BIODISTRIBUTION AND DOSIMETRY

In the review of Corixa's submission of the biodistribution imaging, normal organ dosimetry and tumor dosimetry, CBER has performed the following:

- A review of the imaging findings from the biodistribution imaging studies with I-131 tositumomab
- Analyzed and recalculated the submitted normal organ dosimetry for I-131 tositumomab
- Analyzed and recalculated the submitted normal organ dosimetry I-131 tositumomab
- Analyzed and recalculated the submitted tumor dosimetry

Biodistribution Imaging Findings

Electronic Submission

The whole body biodistribution images were electronically archived and submitted without data compression or data loss. The images have been presented in an electronic dataset within a searchable, interactive database. The supporting datasets have been submitted in SAS transport files.

Biodistribution Imaging – Normal Organs

In the biodistribution imaging, the normal organs are visualized by having uptake of I-131 tositumomab in the organ greater than the adjacent whole body background activity.

The review findings of the biodistribution imaging for the visualized organs are as follows:

Liver and Spleen

The imaging of the liver demonstrates an intense and somewhat grainy uptake pattern seen commonly with I-131 diagnostic imaging. The spleen is seen variably in imaging studies with similar, but occasionally less intense uptake of radiotracer.

Bone Marrow

The bone marrow compartment is variably seen in the expected distribution of the red marrow in adults. In some subjects, the bone marrow imaging demonstrated patchy areas of increased localization, suggesting possible imaging of NHL bone marrow involvement.

Testes

Imaging of the testes is remarkable for the intensity of the radiotracer localization (equivalent to the liver). No asymmetry of the testes or focal localization to suggest imaging of occult, focal NHL was identified.

Kidney, Urinary Bladder

The kidneys and urinary bladder are seen. The urinary bladder is variable in its configuration and partially filled with radiotracer, compatible with the urinary tract function as the clearance pathway of the I-131.

Large Bowel

Variable regions of the large bowel demonstrate localization of I-131 in subjects. Once seen, the localization appears unchanging in its anatomical distribution through later imaging time points. The imaging of the large bowel is compatible with I-131 tositumomab targeting normal sites of lymphoid aggregates in the bowel wall as well as sites of NHL. It must be noted, the imaging of the large bowel may represent the presence of an occult second clearance pathway in the bowel.

Small Bowel

Occasional regions of the small bowel appear to be imaged in some subjects.

Stomach

Diffuse, slight but definite localization in the stomach is seen in some subjects.

Heart, Large Vascular Structures

The cardiac chambers and major vascular structures demonstrate localization in the early imaging with the expected loss of imaging in later imaging. This imaging pattern is compatible with the infusion of I-131 tositumomab, and the expected clearance of the radiolabeled antibody from the vascular space.

Lung Fields

The lung fields demonstrate a modest diffuse to somewhat irregular localization of the radiolabeled antibody as compared to the whole body background activity.

Thyroid

Intense uptake of I-131 is demonstrated in the thyroid gland of many subjects.

Biodistribution Imaging – Tumor Sites

Occasionally tumor sites are seen poorly-defined localization of I-131 tositumomab.

CBER Review Comments

Consistent with the diagnostic imaging characteristics of I-131 but compromised by the variable imaging quality submitted by the sponsor, the I-131 tositumomab whole body biodistribution imaging provided marginal quality whole body and organ imaging at the imaging time points.

If adequate, and well controlled imaging techniques are applied to the biodistribution imaging with I-131 tositumomab, the whole body imaging should be able to provide supportive information for the safe administration of I-131 tositumomab to confirm the presence of the expected pattern of I-131 tositumomab in the normal organs. An alteration in the biodistribution of I-131 tositumomab would suggest the presence of one or more of the following conditions:

- Immune response, HAMA.
- Organ dysfunction, e.g., urinary tract obstruction.
- Improper preparation of the I-131 tositumomab imaging agent.

Imaging of tumor sites was unable to confirm localization of I-131 tositumomab. Thus, the review of the whole body biodistribution images appears to unable to establish routinely the "normal structures at risk" due to the radiation absorbed dose exposures from adjacent tumor sites. In addition, the review of the whole body biodistribution imaging does not appear to allow the following:

- Quantitation of the radiation dose for those tumor sites, which are adjacent to "normal structures at risk."
- Quantitation of the radiation absorbed dose to normal organs and tumor sites.

Normal Organ Dosimetry

Organ Dosimetry

Prior to the therapy administration of I-131 tositumomab therapy, the clinical sites performed biodistribution imaging studies with a diagnostic dose of I-131 tositumomab for each subject. The routine whole body biodistribution studies resulted in whole body images for at least 3 time points (imaging days). Based on the whole body imaging study, the clinical sites determined the therapy dose for the subject.

For the BLA submission, organ dosimetry was performed after 126 infusions in subjects receiving a predose of at least 475 mg of antibody based on regions-of-interest (ROI) counts from the kidneys, liver, lungs, spleen obtained daily after the dosimetric dose. Counts from blood samples, urinary bladder and remainder of the body were additional source organs.

Due to the inadequate and incomplete assignment of regions of interest, a subset of ten subjects were selected to properly estimate radiation-absorbed doses to organs, based on ROIs assigned to all organs demonstrating increased radiotracer localization as compared to the whole body background activity for 6 to 8 time points (imaging days). These subjects were selected to assure that there were at least 5 patients with well-defined thyroid uptake, 5 patients with well-defined stomach uptake, and 5 patients with well-defined large bowel uptake, and approximately 50% male subjects.

Residence times were determined for kidneys, liver, lungs, spleen, bone marrow, heart, lower large intestine (LLI), upper large intestine (ULI), small intestine, stomach, thyroid, testes (for males), urinary bladder, and tumors. The remainder method was used for all other organs.

Organs To Be Evaluated By Time Activity Curves

For the determination of dosimetry by the -------- software, all organs visualized are considered to have greater concentration of the radiolabeled antibody as compared to the whole body background activity. These visualized organs are evaluated by regions of interest (ROIs) with quantification of the radioactivity present in these organs at the multiple time points. The determination of the radioactivity localization in these organs by the ROIs for the multiple time points produces the time-activity curves. By integration of the time activity curves, the residence times are obtained, which are required for the -------- software to estimate the normal organ dosimetry.

