target molecule (CD20) for each of these mechanisms of action is the same across all indications for which US-licensed Rituxan is approved. Comparative analytical

data provided by the Applicant support that ABP 798 has the same mechanism(s) of action as US-licensed Rituxan to the extent known. The foregoing supports the extrapolation of data and information to support licensure of the indications for which US-Rituxan has been previously approved and for which the Applicant is seeking licensure; it also supports extrapolation of data and information to support the applicant's pediatric assessment for pediatric GPA/MPA.

- PK: Pharmacokinetic similarity was demonstrated between ABP 798 and US-licensed Rituxan in Study 20130108 in patients with rheumatoid arthritis. There are no product-related attributes that would increase the uncertainty that the PK may differ between ABP 798 and US-Rituxan across the indications for which US-licensed Rituxan is approved. Therefore, a similar PK profile would be expected between ABP 798 and US-licensed Rituxan in indications for which US-Rituxan has been previously approved and for which the Applicant is seeking licensure as well as in pediatric GPA/MPA.

- Immunogenicity: Patients with rheumatoid arthritis (Study 20130108) and low tumor burden follicular lymphoma (Study 20130109) are considered sensitive populations for detecting potential differences in immunogenicity following treatment with rituximab products. Becaue an adequate scientific bridge was established, the clinical immunogenicity results from studies 20130108 and 20130109 support a demonstration that there are no clinically meaningful differences in terms of immunogenicity between ABP 798 and US-licensed Rituxan. There are no product-related attributes that would increase the uncertainty that the PK may differ between ABP 798 and US-Rituxan across the indications for which the Applicant is seeking licensure and for which US-licensed Rituxan is licensed as well as for pediatric GPA/MPA. Therefore, the incidence of immunogenicity for ABP 798 would be expected to be similar to that of US-licensed Rituxan in each of the indications for which the Applicant is seeking licensure as well as for pediatric GPA/MPA.

- Safety: The results from studies 20130108 and 20130109 showed similar safety profiles between ABP 798, US-Rituxan, and EU-MabThera. Furthermore, the available safety data of US-licensed Rituxan (see USPI) does not indicate that there are any notable differences in expected toxicities for the indications for which US-licensed Rituxan was previously licensed and for which the Applicant is seeking licensure as well as for pediatric GPA/MPA.

The Applicant's proposed scientific justifications noted above are sufficient to support extrapolation of data and information in the application to support licensure of ABP 798 under section 351(k) of the PHS Act for the indications for which US-Rituxan has been previously approved and for which the Applicant is seeking licensure. The proposed scientific justifications are also sufficient to support the Applicant's pediatric assessment for pediatric GPA/MPA; however, the Applicant is not seeking licensure for this indication and the Agency cannot license ABP 798 for this indication until the expiration of US-Rituxan's orphan exclusivity. For additional

information, refer to sections 7.4.1 and 7.4.2.

### 7.4.1 Division of Rheumatology and Transplant Medicine

The Applicant is seeking licensure of ABP 798 for the following indications for which US-Rituxan has been previously approved: Adult Non-Hodgkin's Lymphoma (NHL), Adult Chronic Lymphocytic Leukemia (CLL), adult Granulomatosis with Polyangiitis (GPA) and Microscopic Polyangiitis (MPA). The Applicant also submitted its pediatric assessment for pediatric GPA/MPA in pediatric patients two years of age and older, but is not currently seeking licensure for the indication (see discussion in section 7.4).

The ABP 798 clinical program provides clinical efficacy and safety data from clinical studies in patients with RA in study 20130108 and Grade 1, 2 or 3a follicular B-cell NHL and low tumor burden with the comparative clinical study 20130109. The Division of Hematology Malignancies 2 (DHM2) has determined that the data from this oncology study (20130109) support a demonstration of no clinically meaningful differences between ABP 798 and US-licensed Rituxan and will address the considerations that support licensure of ABP 798 for the oncology indications sought for licensure.

The concept of extrapolation is described in the Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (April 2015). The applicant needs to provide sufficient scientific justification for extrapolation, which should address, for example, the following:

- The mechanism(s) of action (MOA) in each condition of use for which licensure is sought
- The pharmacokinetics (PK) and bio-distribution of the product in different patient populations
- The immunogenicity of the product in different patient populations
- Differences in expected toxicities in each condition of use and patient population
- Any other factor that may affect the safety or efficacy of the product in each condition of use and patient population for which licensure is sought

As a scientific matter, the FDA has determined that differences between conditions of use with respect to the factors addressed in a scientific justification for extrapolation do not necessarily preclude extrapolation. The applicant provided an extrapolation rationale consistent with the principles outlined in the above Guidance. Of these, DRTM reviewed the scientific justification for extrapolation of data to the non-oncology indications of adult and pediatric GPA, and MPA. The justification includes the following:

- Mechanism of action: The known and potential mechanisms of action (MOA) of rituximab include antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), signaling induced cell death (apoptosis), and antibody-dependent cellular phagocytosis (ADCP). The published scientific literature indicates that these Fab-

and Fc-mediated interactions are important for the MOA of rituximab in rheumatic disease indications as well as oncology indications.[91011] The in vitro data provided by the Applicant demonstrated similar activity for these mechanisms, supporting the demonstration that ABP 798 and US-Rituxan utilize the same MOAs.

- PK: PK similarity was demonstrated between ABP 798 and US-Rituxan in patients with RA (Study 20130108). Further, the product quality review team concluded that ABP 798 is highly similar to US-Rituxan based on comparative analytical data and that there are no product-related attributes that would increase the uncertainty that the PK may differ between ABP 798 and US-Rituxan based on the indication. Thus, a similar PK profile would be expected between ABP 798 and US-Rituxan in adult and pediatric patients with GPA and MPA patients.
- Immunogencity: Similar immunogenicity was demonstrated between ABP 798 and US-Rituxan in RA, a reasonably sensitive population. Importantly, across all US-licensed Rituxan approved indications, the incidence of ADA (referred to as HACA in the FDA approved Rituxan labeling) formation was relatively low (1.1% in NHL, 11% in RA and 23% in GPA/MPA) and was not associated with clinically relevant sequelae[12]. Further, no analytical differences were seen in attributes that could potentially impact immunogenicity. Additionally, PK similarity was also demonstrated between ABP-798 and US-Rituxan. Therefore, based on the foregoing, a similar immunogenicity profile would be expected between ABP 798 and US-Rituxan in adult and pediatric patients with GPA and MPA.
- Expected toxicities: The clinical safety profiles of ABP 798, US-Rituxan and EU-MabThera showed no clinically significant differences and were consistent with the established safety profile of US-licensed Rituxan (see USPI). Based on the foregoing, and as analytical and PK similarity were demonstrated between ABP 798 and US-Rituxan, a similar safety profile would be expected between ABP 798 and US-Rituxan in adult and pediatric patients with GPA and MPA.

In aggregate, based on the above considerations, the Applicant provided adequate justification to support extrapolation of data and information in the BLA to support licensure of ABP 798 in adult GPA/MPA. Additionally, the justification was also adequate to support extrapolation of data and information in the BLA to support the pediatric assessment in pediatric GPA and MPA; however, the Applicant is not seeking licensure for this indication and the Agency cannot license ABP 798 for this indication until the expiration of US-Rituxan's orphan exclusivity.

**Authors:**

| | | |
|---|---|---|
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| Medical Officer | Clinical Team Leader, Acting | DRTM, Director |

### 7.4.2 Division of Hematologic Malignancies II

As relevant to DHM2, the Applicant submitted scientific justification for extrapolation of data and information to support licensure of ABP 798 (rituximab-arrx; Riabni) as a biosimilar to US-licensed Rituxan for the following indications: Adult Non-Hodgkin Lymphoma (NHL) and Adult Chronic Lymphocytic Leukemia (CLL). The justification is based on the mechanism of action, PK, immunogenicity, and safety profile of ABP 798 compared to US-licensed Rituxan as described above in Section 7.4.

Licensure of ABP 798 as a biosimilar to US-licensed Rituxan for conditions of use that were not directly studied (i.e., CLL and NHL subtypes such as diffuse large B-cell lymphoma and advanced follicular lymphoma) in the clinical development program is supported by adequate justification for extrapolation. See Section 7.4 and 7.4.1 above for further information .

A scientific bridge was established to justify the relevance of data generated with EU-MabThera as a comparator to the assessment of biosimilarity. In considering the totality of evidence submitted, including the data and information submitted by the Applicant support that ABP 798 is highly similar to U.S.-licensed Rituxan, notwithstanding minor differences in clinically active components, and the collective evidence from the comparative clinical studies to support a demonstration that there are no clinically meaningful differences in terms of safety, purity, and potency between ABP 798 and US-licensed Rituxan, and based on on the above considerations, the applicant has provided adequate data and information to support licensure of ABP 798 for CLL and NHL indications for which the applicant is seeking licensure and for which US-Rituxan has been previously licensed.

| | | |
|---|---|---|
| Pamela Seam | Nicholas Richardson | Nicole Gormley |
| Clinical Reviewer | Clinical Team Leader | DHMII, Director |

# 8 Labeling Recommendations

## 8.1. Proper Name

The Applicants's nonproprietary name for ABP 798, rituximab-arrx, was found to be conditionally accepted by the Agency. The four-letter suffix was considered acceptable by Division of Medication Error Prevention and Analysis (DMEPA) (review dated May 28, 2020).

## 8.2. Proprietary Name

The Applicant's proposed proprietary name for ABP 798, Ribani, has been conditionally approved. This name has been reviewed by DMEPA (review dated March 2, 2020).

## 8.3. Other Labeling Recommendations

ABP 798 is a proposed biosimilar to US-licensed Rituxan. The applicant is proposing the following dosage forms and strengths for intravenous use:

- 100 mg/10 mL (10 mg/mL), injection
- 500 mg/50 mL (10 mg/mL), injection

The proposed prescribing information incorporates relevant data and information from the US-licensed Rituxan prescribing information, with appropriate modifications.

The Applicant is seeking licensure for the following indications for which US-licensed Rituxan has been previously approved:

- Adult patients with non-Hodgkin lymphoma (NHL):
    - Relapsed or refractory, low grade or follicular, CD20-positive B-cell NHL as a single agent;
    - Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single agent maintenance therapy;
    - Non-progressing (including stable disease), low grade, CD20-positive, B-cell NHL as a single agent after first line cyclophosphamide, vincristine, and prednisone chemotherapy;
    - Previously untreated diffuse large B-cell, CD20-positive NHL in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone or other anthracycline-based chemotherapy regimens.
- Adult patients with chronic lymphocytic leukemia (CLL):
    - Previously untreated and previously treated CD20-positive CLL in combination with fludarabine and cyclophosphamide.

- Granulomatosis with polyangiitis and microscopic polyangiitis in adult patients in combination with glucocorticoids.

The Applicant is not seeking licensure for the following indications for which US-Rituxan has been previously approved:

- Rheumatoid arthritis (RA) in combination with methotrexate in adult patients with moderately to severely active RA who have inadequate response to one or more TNF antagonist therapies.
- Granulomatosis with polyangiitis and microscopic polyangiitis in pediatric patients 2 years of age and older in combination with glucocorticoids
- Moderate to severe pemphigus vulgaris in adult patients

It was determined that the proposed labeling is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR), and is consistent with labeling guidance recommendations and CDER/OND best labeling practices and policies, is clinically meaningful and scientifically accurate, and conveys the essential scientific information needed for safe and effective use of the product. The Applicant agreed to changes requested by the Divisions to improve readability, clarity, and accuracy of the prescribing information.

# 9 Advisory Committee Meeting and Other External Consultations

This application was not presented to an FDA Advisory Committee as it was determined that there were no issues where the Agency needed input from the committee.

