

## **EXECUTIVE SUMMARY**

The tositumomab therapeutic regimen consists of a two-part administration of the tositumomab antibody administered 7 to 14 days apart. The first step is administration of the dosimetric dose, consisting of 450 mg of unlabeled tositumomab antibody intravenously over one hour followed by 35 mg of tositumomab labeled with 5 mCi of <sup>131</sup>Iodine. A series of at least 5 gamma camera scans are obtained over the next 5-7 days to derive the dose of <sup>131</sup>Iodine antibody required to deliver 75 cGy to the whole body. The therapeutic dose is administered as the second step, consisting of sequential infusions of 450 mg of unlabeled tositumomab antibody followed by 35 mg of tositumomab labeled with a patient-specific dose of <sup>131</sup>Iodine.

The development plan for the tositumomab therapeutic regimen consisted of a single major efficacy trial (RIT-II-004) supported by evidence of anti-tumor activity in a single Phase 1, several Phase 2 trials and additional safety information obtained from a large expanded access experience. RIT-II-004 was a single arm, multicenter trial conducted in patients with chemotherapy-refractory, CD20 positive, low grade and follicular non-Hodgkin's lymphoma. The original goal of the major efficacy trial was to demonstrate that the tositumomab therapeutic regimen had an effect on the surrogate endpoint of response rate. The sponsor intended to show that the tositumomab therapeutic regimen could provide an overall response rate  $\geq 30\%$ , a complete response rate of  $\geq 10\%$ , and a median duration of response of 8 months in patients whose disease was no longer responding chemotherapy or who had short (<6 months) response durations. In order to put these data in perspective, the sponsor was urged to conduct a controlled trial.

In response to this request, the sponsor noted that, historically, objective response rates and the durations of response decrease with each subsequent chemotherapy. Therefore, the trial was designed also to incorporate comparisons of the response rate and duration with the tositumomab therapeutic regimen to that achieved with the most recent chemotherapy regimen. Using this design, activity (durable tumor responses) would be demonstrated if a higher proportion of patients achieved responses and/or more durable responses after treatment with the tositumomab therapeutic regimen than they had achieved with an adequate trial (as least two cycles) of a standard chemotherapeutic regimen (defined in the protocol as the last qualifying chemotherapy [LQC]). To minimize the potential effects of bias in assessing the results in this open label, single arm trial, the response and duration of response to the LQC and to the tositumomab therapeutic regimen were determined by an independent review panel that was masked to the investigator's assessment of response. Masking to the treatment regimen was unlikely to have been maintained since the frequency and type of evaluations for response were uniform (specified in the protocol) following the tositumomab therapeutic regimen whereas the same evaluations for the LQC were performed according to the individual treating physician's standard medical practice.

This study design, which utilized the patient's response to recent prior chemotherapy as an historical control, was identified by the Biological Response Modifiers Advisory Committee (BRMAC) as an acceptable study design for drugs intended to treat patients with "chemotherapy-refractory" NHL and as an acceptable alternative to a concurrently controlled trial, using best standard of care or alternative therapy of physician choice, as requested by FDA. FDA believes that this historically controlled trial design has a potential design flaw. Based on the selection criteria for the population (i.e., patients with refractory disease), a successful result could have been obtained with a potentially unacceptably low response rate and/or responses of very limited durability (e.g., 32

days). Given that the toxicity profile (high rate and prolonged nature of toxicity, notably hematologic toxicity), the time with toxicity could exceed the time in response in this study design. This trial design flaw was noted in correspondence with the sponsor.

