Combidex®

(ferumoxtran-10)

NDA 21-115

Oncology Drugs Advisory Committee Briefing Document

January 28, 2005

Volume 1 of 2

Advanced Magnetics, Inc.
Cambridge, MA

Available for Public Disclosure Without Redaction

Table of Contents

Table of Tables

Table of Figures

Table of Appendices

LIST OF ABBREVIATONS

ACR	American College of Radiology
AJCC	American Joint Committee on Cancer
BR	Blinded Reader or Blinded Reading
CT	Computed Tomography
CECT	Contrast Enhanced Computed Tomography
Dx	Diagnosis
FDA	Food and Drug Administration
Fe	Iron
FSE	Fast spin echo
GRE	Gradient echo
ITT	Intent-to-treat
MR	Magnetic resonance
MRI	Magnetic resonance imaging
MRI Dx	Lymph node diagnosis based on size criteria
NCCN	National Comprehensive Cancer Network
NDA	New Drug Application
NEJM	New England Journal of Medicine
NPV	Negative predictive value
PPV	Positive predictive value
ROC	Receiver operator characteristic
SI	Signal Intensity
T2	T2 weighted image sequence
T2*	Heavily T2 weighted image sequence

DEFINITIONS

Accuracy	Accuracy is defined as the ability of a procedure to differentiate the patients who have the condition(s) that the procedure is intended to find from those who do not. In this document, accuracy represents the proportion of correct diagnoses made using MR images.
Adjudicator	Radiologist unaffiliated with the study who compared MR images with nodes marked by the Blinded Readers to MR images with nodes marked by the Investigators to match lymph nodes seen by the Blinded Readers with lymph nodes that were sampled at biopsy or surgery.
Blinded Reader	A radiologist or oncologist, unaffiliated with the study, who reviewed the study images and completed a blinded CRF without having access to any clinical information about the patients.
Blinded Reading	Review of study images presented in a randomized fashion to clinicians not affiliated with any of the Combidex clinical trials who were blinded to all clinical data about the patients. The US blind readings were by a team comprised of a radiologist and an oncologist. The role of the radiologist was primarily to provide MRI interpretation for each lymph node evaluated. The radiologist also assisted the oncologist in determining which lymph nodes should have been biopsied, in recommending further diagnostic tests, and in answering questions concerning clinical nodal staging and the impact of Combidex on nodal staging and patient management. The primary role of the oncologist was to provide the clinical nodal stage, to recommend the next course of action regarding treatment of the patient, and to assess the impact of Combidex on nodal staging.
Nodal mapping	The adjudicator compared the nodes identified by the Blinded Readers with the nodes identified by the Investigators to complete nodal mapping. The nodal mapping permitted nodes identified by the Investigators and subsequently sampled at surgery/biopsy to be matched to those identified by the Blinded Readers.
NPV	NPV is defined as the probability that a negative result of a procedure correctly identifies a patient who does not have the condition(s) that the procedure is intended to find. In this document, NPV equals the number of negative (non-metastatic) diagnoses made using MR images which were correct by histology divided by the total number of negative diagnoses made using MR images.

Paired Evaluation	Side-by-side evaluation of images obtained before administration of Combidex and images obtained after administration of Combidex.
Post-Dose Evaluation	An evaluation of the Combidex enhanced images alone performed more than 2 weeks after the pre-dose and paired evaluations.
PPV	PPV is defined as the probability that a positive result of a procedure correctly identifies a patient who has the condition(s) that the procedure is intended to find. In this document, PPV equals the number of positive (metastatic) diagnoses made using MR images which were correct by histology divided by the total number of positive diagnoses made using MR images.
Pre-Dose Evaluation	Evaluation of only the unenhanced MR images obtained before Combidex administration.
Pre-Dose (MRI Dx)	Diagnosis (metastatic or non-metastatic) based solely on the size of lymph nodes seen and measured on pre-dose images. Any node with a short-axis size >10 mm was considered metastatic.
Pre-Dose (Readers Dx)	Diagnosis (metastatic or non-metastatic) based on the Blinded Reader's assessment of each node seen on pre-dose images. If the Blinded Reader's assessment was "metastatic" or "possibly metastatic," the node was considered metastatic.
Sensitivity	Sensitivity is defined as the probability that a procedure can identify patients who have the condition(s) that the procedure is being used to find. In this document, sensitivity equals the number of positive (metastatic) diagnoses made using MR images which were correct divided by the total number of positive diagnoses based on histology.
Specificity	Specificity is defined as the probability that a procedure can identify patients who are free from the condition(s) that the procedure is being used to find. In this document, specificity equals the number of negative (non-metastatic) diagnoses made using MR images which were correct divided by the total number of negative diagnoses based on histology.

