CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761064Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW
## Cross-Discipline Team Leader Review

### Cross-Discipline Team Leader Review

<table>
<thead>
<tr>
<th>Date</th>
<th>see stamp date</th>
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<tr>
<td>From</td>
<td>R. Angelo de Claro, M.D.</td>
</tr>
<tr>
<td>Subject</td>
<td>Cross-Discipline Team Leader Review</td>
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<tr>
<td>NDA/BLA #</td>
<td>BLA 761064</td>
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<tr>
<td>Supplement#</td>
<td>Original</td>
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<tr>
<td>Applicant</td>
<td>Genentech, Inc.</td>
</tr>
<tr>
<td>Date of Submission</td>
<td>25 August 2016</td>
</tr>
<tr>
<td>PDUFA Goal Date</td>
<td>26 June 2017</td>
</tr>
<tr>
<td>Proprietary Name / Established (USAN) names</td>
<td>Rituxan Hycela / rituximab and hyaluronidase human</td>
</tr>
<tr>
<td>Dosage forms / Strength</td>
<td>Injection</td>
</tr>
<tr>
<td></td>
<td>• 1,400 mg rituximab and 23,400 USP units hyaluronidase human per 11.7 mL (120 mg/2000 USP units per mL) solution in a single-dose vial</td>
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<tr>
<td></td>
<td>• 1,600 mg rituximab and 26,800 USP units hyaluronidase human per 13.4 mL (120 mg/2000 USP units per mL) solution in a single dose vial</td>
</tr>
<tr>
<td>Applicant’s Proposed Indication</td>
<td>Refer to Section 2</td>
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<tr>
<td>Intended Population</td>
<td>Patients ≥18 years of age</td>
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<tr>
<td>Recommendation on Regulatory Action</td>
<td>Approval</td>
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<tr>
<td>Recommended Indication</td>
<td>Refer to Section 1</td>
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</table>

### Material Reviewed/Consulted

| Clinical | Alexandria Schwarsin / R. Angelo de Claro |
| Statistical | Jingjing Ye / Lei Nie |
| Pharmacology Toxicology | Natalie Simpson / Christopher Sheth |
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| | Leeza Rahimi / Hina Mehta |
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| OPDP | L. Shenee Toombs / Elaine Cunningham / Kathleen Davis |

Reference ID: 4108798
1. Benefit-Risk Assessment

Regulatory Recommendation: Traditional Approval

Recommended Indications: Rituxan Hycela is a combination\(^1\) of rituximab, a CD20-directed cytolytic antibody, and hyaluronidase human, an endoglycosidase for the treatment of adult patients with:

- **Follicular Lymphoma (FL)**
  - Relapsed or refractory, follicular lymphoma as a single agent
  - Previously untreated follicular lymphoma in combination with first line chemotherapy and, in patients achieving a complete or partial response to rituximab in combination with chemotherapy, as single-agent maintenance therapy
  - Non-progressing (including stable disease), follicular lymphoma as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy

- **Diffuse Large B-cell Lymphoma (DLBCL)**
  - Previously untreated diffuse large B-cell lymphoma in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or other anthracycline-based chemotherapy regimens

- **Chronic Lymphocytic Leukemia (CLL)**
  - Previously untreated and previously treated CLL in combination with fludarabine and cyclophosphamide (FC)

The efficacy and safety of Rituxan Hycela was established for the above recommended indications based on the results from multiple randomized clinical trials, including SABRINA, MabEase, and SAWYER, which demonstrated: (a) non-inferior rituximab trough concentrations (C\(_{\text{trough}}\)) levels for Rituxan Hycela 1,400 mg/23,400 Units compared to a rituximab product 375 mg/m\(^2\) administered intravenously, (b) non-inferior rituximab C\(_{\text{trough}}\) levels for Rituxan Hycela 1,600 mg/26,800 Units compared to a rituximab product 500 mg/m\(^2\) administered intravenously, and (c) comparable efficacy and safety results. Postmarketing ex-US experience with Rituximab (MabThera) for SC injection provides for supportive evidence of safety. Refer to table below for additional details on benefit-risk analysis.

All review teams recommend approval.

Rituxan Hycela is recommended for subcutaneous use only. All patients must receive at least one full dose of a rituximab product by intravenous infusion before receiving Rituxan Hycela by subcutaneous injection. The recommended dosing regimens are:

- **FL/DLBCL**: Administer 1,400 mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human) subcutaneously according to recommended schedule.

- **CLL**: Administer 1,600 mg /26,800 Units subcutaneously according to recommended schedule.

\(^1\) For labeling purposes, the term “combination” is recommended. From a regulatory perspective, the term “fixed-dose combination” is preferred.
Benefit-Risk Summary and Assessment

The Applicant used primarily a PK-bridging approach to establish the safety and effectiveness of a fixed-dose combination of rituximab and hyaluronidase human intended for subcutaneous route of administration. A notable feature of the Applicant’s approach was the targeting of a trough concentration (C_{trough}) for Rituxan Hycela that would be at least as high as that achieved with a rituximab IV product. Additional changes include the use of a fixed-dose regimen instead of BSA-based dosing, and the addition of hyaluronidase human to facilitate absorption and administration.

FDA verified that Rituxan Hycela achieved equal or higher C_{trough} relative to rituximab IV in patients with FL, DLBCL, and CLL. The addition of hyaluronidase human increased the absorption rate of rituximab. The fixed-dosing strategy lead to reasonably consistent C_{trough} across all BSA sizes relative to BSA-based dosing of rituximab IV.

Although the clinical trials were not designed for efficacy hypothesis testing, the efficacy results between Rituxan Hycela and rituximab IV are comparable.

There were no major differences in safety findings between Rituxan Hycela and rituximab IV, with the exception of increase in administration site-related local reactions with Rituxan Hycela. In addition, exposure-response analyses for safety did not show significant relationships between C_{trough} and any of the safety endpoints evaluated.