Subject Population

Ten subjects selected for adequate imaging technique and demonstrated normal organ localization of the radiolabeled antibody.

Regions of Interest

Corixa has evaluated the following listed organs/tissues and total body activity:

1. Total Body
2. Blood
3. Heart
4. Kidneys
5. Lung
6. Liver
7. Small Intestine
8. Large Intestine
9. Spleen
10. Testes
11. Thyroid
12. Humeral head (Bone Marrow)

Route of Excretion

Urine was collected following 49 dosimetric doses.

Samples were collected and counted for the following intervals: 0–12 hours, 12–24 hours, 24–48 hours, 48–72 hours, 72–96 hours, and 96–120 hours.

In the first 120 hours following the dosimetric dose, the whole body clearance of the iodine 131 was 67% ± 13% of the injected dose. The percent of the injected dose collected in the urine was 65% ± 13%.

The percent of total body excretion that was captured in the urine over the 5-day time period was 98% ± 15%.

CBER Review Comment:

CBER's review of the whole body biodistribution images demonstrates localization of the radiotracer in the bowel in several subjects. The possible contribution of activity in the bowel lumen from a second route of clearance in the bowel can not been ruled out.

Tumor Dosimetry

Tumor doses are summarized based on data from 29 patients.

Tumor selection was limited due to the following:

1) no quantification of a tumor site because the tumor was not visualized
2) the tumor could not be clearly delineated from adjacent radiotracer activity

The tumor dosimetry data were calculated based on ROIs drawn over the tumors. Corrections for attenuation and background were performed as for normal organ dosimetry.

Tumor volumes were calculated by outlining individual tumors slice-by-slice on CTs.

For tumors with masses between 10 and 100 g, tumor dosimetry was performed using the table of absorbed fractions for spheres. For tumors greater than 100 g, a splenic mass adjusted model was used. The tumor dose represents the nonpenetrating and penetrating doses from iodine 131 within the tumor plus the expected penetrating dose from the total body.

DOSIMETRY ANALYSIS

This review has been based on the information submitted by Corixa in the Bexxar BLA: CD entitled "Resubmission: Response to Complete Review Letter, Part II. Items: 1, 8, 10, 11, and 20. Dated ----------, Disk 1 of 1.

Study Design

This section assesses the study design for adequate data collection for the dosimetry analysis. It will begin with summary tables of the time-activity data collected for dosimetry, and will acknowledge a standard checklist for adequate data collection for the dosimetry analysis.

Table DA1: Data Collection Summary.

Organ Data Collected	Data Source	n	Reported Number of Time points (Range)	CBER Evaluation
Bone Marrow*	**Gamma Camera/Blood**	**10**	**6-8**	**Good**
Heart	**Gamma Camera**	**10**	**6-8**	**Good**
Kidneys	**Gamma Camera**	**10**	**6-8**	**Good**
Liver	**Gamma Camera**	**10**	**6-8**	**Good**
Lungs	**Gamma Camera**	**10**	**6-8**	**Good**
LLI	**Based on ULI ROI**	**10**	**na**	**Good**
SI	**ICRP-30 GI model**	**10**	**na**	**Good**
Spleen	**Gamma Camera**	**10**	**6-8**	**Good**
Stomach	**Gamma Camera**	**10**	**6-8**	**Good**
Testes	**Gamma Camera**	**6**	**6-8**	**Good**
Thyroid	**Gamma Camera**	**10**	**6-8**	**Good**
Tumors	**Gamma Camera**	**29**	**6-8**	**Good**
ULI	**Gamma Camera**	**10**	**6-8**	**Good**
Urinary Bladder¥	**Gamma Camera**	**10**	**6-8**	**Good**
Whole Body	**Gamma Camera**	**10**	**6-8**	**Good**

*** Corixa Performed analysis using both blood based and ROI based methods. ROI based results were presented in the main table.**
¥ Based on Whole Body Images.

Were an adequate number of subjects utilized? **Yes**

Complete dosimetry was determined for 10 patients.

Were the number and spacing of the data collection time points adequate? **Yes**

The data collected does adequately describe the time activity curves for the listed organs/tissues. Image data were collected for between 6 and 8 time points. To fully describe the time activity curves for all organs/tissues that demonstrate uptake of activity, dosimetry studies require that adequate data be collected, at the appropriate times,

Was whole body activity measured over the course of the study? **Yes**

Did activity quantification methods seem reasonable and adequate? **Yes**

Were all organs showing significant uptake measured and reported? **Yes**

Were excretion data from all significant routes of excretion collected? **Yes**

CBER Review Comment

Study Design is considered appropriate and sufficient.

Image Quantification Validation on 2 patients

This section describes the image quantification methods (transformation of counts to activity in regions of interest) used by Corixa, and compares results obtained by CBER for two patients, to the results obtained by Corixa on the same patients. This analysis is not intended to confirm the results for all organs/tissues, but rather to confirm the general reliability of the Corixa methodology and results by selecting a representative group of organs and comparing the results.

Description of the Image Quantification Methods used by Corixa

Whole body and spot images were collected at 6 to 8 different time points. The eight time points at which data were collected were approximately 1.5, 18, 40, 66, 113, 136, and 161 hours. When time points were excluded, those typically excluded were the 5 and 136 hour time points.

The conversion of counts to activity was performed by Corixa based on a series of phantom studies with I-131. This method modeled the efficiency of the camera as a function of depth. Effective thicknesses in the patients at each region of interest were determined using modified transmission scan data using a Co-57 source. This methodology converts counts to activity, and accounts for attenuation in the patient at each ROI. ROIs were drawn for Bone Marrow (humeral head), Heart, Kidneys (one), Liver, Lungs, Spleen, Stomach, Testes, Thyroid, Tumors, ULI, and Whole Body. This method should result in reasonable activity quantification. Given that no activity standard was used, this methodology requires that consistent camera settings be used. Spot images were used for all of the listed regions of interest except whole body, where whole body scans were used.