# 10 Pediatrics

The applicant included an amended pediatric study plan in its 351(k) BLA submission, which was discussed at PeRC on October 27, 2020. No Pediatric Research Equity Act (PREA) PMRs were recommended.

The Applicant proposed supporting its pediatric assessment for GPA/MPA in pediatric patients two years of age and older by satisfying the statutory requirements for biosimilarity and providing an adequate scientific justification under the BPCI Act to support extrapolation of data and information in the application. The Agency evaluated the pediatric assessment and found the extrapolation justification adequate (see section 7.4, 7.4.1). US-Rituxan is protected by orphan exclusivity, and ABP 798 cannot be licensed for this indication until the expiration of orphan exclusivity in September 2026. Accordingly, the following statement will be included in the labeling for ABP 798: A pediatric assessment for RIABNI demonstrates that RIABNI is safe and effective for pediatric patients in an indication for which Rituxan (rituximab) is

approved. However, RIABNI is not approved for such indication due to marketing exclusivity for Rituxan (rituximab).

The agency has determined at this time that, with respect to the following indications, no pediatric studies will be required under PREA for this applicant's BLA:

- NHL;
- CLL; and
- GPA/MPA in 0 to less than 2 years of age.

Refer to memo dated 08 December 2020.

# 11 REMS and Postmarketing Requirements and Commitments

## 11.1. Recommendations for Risk Evaluation and Mitigation Strategies

None.

## 11.2. Recommendations for Postmarket Requirements and Commitments

Based upon this review, no postmarketing requirements or commitments were recommended by the review divisions.

# 12 Division Director (OND - Clinical) Comments

I agree with the review team's and cross-discipline team leader's recommendation to approve ABP 798 (Riabni, rituximab-arrx) as a biosimilar to US-licensed Rituxan for the Adult Non-Hodgkin lymphoma (NHL), Adult chronic lymphocytic leukemia (CLL), and Adult Granulomatosis with Polyangiitis (GPA) and Microscopic Polyangiitis (MPA) indications that are the same as those previously approved for US-licensed Rituxan.

**Author:**
Nicole Gormley, MD
Division Director, DHMII

# 13 Appendices

## 13.1. Financial Disclosure

**Covered Clinical Study: Study 20130108**

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 335 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____<br>Significant payments of other sorts: _____<br>Proprietary interest in the product tested held by investigator: _____<br>Significant equity interest held by investigator in S<br>Sponsor of covered study: _____ | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☐ | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☒ | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0 | | |
| Is an attachment provided with the reason: | Yes ☐ | No ☐ (Request explanation from Applicant) |

**Covered Clinical Study: 20130109**

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 645 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____<br>Significant payments of other sorts: _____<br>Proprietary interest in the product tested held by investigator: _____<br>Significant equity interest held by investigator in S<br>Sponsor of covered study: _____ | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☐ | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☒ | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0 | | |
| Is an attachment provided with the reason: | Yes ☐ | No ☐ (Request explanation from Applicant) |

## 13.2. Nonclinical Appendices

### 13.2.1 Nonclinical Pharmacology

**Primary Pharmacology**

ABP 798 (Riabni) is a murine/human chimeric immunoglobulin isotype G subclass 1 kappa (IgG1κ) isotype monoclonal antibody directed against against the CD20 antigen that mediates the depletion of B cells.

The Applicant conducted pharmacology studies that evaluated antibody-dependent cell-mediated phagocytosis (ADCP), trogocytosis, CD20 positive cell internalization, binding to FcγRIIIa, and antitumor activity.

**Study title: Similarity Assessment using the Rituxan ADCP (PBMC) Assay**

**Report: FR20-18**

**Key findings**

- ABP 798, EU-Rituxan, and US-Rituxan had similar effects on the ADCP assay.
- The ADCP activity of US-Rituxan was similar to EU-Rituxan, and the activity of ABP 798 was similar to both US-Rituxan and EU-Rituxan.

**Methods**

The Ramos B lymphocyte target cell line was incubated with peripheral blood mononuclear cells (PBMC) from healthy donors and various dilutions of ABP 798, EU-Rituxan, or US-Rituxan (0.09 to 100 ng/mL) at 36$^{O}$C for 1.5 to 3.5 hours. The treated cells were then stained for the CD14 antigen prior to analysis by flow cytometry.

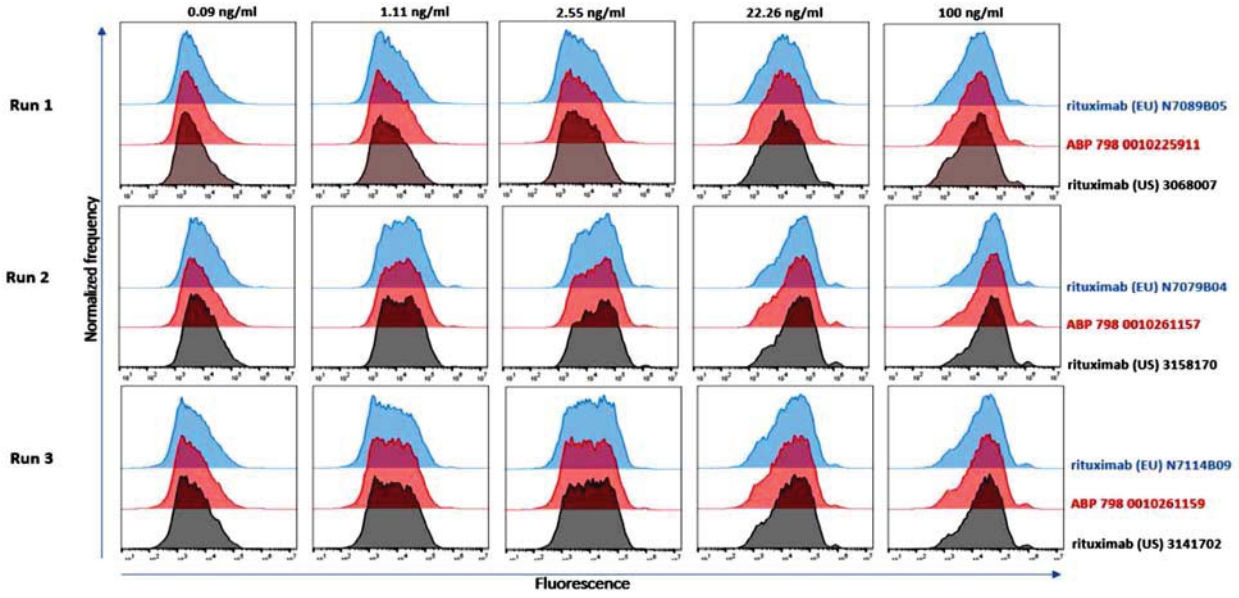
**Drug lots**

**Test article:** APB 798 lots 0010225911, 0010261157, and 0010261159.
**Test article:** US-Rituxan lots 3068007, 3158170, and 3141702.
**Test article:** EU-Rituxan lots N7089B05, N7079B04, and N7114B09.

**Results**

The flow cytometry analysis showed comparable concentration-dependant increases in CD14 staining among ABP 798, US-Rituxan, and EU-Rituxan.

**Figure 13: Histogram overlays of CD14-stained cells after treatment with ABP 798, US-Rituxan, or EU-Rituxan**




**Study title: Evaluation of Target Internalization by ABP 798, US-Rituxan) and EU-Rituxan in Raji cells**

**Report: R20150177**

**Key findings**

- ABP 798, EU-Rituxan, and US-Rituxan were similarly internalized by Raji B lymphocyte cells.
- The internalization of US-Rituxan was similar to EU-Rituxan, and the internalization of ABP 798 was similar to both US-Rituxan and EU-Rituxan.

**Methods**

Flourophor-labelled ABP 798, EU-Rituxan, or US-Rituxan were incubated at 10 μg/mL with Raji cells for 2 hours prior to analysis by flow cytometry.

**Drug lots**

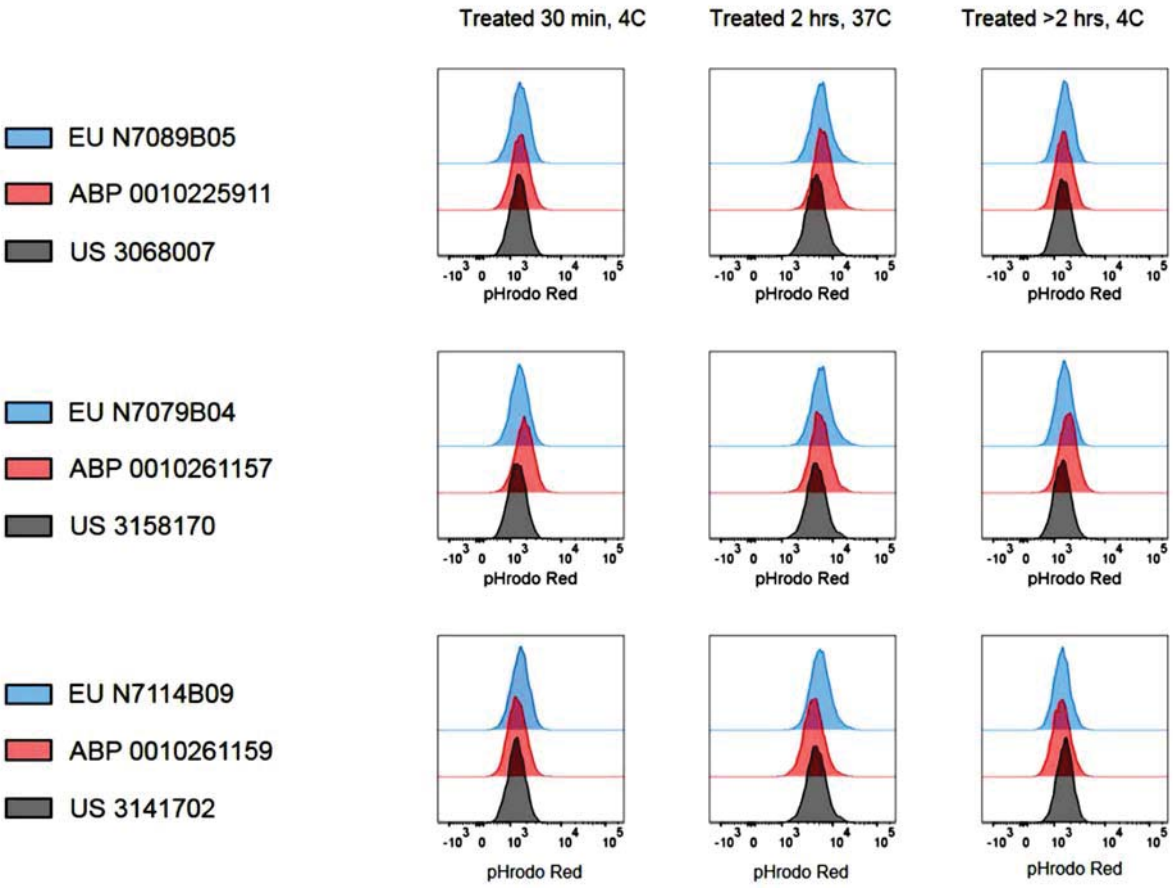
**Test article:** APB 798 lots 0010225911, 0010261157, and 0010261159.
**Test article:** US-Rituxan lots 3068007, 3158170, and 3141702.
**Test article:** EU-Rituxan lots N7089B05, N7079B04, and N7114B09.

**Results**

The flow cytometry analysis showed comparable concentration-dependant increases in

flourophor-labelled antibody staining among ABP 798, US-Rituxan, and EU-Rituxan.