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis of Condition</td>
<td>FL and CLL are indolent diseases with variable clinical courses but are not considered curable. The typical course can include several treatments with the potential for the disease to become unresponsive to treatment. DLBCL is an aggressive non-Hodgkin’s lymphoma with a 5-year relative survival of 62%.</td>
<td>FL, CLL, and DLBCL are life threatening diseases.</td>
</tr>
<tr>
<td>Current Treatment Options</td>
<td>Current treatment options for FL and CLL range from observation to chemotherapy combined immunotherapy. Current treatment options for DLBCL includes chemotherapy and immunotherapy.</td>
<td>Treatment options for FL, CLL and DLBCL vary depending on the disease and stage of disease the patient has. Rituximab can be combined with chemotherapy for treatment of FL, CLL and DLBCL.</td>
</tr>
<tr>
<td>Dimension</td>
<td>Evidence and Uncertainties</td>
<td>Conclusions and Reasons</td>
</tr>
<tr>
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<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Benefit</td>
<td>The benefit of Rituxan Hycela given SC has been demonstrated in clinical trials in FL, DLBCL and CLL to be comparable to that of a rituximab product given IV.</td>
<td>The efficacy of Rituxan Hycela is comparable to a rituximab product given IV.</td>
</tr>
<tr>
<td>Risk</td>
<td>The risk of Rituxan Hycela is comparable to that of a rituximab product given IV with a few notable differences. In each of the disease, FL, DLBCL, and CLL the risk of some adverse events may be increased slightly. Rituxan Hycela was associated with injection site reactions. Across three trials, there was an increased risk of neutropenia and infections both serious and non-serious.</td>
<td>The risks of Rituxan Hycela are comparable to that of a rituximab product given IV with an increased risk of some adverse events including infections. The prescribing information will describe the rates of adverse events in FL, CLL and DLBCL.</td>
</tr>
<tr>
<td>Risk Management</td>
<td>The risk of reactions is minimized by previous intravenous administration of a dose of a rituximab product. Serious and life-threatening toxicities can be managed with appropriate supportive treatment.</td>
<td>The Prescribing Information will clearly state Rituxan Hycela is to be given subcutaneously and all patients must receive a full dose of a rituximab product intravenously prior to starting Rituxan Hycela.</td>
</tr>
</tbody>
</table>
2. **Background**

The Applicant (Genentech, Inc.) submitted a biologic license application (BLA) on August 25, 2016 to support approval for the combination of rituximab and hyaluronidase human for the following oncologic indications:

**a. Follicular Lymphoma (FL)**

TRADENAME (rituximab/hyaluronidase) for subcutaneous injection is a combination of rituximab and recombinant human hyaluronidase (rHuPH20) and is indicated for the treatment of patients with:

- Relapsed or refractory, FL as a single agent.
- Previously untreated FL in combination with first line chemotherapy and, in patients achieving a complete or partial response to TRADENAME™ for subcutaneous injection in combination with chemotherapy, as single-agent maintenance therapy.
- Non-progressing (including stable disease), FL as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy.

**b. Diffuse Large B-Cell Lymphoma (DLBCL)**

TRADENAME (rituximab/hyaluronidase) for subcutaneous injection is indicated for the treatment of patients with previously untreated DLBCL in combination with cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) or other anthracycline-based chemotherapy regimens.

**c. Chronic Lymphocytic Leukemia (CLL)**

TRADENAME (rituximab/hyaluronidase) for subcutaneous injection is indicated, in combination with fludarabine and cyclophosphamide (FC), for the treatment of patients with previously untreated and previously treated CLL.

Rituxan® is an intravenously administered CD20-directed cytolytic antibody approved for the treatment of patients with NHL (Non-Hodgkin lymphoma) and CLL. The initial oncology approval occurred in 1997.

Hyaluronidase is a purified preparation of the enzyme recombinant human hyaluronidase. Hyaluronidase facilitates absorption and dispersion of subcutaneously injected drugs by cleaving glycosidic bonds of hyaluronic acid other acid mucopolysaccharides of the connective tissue. Hyaluronidase has been approved as an adjuvant as follows:

- in subcutaneous fluid administration for achieving hydration
- to increase the dispersion and absorption of other injected drugs
- in subcutaneous urography for improving resorption of radiopaque agent

The fixed-dose combination of rituximab and hyaluronidase human, hereafter referred to as rituximab SC or Rituxan Hycela, is subcutaneously administered, which offers patients a
different route of administration compared to intravenous rituximab, hereafter referred to as rituximab IV.

The clinical development of rituximab SC was based on a pharmacokinetic bridging program to intravenously administered rituximab in patients with DLBCL, FL and CLL. The development approach is consistent with FDA Guidance2 on “Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products”, which states the following:

“In certain cases, effectiveness of an approved drug product for a new indication, or effectiveness of a new product, may be adequately demonstrated without additional adequate and well-controlled clinical efficacy trials. Ordinarily, this will be because other types of data provide a way to apply the known effectiveness to a new population or a different dose, regimen or dosage form.”

When being applied to different doses, regimens, or dosage forms, the above FDA Guidance states that “it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of PK data without an additional clinical efficacy trial”. In the current application, PK data, together with a well-defined PK-efficacy relationship, are used to bridge the established safety and efficacy results of rituximab IV to rituximab SC.

Two different doses of rituximab SC were developed: a 1,400 mg subcutaneous (SC) dose to represent the 375 mg/m$^2$ intravenous (IV) rituximab dose and a 1,600 mg SC dose to represent the 500 mg/m$^2$ IV rituximab dose. This submission contains 5 clinical trials listed in Table 1.

**Table 1 Clinical Trials Submitted**

<table>
<thead>
<tr>
<th>Protocol number and name</th>
<th>Patient Population</th>
<th>Design</th>
<th>Primary Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>BO22334/ SABRINA</td>
<td>FL</td>
<td>Phase 3, 2 stage trial, stage 1 with more intensive PK sampling of 1,400 mg SC dose</td>
<td>Stage 1: Non-inferiority C$_{\text{trough}}$ of rituximab SC vs IV Stage 2: Efficacy overall response rate (ORR) at end of induction</td>
</tr>
<tr>
<td>MO28107/ MabEase</td>
<td>DLBCL</td>
<td>Phase 3b randomized trial</td>
<td>Complete response rate (CRR) at end of treatment</td>
</tr>
<tr>
<td>BO25341/ SAWYER</td>
<td>CLL</td>
<td>Phase 1b; Stage 1: dose-finding single SC injection Stage 2: Dose confirmation of 1,600 mg SC dose</td>
<td>Non-inferiority of C$_{\text{trough}}$ SC vs IV</td>
</tr>
<tr>
<td>BP22333/ SparkThera</td>
<td>FL</td>
<td>Phase 1b; Stage 1: dose finding single SC injection Stage 2: dose confirmation 1,400 mg in maintenance setting</td>
<td>Non-inferiority of C$_{\text{trough}}$ SC vs IV</td>
</tr>
<tr>
<td>MO28457/ PrefMab</td>
<td>FL/DLBCL</td>
<td>Phase 3b randomized cross over trial</td>
<td>Patient preference of SC vs IV</td>
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</table>

The development of rituximab SC is based on the predicate that rituximab SC is “a different dose, regimen, or dosage form” of rituximab IV and that PK data can be used to bridge the two different formulations of the same molecular entity provided the role of hyaluronidase is to serve as an adjunct to facilitate the dispersion and subsequent absorption of rituximab from the subcutaneous tissue. The main differences between the two formulations are shown in Table 2.