CBER Methodology for Image Quantification

Corixa supplied whole body and spot images for 10 patients in the BLA submission. Of the 10, 2 patients were selected at random for the validation (Patient 003-012-003 and Patient 003-012-056) Regions of interest (ROIs) were selected and drawn around the selected group of organs/tissues [whole body, lungs, liver, spleen, kidneys, and heart] in both the whole body and spot images. Activity in each organ/tissue, at each time point, was determined by taking the geometric mean of the anterior and posterior counts in each ROI and dividing by the number of geometric mean whole body counts in the first image. Geometric mean whole body counts in the first spot image were estimated based on the available image area.

Validation and Evaluation of Image Quantification Results

CBER results matched those reported by Corixa to within the limits expected, given the data, and the approximate nature of CBER methodology, which did not account for attenuation or over/underlying activity. Whole body numbers were almost identical, and other organs matched well enough to conclude that the quantification methods performed by Corixa were appropriate and likely conservative. Ratios of CBER to Corixa image quantification results for Patient 003-012-003 where CBER used the spot images are shown in Table 2. Ratios of CBER to Corixa image quantification results for Patient 003-056-003 where CBER used the whole body images are shown in Table 3. There were some discrepancies in some of CBER results for the whole body images, but these were very likely due to the remarkably poor whole body images at the later time points.

Table DA2: Ratio of CBER (using spot images) to Corixa ROI activity determination.

Patient 003-012-003

	1.17	17.08	40.17	65.13	140.83
Heart Wall	**0.53**	**0.47**	**0.52**	**0.65**	**0.63**
Kidneys	**0.55**	**0.43**	**0.45**	**0.34**	**0.17**
Liver	**0.70**	**0.79**	**0.85**	**0.94**	**1.22**
Spleen	**0.72**	**0.65**	**0.69**	**0.75**	**0.78**
Whole Body	**1.00**	**1.03**	**1.03**	**1.02**	**1.09**

Table DA3: Ratio of CBER (using whole body images) to Corixa ROI activity determination.

Patient 003-056-003

	1.22	18.47	43.12	66.83	113.98	145.12
Liver	**0.78**	**0.93**	**0.90**	**0.88**	**1.01**	**0.92**
Kidneys	**0.38**	**0.42**	**0.44**	**0.46**	**0.47**	**0.62**
Spleen	**0.45**	**0.44**	**0.48**	**0.55**	**0.49**	**0.63**
Whole Body	**1.00**	**1.07**	**1.02**	**0.92**	**1.08**	**1.13**

CBER Review Comment

The small image size of the spot and whole body images, and the low quality of the whole body images made region determination somewhat difficult for smaller and low activity uptake regions.

It is difficult to assess if the regions used by Corixa for some organs/tissues, such as GI organs, testes and marrow, would result in accurate dosimetry as the structures were difficult to visualize on the images. However, it was apparent that in the cases where the structures were difficult to visualize, that Corixa would typically use a generous and likely conservative region of interest. Thus it is likely that for the larger and high activity uptake regions that the resulting dosimetry estimates are fairly accurate, and for the small and/or lower activity uptake regions the resulting dosimetry estimates are at least conservative, if somewhat less accurate.

Kinetic Modeling

This sub-section describes and evaluates the methods Corixa used to determine residence times from whatever time activity data was collected using imaging, excreta sampling, and blood sampling.

Mathematical model used to estimate organ residence times

Organ residence times for most organs/tissues quantified were found by fitting the quantified data form imaging with sums of exponentials and integrating the resulting functions. For LLI, residence time was based on ULI region results. SI residence time was estimated using the ICRP-30 GI tract model and the activity seen in stomach. For stomach and thyroid, due to the erratic nature of the data collected, a trapezoidal methodology was used, assuming physical decay only beyond the final data point.

Urine residence times were found using whole body data assuming urinary excretion data only. A previous study compared whole body retention and urinary excretion to validate this method. A 4.8-hour voiding bladder model was then applied to the integration process.

Red marrow residence times were determined using two methodologies. The first method used a humeral head ROI to estimate marrow activity. This was done by assuming that the activity found in this region represented a fixed amount of the total red marrow (9.95 g) The second method used the blood data and the methodology described by Sqouros [J Nuclear Medicine 1993;34:689-694]. This involves curve fitting the blood data using sums of exponentials and assuming that marrow activity is proportional to blood activity. The Sqouros methodology is only appropriate when there is no specific uptake of activity in marrow elements. The ROI method was selected as more appropriate, and the results from this method were used to generate the final dosimetry.

Remainders of body residence times were determined by subtracting organ residence times from whole body residence times.

Were appropriate assumptions made about activity beyond the last time point imaged? Yes
After the last time point imaged, the time-activity curve was assumed to continue to follow mathematical fit (sums of exponentials) that was determined using the data collected, except for stomach and thyroid, where activity was assumed to be lost by physical decay only after the last observed data point.

Does the model conserve activity? Yes
The assumption of all activity not in whole body traveling through an excretion pathway and the determination of remainder of body residence times by subtracting organ residence times from whole body residence times insures that the model accounts for 100% of the injected activity at all times (that is, it conserves activity).

Validation and Evaluation of kinetic modeling

CBER reproduced through independent analysis all residence times for 5 of the 10 patients using the kinetic data as supplied by Corixa. On average, residence times found by CBER matched almost exactly with those found by Corixa.

There were a few exceptions, notably heart wall and SI. The most significant example was the residence time for heart wall for patient 003-012-003 found by Corixa. It appeared to be different by approximately a factor of 2. However, this will have little impact on the final dosimetry for heart wall however, as all other residence times found by CBER for heart wall matched those found by Corixa to within about 3%.

CBER also found different results from Corixa for SI residence times. Corixa found these by assuming the activity in the stomach continued on to the SI following the kinetics of the ICRP-30 GI tract model. Corixa assumed that the fraction of the total activity traveling from Stomach to GI was equal to the ratio of the stomach and whole body residence times. This method appears inconsistent to CBER since transit through the stomach is much faster than whole body retention.