1 EXECUTIVE SUMMARY

Lymph node status is an important part of clinical staging for many types of cancer. The accurate and reproducible detection of lymph node metastasis is important because the presence, number, and location of nodal disease have significant impact on therapy decisions and prognosis. Cross sectional imaging, such as computed tomography (CT) and magnetic resonance imaging (MRI), relies on lymph node size based criteria to differentiate metastatic from non-metastatic lymph nodes. It is widely acknowledged that the current practice of using size for assessing nodal metastasis is inadequate since normal sized nodes may harbor metastatic disease and enlarged nodes may be increased in size for reasons other than the presence of cancer. A more accurate image-based method for the differentiation of metastatic lymph nodes is needed. This fact is reflected by FDA's designation of Combidex® (ferumoxtran-10) for priority review.

Anatomic imaging is presently used to differentiate benign from malignant lymph nodes as stated in consensus guidelines developed by the American College of Radiology (ACR),[1] the National Comprehensive Cancer Network (NCCN)[2] and the American Joint Committee on Cancer Staging (AJCC).[3] Contrast Enhanced Computed Tomography (CECT) and MRI currently are the most often employed imaging modalities. FDG-PET imaging also can provide information on metabolic status of lymph nodes, but is limited by poor spatial resolution, false positives and lack of uptake for certain cancers, such as prostate carcinoma.

Combidex is an intravenous contrast agent composed of an ultra-small, superparamagnetic iron oxide particle covered with a low molecular weight dextran. Combidex allows differentiation of metastatic and benign lymph nodes on the basis of physiological function instead of size. It is phagocytosed by macrophages in normal and reactive lymph nodes resulting in a decrease in nodal signal intensity (darkening the nodes) on post-contrast T2 and T2* weighted MR images. Neoplastic nodes, lacking macrophage activity, do not take up the contrast agent and hence do not show a decrease in signal intensity on post-dose images. This allows for differentiation of metastatic from non-metastatic lymph nodes based on post-

contrast nodal appearance. Combidex improves the accuracy of MR imaging for the differentiation of metastatic from non-metastatic lymph nodes.

The Phase III Combidex clinical trials were designed to compare imaging results obtained from unenhanced MR images (pre-dose) with those from Combidex enhanced images (post-dose), using histopathological confirmation of nodal status as the gold standard.

Combidex was evaluated in a US Phase III study and in Phase III studies conducted in the EU. In each study, the clinical setting was the same (i.e., patients scheduled for surgery or biopsy for pathologic nodal staging), the dose of Combidex was the same (2.6 mg/kg), and efficacy results were obtained via an independent blinded reading of the images. The efficacy of Combidex was compared to pre-dose evaluations using either established nodal size criteria alone (called the MRI Dx) or other subjective criteria (called the Reader's Dx). The comparator for the primary efficacy endpoint was the size based pre-contrast evaluation. Additional support for the clinical utility of Combidex comes from the published literature including the lead article in the New England Journal of Medicine dated June 19, 2003 by Harisinghani et al[4] as well as numerous other published studies.

These studies demonstrate the efficacy of Combidex. Accuracy is consistently improved in the Combidex enhanced image evaluation. Lymph node size determined whether sensitivity or specificity contributed the most to this improvement in accuracy compared to the size based pre-dose evaluation. In studies where most of the nodes evaluated were large (*e.g.*, the EU Phase III study) use of Combidex resulted in a significant increase in specificity. In studies where most of the nodes were small (*e.g.*, the US Phase III study and the NEJM blinded read) use of Combidex resulted in a significant increase in sensitivity.

In the Phase III clinical studies, trade-offs between sensitivity and specificity were observed in the two pre-contrast blind reading results. The pre-contrast evaluations resulted in either high sensitivity or high specificity, but not both. The accuracy was the same for both. However, in the Combidex enhanced blinded evaluations, <u>both</u> sensitivity and specificity

were uniformly high. The accuracy of the post Combidex images was higher than either of the pre-contrast evaluations. The results with Combidex not only improved accuracy but also decreased inter-reader variability compared to the pre-dose Reader's Dx.

Combidex enhanced MR imaging improved the accuracy in differentiating metastatic from non-metastatic lymph nodes as follows.

- Sensitivity is increased from 54% to 85% over the size based diagnosis
- Specificity is increased from 51% to 85% over the Reader's diagnosis
- Increase from 68-71% to 85% in accuracy over either size based or readers diagnosis

The original NDA submission contained safety data for 947 subjects who had received Combidex in two patient populations for two distinct indications: imaging the liver/spleen and evaluation of lymph node disease. All of the patients studied for the lymph node indication were administered Combidex by infusion following dilution (in 50 or 100 ml saline), but most of the patients enrolled in studies for imaging of the liver/spleen were administered Combidex by direct bolus injection. The sponsor has subsequently withdrawn the liver/spleen indication and discontinued the use of bolus injection because the rates of adverse events and serious adverse events are considerably higher with this method of administration. Administering Combidex by infusion following dilution in 100 ml saline over a period of approximately 30 minutes not only significantly reduces the incidence of adverse events, but it also facilitates prompt intervention, when appropriate, in treating those adverse events that may occur. In many cases when a patient experienced an adverse event, discontinuing the infusion was the only treatment required.