### Table 2 Comparison between rituximab IV and rituximab SC

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Rituximab IV</th>
<th>Rituximab SC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration</td>
<td>IV infusion over 1.5 to 2.5 hours</td>
<td>SC injection over 5 minutes</td>
</tr>
<tr>
<td>Rituximab Concentration</td>
<td>10 milligrams (mg)/milliliters (mL)</td>
<td>120 mg/mL</td>
</tr>
<tr>
<td>Dosing regimen</td>
<td>Body surface area - based</td>
<td>Fixed</td>
</tr>
<tr>
<td>Combination with hyaluronidase human</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Doses</td>
<td>375 mg/m² and 500 mg/m²</td>
<td>1,400 mg and 1,600 mg</td>
</tr>
</tbody>
</table>

### 3. Product Quality

**Source: CMC Review**

**CMC Team Recommendation: Approval**

- General product quality considerations

Rituxan Hycela is a combination of rituximab and hyaluronidase human. Rituximab is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen. Rituximab has an approximate molecular weight of 145 kD. Rituximab has a binding affinity for the CD20 antigen of approximately 8.0 nM. Rituximab is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

Recombinant hyaluronidase human is an endoglycosidase used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously. It is produced by mammalian (Chinese Hamster Ovary) cells containing a DNA plasmid encoding for a soluble fragment of hyaluronidase human (PH20). It is a glycosylated single-chain protein with an approximate molecular weight of 61 kD. Rituxan Hycela (rituximab and hyaluronidase human) Injection is a colorless to yellowish, clear to opalescent solution supplied in sterile, preservative-free, single-dose vials for subcutaneous administration.

Rituxan Hycela is supplied as 1,400 mg rituximab and 23,400 Units hyaluronidase human per 11.7 mL in single-dose vials or 1,600 mg rituximab and 26,800 Units hyaluronidase human per 13.4 mL in single-dose vials. Each mL of solution contains...
rituximab (120 mg), hyaluronidase human (2,000 Units), L-histidine (0.53 mg), L-
histidine hydrochloride monohydrate (3.47 mg), L-methionine (1.49 mg), polysorbate
80 (0.6 mg), α,α-trehalose dihydrate (79.45 mg), and water for Injection

The shelf life for drug product in both strengths is 30 months at 2-8°C.

- Facilities review/inspection

  All facilities inspections have been completed. According to Office of Process and
  Facilities, the overall manufacturing inspection recommendation is acceptable.

- Other notable issues: None

4.  Clinical Microbiology

  Not applicable.

5.  Nonclinical Pharmacology and Toxicology

  Source: Pharmacology and Toxicology Review

  Pharmacology Toxicology Team Recommendation: Approval

  - General nonclinical pharmacology/toxicology considerations (including pharmacologic
    properties of the product, both therapeutic and otherwise).

  Pharmacology studies in mantle cell lymphoma xenograft mice and a monkey B-cell
  depletion model were submitted comparing IV and subcutaneous (SC) rituximab
  formulations. Despite exposure differences, there were no major differences in
  pharmacodynamic (PD) effects of tumor growth inhibition or B-cell depletion in mice
  or monkeys, respectively. Also, several rHuPH20 pharmacology studies were
  submitted (which were previously reviewed under NDA 21859 (HYLENEX), to
  emphasize the transient, locally acting effects of rHuPH20 in animals at concentrations
  (and doses) within the range proposed for humans, 2000 U/mL rHuPH20 (390 to 447
  U/kg, assuming a 60 kg adult). In mice, 100 to 500 U/mL rHuPH20 (87 to 435 U/kg,
  assuming a 0.023 kg mouse), increased dye dispersion approximately 40-66% compared
to controls within 5 minutes, which is a time frame relevant for SC injections. In mice,
dispersion of dye following intradermal administration of 100 U/mL rHuPH20 (174 U/kg) was
complete within 6 to 18 hours and up to 30,000 U/mL rHuPH20 (52,000 U/kg) did not act distally.

  Dedicated safety pharmacology studies were not performed for rituximab SC; however,
cardiovascular endpoints were included as part of the 8-week general toxicology study with
rituximab SC described below.
The following pharmacokinetic (PK) studies with SC administration of rituximab were reviewed:

- SC bioavailability study in female Göttingen Minipigs with rituximab (with 2000, 4000, or 6000 U rHuPH20 or 230, 460, and 690 U/kg rHuPH20, respectively);
- comparative PK study between rituximab administered intravenously, or subcutaneously with 6000 U/mL rHuPH20 (30,000 U/kg), in severe combined immunodeficiency (SCID) beige mice; and,
- PK/PD study with subcutaneously administered rituximab with 6000 U/mL rHuPH20 (1000 U/kg) in cynomolgus monkeys.

The minipig study provides evidence to support that the addition of rHuPH20 to rituximab formulations administered subcutaneously improved the absorption rate of rituximab in minipigs (compared to a SC formulation without rHuPH20), reducing Tmax from 48 to 24 hours. There were no major differences in systemic exposure in minipigs administered 10 mg/kg rituximab intravenously or 14 mg/kg (120 mg/mL rituximab with 2000 U/mL rHuPH20) rituximab SC. However, maximum plasma levels following IV administration of 10 mg/kg rituximab could not be achieved with rituximab SC in minipigs (or in mice administered 30 mg/kg rituximab with 6000 U/mL rHuPH20 subcutaneously, compared to 30 mg/kg IV rituximab). The minipig study also demonstrated that the addition of more concentrated rHuPH20 to the formulation did not increase Cmax. However, in monkeys administered 20 mg/kg rituximab with 6000 U/mL rHuPH20 (1000 U/kg) subcutaneously, maximum plasma concentrations were achieved at 24 hours and they were comparable to levels observed in studies reviewed with the BLA for rituximab IV. Overall, the animal pharmacology and PK data supports that there is a need for rHuPH20 to improve the absorption rate of rituximab administered subcutaneously, that rHuPH20 is locally acting, and rHuPH20 does not appear to affect the activity of rituximab.