CBER assumed that the maximum activity seen in stomach was passed through to SI using ICRP-30 kinetics. Both of these methods have problems however. Since the SI region was not quantifiable, and activity uptake in GI was not apparent in the two patients evaluated, it is difficult to assess the methodology selected by Corixa or CBER. Especially given the fact that lymphoid aggregates in GI might have uptake of the activity. However, if this were the case, it was not apparent from either the spot or whole body images. In addition, the uptake in stomach could have been from free iodine, and would not be as likely to pass completely into SI.

Given that GI uptake was not apparent in the two image sets studied, CBER would be inclined to treat the SI, ULI, and LLI as remainder organs, which would result in much lower doses than those found by Corixa. However, it should be noted that GI uptake might have occurred in other patients than the 2 examined here. Thus CBER choose the more conservative assumption similar to the one chosen by Corixa, using the ICRP-30 model

If the uptake actually was in lymphoid aggregates in the GI tract, a better method for SI might be to assume similar uptake in SI as in ULI which would result in higher absorbed dose estimates. This would result in final dosimetry estimates for SI that would be very similar to those found for ULI and LLI.

Cber Review Comments

With the possible exception of SI, the kinetic modeling was appropriate and correct.

Physics (S-value) Modeling

This section describes and evaluates the methodology used by Corixa to obtain S-values. Most S-values used by Corixa are those using the Cristy-Eckerman Mathematical phantom as implemented in -------- 3.1. There were some exceptions to this as follows:

GI tract organ S-values for the assumption of activity in wall

-------- 3.1 assumes that for GI organs, activity is contained in the contents of the GI tract. There is no built in methodology for putting activity in the GI walls using -------- 3.1. Corixa corrected the GI tract S-values by removing the non-penetrating component due to activity in the contents, and then adding a non-penetrating component assuming that the activity was located in the walls. For example, for LLI:

$$S_{corrected}(\text{LLI wall} \leftarrow \text{LLI contents}) = S_{MIRDose}(\text{LLI wall} \leftarrow \text{LLI contents}) - \frac{\Delta_{np}}{2m_{contents}} + \frac{\Delta_{np}}{m_{wall}}$$

This method is appropriate and correct.

Spleen S-values

Spleen S-values from -------- were modified to account for large mass differences from reference man values found in some patients using a well-known technique that accounts for photon and non-penetrating differences. This method is appropriate and correct.

Tumor S-values

Tumor S-values were based on published photon absorbed fractions for spheres, and the assumption of 100% absorption of electron emissions. This method is appropriate and correct for the range of tumor sizes in this study. Values found by Corixa match those found by using nodule module in -------- almost exactly.

CBER Review Comments

Methods for S-value determination were appropriate and correct.

Normal Organ Dosimetry Methods and Results

This section describes and evaluates the methodology used by Corixa to obtain radiation absorbed doses using the residence times as described in the kinetic modeling section. This section shall also compare the absorbed dose results obtained by Corixa to the

absorbed dose results obtained by CBER. The results obtained by CBER in this sub-section are based on the time-activity data exactly as provided by Corixa.

Description of Dosimetry Methods

Normal organ dosimetry estimates were determined by Corixa using the residence times as found and explained in the kinetic modeling section and the -------- 3.1 software.

For GI organs, dosimetry was calculated under 3 different scenarios:

1) assuming 100% of the activity was in contents,
2) assuming activity was distributed 50% in contents 50% in walls, and
3) assuming activity was distributed 100% in walls.

SOURCE OF S-VALUES: -------- 3.1

Was the remainder of body correction appropriately applied? Yes

VALIDATION RESULTS: CORIXA VS. CBER. Based on kinetic data as supplied by Corixa.

Table 4A shows the results obtained by Corixa and CBER, and the ratio of these results in cGy/mCi. Table 4B shows the same results in mGy/MBq. Table 5A shows the dose estimates in cGy/mCi determined by Corixa in the GI organs under the 3 different distribution (wall vs. contents) assumptions. Table 5B shows the same results in mGy/MBq.

TABLE DA4A: COMPARISON OF CORIXA RESULTS AND CBER RESULTS, BOTH BASED ON TIME-ACTIVITY DATA AS SUPPLIED BY CORIXA IN RADS/MCI.

	Source of Data for Dosimetry	cGy/mCi Corixa	cGy/mCi CBER	Ratio of Corixa to CBER
Adrenals	Whole Body ROI	1.1	1.0	1.09
Brain	Whole Body ROI	0.5	0.4	1.10
Breasts	Whole Body ROI	0.6	0.5	1.07
Gallbladder Wall	Whole Body ROI	1.1	1.0	1.08
LLI Wall †	Based on ULI ROI	4.6	4.8	0.97
Small Intestine†	ICRP Model	0.8	0.8	1.04
Stomach†	Organ ROI	1.7	1.7	1.02
ULI Wall †	Organ ROI	4.8	4.9	0.98
Heart Wall	Organ ROI	4.4	4.6	0.94
Kidneys	Organ ROI	7.3	7.0	1.05
Liver	Organ ROI	3.0	2.7	1.11
Lungs	Organ ROI	2.9	3.0	0.95
Muscle	Whole Body ROI	0.6	0.6	1.07
Ovaries	Whole Body ROI	0.9	0.9	1.03
Pancreas	Whole Body ROI	1.1	1.1	1.06
Red Marrow*	Organ ROI	2.6	2.2	1.19
Bone Surfaces	Whole Body ROI	1.7	1.4	1.16
Skin	Whole Body ROI	0.5	0.4	1.08
Spleen	Organ ROI	4.3	5.4	0.80
Testes	Organ ROI	3.0	2.5	1.21
Thymus	Whole Body ROI	0.8	0.8	1.04
Thyroid	Organ ROI	11.7	18.5	0.63
Urine Bladder Wall	Whole Body ROI**	2.7	2.6	1.00
Uterus	Whole Body ROI	0.7	0.7	1.00
Total Body	Whole Body ROI	0.9	0.8	1.08

* Humerus ROI results

** All excretion assumed to be urinary.

† Assumes 100% in contents.

TABLE DA4B: COMPARISON OF CORIXA RESULTS AND CBER RESULTS, BOTH BASED ON TIME-ACTIVITY DATA AS SUPPLIED BY CORIXA IN MGY/MBQ.