Since the original NDA, complete safety and demographic data from an additional 1,114 subjects enrolled in clinical studies with Combidex have been submitted. The safety database for Combidex now includes over 2,000 subjects. The rate of serious adverse events associated with infusion of Combidex following dilution is lower than that for iodinated contrast agents used with computed tomography for anatomic imaging of tumors and lymph nodes. The safety profile of Combidex resembles that of iodinated contrast

agents, with a small but definite risk of anaphylactoid-type events that must be weighed against the improved efficacy over current practice.

In the assessment of the balance of risks and benefits of imaging agents, the FDA's Medical Imaging Guidance[5] notes that potential risks include both the risks related to the administration of the drug and the risks of incorrect diagnostic information. The shortcomings of current imaging procedures for diagnosing nodal metastasis were demonstrated very clearly during the clinical trials of Combidex. Whether one uses size criteria or more subjective methods of interpretation, current imaging techniques provide high sensitivity *or* high specificity, *but not both*, which results in poor to moderate accuracy. The impact of a false diagnosis is the same regardless of the technology used to reach the diagnosis–CT or MR, enhanced or not. False diagnoses of lymph node status can lead to inappropriate treatment (with attendant morbidity) of the patient. Combidex reduces the number of both false positive and false negative diagnoses when evaluating lymph node status and significantly improves the accuracy of clinical nodal staging.

Combidex fills an unmet medical need as there is no other FDA approved contrast agent that accurately differentiates metastatic from non-metastatic lymph nodes. More accurate diagnosis of lymph node status has the potential to reduce morbidity and improve patient care.

2 INTRODUCTION

Lymph node status is an important part of clinical staging for many types of cancer. The accurate and reproducible detection of lymph node metastasis is important because the presence, number, and location of nodal metastases have significant impact on therapy decisions and prognosis. Cross sectional imaging techniques such as CT and MRI rely on size based criteria to differentiate metastatic from non-metastatic lymph nodes. A large body of work has appeared over the last decade supporting the use of short axis nodal diameter of 10 mm as the appropriate threshold for image-based identification of metastatic lymph nodes. The current practice of using size for assessing nodal metastasis is inadequate since normal sized nodes may harbor metastatic disease and enlarged nodes may be increased in size for reasons other than the presence of cancer (e.g. inflammation). Thus, a more accurate image-based method for the differentiation of metastatic lymph nodes is needed. Combidex has been developed to improve the current methodology for assessing nodal metastasis.

Combidex is an intravenous contrast agent composed of an ultra-small, superparamagnetic iron oxide particle covered with a low molecular weight dextran. As it is incorporated into various organs of the reticuloendothelial system, it is useful for imaging lymph nodes in the late phase distribution (24 to 36 hours post-dose). Combidex is phagocytosed by macrophages in normal and reactive lymph nodes resulting in a decrease in nodal signal intensity (darkening the image) on post-contrast T2 and T2* weighted MR images. Neoplastic nodes in which cancer cells either partially or completely replace macrophages do not take up the contrast agent and hence do not show a decrease in signal intensity on Combidex enhanced post-dose images. This allows for differentiation of metastatic from non-metastatic lymph nodes based on post-contrast nodal appearance rather than size. An example of positive and negative nodes is shown in Figure 1.