Single dose toxicology studies were not performed for rituximab SC. A GLP-compliant 8-week repeat dose general toxicology, with a 13-week recovery phase, study with rituximab SC in cynomolgus monkeys was submitted. Monkeys were administered vehicle control (containing 2000 U/mL rHuPH20 (340 U/kg)) or 20 mg/kg rituximab SC (containing 120 mg/mL rituximab and 2000 U/mL rHuPH20 (340 U/kg)). Toxicities with SC administration are overall consistent with what is known historically with rituximab IV administration. Decreases in neutrophils, cardiac arrhythmias (increases in QRS complex R and S waves in recovery animals only), and liver toxicity (liver enzyme elevations, hepatomegaly, and marked multifocal hepatocellular necrosis) were observed in this study that were not observed in nonclinical studies submitted to support the rituximab IV BLA; but, neutropenia, cardiac arrhythmias, and liver toxicity have been observed in patients administered rituximab IV. There were some injection site findings that could be related to SC administration (inflammation, with only minimal necrosis in the draining axillary lymph nodes); however, they were not adverse. The 20 mg/kg rituximab SC dose
resulted in exposure levels in monkeys that were comparable to those achieved at the highest doses in the corresponding nonclinical IV safety program.

In a local tolerance study in male New Zealand White Rabbits, there were no adverse injection site findings related to rituximab SC treatment (120 mg/mL rituximab and 2000 U/mL rHuPH20 (~300 U/kg, assuming a 3 kg rabbit)), but there was edema and mixed cell infiltrates at a higher incidence/severity at the rituximab SC injection sites compared to controls.

Overall, the pharmacodynamic, pharmacokinetic and toxicity profile of SC administered rituximab is consistent with IV administered rituximab. Cardiac arrhythmias, liver toxicity, and decreases in neutrophils observed with rituximab SC that were not observed in toxicity studies submitted with the rituximab IV BLA have been observed as adverse events in patients treated with rituximab IV. Injection site reactions are clinically relevant, but based on the nonclinical data, are not expected to be adverse.

- Carcinogenicity
  No genetic toxicology or carcinogenicity studies were submitted or are required since rituximab SC is a biologic [ICH Guidance S6(R1)].

- Reproductive toxicology
  No new reproductive and developmental toxicology studies were reviewed since there were no changes to the reproductive and developmental toxicology data from the RITUXAN and HYLENEX labels except for updating of language and animal:human exposure margins for rHuPH20 in order to comply with the Pregnancy and Lactation Labeling Final Rule (PLLFR) (see Table 19 of Pharmacology-Toxicology Review).

- Other notable issues: None

6. Clinical Pharmacology

Source: Clinical Pharmacology Review

Clinical Pharmacology Team Recommendation: Approval

- General clinical pharmacology considerations

The PK of rituximab in patients with NHL and CLL was described by a using a two-compartment model with time-independent clearance and additional target-mediated (time-dependent) elimination with a non-renewable target. The subcutaneous absorption was characterized using a first-order absorption process. A summary of the clinical pharmacokinetics of rituximab SC is provided in Table 3.

In the SABRINA trial, the geometric mean C_{trough} (%CV) in the Rituxan Hycela arm was higher than in the rituximab arm with a geometric mean ratio (C_{trough}) RITUXAN
HYCELA (C\textsubscript{trough}, rituximab) of 1.52 (90% CI: 1.36, 1.70) at Cycle 7. In the SAWYER trial, the geometric mean C\textsubscript{trough} in the Rituxan Hycela arm was higher than in the rituximab arm with an adjusted geometric mean ratio of 1.53 (90% CI: 1.27-1.85) at Cycle 5.

Table 3 Pharmacokinetic Parameters of Rituximab SC

<table>
<thead>
<tr>
<th></th>
<th>FL</th>
<th>CLL</th>
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</thead>
<tbody>
<tr>
<td><strong>Absorption</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated Absolute Bioavailability\textsuperscript{b}</td>
<td>0.646 (NA)</td>
<td>0.633 (21)</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume of Central compartment\textsuperscript{c} (L)</td>
<td>4.06 (26)\textsuperscript{d}</td>
<td>4.80 (18)</td>
</tr>
<tr>
<td>Apparent Volume of Distribution at steady state\textsuperscript{c} (L)</td>
<td>8.09 (19)\textsuperscript{d}</td>
<td>8.52 (13)</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terminal Half-life (hours)</td>
<td>34.1 (27)</td>
<td>32 (24)</td>
</tr>
<tr>
<td>Effective Clearance (L/day)</td>
<td>0.18 (34)</td>
<td>0.204 (31)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Parameters represented as geometric mean (%CV) unless otherwise specified;  
\textsuperscript{b} Compared to rituximab IV  
\textsuperscript{c} Volume of central compartment and peripheral compartment  
\textsuperscript{d} NA=Not available

- Drug-drug interactions
  Since rituximab is not given orally, food-drug interactions are not anticipated or applicable. Drug-drug interactions are not expected based on the CYPs, other metabolizing enzymes, or transporters. As such, no in vivo or in vitro drug-drug interaction studies were conducted.

- Pathway of elimination
  Refer to General Clinical Pharmacology considerations.

- Intrinsic factors potentially affecting elimination, Demographic interactions, and Special populations
  Rituximab IV is dosed using body surface area (BSA) and BSA was a significant covariate in the population PK analysis of rituximab. The proposed doses of 1,400 mg for patients with NHL and 1,600 mg for patients with CLL provided consistently higher exposure than the 375 mg/m2 and 500 mg/m2 IV doses, respectively. Because rituximab has a wide therapeutic window, the higher C\textsubscript{trough} following the fixed rituximab SC doses is not expected to influence the safety profile of rituximab. No dose individualization is required for adult patients.

- Other notable issues: Immunogenicity
  The post-baseline incidence of anti-rituximab antibodies (treatment-induced and treatment-enhanced human-antichimeric antibody responses) was 1-4% in the IV group versus 1-2 % in the SC arm in patients with FL. In patients with CLL, the incidence of anti-rituximab antibodies was ~ 7% (6/89 patients) in the IV group compared with 2% (2/85 patients) in the SC group.
7. Clinical/Statistical- Efficacy

Source: Statistical and Clinical Reviews

Statistical Team Recommendation: Approval

Clinical Team Recommendation: Approval

SABRINA (Follicular Lymphoma)

Patient Population
The patient population was ≥18 year of age with histologically confirmed CD20-positive follicular lymphoma grade 1, 2, or 3a according to WHO classification. Patients with 3b follicular lymphoma, transformation to high-grade, presence of CNS disease (lymphoma or lymphomatous meningitis) or other types of NHL were excluded. Patients could not have received prior treatment.

Trial Design
The trial was a two-stage, international, multicenter, randomized, controlled, open-label trial to evaluate PK, efficacy, and safety. Patients received induction treatment of rituximab in combination with CHOP or CVP followed by maintenance treatment with rituximab monotherapy. The randomization ratio was 1:1 and randomization was stratified by selected chemotherapy (CHOP or CVP), FLIPI score (low-risk, intermediate-risk, or high-risk), and region, (Europe and North America, South and Central America, and Asia).