	Source of Data for Dosimetry	mGy/MBq Corixa	mGy/MBq CBER	Ratio of Corixa to CBER
Adrenals	Whole Body ROI	0.3	0.3	1.09
Brain	Whole Body ROI	0.1	0.1	1.10
Breasts	Whole Body ROI	0.2	0.1	1.07
Gallbladder Wall	Whole Body ROI	0.3	0.3	1.08
LLI Wall †	Based on ULI ROI	1.2	1.3	0.97
Small Intestine†	ICRP Model	0.2	0.2	1.04
Stomach†	Organ ROI	0.5	0.5	1.02
ULI Wall †	Organ ROI	1.3	1.3	0.98
Heart Wall	Organ ROI	1.2	1.3	0.94
Kidneys	Organ ROI	2.0	1.9	1.05
Liver	Organ ROI	0.8	0.7	1.11
Lungs	Organ ROI	0.8	0.8	0.95
Muscle	Whole Body ROI	0.2	0.2	1.07
Ovaries	Whole Body ROI	0.2	0.2	1.03
Pancreas	Whole Body ROI	0.3	0.3	1.06
Red Marrow*	Organ ROI	0.7	0.6	1.19
Bone Surfaces	Whole Body ROI	0.5	0.4	1.16
Skin	Whole Body ROI	0.1	0.1	1.08
Spleen	Organ ROI	1.2	1.5	0.80
Testes	Organ ROI	0.8	0.7	1.21
Thymus	Whole Body ROI	0.2	0.2	1.04
Thyroid	Organ ROI	3.2	5.0	0.63
Urine Bladder Wall	Whole Body ROI**	0.7	0.7	1.00
Uterus	Whole Body ROI	0.2	0.2	1.00
Total Body	Whole Body ROI	0.2	0.2	1.08

* Humerus ROI results

** All excretion assumed to be urinary.

† Assumes 100% in contents.

TABLE DA5A: GI WALL DOSE ESTIMATES IN CGY/MCI UNDER DIFFERING ACTIVITY DISTRIBUTION ASSUMPTIONS.

	100% Contents	50% Wall, 50% Contents	100% Wall
Stomach Wall	1.7	3.0	4.2
LLI Wall	4.6	6.8	8.5
ULI Wall	4.8	6.9	8.6

TABLE DA5B: GI WALL DOSE ESTIMATES IN MGY/MBQ UNDER DIFFERING ACTIVITY DISTRIBUTION ASSUMPTIONS.

	100% Contents	50% Wall, 50% Contents	100% Wall
Stomach Wall	0.5	0.8	1.1
LLI Wall	1.2	1.8	2.3
ULI Wall	1.3	1.9	2.3

CBER Review Comments

The dosimetry methods for normal organs used by Corixa were appropriate and correct. The final results matched those found by CBER (based on kinetic data as supplied by Corixa within about 10%) in all cases except red marrow, bone surfaces, testes, thyroid, and spleen.

The differences in red marrow and bone surface dosimetry (about 20%) are consistent with the smaller sample size used by CBER, which by pure chance contained the patients showing lower red marrow uptake Comparing patient by patient for the red marrow and bone surface dosimetry, Corixa and CBER results match almost exactly.

The differences in testes dosimetry (about 20%) were consistent with the result of the smaller sample size used by CBER, which by chance contained the patients showing lower testes uptake. Comparing patient by patient for the testes dosimetry, Corixa and CBER results match almost exactly.

The differences in thyroid dosimetry (about 40%) were consistent with the result of the smaller sample size used by CBER, which by chance contained the patients showing lower thyroid uptake. Comparing patient by patient for the thyroid dosimetry, Corixa and CBER results match almost exactly.

CBER recalculated and confirmed the dosimetry results for GI organs under the 3 different distribution (wall vs. contents) assumptions (Table 5). Results were not an exact match, but were close enough to confirm that the methodology was likely correctly applied. Differences were likely due to the use of slightly different residence times and I-131 np delta for the calculation. It is the tentative conclusion of CBER, based on the lack of observable uptake in intestine that the GI organ estimates given in Tables 4 and 5 likely represent overestimates.

The differences in spleen dosimetry (about 20%) were a result of the smaller sample size used by CBER, and the slightly difference methodology for mass correction of the dose.

Tumor Dosimetry Verification

Tumor dosimetry was recalculated by CBER for 16 tumors, based on kinetic data, and tumor mass data supplied by Corixa. For absorbed fraction determination, the tumors were assumed to be spherical. Results are shown in Tables 6A and 6B. Average tumor dose found by CBER was within 10% of that found by Corixa. The absorbed dose found by CBER for 13 of the 16 tumors, was within about 15% of the absorbed dose estimated by Corixa. Differences were likely due to slightly different kinetic modeling and S-values.

Table DA6A: Tumor Dose Estimates (cGy/mCi)

Study	Patient	Mass grams	CBER cGy/mCi	Corixa cGy/mCi	Review/Corixa
RIT-II-001	001-003-004	806.7	5.5	5.3	1.04
RIT-II-001	001-003-004	19.0	21.2	21.0	1.01
RIT-II-003	003-012-003	135.7	4.0	4.4	0.92
RIT-II-003	003-012-003	91.8	4.3	4.9	0.88
RIT-II-003	003-012-009	47.6	10.1	8.7	1.16
RIT-II-003	003-012-009	81.5	8.8	11.4	0.77
RIT-II-003	003-012-010	314.8	2.0	2.9	0.69
RIT-II-003	003-012-010	104.8	6.1	6.9	0.90
RIT-II-003	003-012-038	57.1	6.8	7.8	0.88
RIT-II-003	003-012-051	28.2	10.3	11.5	0.90
RIT-II-003	003-012-053	390.5	5.0	5.4	0.92
RIT-II-003	003-012-056	59.0	12.1	13.6	0.89
RIT-II-003	003-012-057	66.0	10.4	11.6	0.90
RIT-II-003	003-012-057	139.3	5.3	5.9	0.91
RIT-II-003	003-012-065	68.5	7.7	8.7	0.88
RIT-II-003	003-012-065	32.1	40.6	41.2	0.98

Table DA6B: Tumor Dose Estimates (mGy/MBq)