**Figure 14: Histogram overlays of flourophor-labelled antibody-stained cells after treatment with ABP 798, US-Rituxan, or EU-Rituxan**




**Study title: Similarity Assessment using the Rituximab Trogocytosis (PBMC) Assay**

**Report: FR20-3C**

**Key findings**

- ABP 798, EU-Rituxan, and US-Rituxan exhibited similar levels of trogocytosis activity with PBMCs.
- The activity of US-Rituxan was similar to EU-Rituxan, and the activity of ABP 798 was similar to both US-Rituxan and EU-Rituxan.

**Methods**

Flourophor-labelled Ramos cells were incubated with PMBCs and ABP 798, EU-Rituxan, or US-

Rituxan at 0.3 to 300 μg/mL for 30 to 120 minutes prior to analysis by flow cytometry.

**Drug lots**
**Test article:** APB 798 lots 0010225911, 0010261157, and 0010261159.
**Test article:** US-Rituxan lots 3155137, 3158170, and 3141702.
**Test article:** EU-Rituxan lots N7089B05, N7079B04, and N7114B09.

**Results**
The flow cytometry analysis showed comparable concentration-dependant increases in Ramos cell uptake among ABP 798, US-Rituxan, and EU-Rituxan.

**Table 46: Mean relative trogocytosis results of PBMC-engulfed Ramos cells after treatment with ABP 798, US-Rituxan, or EU-Rituxan**

| Group | % Trogocytosis | | |
|---|---|---|---|
| | Mean (%) | %CV | Range (%) |
| ABP 798 | 97.3 | 6.0 | 92.6-103.6 |
| EU-Rituxan | 101.1 | 4.0 | 97.6-105.5 |
| US-Rituxan | 102.1 | 8.0 | 97.0-111.4 |

**Study title: Comparative Assessment of ABP 798 and US-Rituxan Binding to Fcγ Receptors on Primary Natural Killer Cells**

**Report: R20180007**

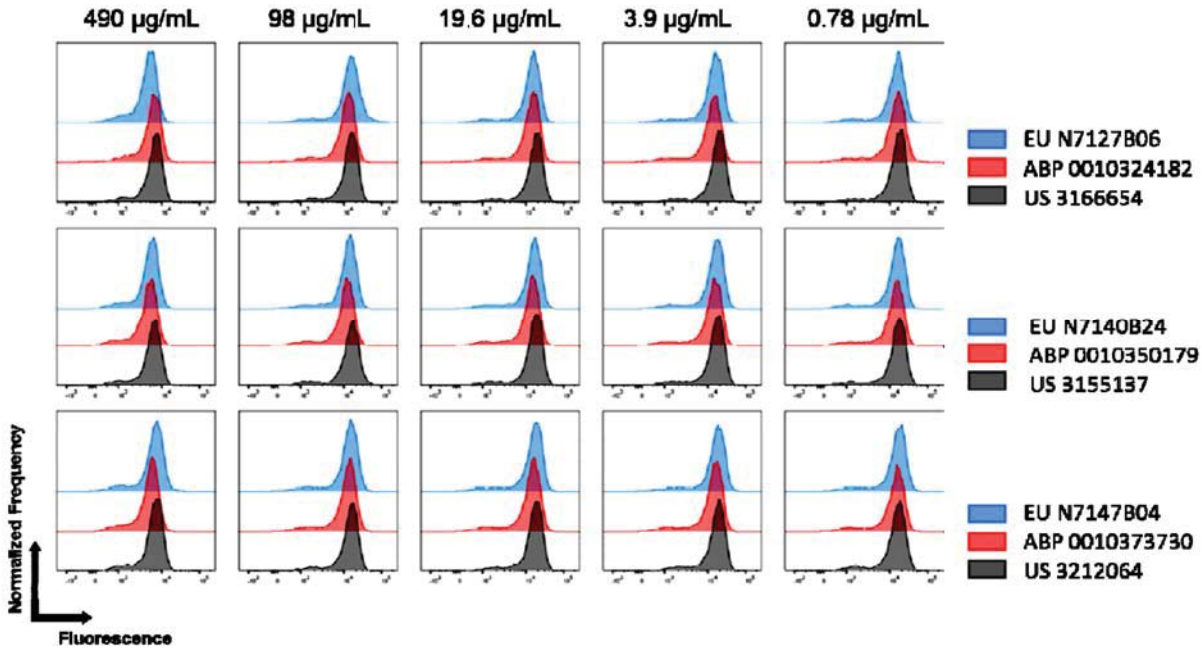
**Key findings**
- ABP 798, EU-Rituxan, and US-Rituxan exhibited similar binding to Fcγ receptors on NK cells.
- The binding to Fcγ receptors of US-Rituxan was similar to EU-Rituxan, and the binding of ABP 798 was similar to both US-Rituxan and EU-Rituxan

**Methods**
A competitive binding assay was performed wherein NK cells from healthy donors were incubated with Flourophor-labelled ABP 798 prior to incubation with unlabeled ABP 798, EU-Rituxan, or US-Rituxan at concentrations ranging from 0.78 to 480 μg/mL for 1 hour prior to analysis by flow cytometry where higher fluorescence indicated lower test article binding.

**Drug lots**
**Test article:** APB 798 lots 0010324182, 0010350179, and 0010373730.
**Test article:** US-Rituxan lots 3155137, 3166654, and 3212064.
**Test article:** EU-Rituxan lots N7127B06, N7140B24, and N7147B04.

**Results**
The flow cytometry analysis showed comparable binding to NK cells among ABP 798, US-Rituxan, and EU-Rituxan.

**Figure 15: Histogram overlays of flourophor-labelled antibody displacement on NK cells by ABP 798, US-Rituxan, or EU-Rituxan**




**Study title: In Vivo Evaluation of Efficacy and Safety of Test Articles in the Treatment of Subcutaneous RL Subcutaneous Human Non-Hodgkin's Lymphoma Xenograft Model**

**Report: E0520-U1738**

**Key findings**

- ABP 798 and US-Rituxan exhibited similar levels of antitumor activity in an RL human non-Hodgkin's lymphoma (NHL) xenograft tumor model.

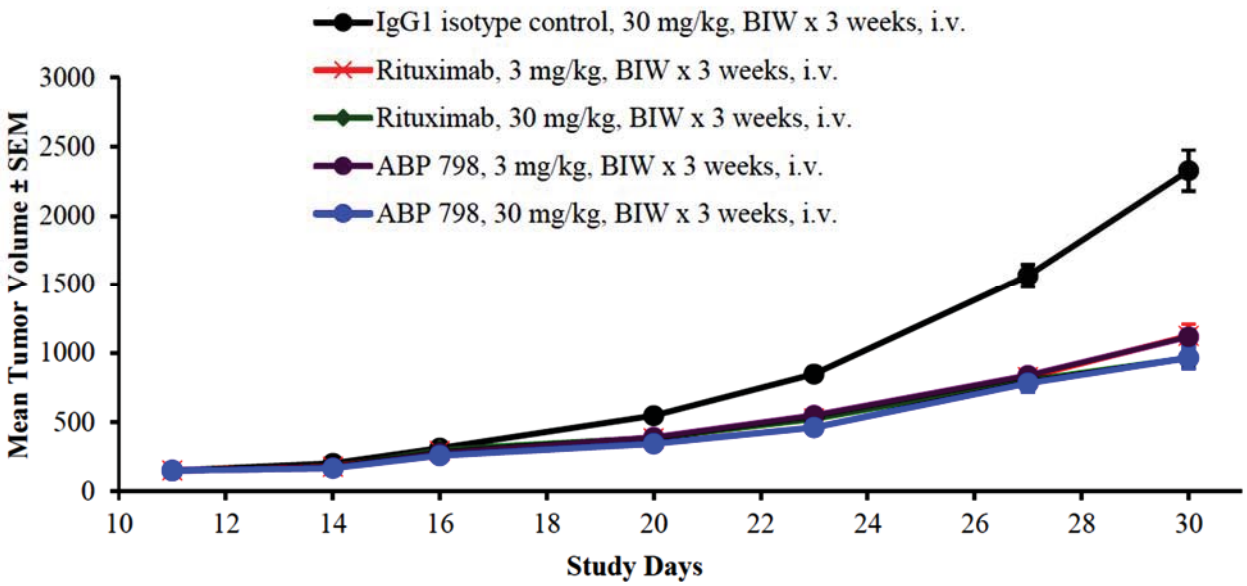
**Methods**
RL cell tumors were established subcutaneously in NOD/SCID mice prior to 3 weeks of twice-weekly IV dosing with ABP 798 or US-Rituxan at 3 or 30 mg/kg, or an IgG1 isotype control at 30 mg/kg. Tumor measurements were taken twice per week. The study was terminated on day 30.

**Drug lots**
**Test article:** APB 798 lot 0010261169.

**Test article:** US-Rituxan lot 3158170.

**Results**
The tumor volume analyses showed comparable dose-dependent antitumor activity for ABP 798 and US-Rituxan.

**Table 47: Tumor growth curves of RL xenografts dosed with ABP 798 or US-Rituxan**




### 13.2.2 Nonclinical Pharmacokinetics and Pharmacodynamics

Nonclinical toxicokinetics from the 4-week toxicology study in Cynomolgus monkeys (report 116362; discussed in the general toxicology section below) demonstrated that ABP 798 and US-Rituxan have similar toxicokinetic parameters. Antidrug antibodies were assessed and shown to correlate with exposure levels. Separate nonclinical ADME studies were not conducted.

### 13.2.3 General Toxicology

A GLP-compliant repeat-dose toxicology/toxicokinetics study was conducted in Cynomolgus monkeys to compare ABP 798 with US-Rituxan.

**Repeat-Dose Toxicity/Toxicokinetics**

Cynomolgus monkeys (n=3/sex/dose group) were administered 20 mg/kg ABP 798 or US-Rituxan once weekly on days 1, 8, 15, and 22 prior to euthanasia on day 29. The control animals were administered vehicle comprised of 154 mM sodium chloride, 25 mM sodium citrate

dihydrate, and 0.07% polysorbate 80 at pH 6.5. There were no recovery groups in this study.

Both ABP 798 and US-Rituxan produced similar toxicokinetic parameter values and similar on- and off-target effects. There were similar mild decreases in circulating lymphocytes and lymphoid depletion of the follicular region of lymphoid tissues. There were no effects on clinical signs, body weight, food consumption, ophthalmic, electrocardiogram (ECG), body temperature, respiration rate, clinical chemistry, coagulation, urinalysis, organ weights, organ weight ratios, or macroscopic necropsy observations for ABP 798 or US-Rituxan.

The toxicity study demonstrated a similar toxicity and toxicokinetic profile with responses of a similar magnitude for ABP 798 and US-Rituxan. The study supports a determination of biosimilarity.

**Study title: ABP 798: A 1-month Intravenous Toxicology Study in the Cynomolgus Monkey**

| | |
|---|---|
| **Study number:** | **116362** |
| Study report location: | Module 4.2.3.2 |
| Conducting laboratory and location: | (b) (4) |
| Date of study initiation: | 11/11/2013 |
| GLP compliance: | Yes |
| Quality assurance (QA) statement: | Yes |
| Drug/lot #/% purity: | ABP 798/0010174220/99.2%<br>US-Rituxan/548425/100% |

**Key study findings**

- ABP 798 and US-Rituxan produced similar results when administered IV to Cynomolgus monkeys once weekly for 4 weeks (days 1, 8, 15, and 22) at 20 mg/kg (n=3 animals/sex/dose group).
- Similar drug toxicokinetic parameters were obtained between both drugs.
- There were comparable on-target decreases in circulating B cells, and evidence of B cell depletion in the lymph nodes, tonsil, gut-associated lymphoid tissue (GALT), and spleen in both the ABP 798 and US-Rituxan groups.
- There were no significant off-target effects observed with either ABP 798 or US-Rituxan dosing.
- The findings support the biosimilarity of ABP 798 and US-Rituxan.

