

FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Oncologic Drugs Advisory Committee (ODAC) Meeting

Sheraton College Park North Hotel
4095 Powder Mill Road, Beltsville, Maryland
March 29, 2017

DRAFT QUESTION

BLA 761064
rituximab and hyaluronidase injection
for subcutaneous use
APPLICANT: Genentech, Inc.

PROPOSED INDICATIONS:

- (1) For the treatment of patients with relapsed or refractory, follicular lymphoma (FL) as a single agent;
 - (2) For previously untreated FL in combination with first line chemotherapy and, in patients achieving a complete or partial response to rituximab/hyaluronidase for subcutaneous injection in combination with chemotherapy, as single-agent maintenance therapy;
 - (3) For non-progressing (including stable disease), FL as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy;
 - (4) For the treatment of patients with previously untreated diffuse large B-cell lymphoma (DLBCL) in combination with cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) or other anthracycline based chemotherapy regimens; and
 - (5) In combination with fludarabine and cyclophosphamide (FC), for the treatment of patients with previously untreated and previously treated chronic lymphocytic leukemia (CLL).
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The Applicant (Genentech, Inc.) submitted a biologic license application (BLA) to support approval for a co-formulation of rituximab and hyaluronidase for the above proposed indications.

The co-formulation of rituximab and hyaluronidase (rituximab SC) is subcutaneously administered, which offers patients a different route of administration compared to intravenous rituximab (rituximab IV).

The clinical development of rituximab SC was based on a pharmacokinetic bridging program to intravenously administered rituximab. Two different doses of rituximab SC were developed: a 1400 mg subcutaneous (SC) dose to compare to the 375 mg/m² intravenous (IV) rituximab dose and a 1600 mg SC dose to compare to the 500 mg/m² IV rituximab dose. This submission contains 5 clinical trials listed in Table 1.

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Table 1 Clinical Trials Submitted

Protocol number /name	Patient Population	Design
1. BO22334/SABRINA	FL	Phase 3, 2 stage trial, stage 1 with more intensive PK sampling of 1400 mg SC dose
2. MO28107/MabEase	DLBCL	Phase 3b randomized trial
3. BO25341/SAWYER	CLL	Phase 1b Stage 1: dose-finding single SC injection Stage 2: Dose confirmation of 1600 mg SC dose
4. BP22333/ SparkThera	FL	Phase 1b Stage 1: dose finding single SC Injection Stage 2: dose confirmation 1400 mg in maintenance setting
5. MO28457/PrefMab	FL/DLBCL	Phase 3b randomized cross over trial

Clinical Pharmacology and Pharmacokinetic (PK) Bridging. A PK-bridging approach was used to establish the safety and effectiveness of a rituximab and hyaluronidase product intended for subcutaneous route of administration. A notable feature of the Applicant's approach was the targeting of a trough concentration (C_{trough}) for the rituximab SC product that would be at least as high as that achieved with the rituximab IV product. Additional changes include the use of a fixed-dose regimen instead of BSA (body surface area)-based dosing, and the addition of hyaluronidase to facilitate absorption and administration.

FDA verified that rituximab SC achieved equal or higher C_{trough} relative to rituximab IV. The addition of hyaluronidase 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.

Efficacy and Safety. The clinical trials were not designed for efficacy hypothesis testing, however, the efficacy results between rituximab SC and rituximab IV are comparable. There were no major differences in safety findings between rituximab SC and rituximab IV, with the exception of increase in administration site-related local reactions with rituximab SC. In addition, exposure-response analyses for safety did not show significant relationships between C_{trough} and any of the safety endpoints evaluated.

Patient Preference. Results based on the patient preference questionnaire (PPQ) instrument from the PrefMab clinical trial, demonstrate that 80% of the patients preferred rituximab SC over rituximab IV.

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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)?

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