**The results of the major efficacy trial demonstrated a significantly higher proportion of patients with a longer duration of response following iodine I 131 tositumomab therapy as compared to the most recent standard chemotherapy regimen ( $p < 0.001$ , McNemar’s test). Treatment with the tositumomab therapeutic regimen yielded an overall response rate of 47%, a median duration of response of 11.7 months and a complete response rate (CR plus CCR) of 20%. As shown in the table below, response rates ranging from 47% to 68% with a median duration of approximately one year and complete response rates ranging from 20% to 34% were observed in clinical trials conducted in patients with previously treated, follicular and low grade NHL. Summary of Efficacy Outcomes by Study**

Study Number	Median # of Prior Chemotherapy Regimens (range)	Overall Response Rate (95% CI)	Complete Response Rate (CR +CCR)	Median Duration of Response (yrs)	Duration of Response 25 <sup>th</sup> & 75 <sup>th</sup> quartiles (yrs)
<b>Primary Efficacy Studies</b>					
RIT-II-004 (N=62)	4 (2-13)	46% (33%, 59%)	20%	1.0	0.3, 3.9
CP-97-012 (N = 43)	4 (1–11)	63% (47%, 77%)	30%	1.3	0.8; NR
<b>Supportive Studies</b>					
RIT-I-000 (N=59)	3 (1-11)	48% (34%, 61%)	27%	1.0	0.6; 3,8
RIT-II-001 (N = 47)	4 (1–8)	49% (34%, 64%)	26%	1.2	0.4; 4.9
RIT-II-002 (N = 42)	2 (1–4)	55% (39%, 70%)	33%	NR	0.4; NR

The toxicities of this product are related both the radioisotope (131-Iodine) component and to the murine monoclonal antibody. The toxicities which appear due to the radioisotope include marrow suppression with a median time to nadir of 4 to 6 weeks and duration of nadir (NCI CTC grade 3-4) of approximately 4-6 weeks in 64%, 54%, and 29% of the patients (neutropenia, thrombocytopenia, and anemia, respectively). In addition, secondary leukemias, solid tumors and myelodysplasia have been observed. Finally, hypothyroidism has been observed with a cumulative rate of 30% at 5 years and 45% at 7 years across the clinical studies. In addition, there are toxicities which appear

to be due to the tositumomab (antibody) component. These include infusion reactions, which occur in approximately 20% of patients and can be severe, gastrointestinal toxicity due to binding in lymphocytes in the GI tract which is both acute (antibody mediated), a decrease in circulating CD20+ cells, and delayed (131-Iodine), and the development of an immune response to the murine antibody, which reaches a cumulative incidence of 20% at approximately one year (as lymphocyte recovery occurs). In addition, there may be an interaction between the lymphopenia due to tositumomab and the neutropenia due to 131-Iodine to result in an increased risk of infection (up to 55% in one study).

1. FDA will seek advice as to whether the durable responses observed, in the face of the toxicities described, are likely to predict clinical benefit for this agent in patients with low grade and follicular NHL, with or without transformation, where the disease is refractory to chemotherapy.
2. At the time of the original submission of BLA 125011, several of the trials listed above were ongoing. In responding to FDA's requests for additional safety and efficacy information, the final study report for CP97-012 was filed along with other clinical data. This is the only study that assesses the activity of the tositumomab therapeutic regimen in patients whose disease is refractory to, or only transiently responsive to, Rituximab. In this study, the overall response rate in the entire study was 63% with a median duration of response of 1.3 years. The requested indication is in patients with follicular lymphoma, a subset of the patients enrolled. In this subpopulation, the activity was similar (ORR 63%, median duration of response 2.1 years). FDA will seek the committee's advice as to whether the data from this study, supported by the activity in other studies in patients with chemotherapy-refractory disease, are adequate and are reasonably likely to predict clinical benefit for the treatment of patients with follicular NHL that has relapsed following chemotherapy and is refractory to Rituxan.
3. FDA will seek the Committee's advice regarding the value of the findings of the retrospectively identified subset of responding patients whose time to disease progression has exceeded one year, in establishing clinical benefit. FDA notes that these responding patients, differ from the general study population in several prognostic factors, have particularly long-lasting responses (median response duration 4.9 years). In particular, FDA seeks advice on the design (e.g., prospective, randomized trial) and appropriate control arm to establish whether treatment with the tositumomab therapeutic regimen reliably produces very durable (>1 year) responses that would support promotional claims for this effect.
4. FDA will seek the Committee's advice on the types of studies needed to further assess the safety profile of this agent, particularly with respect to delayed toxicities such as MDS and secondary malignancies, hypothyroidism, and HAMA.