**Methods**

| | |
|---|---|
| Dose: | 0 (control), ABP 789 at 20 mg/kg, US-Rituxan at 20 mg/kg. |
| Dosing frequency: | Once weekly for 4 injections. |
| Route of administration: | Intravenous. |
| Dose volume: | 2 mL/kg. |
| Formulation/vehicle: | 154 mM sodium chloride, 25 mM sodium citrate dihydrate, |

0.07% polysorbate 80 at pH 6.5.

Species/strain: Monkey/Cynomolgus

Age: 5.5-7.5 years old.

Weight: Males: 7.2-9.6 kg.
Females: 3.6-4.4 kg.

Experimental design:

| Group | Dose (mg/kg) | Volume (mL/kg) | Concentration (mg/mL) | Number of animals/sex/group |
|---|---|---|---|---|
| Control | 0 | 2 | 0 | 3 |
| ABP 798 | 20 | 2 | 10 | 3 |
| US-Rituxan | 20 | 2 | 10 | 3 |

**Obserations and results**

**Mortality**
Animals were checked twice daily.
There were no unscheduled deaths.

**Clinical signs**
Animals were checked at cageside at least once daily and removed from their cages for detailed observations once weekly.
There were no clinical signs attributed to ABP 798 or US-Rituxan.

**Body weights**
Animals were weighed once weekly.
There were no changes in body weight or weight change attributed to ABP 798 or US-Rituxan.

**Food consumption**
Food consumption was determined once daily.
There were no changes in food consumption attributed to ABP 798 or US-Rituxan.

**Ophthalmology**
Ophthalmic examinations were conducted at prestudy and in the final week of the study.
There were no changes in ophthalmic findings that were considered treatment-related.

**Electrocardiology**
ECG readings were recorded at predose and during week 4.
There were no treatment-related changes.

**Body temperature**
Body temperatures were recorded at predose and during week 4.
There were no treatment-related changes.

**Respiration rate**
Respiration rates were recorded at predose and during week 4.
There were no treatment-related changes.

**Hematology**
Blood was collected by venipuncture.
ABP 798 and US-Rituxan dosing resulted in comparable mild decreases in lymphocytes on day 2 but not day 22. Flow cytometry showed that the lymphocytes were positive for CD45, CD3, CD20, and CD19 antigens.

**Table 48: White blod cell and lymphocyte findings**

| Cell counts ($10^3/\mu L$) | Group | Day -6 | | Day 2 | | Day 22 | |
|---|---|---|---|---|---|---|---|
| | | Male | Female | Male | Female | Male | Female |
| WBC | Vehicle | 11.82 | 7.74 | 14.08 | 9.01 | 11.44 | 8.66 |
| | ABP 798 | 11.70 | 9.35 | **9.55** | 11.35 | 10.99 | 15.44 |
| | US-Rituxan | 11.96 | 8.96 | 14.16 | 8.85 | 13.41 | 10.51 |
| Lymphocytes | Vehicle | 4.82 | 4.55 | 3.40 | 3.60 | 3.03 | 3.73 |
| | ABP 798 | 6.68 | 4.79 | 3.08 | **2.10** | 4.10 | 2.77 |
| | US-Rituxan | 4.20 | 5.98 | 3.45 | **2.14** | 3.71 | 2.68 |

**Significant differences are in bold type**
**US-Rituxan refers to US-licensed Rituxan**

**Clinical chemistry**
Blood was collected by venipuncture.
There were no changes to clinical chemistry measurements due to ABP 798 or US-Rituxan dosing.

**Urinalysis**
Urine was collected overnight before necropsy.
There were no ABP 798 or US-Rituxan treatment effects of urinalysis parameters.

**Organ weights**
Organ weights were measured at necropsy.
There were no organ weight changes associated with ABP 798 or US-Rituxan.

**Gross pathology**
Study animals were subjected to a complete necropsy examination after euthanasia.
There were no macroscopic changes associated with ABP 798 or US-Rituxan.

**Histopathology**
Adequate battery: Yes.
Peer review: Yes. The evaluation was performed by a board-certified veterinary pathologist.

Lymphoid depletion was observed in the lymph nodes, tonsil, GALT, and spleen of the ABP 798 and US-Rituxan groups. The lymphoid depletion was an expected on-target effect.

**Table 49: Summary of Microscopic Changes**

| | Males | | | Females | | |
|---|---|---|---|---|---|---|
| **Group** | **1** | **2** | **3** | **1** | **2** | **3** |
| **Dose (mg/kg)** | **0** | **20 ABP 798** | **20 Rituximab** | **0** | **20 ABP 798** | **20 Rituximab** |
| **No. animals examined** | **3** | **3** | **3** | **3** | **3** | **3** |
| **Lymph Node, Axillary** | | | | | | |
| Depletion lymphoid, follicular | | | | | | |
| Mild | 0[a] | 1 | 2 | 0 | 3 | 2 |
| Moderate | 0 | 2 | 1 | 0 | 0 | 1 |
| **Lymph Node, Inguinal** | | | | | | |
| Depletion lymphoid, follicular | | | | | | |
| Mild | 0 | 3 | 2 | 0 | 3 | 2 |
| Moderate | 0 | 0 | 0 | 0 | 0 | 1 |
| **Lymph Node, Mesenteric** | | | | | | |
| Depletion lymphoid, follicular | | | | | | |
| Mild | 0 | 0 | 2 | 0 | 2 | 1 |
| Moderate | 0 | 3 | 1 | 0 | 1 | 2 |
| **GALT** | | | | | | |
| Depletion lymphoid, follicular | | | | | | |
| Minimal | 0 | 0 | 1 | 0 | 0 | 0 |
| Mild | 0 | 3 | 1 | 0 | 3 | 0 |
| **Spleen** | | | | | | |
| Depletion lymphoid, follicular | | | | | | |
| Mild | 0 | 0 | 2 | 0 | 0 | 0 |
| Moderate | 0 | 3 | 1 | 0 | 3 | 3 |
| **Tonsil** | | | | | | |
| Depletion lymphoid, follicular | | | | | | |
| Mild | 0 | 1 | 2 | 0 | 1 | 0 |
| Moderate | 0 | 2 | 1 | 0 | 2 | 3 |
| [a] = number of animals with the finding. | | | | | | |

**Toxicokinetics**

Blood was collected by venipuncture on days 1 and 22 at predose and 0.25, 1, 4, 8, 24, 48, 72, and 168 hours postdose. ABP 798 and US-Rituxan levels were measured by a validated electrochemiluminescent (ECL) immunoassay.

The sex-related differences were less than 2-fold and therefore, the data for males and females were grouped together. Overall, the $T_{max}$, $C_{max}$, and $AUC_{0-168}$ values for ABP 798 and US-Rituxan were similar. Accumulation ratios (AR) between days 1 and 22 were low and suggested minimal accumulation with repeated dosing.

**Table 50: Mean (SD) Toxicokinetic Parameter Estimates on Days 1 and 22 Following IV Administration of 20 mg/kg ABP 798 or US-Rituxan to Cynomolgus Monkeys**

| Route | Treatment Description | Day | N | $t_{max}$ [1] (hr) | $C_{max}$ (ug/mL) | $AUC_{0-168}$ (ug*hr/mL) | AR |
|---|---|---|---|---|---|---|---|
| IV | ABP 798 | 1 | 6 | 0.25 (0.25-0.25) | 608 (52.3) | 37700 (4120) | NC |
| | | 22 | 6 | 0.62 (0.25-4.00) | 1100 (271) | 57000 (40600) | 1.50 (0.983) |
| | Rituximab | 1 | 6 | 0.25 (0.25-1.00) | 618 (157) | 41400 (8870) | NC |
| | | 22 | 6 | 0.62 (0.25-4.00) | 687 (320) | 39200 (31600) | 1.01 (0.763) |

[1] $t_{max}$ (hr) is Median (min - max)

## 13.3 Office of Clinical Pharmacology Appendices

### 13.3.1 Summary of Bioanalytical Method Validation and Performance

## Pharmacokinetics

For the PK similarity study (Study 20130108), serum ABP 798, US-Rituxan, and EU-MabThera concentrations measured using a validated electrochemiluminescent (ECL) method were suitable for assessment of PK similarity. In this method, biotinylated mouse anti-ABP 798 monoclonal antibody (clone 1.15.1, Amgen, Inc., CA) was used as the capture antibody and ruthenium-labeled mouse anti-ABP 798 monoclonal antibody (clone no. 1.26.2, Amgen, Inc., CA) was used as the detection antibody. During method validation, ABP 798 was used to establish the calibration curves, and the accuracy and precision (±20%, ±25% for lower limit of quantification (LLOQ) and upper limit of quantification (ULOQ)) was evaluated using ABP 798, US-Rituxan, and EU-MabThera as QC samples. Both the method validation (method qualification report number: 120191; method validation report number: 120192, 120192 addendum #1) and sample analysis for Studies 20130108 and 20130109 were performed at (b) (4) All study samples were analyzed within the established long-term stability period. The method validation and in-study performance are summarized in the table below.

In the accuracy and precision (A&P) assessment, each A&P run microwell plate contained blank samples, 8 calibrators, and 6 QC levels for ABP 798, US-Rituxan, and EU-MabThera. Only 2 replicates per QC level were included in each run. The OSIS reviewer clarified that given the number of calibrators and QC levels in each A&P run, only limited QC replicates could be placed on each plate.

In the A&P analysis, the Applicant excluded 4 replicates which were considered to be outliers. A single replicate was excluded from each of the ABP 798 and US-Rituxan A&P analysis and 2 replicates were excluded from the EU-MabThera A&P analysis. The OSIS reviewer clarified that the validation protocol specified that outliers could be removed from the A&P analysis with an appropriate statistical test and therefore it was appropriate to exclude these outliers from the overall A&P analysis (refer to Section 4.4 for further information).