Study	Patient	Mass grams	CBER mGy/MBq	Corixa mGy/MBq	Review/Corixa
RIT-II-001	001-003-004	806.7	1.5	1.4	1.04
RIT-II-001	001-003-004	19.0	5.7	5.7	1.01
RIT-II-003	003-012-003	135.7	1.1	1.2	0.92
RIT-II-003	003-012-003	91.8	1.2	1.3	0.88
RIT-II-003	003-012-009	47.6	2.7	2.3	1.16
RIT-II-003	003-012-009	81.5	2.4	3.1	0.77
RIT-II-003	003-012-010	314.8	0.5	0.8	0.69
RIT-II-003	003-012-010	104.8	1.6	1.9	0.90
RIT-II-003	003-012-038	57.1	1.8	2.1	0.88
RIT-II-003	003-012-051	28.2	2.8	3.1	0.90
RIT-II-003	003-012-053	390.5	1.4	1.5	0.92
RIT-II-003	003-012-056	59.0	3.3	3.7	0.89
RIT-II-003	003-012-057	66.0	2.8	3.1	0.90
RIT-II-003	003-012-057	139.3	1.4	1.6	0.91
RIT-II-003	003-012-065	68.5	2.1	2.4	0.88
RIT-II-003	003-012-065	32.1	11.0	11.1	0.98

Tumor radiation absorbed dose estimates found by both Corixa and CBER were obtained using absorbed fractions that were based on the average beta energy emission of I-131, and the assumption that the tumors could be modeled as spheres for radiation transport

purposes. Both of these assumptions are very slightly conservative, that is they will result in an overestimate of the actual radiation absorbed dose to the tumors.

CBER Review Comment

The dosimetry methods for tumors used by Corixa were appropriate and correct. The final results matched those found by CBER (based on kinetic data as supplied by Corixa) (within about 15%) in almost all cases.

Absorbed Dose to Surrounding Tissues From Activity in Tumors

This section reviews the use of some relatively simple geometric models and radiation transport simulations to estimate radiation absorbed dose to structures adjacent to tumors.

Given the possibility for large absorbed doses in tumors in RIT therapy, there exists a possibility of large absorbed doses to the tissue immediately surrounding the tumors. Three models were constructed with 3 tumor sizes each to investigate various situations including dose to generic tissue surrounding tumor, tumor around a small cylinder such as a nerve, and tumor against the pericardium or bowel wall.

Depth absorbed dose profiles for all models were calculated for I-131. This was performed by determining absorbed fractions using Monte Carlo simulation of the radiation transport the models. For each simulation between 100 thousand and 25 million particle histories were run. Full beta spectrum was generated for the simulations. For all simulations, sufficient numbers of histories were run such that the relative errors were less than 5%. The MCNP relative error criteria for generally reliable results is 10% or less. Listed below are methods and results for each of the models. These results are based on a paper submitted to the Journal of Nuclear Medicine for publication and is currently under review. [----------
---------- Under Review].

Nerve Surrounded by Spherical Tumor

This simulation was designed to model the irradiation of a small nerve surrounded by tumor. The model consisted of a spherical source (representing tumor) encasing a small cylindrical nerve. Table 7 lists the depth absorbed dose profile into surrounding generic tissue using 10, 20 and 40-gram tumor models.

Table DA7: Depth Dose Profile for ^{131}I: Nerve surrounded by spherical tumor.

Depth (cm)	% Source dose 10 gram Tumor	% Source dose 20 gram Tumor	% Source dose 40 gram Tumor
(Source)	100%	100%	100%
0.0085	50%	51%	52%
0.025	36%	37%	39%
0.042	31%	31%	35%

Generic Tissue Surrounding Spherical Tumor

This simulation was designed to model the irradiation of generic tissue surrounding a tumor. The model consisted of a spherical source (representing tumor) with surrounding concentric spherical shells. Table 8 lists the depth absorbed dose profile into surrounding generic tissue for 10, 20 and 40-gram tumor models.
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Table DA8: Depth Dose Profile for 131I: Generic Tissue Surrounding Spherical Tumor

Depth (cm)	% Source dose 10 gram Tumor	% Source dose 20 gram Tumor	% Source dose 40 gram Tumor
-	100%	100%	100%
	43%	43%	44%
0.01	31%	31%	32%
0.02	21%	21%	22%
0.03	15%	16%	17%
0.04	11%	12%	13%
0.05	8%	9%	11%
0.06	7%	8%	9%
0.07	5%	6%	7%
0.08	5%	6%	7%
0.09	4%	5%	6%
0.1	4%	5%	6%
0.15	3%	4%	5%
0.25	2%	3%	4%
0.4	2%	3%	4%
0.6	2%	2%	3%

Hemispherical Tumor Adjacent to Bowel Wall or Pericardium

This simulation was designed to model the irradiation of tissue such as bowel wall or pericardium adjacent to a hemispherical tumor. The model consisted of a hemispherical source (representing tumor) adjacent to a series of cylindrical disks. Table 9 lists the depth absorbed dose profile into surrounding generic tissue for 10, 20 and 40-gram tumor models.

Table DA9: Depth Dose Profile for 131I Hemispherical Tumor Adjacent to Bowel or Pericardium.

Depth (cm)	% Source dose 10 gram Tumor	% Source dose 20 gram Tumor	% Source dose 40 gram Tumor
-	100%	100%	100%
0.0025	46%	46%	47%
0.01	32%	33%	34%
0.02	22%	24%	24%
0.03	17%	18%	19%
0.04	13%	14%	15%
0.05	10%	11%	12%
0.06	8%	9%	10%
0.07	7%	8%	9%
0.08	6%	7%	8%
0.09	5%	6%	8%
0.1	5%	6%	7%
0.15	4%	5%	6%
0.25	3%	4%	6%
0.4	3%	4%	5%
0.6	2%	3%	4%

CBER Review Comment

Results for these estimates reported by Corixa are identical, which is as expected since Corixa consultant Dr. ---------- participated in the analysis. Corixa did not, however, report the dose depth estimates to the nerve surrounded by tumor case.

