

BIORESEARCH MONITORING INSPECTION RESULTS

Inspections of five clinical sites were performed in support of BLA 99-0813 for Protocol RIT-II-004 entitled “Multicenter, Pivotal Phase III Study of Iodine-131 Anti-B1 Antibody (Murine) Radioimmunotherapy for Chemotherapy-Refractory Low-Grade B-Cell Lymphomas and Low-Grade Lymphomas that have Transformed to Higher Grade Histologies.” In addition one of the sites (University of Nebraska) was also inspected for Protocol RIT-II-001, entitled “Multicenter, Phase II Dosimetry/Validation Study of 131Iodine-AntiB1(murine) Radioimmunotherapy for Chemotherapy-Refractory Low-Grade B-Cell Lymphomas and Low-Grade Lymphomas that have Transformed to Higher Grades” after the sponsor reported that data was missing. The inspections were conducted in accordance with CPGM 7348.811, the Inspection Program for Clinical Investigators.

Specific questions concerning the studies were included. Data audits were performed at the following five sites:

Site	Investigator	Form 483	Classification
Kaiser - Vallejo	Dr. Fehrenbacher	No	VAI
Stanford University	Dr. Knox	Yes	VAI
University of Michigan	Dr. Kaminski	Yes	VAI
University of Washington	Dr. Press	Yes	VAI
University of Nebraska	Dr. Vose	Yes	VAI

INSPECTIONAL FINDINGS

1. Kaiser–Vallejo / Dr. Fehrenbacher and Stanford University / Dr. Knox

For subject 001, the diagnosis of mantle cell lymphoma was confirmed after enrollment at Kaiser. This subject was referred to Dr. Knox, at Stanford University, for administration of the investigational product. As a result of this protocol violation, the subject was inappropriately treated with a test article for which he was not eligible.

At Stanford University, the therapeutic doses for subjects 001 and 002 were calculated incorrectly.

Stanford University study records did not contain a signed consent form approved by the IRB.

2. University of Michigan / Dr. Kaminski

Staff did not perform gamma camera background counts according to protocol.

Six subjects received pre-treatment doses of potassium iodide on the day of infusion of the test article, rather than 24 hours prior to that time, as specified in the protocol.

The residual activity in the infusion set was not measured with a dose calibrator, as required by protocol.

3. University of Washington / Dr. Press

Three subjects received erroneously high doses: 006 and 007 because of failure to lower the dose for thrombocytopenia; 005 due to an infusion error.

4. University of Nebraska / Dr. Vose

Staff did not perform gamma camera background counts according to protocol.

Inspectional Summary Statement

The results of bioresearch monitoring inspections indicate that the deviations are not substantive, with the exceptions noted, and that the submitted data can be considered reliable and accurate.

ADDITIONAL INSPECTIONS PERFORMED

Inspections of two clinical investigators were performed in support of BLA STN 125011 for Protocol CP-98-020, EXPANDED ACCESS STUDY OF IODINE-131 ANTI-B1 ANTIBODY FOR RELAPSED / REFRACTORY LOW-GRADE AND TRANSFORMED LOW-GRADE NON-HODGKIN'S LYMPHOMA. The inspections were conducted in with CPGM with 7348.811, the Inspection Program for Clinical Investigators.

Specific questions concerning the studies were included. Data audits were performed at the following two sites:

Site	INVESTIGATOR	Date	Form 483	Classification
Rush-Presbyterian Medical Center	Dr. Gregory	4/01	Yes	VAI
Carolinas Medical	Dr. Frenette	7/01	Yes	VAI

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INSPECTIONAL FINDINGS

1. Rush-Presbyterian Medical Center / Dr. Gregory

A Form FDA 483 was issued to Dr. Gregory for administering incorrect doses of ¹³¹Iodine-Tositumomab to 4 subjects, not listing the nuclear medicine physician subinvestigator on the Form FDA 1572, performing HAMA titers on 15 subjects prior to having them sign informed consent documents, failure to maintain source documents to support adverse events (rashes) for two subjects, and incorrectly reporting a WBC of 3.61 as 4.64 to the sponsor.

2. CAROLINAS MEDICAL CENTER / DR. FRENETTE

A Form FDA 483 was issued to Dr. Frenette for failure to perform a CT scan on subject 062 prior to enrollment, and failure to provide written documentation that the test article was stored at the proper temperature.

The EIR stated that data in the BLA line listings did not always match CRF and source data for laboratory results. Also, for several study subjects, there appeared to be a difference of one week between the BLA line listing data points and the corresponding CRF data for laboratory values.

Because of questions about dosimetry at this site, a second inspection was planned.

A second Form FDA 483 was issued to Dr. Frenette for the following: failure to document the residual activity in the infusion set after administration of the investigational product; providing inaccurate reports to the sponsor, including the actual administered doses of the investigational product; and failure to perform dosimetry calculations accurately. The inspection revealed that, when the residual activity in the infusion set was measured, the values ranged from 0% to 19% of the original assayed dose prior to administration.

A Warning Letter was issued to Dr. Frenette for failure to furnish accurate reports to the sponsor
(http://www.fda.gov/foi/warning_letters/g3628d.pdf).

3. UNIVERSITY OF ARKANSAS FOR MEDICAL SCIENCES / DR. MADDOX

A Form FDA 483 was issued to Dr. Maddox for: failure to ensure that the study was conducted according to the protocol; enrollment of an ineligible subject; failure to perform dosimetry calculations accurately; discrepancies between data in the Case Report Forms compared to that in the source documents; and failure to report all adverse events to the sponsor, as required by the protocol. In addition, the inspection revealed that Dr. Maddox failed to document the residual activity in the infusion set after administration of the investigational product.

4. SPONSOR INSPECTION / CORIXA

A Form FDA 483 was issued on November 19, 2002 to the sponsor for: failure to ensure that the investigation was conducted according to the protocol; failure to document changes of the in-line filter during infusion of the investigational product; failure to adequately monitor clinical studies (RIT-II-000, RIT-II-001, RIT-II-002, RIT-II-003, RIT-II-004, CP-97-012, and CP-98-020); and failure to follow the Standard Operating Procedure for monitoring.

INSPECTIONAL SUMMARY STATEMENT

The results of bioresearch monitoring inspections of Dr. Gregory, Dr. Frenette, Dr. Maddox, and the Sponsor indicate that with the exceptions noted, the submitted data can be considered reliable and accurate.