Figure 1 Trial Design in Follicular Lymphoma (SABRINA)

The primary endpoint in the study was investigator-assessed objective response rate (ORR). ORR was defined as CR, CRu and PR in each treatment arm at the end of completion of induction treatment. The secondary endpoints are CRR (CR and CRu) at the end of completion of induction treatment, ORR and CRR at the end of completion of maintenance treatment, and
time-to-event endpoints (Progression-free survival (PFS), Event-free survival (EFS), Overall Survival (OS)).

**Efficacy Results**
A total of 410 patients with previously untreated, CD20-positive follicular lymphoma of Grade 1, 2 or 3a requiring therapy were enrolled in a two-stage, open-label, multicenter, randomized trial. Of all randomized patients, the median age was 57 years, median BSA was 1.83 m2, 53% were females, and 86% were Caucasian, 45% had high risk or 34% had intermediate risk FLIPI score and 54% had Ann Arbor Stage IV disease at study entry. Ninety percent of patients completed all 8 cycles of induction treatment and 70% of patients completed 20 cycles of maintenance treatment. Median treatment duration was 27.1 months in both groups. The median number of cycles received was 20 in both groups.

The PK results for the primary endpoint in Stage 1, rituximab C_{trough} at Cycle 7 (i.e., 21 days after Cycle 7 rituximab administration), demonstrated that Rituxan Hycela 1,400 mg/23,400 Units was non-inferior compared with rituximab at 375 mg/m2 in patients receiving induction treatment. The efficacy results for Rituxan Hycela were comparable with rituximab and are presented in Table 4.

**Table 4 Efficacy Results for SABRINA Trial**

<table>
<thead>
<tr>
<th></th>
<th>Rituxan Hycela</th>
<th>Rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Response Rate at End of Induction</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of responders (CR/CRu, PR)</td>
<td>173</td>
<td>174</td>
</tr>
<tr>
<td>Overall response (CR/CRu, PR) rate (% [95% CI])</td>
<td>84% [79;89]</td>
<td>85% [79;90]</td>
</tr>
<tr>
<td>Difference in overall response ratesb [95% CI]</td>
<td>-0.5% [-7.7;6.8]</td>
<td></td>
</tr>
<tr>
<td>Number of complete responders (CR/CRu)</td>
<td>66</td>
<td>66</td>
</tr>
<tr>
<td>Complete response (CR/CRu) rate (% [95% CI])</td>
<td>32% [26;39]</td>
<td>32% [26;39]</td>
</tr>
<tr>
<td>Difference in complete response ratesb [95% CI]</td>
<td>0.0% [-9.3;9.3]</td>
<td></td>
</tr>
</tbody>
</table>

| **Overall Response Rate at End of Maintenance** |                |           |
| Number of patients treated in maintenance (n) | 172            | 178       |
| Number of responders (CR/CRu, PR)  | 134            | 139       |
| Overall response (CR/CRu, PR) rate (% [95% CI]) | 78% [71;84]    | 78% [71;84]|
| Difference in overall response ratesb [95% CI] | -0.2 [-9.2;8.8] |           |
| Number of complete responders (CR/CRu) | 87             | 100       |
| Complete response (CR/CRu) rate (% [95% CI]) | 51% [43;58]    | 56% [49;64]|
| Difference in complete response ratesb [95% CI] | -5.6 [-16.4;5.2] |           |

| **Progression-free survival** |                |           |
| Number of patients with event | 50 (24%)       | 57 (28%)  |
| Hazard Ratio [95% CI] (unstratified Cox model) | 0.84 [0.57;1.23] |           |

Reference ID: 4108798
MabEase (Diffuse Large B Cell Lymphoma)

Patient Population
The trial population was patients aged 18-80 (both inclusive) with untreated histologically confirmed CD20-positive DLBCL according to the World Health Organization (WHO) classification system. Patients need an IPI score of 1-5 or a score of 0 with bulky disease defined as one lesion ≥ 7.5 cm. Patients with primary CNS lymphoma, blastic variant of mantle cell lymphoma, evidence of transformation to Burkitt’s lymphoma, primary mediastinal DLBCL, primary effusion lymphoma, primary cutaneous DLBCL or primary DLBCL of the testis were excluded. Also excluded was transformed lymphoma or follicular lymphoma IIIB. Patients with prior therapy for DLBCL except biopsy or local irradiation were also excluded.

Trial Design
This was a phase IIIb, multi-center, international, open label trial in patients randomized 2:1 to rituximab SC + CHOP and rituximab IV + CHOP. Patients were stratified by age (<60 and ≥60 years), IPI risk category (low, low-intermediate, high-intermediate, and high), and chemotherapy regimen (CHOP-21 and CHOP-14). Patients were to receive 8 cycles of rituximab with 6 or 8 cycles of CHOP-21 or 6 or 8 cycles of CHOP-14. Response was assessed approximately one month after day 1 of the last cycle. An interim staging was done after 4 cycles. All patients received the first cycle with rituximab IV. The trial schema is displayed in Figure 2.

The primary objective of the study is to estimate the efficacy of rituximab SC or IV in combination with CHOP as measured by CR/CRu approximately one month after the end of rituximab-based treatment. The primary endpoint of the study is complete response rate (CR/CRu) based on investigator’s assessment according to the international working group response criteria at the end of the induction treatment. The secondary endpoints are PFS, EFS, DFS, and OS. PFS, EFS, and OS are defined similarly to BO22334 study. DFS is defined as the time from the date of the initial CR/CRu until the date of progression or death from any cause.
Efficacy Results
Of all randomized patients, 54% of patients were male, the median age was 64 years, 79% Caucasians, median BSA was 1.83 m2, 31% low risk or 30% low intermediate risk IPI score, 24% high intermediate risk, or 15% high risk IPI score and 42% of patients had Ann Arbor Stage IV disease. A total of 470 patients (82%) received 8 cycles of treatment. Median duration of exposure to treatment was 4.9 months in both treatment groups. The median number of administrations/cycles (Rituxan Hycela or rituximab) was 8 in both groups.

The efficacy results for Rituxan Hycela were comparable with rituximab and are presented in Table 5. The median observation time was approximately 28 months.