ABNORMAL SITUATION DOSIMETRY

Dosimetry for Kidney Obstruction: Uptake and Indefinite Retention in the Kidneys

This section estimates the radiation-absorbed dose to the kidneys assuming indefinite retention of some level of percent-injected dose. The S-value for a single kidney was estimated using a 150-gram sphere with the -------- nodule module. Residence time was estimated assuming no biological removal of an instantaneous uptake of activity in a single kidney. The radiation-absorbed doses in a single kidney, for different levels of indefinite retention are shown in Table 10 below.

A similar analysis was discussed but not performed by Corixa.

Table DA10: I-131 Doses in Obstructed Kidney

% Injected Dose Retained	Single Kidney Absorbed Dose	
	cGy/mCi	mGy/MBq
1%	8	2
2%	16	4
3%	24	6
4%	32	9
5%	40	11

Dosimetry for Kidney Obstruction: Kidneys Fail to Process Activity

This section estimates the impact of renal obstruction for the first 24 hours, where the kidneys are assumed to stop functioning during this period, and then to resume normal function after this time. This will have the effect of increasing whole body residence time. It is assumed that all organ and remainder tissues residence times will increase roughly at the same percentage as whole body residence time increases, except for kidneys and urinary bladder residence times, which will decrease slightly, due to loss of about 8% of the activity by physical decay during the 24 hour period with no renal function, and no activity transfer to kidneys or bladder. For the average whole body half life of 90 hours, CBER found that the whole body residence time will show an increase of roughly 20%, which is in agreement with the number calculated by Corixa. CBER agrees with Corixa's assessment that a 20% increase in organ and remainder residence times will result in approximately a 20% increase in absorbed dose, except for kidneys and bladder wall, which will show a smaller increase in absorbed dose.

Dosimetry for Urinary Bladder Obstruction: 0-24 Hour Blockage

This section estimates the radiation-absorbed dose to the urinary bladder wall assuming a urinary bladder blockage lasting from 0 to 24 hours. This dose estimate assumes that he urinary bladder wall dose will be the most impacted by such a blockage, and that other organ, and remainder of body residence times will be impacted only slightly. Corixa performed this analysis with a series of assumed total body half lives. CBER verified this calculation based on the average whole body half-life of 90 hours in the 10 patients submitted. Results found by CBER and Corixa for a total body effective half-life of 90 hours are shown in Table 11 below. CBER and Corixa results are in excellent agreement.

Table DA11: Urinary Bladder Wall Absorbed Doses With and Without Bladder Obstruction.

	CBER cGy/mCi mGy/MBq		Corixa cGy/mCi mGy/MBq		CBER/Corixa
Bladder Dose without Obstruction	**2.6**	**0.7**	**2.8**	**0.8**	**0.93**
Bladder Dose with 0 to 24 hour Obstruction	**4.6**	**1.2**	**4.6**	**1.2**	**1.0**

Dosimetry Assuming Colloid Type Distribution

Dosimetry estimates for I-131 were determined using a colloid type distribution, based on the models described in ICRP-53 [ICRP 1988], by both CBER and Corixa.

The first model assumes "large" colloids (100-1000 nm diameter), with distributions of 70% in liver, and 10% each in spleen, red marrow, and remaining tissue.

The second model assumes "small" colloids (<100 nm diameter), with distributions of 70% in liver, and 10% in spleen, 15% in red marrow, and 5% remaining tissue.

In both models the colloid is assumed to break down with biological half lives of 3 hours and 5 days, for 80% and 20% of the total colloid, respectively. However, Corixa failed to account for the free iodide after the breakdown, and failed to account for the excretion of the activity in the bladder. These are clearly illustrated in ICRP-53 (Which was used by Corixa, but incorrectly called ICRP-50). This led to the rather large discrepancies seen below in Tables 12A and 12B. It should be noted that all estimates below assume complete blocking of the thyroid.

Table DA12A: Dosimetry Estimates Assuming Large and Small Colloids (cGy/mCi).

	CBER (cGy/mCi)		Corixa (cGy/mCi)		Ratio CBER/Corixa	
	Large Colloids	Small Colloids	Large Colloids	Small Colloids	Large Colloids	Small Colloids
Adrenals	0.5	0.5	0.4	0.4	1.3	1.3
Brain	0.1	0.1	0.03	0.03	3.3	3.3
Breasts	0.2	0.2	0.08	0.07	2.5	2.9
Gallbladder Wall	0.7	0.7	0.6	0.6	1.2	1.2
LLI Wall	0.2	0.2	0.06	0.06	3.3	3.3
Small Intestine	0.3	0.3	0.1	0.1	3.0	3.0
Stomach	0.3	0.3	0.2	0.2	1.5	1.5
ULI Wall	0.3	0.3	0.2	0.2	1.5	1.5
Heart Wall	0.3	0.3	0.2	0.2	1.5	1.5
Kidneys	0.5	0.5	0.3	0.3	1.7	1.7
Liver	5.0	5.0	4.9	4.9	1.0	1.0
Lungs	0.3	0.3	0.2	0.2	1.5	1.5
Muscle	0.2	0.2	0.09	0.09	2.2	2.2
Ovaries	0.2	0.2	0.08	0.08	2.5	2.5
Pancreas	0.5	0.5	0.4	0.4	1.3	1.3
Red Marrow	0.7	0.9	0.6	0.8	1.2	1.1
Bone Surfaces	0.5	0.6	.4	.5	1.3	1.2
Skin	0.1	0.1	0.06	0.06	1.7	1.7
Spleen	6.5	6.5	6.4	6.4	1.0	1.0
Testes	0.2	0.1	0.03	0.02	6.7	5.0
Thymus	0.2	0.2	0.08	0.07	2.5	2.9
Thyroid	0.1	0.1	0.04	0.03	2.5	3.3
Urine Bladder Wall	1.9	1.9	0.05	0.04	38.0	47.5
Uterus	0.3	0.2	0.07	0.07	4.3	2.9
Total Body	0.4	0.4	0.3	0.3	1.3	1.3

Table DA12B: Dosimetry Estimates Assuming Large and Small Colloids (mGy/MBq).