**Table 51: Summary of the Bioanalytical Method Validation (report number: 120192, 120192 addendum #1) and In-Study Performance for Measurement of ABP 798, US-Rituxan, EU-MabThera in Human Serum (Studies 20130108 and 20130109)**

| | | | |
|---|---|---|---|
| **Bioanalytical method validation report name, amendments, and hyperlinks** | Method Validation of an Electrochemiluminescent Method for the Quantitation of ABP 798 or Rituximab in Human Serum | | |
| **Method description** | ICD 594 Version 1.00, An Electrochemiluminescent Method for the Quantitation of ABP 798 or Rituximab in Human Serum | | |
| **Materials used for calibration curve and concentration** | Prepared in human serum at nominal ABP 798 concentrations of 250, 500, 1000, 2000, 4000, 8000, 12500, and 16000 ng/mL | | |
| **Validated assay range** | 250 to 16,000 ng/mL | | |
| **Material used for QCs and concentration** | Prepared in human serum at nominal ABP 798 or Rituximab concentrations of 250, 600, 2400, 12000, 16000 ng/mL | | |
| **Minimum required dilutions (MRDs)** | 1:100 | | |
| **Source and lot of reagents (LBA)** | • ABP 798, Amgen, Lot 0010261175 / PRDS-002156 (9.80 mg/mL)<br>• Rituximab US, Genentech USA, Lot 3006207 (10.0 mg/mL)<br>• Rituximab EU, Roche USA, Lot N7033 (10.0 mg/mL)<br>• Mu Anti- ABP 798 1.15.1 Mab (Biotin Capture Antibody), Amgen, Lot PL-40578 (0.750 mg/mL)<br>• Mu Anti- ABP 798 1.26.2 Mab (Ruthenium Detection Antibody), Amgen, Lot PL-35425 (1.03 mg/mL)<br>• Mu Anti- ABP 798 1.26.2 Mab (Ruthenium Detection Antibody), Amgen, Lot PL-45891 (1.60 mg/mL) | | |
| **Regression model and weighting** | Four-parameter logistic, 1/response² weighted | | |
| **Validation parameters** | **Method validation summary** | | **Source location (hyperlinked)** |
| **Calibration curve performance during accuracy and precision** | Number of standard calibrators from LLOQ to ULOQ | 8 | Method Validation Report 120192 |
| | Cumulative accuracy (%bias) from LLOQ to ULOQ<br>ABP 798 | -1 to 2% | Method Validation Report 120192 |
| | Cumulative precision (%CV) from LLOQ to ULOQ<br>ABP 798 | 1 to 3% | Method Validation Report 120192 |

| | | |
|---|---|---|
| **QCs performance during accuracy and precision** | **Cumulative accuracy (%bias) in 5 QCs**<br>QCs: ABP 798 -1 to 7%<br>Rituximab US 2 to 9%<br>Rituximab EU 1 to 13% | Method Validation Report 120192 |
| | **Inter-batch %CV**<br>QCs: ABP 798 5 to 8%<br>Rituximab US 7 to 10%<br>Rituximab EU 7 to 11% | Method Validation Report 120192 |
| | **Total Error (TE)**<br>QCs: ABP 798 7 to 15%<br>Rituximab US 9 to 17%<br>Rituximab EU 8 to 24% | Method Validation Report 120192 |
| **Selectivity and matrix effect** | 10 individual lots of healthy, rheumatoid arthritis (RA), and non-Hodgkin's lymphoma (NHL) human serum tested unspiked and spiked at the low-quality control (LQC; 600 ng/mL) and LLOQ (250 ng/mL) levels in ABP 798, Rituximab US, and Rituximab EU.<br>No matrix effect observed in healthy, RA, and NHL male and female individuals. | Method Validation Report 120192 |
| **Interference and specificity** | No interference observed from ABP 798<br>CD 20 lipoparticles at concentrations of 240,000 ng/mL or molar ratios of 455 (CD 20: ABP 798) interfered in the measurement of ABP 798 | Method Validation Report 120192 |
| **Hemolysis effect** | Not applicable | |
| **Lipemic effect** | Not applicable | |
| **Dilution linearity and hook effect** | Dilutional linearity was performed by preparing samples in 100% human serum at nominal concentrations of 16,000 and 500,000 ng/mL of ABP 798, Rituximab US, and Rituximab EU. Samples were diluted in 100% healthy human serum matrix manually and using the Tecan EVO workstation:<br>Up to 400 fold dilution for manual analysis<br>Up to 1000 fold dilution for Tecan analysis<br>High-end hook (prozone) effect was evaluated at the 25,000, 50,000, and 500,000 ng/mL concentrations of ABP 798, Rituximab US, and Rituximab EU. No hook effect was observed. | Method Validation Report 120192 |
| **Bench-top/process stability** | Bench-top Process Stability<br>24 hours in 1:100 MRD in Sample Diluent<br>30 days in 100% human serum<br>2°C to 8°C Process Stability<br>24 hours in 1:100 MRD in Sample Diluent<br>30 days in 100% human serum | Method Validation Report 120192 |

| | | |
|---|---|---|
| **Freeze-Thaw stability** | Stable up to 5 freeze-thaw cycles (100% human serum) for ABP 798, Rituximab US and Rituximab EU. | Method Validation Report 120192 |
| **Long-term storage** | -80°C (-90°C to -60°C)<br>Stable up to 897 days for ABP 798 and Rituximab US; Stable up to 883 days for Rituximab EU<br><br>-25°C (-30°C to -15°C)<br>Stable up to 563 days for ABP 798; Stable up to 549 days for Rituximab US and Rituximab EU | Method Validation Report 120192 Addendum #1 |
| **Parallelism** | Not applicable | |
| **Carry over** | Not applicable | |
| **Method performance in Study 20130108<br>A Randomized, Double-Blind Study to Compare Pharmacokinetics and Pharmacodynamics, Efficacy and Safety of ABP 798 with Rituximab in Subjects with Moderate to Severe Rheumatoid Arthritis** | | |
| **Assay passing rate** | Overall assay pass rate: 94.7% | |
| **Standard curve performance** | • Cumulative bias range: -1 to 1%<br>• Cumulative precision: 1 to 4% CV | |
| **QC performance** | • Cumulative bias range: -2 to 2%<br>• Cumulative precision: 5 to 6% CV<br>• TE: 7% | |
| **Method reproducibility** | Incurred sample reanalysis was performed in 343 study samples (5.96% of total sample size) and 95.9% of samples met the pre-specified criteria | |
| **Study sample analysis/ stability** | Samples were stored for a maximum of 463 days between sample collection and analysis.<br>Standard/QCs and study samples stable up to 897 days for ABP 798 and Rituximab US, and up to 883 days for Rituximab EU when stored at -80°C (-90°C to -60°C). | |
| **Method performance in Study 20130109<br>A Randomized, Double-Blind Study Evaluating the Efficacy, Safety and Immunogenicity of ABP 798 Compared with Rituximab in Subjects with CD20 Positive B-Cell Non-Hodgkin Lymphoma (NHL)** | | |
| **Assay passing rate** | Overall assay pass rate: 96.9% | |
| **Standard curve performance** | • Cumulative bias range: -1 to 1%<br>• Cumulative precision: 1 to 4% CV | |
| **QC performance** | • Cumulative bias range: -2 to 2%<br>• Cumulative precision: 5% CV<br>• TE: 6 to 7% | |

| | |
|---|---|
| **Method reproducibility** | Incurred sample reanalysis was performed in 166 study samples (7.54% of total sample size) and 94.6% of samples met the pre-specified criteria |
| **Study sample analysis/ stability** | Samples were stored for a maximum of 532 days between sample collection and analysis.<br>Standard/QCs and study samples stable up to 897 days for ABP 798 and Rituximab US, and up to 883 days for Rituximab EU when stored at -80 °C (-90 °C to -60 °C). |

CV = coefficient of variation; Bias = Percent difference; EU = European Union; LBA = ligand binding assay; LCQ = low-quality control; LLOQ = lower limit of quantification; MRD = minimum required dilutions; NHL = non-Hodgkin's lymphoma; QC = quality check; RA = rheumatoid arthritis; ULOQ = upper limit of quantification; US = United States
Interference and Specificity Assessment: It should read 'No interference observed from ABP 710'
Bench-Top/Process Stability:

- Stability established for ABP 798, US-Rituxan, and EU-MabThera;
- Stability was established for only 7 days at ambient room temperature in 100% human serum

**Source:** Appendix Table 5 of Summary of Biopharmaceutic Studies and Associated Analytical Methods

## 13.4 Office of Biostatistics Appendices

### 13.4.1 Tipping Point Analysis Methodology

The goal is to evaluate the potential effect of violations in assumptions about missing data on the reliability of conclusions. Suppose that outcomes Y are independently distributed on the control and test drug arms. The parameter of interest is the difference in means θ. Consider the following parameterization and notation to describe the probabilities of completing the study (non-missingness), the true means in completers and dropouts, and the numbers of completers and total patients on the two treatment arms:

**Table 52: Parameters and Notation for Tipping Point Analysis in Presence of Missing Data**

| Arm | Probability of non-missing | Mean among completers | Mean among dropouts | Number of completers | Sample size per arm |
|---|---|---|---|---|---|
| Placebo | $\pi_c$ | $\mu_c$ | $\mu_c + \delta_c$ | $N_c$ | $n_c$ |
| Treated | $\pi_t$ | $\mu_t$ | $\mu_t + \delta_t$ | $N_t$ | $n_t$ |

Given this parameterization, the target of inference is $\theta = [\pi_t\mu_t + (1 - \pi_t)(\mu_t + \delta_t)] - [\pi_c\mu_c + (1 - \pi_c)(\mu_c + \delta_c)] \equiv \mu_t + (1 - \pi_t)\delta_t - [\mu_c + (1 - \pi_c)\delta_c]$ An analysis based on completers will provide reliable inference on $\theta$ if the missing-at random assumption, i.e., the assumption that $\delta_c = \delta_t = 0$, is valid. We will perform sensitivity analyses that allow for the possibility that outcomes among dropouts are not missing-at-random by performing inference under different assumed values of the parameters $\delta_c$ and $\delta_t$.
Denote $M_{ij}$ to be an indicator that patient j on treatment i is a completer, i.e., his or her outcome is observed where $i = c, t$, and $j = 1, \cdots, n_i$. By assuming fixed values of sensitivity parameters $\delta_c$ and $\delta_t$, an estimator of θ can be represented by

$$\hat{\theta} = \hat{\mu}_t + (1 - \hat{\pi}_t)\delta_t - [\hat{\mu}_c + (1 - \hat{\pi}_c)\delta_c]$$

where $\hat{\mu}_i = \frac{1}{N_i}\sum_{k=1}^{n_i} Y_{ik}|M_{ik} = 1$ is the sample mean in the completers and $\hat{\pi}_i = \frac{N_i}{n_i} \equiv \sum_{k=1}^{n_i} M_{ik}/n_i$ is the sample proportion of completers on the treatment arm i, with i taking values c or t.

The test statistic can be constructed as follows:

$$\frac{\hat{\theta} - \theta}{\sqrt{\frac{s_t^2}{N_t} + \frac{s_c^2}{N_c} + \frac{\delta_t^2\hat{\pi}_t(1-\hat{\pi}_t)}{n_t} + \frac{\delta_c^2\hat{\pi}_c(1-\hat{\pi}_c)}{n_c}}}$$

where $s_i^2$ is the sample variance of the outcome. Under suitable conditions, the sampling test statistic is asymptotically normal with mean 0 and standard deviation 1.

The Wald-based 100 (1-α) % confidence interval of the form $\hat{\theta} \pm z_{1-\alpha/2}\sqrt{\frac{s_t^2}{N_t} + \frac{s_c^2}{N_c} + \frac{\delta_t^2\hat{\pi}_t(1-\hat{\pi}_t)}{n_t} + \frac{\delta_c^2\hat{\pi}_c(1-\hat{\pi}_c)}{n_c}}$ can be constructed where $z_q$ is the q quantile of the standard normal distribution.

### 13.4.2 Additional Tables and Figures for Study 20130108

**Table 53: Study 20130108 Difference (90% CI) in the LS Mean Change from Baseline in DAS28(CRP) by Treatment Group, Sensitivity Analyses**

| | Week | ABP-798 vs EU-MabThera | ABP-798 vs US-Rituxan | ABP-798 vs Pooled US-Rituxan and EU-MabThera |
|---|---|---|---|---|
| Per protocol Analysis[1] | 8 | 0.02 (-0.24, 0.29) | -0.16 (-0.43, 0.10) | -0.07 (-0.30, 0.16) |
| | 12 | 0.51 (0.23, 0.78) | 0.25 (-0.02, 0.53) | 0.38 (0.14, 0.62) |
| | 24 | 0.13 (-0.15, 0.41) | -0.07 (-0.35, 0.21) | 0.03 (-0.21, 0.28) |
| ANCOVA[2] | 8 | 0.06 (-0.20, 0.33) | -0.15 (-0.41, 0.12) | -0.04 (-0.27, 0.19) |
| | 12 | 0.50 (0.23, 0.77) | 0.27 (0.00, 0.54) | 0.39 (0.15, 0.62) |
| | 24 | 0.13 (-0.15, 0.41) | -0.06 (-0.34, 0.22) | 0.03 (-0.21, 0.28) |

1: The change from baseline in DAS28(CRP) was fit using a mixed model repeated measures regression adjusting for baseline, stratification factors, visit, treatment, interaction of categorical visit and treatment, with unstructured covariance matrix, and Kenward-Roger degrees of freedom was used to estimate the denominator degrees of freedom.