Table 5 Efficacy Results for MabEase Trial

<table>
<thead>
<tr>
<th></th>
<th>Rituxan Hycela n=381</th>
<th>Rituximab n=195</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete Response Rate (CR/CRu)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of responders (CR/CRu achieved) *</td>
<td>179</td>
<td>82</td>
</tr>
<tr>
<td>Response rate (%, [95% CI])</td>
<td>47% [42;52]</td>
<td>42% [35;49]</td>
</tr>
<tr>
<td>Difference in response rates [95% CI] b</td>
<td>4.9% [-3.6;13.5]</td>
<td></td>
</tr>
<tr>
<td><strong>Progression-free survival c</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients with event</td>
<td>104 (27%)</td>
<td>44 (23%)</td>
</tr>
<tr>
<td>Hazard Ratio [95% CI] (unstratified Cox model)</td>
<td>1.22 [0.85;1.73]</td>
<td></td>
</tr>
<tr>
<td><strong>Overall survival d</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients with event</td>
<td>63 (17%)</td>
<td>29 (15%)</td>
</tr>
<tr>
<td>Hazard Ratio [95% CI] (unstratified Cox model)</td>
<td>1.08 [0.70;1.68]</td>
<td></td>
</tr>
</tbody>
</table>

a Four patients in the Rituxan Hycela group and 1 patient in the rituximab group had their response downgraded due to their bone marrow data.

b Difference in response rates (Rituxan Hycela minus rituximab).

c Progression-free survival is defined as the time from randomization to the first occurrence of disease progression or relapse, or death from any cause.

d Overall survival is defined as the time from randomization until death from any cause.
SAWYER (Chronic Lymphocytic Leukemia)

Patient Population
Patients in this trial were ≥18 years of age and had CD20-positive B cell CLL confirmed according to International Workshop on CLL (iwCLL) criteria and required treatment according to iwCLL criteria. Patients with transformation to an aggressive B-cell malignancy such as DLBCL, Richter’s syndrome or prolymphocytic leukemia were excluded. Patients with previous treatment for CLL were excluded from part 2.

Trial Design
For part 2 patients with untreated CLL were randomized 1:1 to rituximab IV (cohort B) or rituximab SC (cohort C). Cohort A was part 1 and is not discussed here. Treatment was rituximab 375 mg/m² for the first cycle for both treatment arms combined with FC followed by rituximab IV 500 mg/m² + FC in the rituximab IV arm and rituximab 1,600 mg SC + FC in the rituximab SC arm. Cycles were every 28 days for 6 cycles. Patients could receive FC either orally or intravenously. For fludarabine, the IV dose was 25 mg/m² IV days 1-3 or the oral regimens of 24 mg/m² days 1-5 or 30-40 mg/m² on day 1-3. Cyclophosphamide was 250 mg/m² IV on days 1-3 or 150 mg/m² orally on days 1-5 or 200-250 mg/m² orally on days 1-3. Patients were stratified by Binet stage (A, B or C) and route of chemotherapy (IV or oral). The schema for the trial is displayed in Error! Reference source not found.

Figure 3 Trial Design in CLL (SAWYER)

The primary objective of the BO25341/SAWYER study is non-inferiority in Cₜₐ₉₀ between rituximab SC over rituximab IV arm. Please refer to section Error! Reference source not found. for the results. The secondary endpoint is response rate including complete response (CR), complete response with incomplete bone marrow recovery (CRi), and partial response (PR).

Efficacy Results
A total of 176 patients with previously untreated CLL were enrolled in a multicenter, two-part randomized, open-label study. The patient population comprised 96% Caucasians, 65% males,
a median age of 60 years (range, 25-78 years), median BSA of 1.9 m², 62% had Binet Stage B disease and 93% had typical CLL characterization.

The PK results demonstrated that Rituxan Hycela 1,600mg /26,800 Units mg rituximab serum rituximab $C_{\text{trough}}$ level was non-inferior compared with rituximab at 500 mg/m² in patients receiving induction treatment.

An additional outcome measure in Part 2 was investigator-assessed response rates. Overall response rate was 85% (95% CI: 76; 92) in Rituxan Hycela and 81% (95% CI: 71; 88) in the rituximab groups. Overall the response rates were comparable between Rituxan Hycela and rituximab with a difference in response rate of 4.6% (95% CI: -7.2; 16.3). Complete response rate point estimates were 26% (95% CI: 17; 37) and 33% (95% CI: 23; 44) in the Rituxan Hycela and rituximab groups, respectively.

**Conclusions on the Substantial Evidence of Effectiveness:** Substantial evidence of effectiveness for all of the proposed indications was established based on demonstration of (a) non-inferior rituximab $C_{\text{trough}}$ levels for Rituxan Hycela 1,400 mg/23,400 Units compared to a rituximab product 375 mg/m² administered intravenously, (b) non-inferior rituximab $C_{\text{trough}}$ levels for Rituxan Hycela 1,600 mg/26,800 Units compared to a rituximab product 500 mg/m² administered intravenously, and (c) descriptive efficacy results from 3 randomized clinical trials (SABRINA, MabEase, and SAWYER) which demonstrated comparable efficacy between Rituxan Hycela and a rituximab product administered intravenously.

8. **Safety**

*Source: Clinical Review*

**Clinical Team Recommendation:** Approval

The safety population for Rituxan Hycela consisted of 892 patients in four controlled trials with exposures ranging from a single injection up to 27 months of treatment.

The population included 382 patients with follicular lymphoma (FL), 369 patients with diffuse large B-cell lymphoma (DLBCL), and 141 patients with chronic lymphocytic leukemia (CLL). The population was aged 18–85 years (with a median age of 60 years), 53% male and 47% female. Most of the patients were Caucasians (84%).

In the SABRINA trial, patients with FL received a full dose of a rituximab product by intravenous infusion, followed by Rituxan Hycela (1,400 mg rituximab/23,400 Units hyaluronidase human), in combination with chemotherapy for up to 7 doses (i.e. total of 8 doses of induction treatment), or as monotherapy for up to 12 doses (maintenance treatment). Patients with DLBCL in the MabEase trial received a full dose of a rituximab product by intravenous infusion, followed by Rituxan Hycela (1,400 mg rituximab/23,400 Units hyaluronidase human), given in combination with chemotherapy for up to 7 doses (i.e. up to a total of 8 doses). Patients with CLL on part 2 of the SAWYER trial received a full dose of a rituximab product by intravenous infusion, followed by Rituxan Hycela (1,600 mg
Cross Discipline Team Leader Review
BLA 761064 Rituxan Hycela (fixed-dose combination of rituximab and hyaluronidase human)

rituximab/26,800 Units hyaluronidase human) for up to 5 doses, in combination with fludarabine and cyclophosphamide (i.e. total of 6 doses).

The most common adverse reactions (≥20%) of Rituxan Hycela observed in patients with FL in the SABRINA trial were: infections, neutropenia, nausea, constipation, cough, and fatigue.

The most common adverse reactions (≥20%) of Rituxan Hycela observed in patients with DLBCL in the MabEase trial were: infections, neutropenia, alopecia, nausea, and anemia.