	CBER (mGy/MBq)		Corixa (mGy/MBq)		Ratio CBER/Corixa	
	Large Colloids	Small Colloids	Large Colloids	Small Colloids	Large Colloids	Small Colloids
Adrenals	0.14	0.14	0.11	0.11	1.3	1.3
Brain	0.03	0.03	0.01	0.01	3.3	3.3
Breasts	0.05	0.05	0.02	0.02	2.5	2.9
Gallbladder Wall	0.19	0.19	0.16	0.16	1.2	1.2
LLI Wall	0.05	0.05	0.02	0.02	3.3	3.3
Small Intestine	0.08	0.08	0.03	0.03	3.0	3.0
Stomach	0.08	0.08	0.05	0.05	1.5	1.5
ULI Wall	0.08	0.08	0.05	0.05	1.5	1.5
Heart Wall	0.08	0.08	0.05	0.05	1.5	1.5
Kidneys	0.14	0.14	0.08	0.08	1.7	1.7
Liver	1.35	1.35	1.32	1.32	1.0	1.0
Lungs	0.08	0.08	0.05	0.05	1.5	1.5
Muscle	0.05	0.05	0.02	0.02	2.2	2.2
Ovaries	0.05	0.05	0.02	0.02	2.5	2.5
Pancreas	0.14	0.14	0.11	0.11	1.3	1.3
Red Marrow	0.19	0.24	0.16	0.22	1.2	1.1
Bone Surfaces	0.14	0.16	0.11	0.14	1.3	1.2
Skin	0.03	0.03	0.02	0.02	1.7	1.7
Spleen	1.76	1.76	1.73	1.73	1.0	1.0
Testes	0.05	0.03	0.01	0.01	6.7	5.0
Thymus	0.05	0.05	0.02	0.02	2.5	2.9
Thyroid	0.03	0.03	0.01	0.01	2.5	3.3
Urine Bladder Wall	0.51	0.51	0.01	0.01	38.0	47.5
Uterus	0.08	0.05	0.02	0.02	4.3	2.9
Total Body	0.11	0.11	0.08	0.08	1.3	1.3

I-131 Dosimetry for Free Label

Dosimetry estimates for I-131 were determined by CBER for unbound Iodine, based on the model described in ICRP-53 [ICRP 1988]. Assumes 5% uptake by thyroid. Results are shown in Table 13.

Corixa did not perform this analysis.

Table DA13: Dosimetry Estimates Assuming Free Label

	cGy/mCi	mGy/MBq
Adrenals	**0.1**	**0.03**
Brain	**0.1**	**0.03**
Breasts	**0.1**	**0.03**
Gallbladder Wall	**0.1**	**0.03**
LLI Wall	**0.2**	**0.05**
Small Intestine	**1.0**	**0.27**
Stomach	**1.6**	**0.43**
ULI Wall	**0.2**	**0.05**
Heart Wall	**0.1**	**0.03**
Kidneys	**0.2**	**0.05**
Liver	**0.1**	**0.03**
Lungs	**0.1**	**0.03**
Muscle	**0.1**	**0.03**
Ovaries	**0.2**	**0.05**
Pancreas	**0.2**	**0.05**
Red Marrow	**0.1**	**0.03**
Bone Surfaces	**0.2**	**0.05**
Skin	**0.1**	**0.03**
Spleen	**0.1**	**0.03**
Testes	**0.1**	**0.03**
Thymus	**0.2**	**0.05**
Thyroid	**252.0**	**68.11**
Urine Bladder Wall	**2.0**	**0.54**
Uterus	**0.2**	**0.05**
Total Body	**0.2**	**0.05**

CBER Review Comments

Dosimetry for Kidney Obstruction: Uptake and Indefinite Retention in the Kidneys: Not reported by Corixa.

Dosimetry for Kidney Obstruction: Kidneys Fail to Process Activity:
Corixa methods are appropriate and correct. CBER results matched very closely.

Dosimetry for Urinary Bladder Obstruction:
0-24 Hour Blockage. Corixa methods are appropriate and correct. CBER results matched very closely.

Dosimetry Assuming Colloid Type Distribution.
Corixa failed to account for the free iodide after the breakdown, and failed to account for the excretion of the activity in the bladder. This led to the rather large discrepancies between CBER results and Corixa results.

I-131 Dosimetry for Free Label. Not reported by Corixa.

Tolerance Doses per External Radiation Therapy

The following table lists the radiation-absorbed doses for external beam radiation therapy required to produce the listed effects in the listed organs. It must be emphasized that the primary source of these data is from external beam applications. The association and applicability of these values to unsealed source radiation therapy are unknown and not established.

TD 5/5 is the absorbed dose level required to produce the described injury within 5 years in 5% of those so exposed.

TD 50/5 is the absorbed dose level required to produce the described injury within 5 years in 50% of those so exposed.

The %-irradiated column describes the amount of the organ that was exposed to the radiation.

Table DA14: Tolerance Doses*

Organ	Injury	TD 5/5 (cGy)	TD 50/5 (cGy)	% irradiated
Gastrointestinal Epithelial Cells	enteritis	500	1000	whole
Peripheral Nerve	neuropathy	1500	2000	whole
Heart	pericarditis and pancarditis	4500	5500	60%
Heart	pericarditis and pancarditis	7000	8000	25%
Intestine	ulcer, perforation, hemorrhage	4500	5500	400 square cm
Intestine	ulcer, perforation, hemorrhage	5000	6500	100 square cm
Large Arteries and Veins	sclerosis	>8000	>10000	10 square cm
Peripheral Nerves	neuritis	6000	10000	10 cm
Small Intestine	Obstruction, perforation, fistula	5000	6000	1/3
Small Intestine	Obstruction, perforation, fistula	none	none	2/3
Small Intestine	Obstruction, perforation, fistula	4000	5500	3/3

*Sources:

1) Vaeth JM, Meyer JL (eds) Radiation Tolerance of Normal Tissues. 23rd Annual San Francisco Cancer Symposium. 1988.

2) Bentel GC, Nelson CE, Noell KT. Treatment Planning and Dose Calculation in Radiation Oncology. 4th Edition. Pergamon Press,1989.

3) Emani B, Lyman J, et al. Tolerance of Normal Tissue to Therapeutic Irradiation. Int J Rad Onc Biol Phys. Vol 21:1;109-122. 1991