2: The linear regression model fit to the change from baseline in DAS28(CRP) adjusting for baseline, stratification factors, and treatment.

Data through Week 24 prior to the second infusion were used in the regression.

Abbreviations: LS=least squares; DAS28(CRP)=Disease Activity Score-28–C-reactive protein

[Source: Statistical Reviewer]

**Table 54: Study 20130108 Reasons for Missing DAS28(CRP) Assessment at Week 24**

| Patients with missing DAS28(CRP) | ABP-798 (N=104) | EU-MabThera (N=104) | US-Rituxan (N=103) |
|---|---|---|---|
| Missing DAS28(CRP) Change from Baseline at Week 24 | 9 | 6 | 8 |
| Missing Baseline | 1 | 2 | |
| Early Study Discontinuation Prior to Week 24 | 4 | 2 | 5 |
| Incomplete DAS28(CRP) assessment | 3 | 2 | 1 |
| Missing Week 24 DAS28(CRP) component assessments | 1 | | 2 |

Abbreviations: DAS28(CRP)=disease activity score in 28 joints–C-reactive protein
[Source: Statistical Reviewer]

**Table 55: Study 20130108 Individual Components of DAS28(CRP) at Visit Weeks by Treatment Arm**

| Visit | Treatment Arm | Descriptive Statistics | Patient Global | SJC28 | TJC28 | CRP | DAS28(CRP) |
|---|---|---|---|---|---|---|---|
| Week 8 | ABP-798 (N=104) | Mean (SD); n | -26.8 (25.8); 102 | -6.9 (6.5); 102 | -9.2 (7.7); 102 | -6.1 (15.9); 100 | -1.8 (1.3); 98 |
| | | Med (Min, Max) | -28.0 (-83.0, 33.0) | -6.0 (-28.0, 10.0) | -7.5 (-28.0, 8.0) | -1.3 (-83.6, 42.4) | -1.7 (-6.1, 0.6) |
| | EU-MabThera (N=104) | Mean (SD); n | -26.2 (27.9); 100 | -7.4 (5.7); 100 | -8.5 (6.2); 100 | -5.7 (17.0); 96 | -1.7 (1.1); 94 |
| | | Med (Min, Max) | -24.5 (-89.0, 46.0) | -7.0 (-26.0, 3.0) | -8.0 (-26.0, 8.0) | -1.5 (-70.5, 69.9) | -1.7 (-5.1, 0.8) |
| | US-Rituxan (N=103) | Mean (SD); n | -24.4 (22.6); 96 | -7.4 (6.1); 97 | -8.7 (7.3); 97 | -4.5 (18.8); 98 | -1.6 (1.1); 96 |
| | | Med (Min, Max) | -24.0 (-75.0, 36.0) | -8.0 (-24.0, 9.0) | -9.0 (-24.8, 6.2) | -1.5 (-56.1, 108.2) | -1.8 (-3.7, 2.5) |
| Week 12 | ABP-798 (N=104) | Mean (SD); n | -27.9 (27.1); 102 | -7.1 (7.0); 102 | -9.7 (7.4); 102 | -6.8 (21.9); 100 | -1.8 (1.3); 99 |
| | | Med (Min, Max) | -28.0 (-88.0, 65.0) | -7.0 (-28.0, 13.5) | -9.0 (-28.0, 5.2) | -1.8 (-91.4, 116.4) | -1.7 (-5.9, 0.8) |
| | EU-MabThera (N=104) | Mean (SD); n | -31.2 (25.3); 101 | -8.7 (5.6); 101 | -9.9 (6.0); 101 | -7.6 (24.8); 101 | -2.2 (1.1); 99 |
| | | Med (Min, Max) | -32.0 (-86.0, 30.0) | -8.0 (-24.0, 1.0) | -9.0 (-25.0, 2.0) | -1.7 (-79.5, 131.2) | -2.1 (-4.9, 0.7) |
| | US-Rituxan (N=103) | Mean (SD); n | -29.6 (25.9); 98 | -8.7 (6.6); 98 | -10.5 (8.1); 98 | -6.9 (18.7); 97 | -2.1 (1.3); 97 |
| | | Med (Min, Max) | -28.0 (-83.0, 38.0) | -8.3 (-24.0, 9.0) | -10.5 (-28.0, 13.0) | -2.4 (-87.4, 83.2) | -2.1 (-5.4, 1.2) |
| Week 24 | ABP-798 (N=104) | Mean (SD); n | -29.4 (29.5); 99 | -8.4 (6.9); 99 | -11.0 (8.2); 99 | -9.0 (18.8); 96 | -2.2 (1.4); 95 |
| | | Med (Min, Max) | -31.0 (-86.0, 63.0) | -8.0 (-28.0, 16.6) | -10.0 (-28.0, 9.3) | -2.6 (-88.3, 37.6) | -2.2 (-6.1, 0.8) |
| | EU-MabThera (N=104) | Mean (SD); n | -29.2 (27.3); 101 | -8.5 (6.7); 101 | -9.9 (7.8); 101 | -9.8 (20.0); 99 | -2.2 (1.4); 97 |
| | | Med (Min, Max) | -29.0 (-85.0, 28.0) | -8.0 (-24.0, 16.0) | -10.0 (-26.0, 14.0) | -2.7 (-85.4, 23.7) | -2.3 (-6.0, 1.3) |
| | US-Rituxan (N=103) | Mean (SD); n | -28.5 (27.3); 96 | -9.1 (6.3); 96 | -10.6 (7.8); 96 | -7.2 (18.7); 95 | -2.1 (1.3); 95 |
| | | Med (Min, Max) | -25.5 (-85.0, 25.0) | -9.0 (-24.0, 9.0) | -10.0 (-25.8, 14.0) | -1.8 (-86.7, 45.6) | -2.1 (-5.5, 0.9) |

Data for the change from baseline in the individual components, collected through Week 24 prior to the second infusion, were summarized descriptively.
Abbreviations: SD=standard deviation; SJC28=swollen joint counts out of 28=least squares; TJC28=tender joint counts out of 28; CRP=C-reactive protein; DAS28(CRP)=disease activity score in 28 joints–C-reactive protein;
[Source: Statistical Reviewer]

**Table 56: Study 20130108 Individual Components of ACR endpoint not captured in DAS28(CRP), by Treatment Arm**

| Visit | Treatment Arm | Descriptive | HAQDI | Physician Global | Patient Pain | SJC66 | TJC68 |
|---|---|---|---|---|---|---|---|

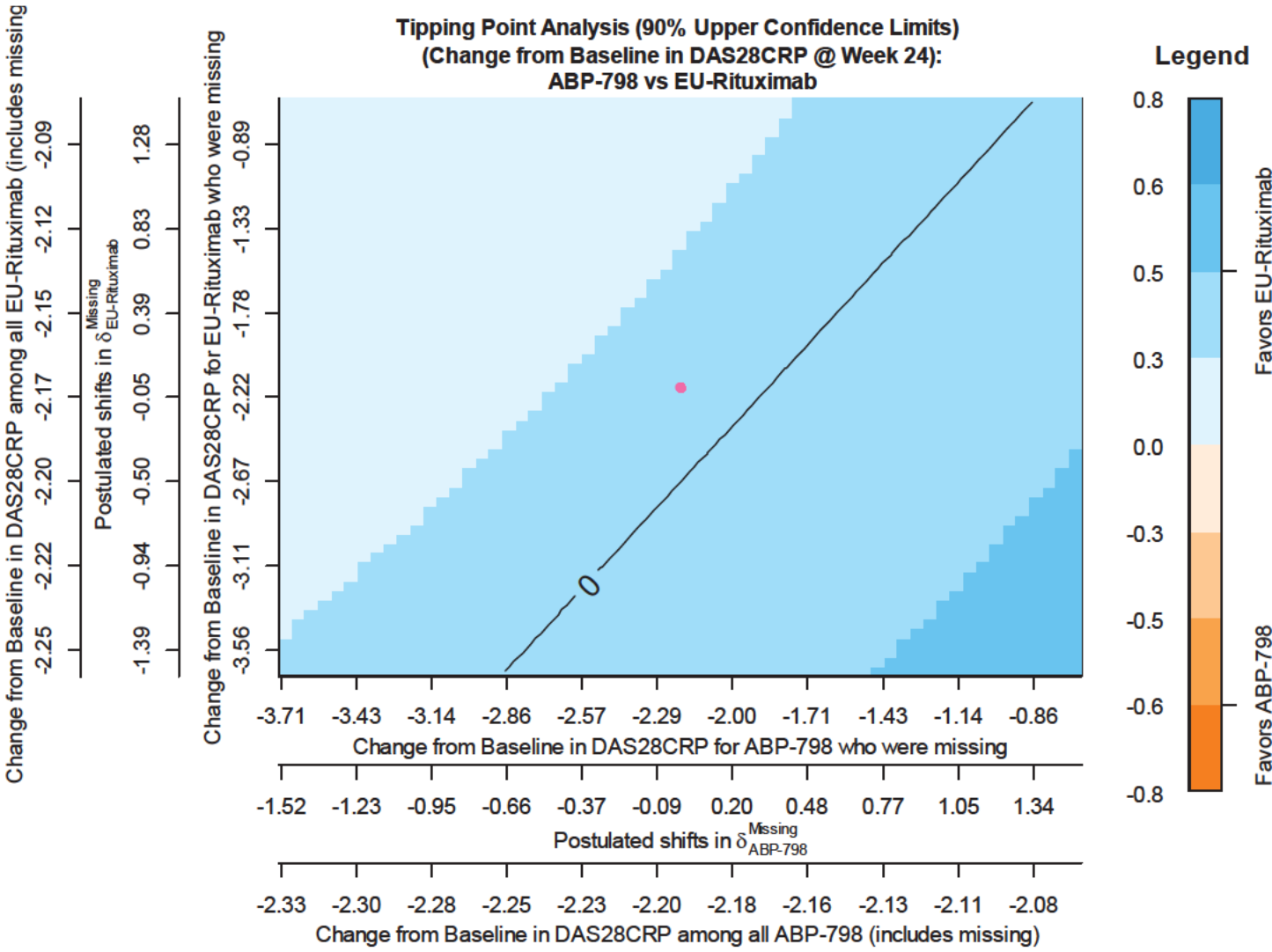
| | | Statistics | | | | | |
|---|---|---|---|---|---|---|---|
| Week 8 | ABP-798 (N=104) | Mean (SD); n | -0.4 (0.5); 102 | -32.3 (20.5); 101 | -24.6 (26.1); 100 | -10.9 (10.3); 102 | -15.6 (13.7); 102 |
| | | Med (Min, Max) | -0.4 (-2.1, 0.5) | -30.0 (-75.0, 8.0) | -25.0 (-82.0, 47.0) | -10.0 (-58.0, 15.0) | -12.0 (-64.0, 14.0) |
| | EU-MabThera (N=104) | Mean (SD); n | -0.4 (0.5); 100 | -32.5 (19.2); 100 | -25.3 (25.1); 99 | -11.2 (9.4); 100 | -14.3 (10.4); 100 |
| | | Med (Min, Max) | -0.2 (-2.2, 0.5) | -33.5 (-70.0, 21.0) | -25.0 (-82.0, 40.0) | -9.9 (-50.0, 9.0) | -12.5 (-43.0, 8.0) |
| | US-Rituxan (N=103) | Mean (SD); n | -0.3 (0.5); 95 | -31.6 (20.7); 97 | -24.0 (23.1); 94 | -10.9 (10.1); 97 | -15.3 (12.7); 97 |
| | | Med (Min, Max) | -0.2 (-1.8, 0.6) | -36.0 (-70.0, 44.0) | -24.0 (-76.0, 32.0) | -9.0 (-52.0, 9.0) | -14.0 (-54.0, 15.2) |
| Week 12 | ABP-798 (N=104) | Mean (SD); n | -0.5 (0.5); 102 | -36.2 (20.4); 102 | -27.4 (26.7); 101 | -11.2 (11.6); 102 | -17.3 (14.5); 102 |
| | | Med (Min, Max) | -0.4 (-2.1, 1.1) | -36.5 (-79.0, 18.0) | -29.0 (-89.0, 35.0) | -10.0 (-58.0, 17.3) | -14.2 (-64.0, 12.0) |
| | EU-MabThera (N=104) | Mean (SD); n | -0.5 (0.5); 101 | -37.8 (20.1); 101 | -32.2 (25.2); 101 | -13.1 (8.8); 101 | -16.7 (11.0); 101 |
| | | Med (Min, Max) | -0.4 (-2.0, 1.0) | -40.0 (-79.0, 20.0) | -35.0 (-82.0, 31.0) | -10.0 (-42.0, 2.0) | -15.0 (-50.0, 4.0) |
| | US-Rituxan (N=103) | Mean (SD); n | -0.4 (0.5); 97 | -35.6 (20.9); 98 | -29.4 (24.7); 97 | -12.1 (10.4); 98 | -17.3 (13.0); 98 |
| | | Med (Min, Max) | -0.4 (-1.9, 0.8) | -38.0 (-82.0, 36.0) | -29.0 (-81.0, 20.0) | -10.0 (-50.0, 12.0) | -16.1 (-56.0, 12.0) |
| Week 24 | ABP-798 (N=104) | Mean (SD); n | -0.5 (0.5); 99 | -38.2 (22.9); 99 | -30.3 (27.8); 98 | -13.2 (11.6); 99 | -19.1 (15.8); 99 |
| | | Med (Min, Max) | -0.5 (-2.1, 0.6) | -38.0 (-78.0, 35.0) | -31.5 (-91.0, 36.0) | -12.0 (-58.0, 17.3) | -14.0 (-64.0, 29.9) |
| | EU-MabThera (N=104) | Mean (SD); n | -0.4 (0.5); 101 | -37.8 (22.4); 101 | -29.7 (28.0); 101 | -12.4 (11.1); 101 | -16.2 (14.2); 101 |
| | | Med (Min, Max) | -0.4 (-2.0, 1.0) | -42.0 (-79.0, 36.0) | -30.0 (-85.0, 47.0) | -10.0 (-48.0, 36.0) | -13.4 (-50.7, 25.0) |
| | US-Rituxan (N=103) | Mean (SD); n | -0.4 (0.5); 95 | -37.5 (20.9); 96 | -27.9 (25.7); 95 | -12.1 (9.6); 96 | -17.1 (12.8); 96 |
| | | Med (Min, Max) | -0.4 (-2.1, 0.5) | -40.0 (-86.0, 18.0) | -26.0 (-76.0, 21.0) | -10.6 (-42.0, 11.0) | -18.0 (-46.0, 10.0) |