The most common adverse reactions (≥20%) of Rituxan Hycela observed in patients with CLL on part 2 of the SAWYER trial were: infections, neutropenia, nausea, thrombocytopenia, pyrexia, vomiting, and injection site erythema.

**SABRINA (Follicular Lymphoma).** Treatment in this trial consisted of up to 8 cycles of induction treatment followed by 12 cycles of maintenance treatment. The mean number of cycles overall was 16.8, this was balanced between the two arms. A total of 1.4% on the rituximab IV arm died within 30 days of last dose compared to 2.0% on the rituximab SC arm. The common nonfatal SAEs on the rituximab SC arm were pneumonia and febrile neutropenia. There was not a nonfatal SAE with a difference in overall incidence greater than 2% between the two arms. More patients on the rituximab SC arm discontinued treatment secondary to an adverse event (7.1% on rituximab SC compared to 4.8% on rituximab IV) and disease progression (14.2% on rituximab SC compared to 11.9% on rituximab IV). For nonfatal treatment-emergent adverse events (TEAE) that occurred in 10% or greater or either arm, 5 had a difference in overall incidence ≥5%. Of these, nausea, pneumonia, injection site erythema and cough were more common on the rituximab SC arm and urinary tract injection was more common the rituximab IV arm. In evaluating TEAE with a difference in incidence >4%, the majority are more common of the rituximab IV arm.

**MabEase (Diffuse Large B Cell Lymphoma).** Treatment in this trial consisted of 8 cycles of rituximab with a maximum of 8 cycles of CHOP chemotherapy. The mean number of cycles was 7.4 for rituximab and 6.7 for rituximab SC. This was balanced between the two arms. For deaths within 30 days, 3.9% on the rituximab IV arm died compared to 3.5% on the rituximab SC arm. For the SAE of febrile neutropenia there was a 2% higher incidence on the rituximab SC arm (13.0% on rituximab SC compared to 10.8% on rituximab IV). The two most common reasons for withdrawal from study treatment was adverse event and progressive disease both of which were more common on the rituximab IV arm. For nonfatal TEAE that occurred in 5% of patients on the rituximab SC arm, none had a difference >5% between the two arms. The TEAE of grade 3 and 4 neutropenia was approximately 5% higher on the rituximab SC arm.

**SAWYER (Chronic Lymphocytic Leukemia).** Treatment in this trial consisted of 6 cycles of rituximab combined with CVP. The mean number of cycles was 5.4 on rituximab IV and 5.6 on rituximab SC. There were no deaths within 30 days of last dose in part 2 of this trial. The SAE of febrile neutropenia was increased 6.1% on the rituximab SC arm (10.6% on rituximab SC compared to 4.5% on rituximab IV). More patients on the rituximab SC arm withdrew from treatment secondary to an adverse event (10.6% on rituximab SC compared to 7.9% on rituximab IV). Nonfatal TEAE that occurred in >10% on either arm with a difference in all
grades greater than 5% were neutropenia, pyrexia, injection site erythema, injection site pain, and erythema which were greater on the rituximab SC arm and asthenia and anemia which were greater on the rituximab IV arm.

**Neutropenia and Infections.** Across the three trials (SABRINA, MabEase, and SAWYER), grade 3 and 4 neutropenia and the TEAEs and SAEs in the System Organ Class (SOC) of infections and infestations were increased. Grade 3 or 4 neutropenia was increased 6.9% in SABRINA, 2.1% in MabEase, and 5.3% in SAWYER. TEAE in the SOC of infections and infestations was increased 4.1% in SABRINA, 6.7% in MabEase, and 7.0% in SAWYER. Nonfatal SAEs in the SOC infections and infestations was increased across the trials as well, 5.2% in SABRINA, 6.1% in MabEase, and 1.7% in SAWYER.

**CDTL Comment:** The text below is taken from the Applicant’s ODAC briefing document.

**Post-Marketing Experience (Ex-US) with Rituximab (MabThera) for SC injection.** Rituximab (MabThera) 1400 mg solution for SC injection was first approved in the European Union (EU) on 21 March 2014, for the treatment of patients with Non-Hodgkin Lymphoma and has since been approved in approximately 50 other countries. In May 2016, MabThera 1600 mg for SC injection gained its first approval in the EU for the treatment of patients with CLL. The Applicant noted 34,179 patients had been exposed to rituximab SC 1400 mg compared with approximately 4.4 million exposed to rituximab IV. Post-marketing information with rituximab SC 1600 mg in CLL is currently not available as it was recently approved in the EU and is under review elsewhere globally. Overall, the observations from the post-marketing setting with rituximab SC 1400 mg in NHL were consistent with the safety profile established in the clinical trials. No new safety signals have emerged from the post-marketing experience with rituximab SC, and the overall safety profile of rituximab SC remains consistent with that of RITUXAN.

9. **Advisory Committee Meeting**

FDA requested discussion at the Oncologic Drugs Advisory Committee (ODAC) to obtain feedback and insights on the acceptability of the above development approach to support the approval of Rituxan Hycela for the same oncologic indications as intravenous rituximab (Rituxan).

The ODAC meeting occurred on March 29, 2017. After FDA and Applicant presentation, and clarifying questions to FDA and Applicant, and discussion, ODAC voted on the following question:

**VOTE:** Is the benefit-risk favorable for the above drug product for the proposed indications in follicular lymphoma (FL), diffuse large B cell lymphoma (DLBCL), and chronic lymphocytic leukemia (CLL).

**YES: 11**  **NO: 0**  **ABSTAIN: 0**

The committee unanimously voted in favor of the benefit-risk for biologics license application (BLA) 761064, rituximab and hyaluronidase human injection for subcutaneous use for the
proposed indications in follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), and chronic lymphocytic leukemia (CLL).

One committee member noted concern about a fixed-dose being used for those patients who have a small body surface area relative to the difference in area under the curve and suggested the product be dose adjusted for those with a smaller body surface area. Committee members commented that the data presented by the sponsor was compelling, and availability of the subcutaneous formulation will allow patients to receive rituximab treatment in approximately five minutes versus 1-2 hours for the intravenous product. The committee members also stated that there would be a role for the subcutaneous formulation in clinical practice.

10. Pediatrics

Rituxan Hycela (rituximab and hyaluronidase human) is exempt from pediatric study requirements described in 21 CFR 314.55. FDA granted Orphan Drug Designation for rituximab and hyaluronidase for the following indications (designation date): follicular lymphoma (22 August 2016), diffuse large B cell lymphoma (7 September 2016), and chronic lymphocytic leukemia (22 August 2016).