The change from baseline of the individual components were summarized above based on data collected through Week 24 prior to second infusion.

Abbreviations: ACR=American College of Rheumatology; CRP=C-reactive protein; Max=maximum; Med=median; Min=minimum; SD=standard deviation; SJC=swollen joint counts; TJC=tender joint counts; HAQ-DI=health assessment questtionare; DAS28(CRP)=disease activity score in 28 joints–C-reactive protein

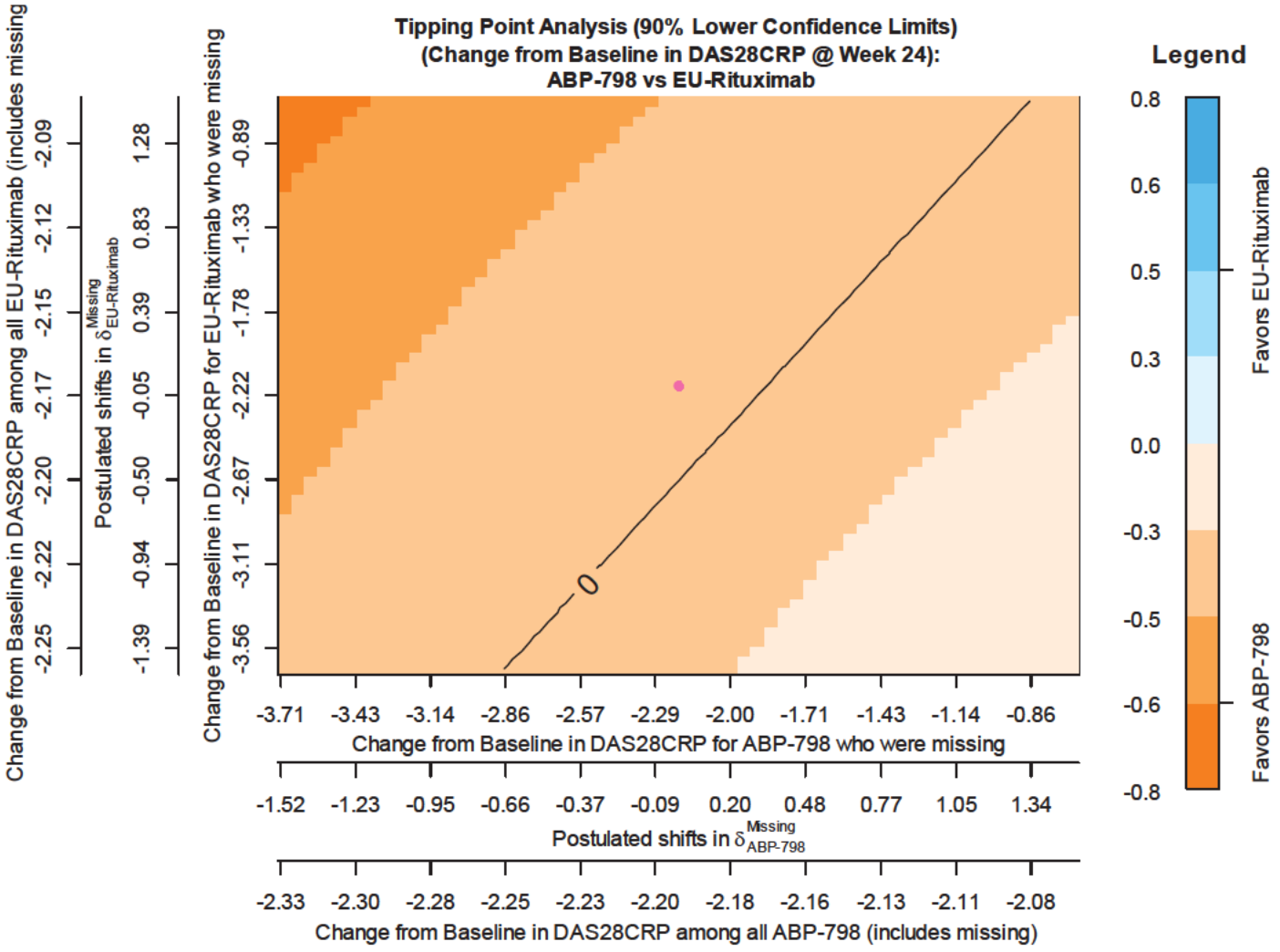
[Source: Statistical Reviewer]

**Figure 16: Study 20130108 Tipping Point Analyses Results for 90% Upper CL (Heatmap) and Point Estimates (Contour Lines) Comparing ABP-798 with EU-MabThera using Change from Baseline in DAS28(CRP)**



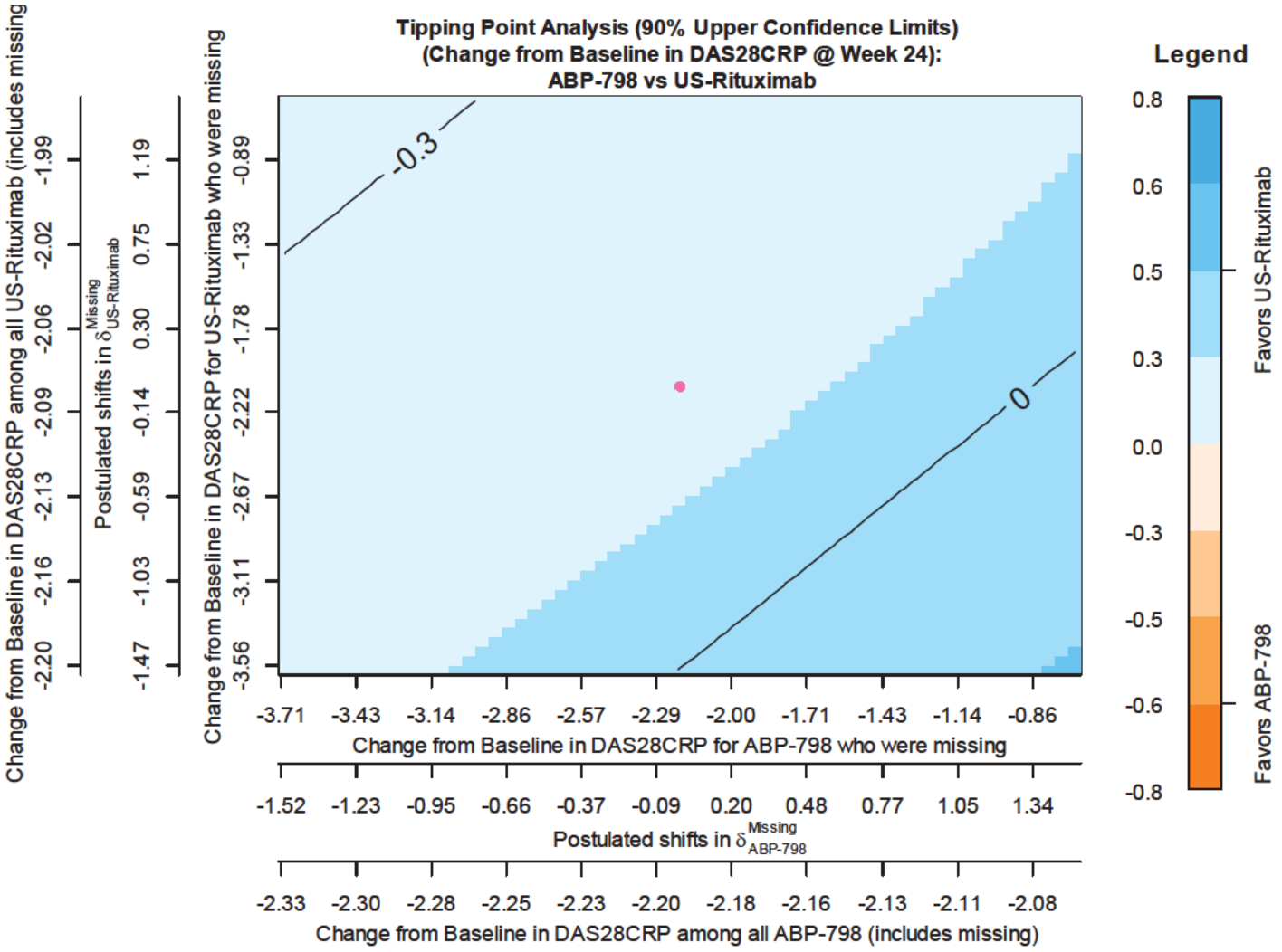

[Source: Statistical Reviewer]

**Figure 17: Study 20130108 Tipping Point Analyses Results for 90% Lower CL (Heatmap) and Point Estimates (Contour Lines) Comparing ABP-798 with EU-MabThera using Change from Baseline in DAS28(CRP)**