11. Other Relevant Regulatory Issues

- Application Integrity Policy (AIP): No issues.
- Exclusivity or Patent Issues of Concern: No issues.
- Financial Disclosures: In accordance with 21 CFR 54.4, the applicant submitted the required financial disclosure requirement and certification for the following clinical trials: Study BO22334/SABRINA, Study MO28107/MabEase, Study BO25341/SAWYER, Study MO28457/PrefMab and Study BP22333/Spark Thera.
- Other GCP Issues: None
- Office of Scientific Investigation (OSI) Audits: Two clinical sites (Drs. Mercadal Vilchez and Tani) were selected for inspection. Additionally the contract research organization (CRO), responsible for site monitoring and monitoring record retention for Study MO28107 and sponsor, Genentech Inc. (South San Francisco, CA), were inspected.

The preliminary classification for the inspections of Drs. Mercadal Vilchez, (CRO) and sponsor (Genentech, Inc., a Member of the Roche Group) is No Action Indicated (NAI). The preliminary classification for Dr. Tani is Voluntary Action Indicated (VAI) based on communications with the field investigator. The study data derived from these clinical sites are considered reliable in support of the requested indication.

- Other outstanding regulatory issues: None
12. Labeling

The following are the key labeling recommendations for the Rituxan Hycela prescribing information:

Highlights
- Rituximab and hyaluronidase human are both considered as active ingredients as per 21 CFR 210.3(a)(7).  
- Recommended terminology would be “combination of rituximab and hyaluronidase human”.

Box Warning
- Recommend to have Severe Mucocutaneous Reactions, Hepatitis B Virus Reactivation, and Progressive Multifocal Leukoencephalopathy for the Box Warning. Hepatitis B Reactivation and Progressive Multifocal Leukoencephalopathy are also Box Warnings for other anti-CD20 monoclonal antibody products, Rituxan, Arzerra, and Gazyva. Box Warning for Fatal Infusion Reactions is not recommended because Rituxan Hycela is not administered intravenously.

Section 1: Indications and Usage
- Follicular lymphoma was used instead of indolent non-Hodgkin lymphoma (iNHL), because iNHL is not a clearly defined indication and is also too broad, and the SABRINA clinical trial was conducted in patients with follicular lymphoma. The indication did not include “CD20-positive” because assessment for CD20 expression is part of the standard diagnostic evaluation for patients with FL, DLBCL, and CLL.
- Limitation of use was added for the following conditions:
  i. Initiate treatment with Rituxan Hycela only after patients have received at least one full dose of a rituximab product by intravenous infusion
  ii. Rituxan Hycela is not indicated for the treatment of non-malignant conditions.

Section 2: Dosage and Administration
- All patients must first receive at least one full dose of a rituximab product by intravenous infusion without experiencing severe adverse reactions before starting treatment with Rituxan Hycela.

  *CDTL Comment: The randomized clinical trials used a non-US-licensed rituximab product for the comparator arms, hence, the comparator product and the rituximab product to be administered by intravenous infusion prior Rituxan Hycela, would be identified as “rituximab product” or “rituximab product by intravenous infusion”.*

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3 *Active ingredient* means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals.

4 The applicable regulations would be 21 CFR 300.50 Fixed-combination prescription drugs for humans. For labeling purposes, the term “combination” is recommended.
Section 5: Warnings and Precautions (W&P)
- General structure follows that for Rituxan prescribing information, with the following changes:
  i. Removal of Warning and Precaution items (b)(4)
  ii. Removal of (b)(4), and addition of new W&P on Hypersensitivity Reactions and Other Administration Reactions, which cover systemic and local cutaneous reactions.

Section 8: Use in Specific Populations
- Pregnancy and Lactation Labeling Rule (PLLR) applied.

Section 14: Clinical Studies
- Descriptive approach used to describe efficacy results for SABRINA, MabEase, and SAWYER clinical trials. P-values are not presented because the trials were not designed for efficacy hypothesis testing.
- PrefMab trial results were described in Section 14.4 Patient Experience to describe patient preference results.

Labeling Consults
- Proprietary name: On 10 March 2017, OSE/DMEPA concluded that the proposed proprietary name, Rituxan Hycela, was found conditionally acceptable.
- Patient labeling/Medication guide: DMPP and OPDP participated in the labeling discussions, and reviewed the medication guide (MG).
- Carton and immediate container labels: OBP and DMEPA participated in the labeling discussions and provided recommendations for the container labels, carton and insert labeling.

13. Postmarketing Recommendations
- Risk Evaluation and Management Strategies (REMS): The review teams did not identify a need for REMS to ensure the safe use of Rituxan Hycela.
- Postmarketing Requirements (PMRs) and Commitments (PMCs): No PMRs or PMCs were requested.
- The Applicant will conduct routine pharmacovigilance.

14. Recommended Comments to the Applicant
None
15. Patient Experience Data

PrefMab Clinical Trial

The PrefMab (MO28457) study was designed to evaluate patient preference (measured by using the Patient Preference Questionnaire [PPQ]) of subcutaneous (SC) administration of rituximab versus intravenous (IV) rituximab. This study also evaluated patient satisfaction as secondary endpoints using two patient-reported outcome (PRO) instruments, Cancer Therapy Satisfaction Questionnaire (CTSQ) and Rituximab Administration Satisfaction Question (RASQ).

Previously untreated adult patients outside of the United States with CD20+ diffuse large B-cell lymphoma (DLBCL) or CD20+ follicular non-Hodgkin’s lymphoma (FL) Grades 1, 2, or 3a were randomized to receive a standard chemotherapy regimen (CHOP, CVP, or bendamustine) and either RITUXAN HYCELA 1,400mg/23,400 Units at Cycles 2–4 (after the first cycle with intravenous rituximab) or a rituximab product by intravenous infusion at Cycles 1–4. After the fourth cycle, patients were crossed over to the alternative route of administration for the remaining 4 cycles. After Cycle 8, 477 of 620 patients (77%) reported preferring subcutaneous administration of RITUXAN HYCELA over intravenous rituximab and the most common reason was that administration required less time in the clinic. After Cycle 8, 66 of 620 patients (11%) preferred rituximab intravenous administration and the most common reason was that it felt more comfortable during administration. Forty eight of 620 patients (7.7%) had no preference for the route of administration. Twenty nine subjects of 620 (4.7%) received cycle 8 but did not complete the preference questionnaire.

Multiple issues were identified with interpretation of the RASQ and CTSQ results. These include issues regarding content validity and concerns with timing of administration. In addition, the concept of satisfaction may not be interpreted consistently by health care providers and patients.
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/s/

ROMEO A DE CLARO
06/07/2017