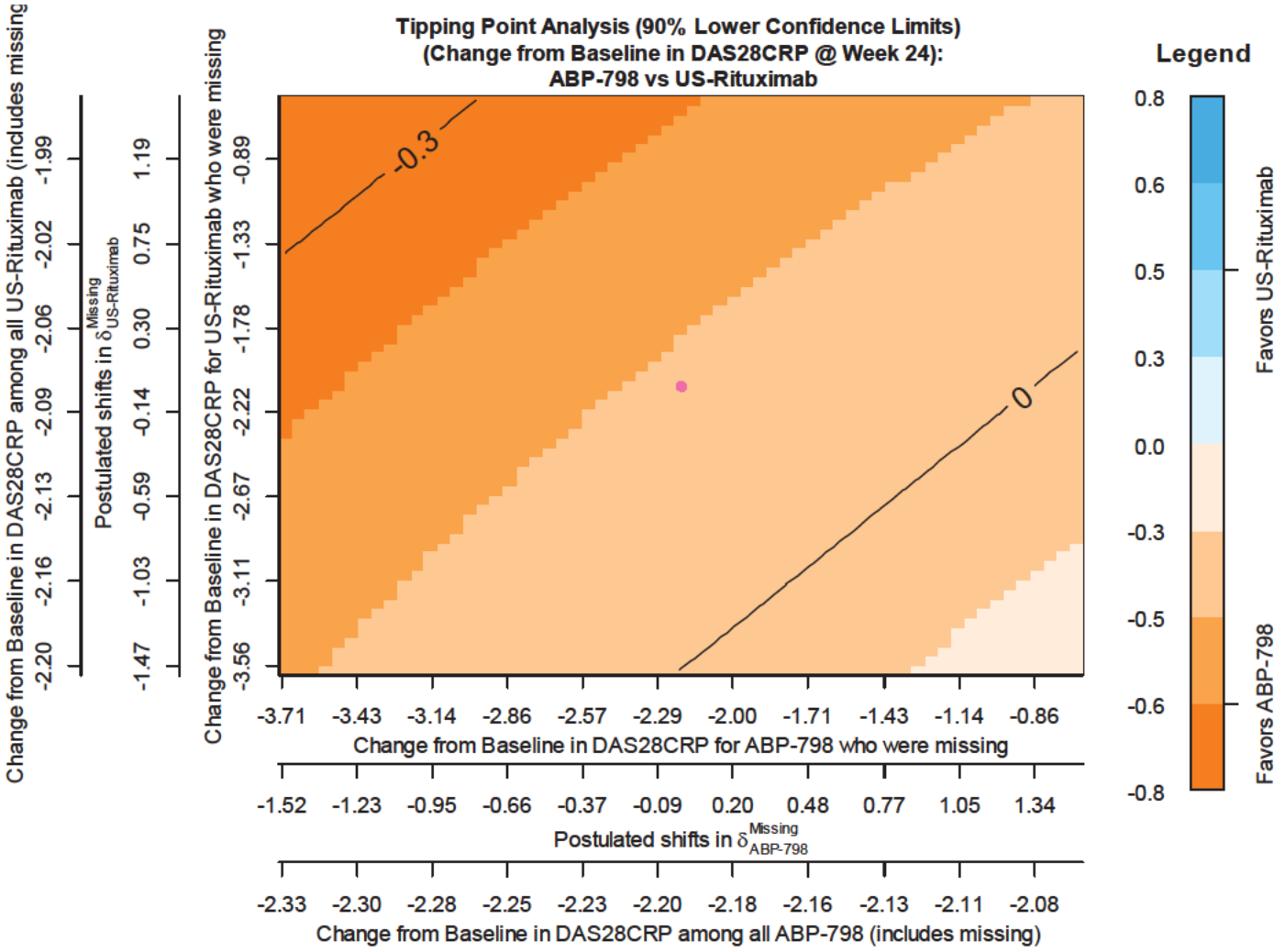

[Source: Statistical Reviewer]

**Figure 18: Study 20130108 Tipping Point Analyses Results for 90% Upper CL (Heatmap) and Point Estimates (Contour Lines) Comparing ABP-798 with US-Rituxan using Change from Baseline in DAS28(CRP)**




[Source: Statistical Reviewer]

**Figure 19: Study 20130108 Tipping Point Analyses Results for 90% Lower CL (Heatmap) and Point Estimates (Contour Lines) Comparing ABP-798 with US-Rituxan using Change from Baseline in DAS28(CRP)**




[Source: Statistical Reviewer]

| [BLA 761140] Riabni (rituximab-arrx) | | | | |
|---|---|---|---|---|

## Multidisciplinary Signature Review

| DISCIPLINE | REVIEWER | OFFICE/DIVISION | SECTIONS AUTHORED/ APPROVED | AUTHORED/ APPROVED |
|---|---|---|---|---|
| Nonclinical Reviewer | Simon Williams, PhD | OOD/DHOT | Sections: 5 and 13.2 | Select one:<br>☑ Authored<br>☐ Approved |
| | Signature: Simon Williams -S<br>Digitally signed by Simon Williams -S<br>DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Simon Williams -S, 0.9.2342.19200300.100.1.1=2001572753<br>Date: 2020.12.16 12:27:54 -05'00' | | | |
| Nonclinical Team Leader | Brenda Gehrke, PhD | OOD/DHOT | Sections: 5 and 13.2 | Select one:<br>☑ Authored<br>☑ Approved |
| | Signature: Brenda Gehrke -S<br>Digitally signed by Brenda Gehrke -S<br>DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Brenda Gehrke -S, 0.9.2342.19200300.100.1.1=0012062023<br>Date: 2020.12.16 16:21:46 -05'00' | | | |
| Clinical Pharmacology Reviewer | Shalini Wickramaratne Senarath Yapa, PhD | OCP/DCPI | Sections: 6 and 13.3 | Select one:<br>☑ Authored<br>☐ Approved |
| | Signature: Shalini Wickramaratne -S<br>Digitally signed by Shalini Wickramaratne -S<br>DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001808888, cn=Shalini Wickramaratne -S<br>Date: 2020.12.16 13:37:28 -05'00' | | | |
| Clinical Pharmacology Team Leader | Ping Ji, PhD | OCP/DCPI | Sections: 6 and 13.3 | Select one:<br>☑ Authored<br>☑ Approved |
| | Signature: Ping Ji<br>Digitally signed by Ping Ji<br>DN: cn=Ping Ji, o=FDA, ou=FDA, email=ping.ji@fda.hhs.goc, c=US<br>Date: 2020.12.16 13:24:40 -05'00' | | | |
| Clinical Reviewer | Pamela Seam, MD | OOD/DHMII | Sections: 2, 3, 7, 8, 10, 11, and 13.1 | Select one:<br>☑ Authored<br>☐ Approved |
| | Signature: Pamela Seam -S<br>Digitally signed by Pamela Seam -S<br>DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Pamela Seam -S, 0.9.2342.19200300.100.1.1=0011634625<br>Date: 2020.12.16 13:55:15 -05'00' | | | |
| Clinical Reviewer | Juwaria Waheed, MD | OII/DRTM | Sections: 2, 3, 7, 8, 10, 11, and 13.1 | Select one:<br>☑ Authored<br>☐ Approved |
| | Signature: Juwaria Waheed -S<br>Digitally signed by Juwaria Waheed -S<br>DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Juwaria Waheed -S, 0.9.2342.19200300.100.1.1=0011401008<br>Date: 2020.12.16 12:33:27 -05'00' | | | |
| Clinical Team Leader (DRTM) | Anil Rajpal, MD | OII/DRTM | Sections: 2, 3, 7, 8, 10, 11, and 13.1 | |
| | | | | ☑ Authored<br>☑ Approved |
| | Signature: Anil K. Rajpal -S<br>Digitally signed by Anil K. Rajpal -S<br>DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Anil K. Rajpal -S, 0.9.2342.19200300.100.1.1=1300170204<br>Date: 2020.12.16 12:23:29 -05'00' | | | |
| Statistical Reviewer | Laura Fernandes, PhD | OOD/DHMII | Section: 7 | Select one:<br>☑ Authored<br>☐ Approved |

| | | | | |
|---|---|---|---|---|
| | Signature: Laura Fernandes -S Digitally signed by Laura Fernandes -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001528044, cn=Laura Fernandes -S Date: 2020.12.16 17:57:56 -05'00' | | | |
| Statistical Reviewer | William Koh, PhD | OII/DRTM | Section: 6 | **Select one:**<br>☑ Authored<br>☐ Approved |
| | Signature: William Jen Hoe Koh -S Digitally signed by William Jen Hoe Koh -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002137835, cn=William Jen Hoe Koh -S Date: 2020.12.16 13:59:38 -05'00' | | | |
| Statistical Team Leader | Yu-te Wu, PhD | OB/DBIX | Section: 7 | **Select one:**<br>☑ Authored<br>☑ Approved |
| | Signature: Yute Wu -S Digitally signed by Yute Wu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yute Wu -S, 0.9.2342.19200300.100.1.1=1300389006 Date: 2020.12.16 12:37:44 -05'00' | | | |
| Statistical Team Leader | Yongman Kim, PhD | OII/DRTM | Section: 6 | **Select one:**<br>☑ Authored<br>☑ Approved |
| | Signature: Yongman Kim -S Digitally signed by Yongman Kim -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yongman Kim -S, 0.9.2342.19200300.100.1.1=1300218531 Date: 2020.12.16 13:01:36 -05'00' | | | |
| Associate Director of Labeling | Stacy Shord, PharmD | OOD/DHMII | Section: 8 | **Select one:**<br>☑ Authored<br>☑ Approved |
| | Signature: Stacy Shord -S Digitally signed by Stacy Shord -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Stacy Shord -S, 0.9.2342.19200300.100.1.1=2000356537 Date: 2020.12.16 14:03:43 -05'00' | | | |
| Cross-Disciplinary Team Leader (CDTL) | Nicholas Richardson, DO, MPH | OOD/DHMII | Sections: 1, 2, 3, 4, 7, 8, 9, 10, 11, and 13.1 | **Select one:**<br>☑ Authored<br>☑ Approved |
| | Signature: Nicholas C. Richardson -S Digitally signed by Nicholas C. Richardson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002040136, cn=Nicholas C. Richardson -S Date: 2020.12.16 14:52:29 -05'00' | | | |
| Division Director (Clinical DRTM) | Nikolay Nikolov, MD | OII/DRTM | Sections: 7 and 12 | **Select one:**<br>☑ Authored<br>☑ Approved |
| | Signature: Nikolay P. Nikolov -S Digitally signed by Nikolay P. Nikolov -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011314790, cn=Nikolay P. Nikolov -S Date: 2020.12.16 12:56:30 -05'00' | | | |
| Division Director (Clinical DHMII) | Nicole Gormley, MD | OOD/DHMII | Sections: 7 and 12 | ☑ Authored |
| | | | ☐ Approved | ☑ Approved |
| | Signature: Nicole J. Gormley -S | | | |
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| OCP = Office of Clinical Pharmacology | | | | |

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|---|---|---|---|---|
| DCPI = Division of Cancer Pharmacology I | | | | |
| OB = Office of Biostatistics | | | | |
| DBIX = Division of Biometrics IX | | | | |
| OOD = Office of Oncologic Diseases | | | | |
| DHM2 = Division of Hematologic Malignancies II | | | | |
| DRTM = | | | | |

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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LAURA C WALL
12/16/2020 06:35:07 PM

NICHOLAS C RICHARDSON
12/16/2020 06:54:02 PM

NICOLE J GORMLEY
12/17/2020 11:58:35 AM