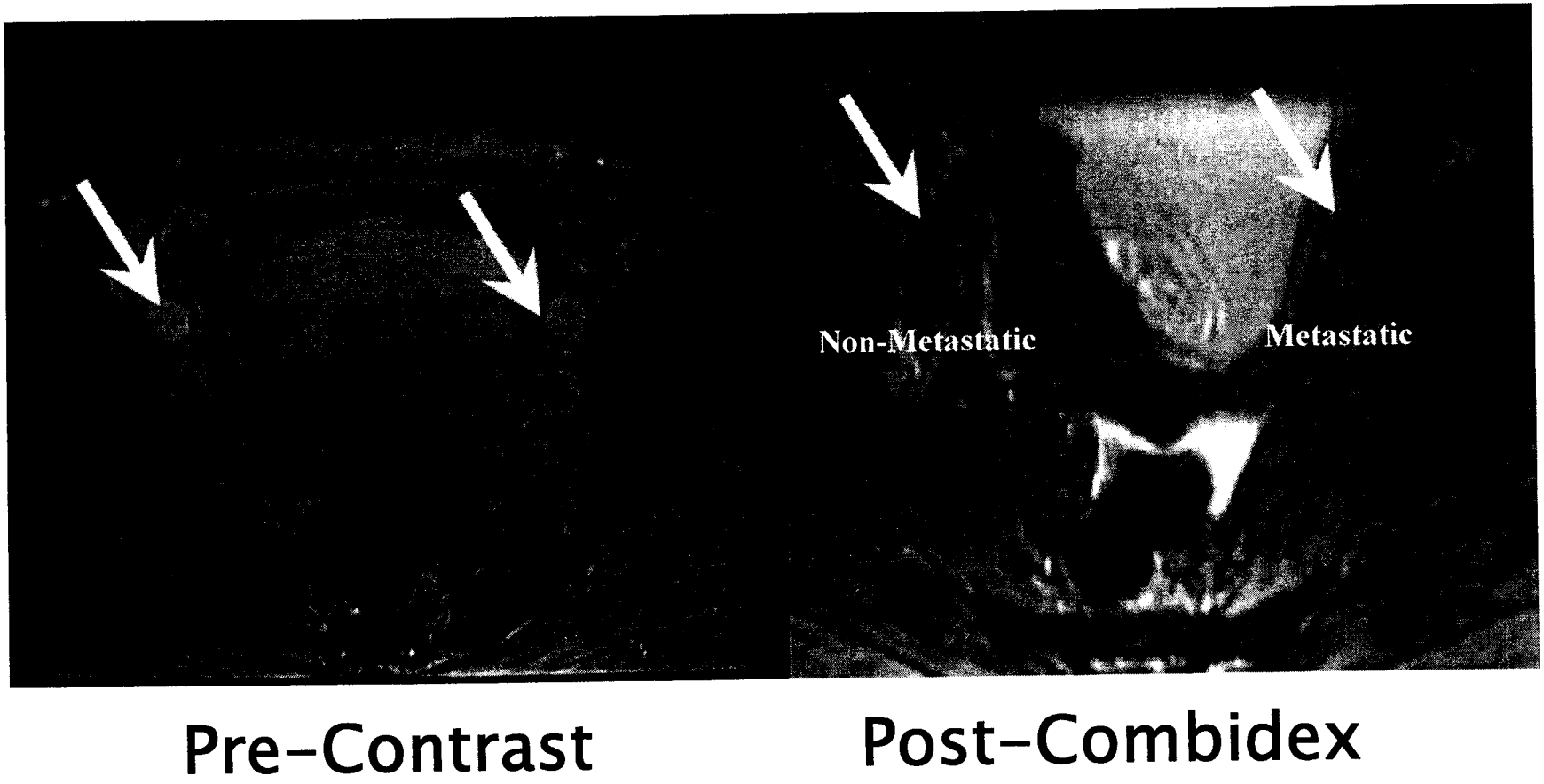


Figure 1. Example of the effect of Combidex in normal and metastatic nodes

Pre-contrast image shows bilateral nodes of approximately the same size and morphology, providing no way to evaluate if they are metastatic or not. Post-Combidex, the MR signal intensity decreases in the normal lymph node. The metastatic node shows uptake only in a thin rim of normal tissue.

The approval being sought for Combidex is consistent with the FDA Guidance for Developing Medical Imaging Drug Products[5] for a disease or pathology detection indication. According to this guidance:

> *In general, establishing effectiveness has two components: (1) establishing the accuracy of the test and (2) establishing the clinical value of the test. In some cases, a test that provides accurate information in describing a clinical condition is of well established value. Generally, this is true for proposed indications for structure delineation and disease or pathology detection or assessment. When there are established methods of seeking similar information and the only issue is comparing the accuracy of the new and old methods, the clinical usefulness of the indication need not be reestablished.*

Contrast Enhanced Computed Tomography (CECT) and MRI using size criteria to differentiate benign from malignant lymph nodes is widely recommended in consensus guidelines developed by the American College of Radiology (ACR)[1], the National Comprehensive Cancer Network (NCCN)[2] and the American Joint Committee on Cancer Staging (AJCC).[3] Combidex improves the accuracy of nodal differentiation over both assessments of non-contrast images (size based and more subjective methods). The improved ability to differentiate normal and metastatic lymph nodes can assist in determining the extent and location of disease, thereby adding value to current diagnostic procedures and more effectively providing guidance in the management of the patient.

The clinical program for Combidex, to date, has included evaluation of the product in over 2,000 subjects. The focus of this briefing document is two Phase III clinical trials where Combidex was evaluated for use in assisting in the differentiation of metastatic and non-metastatic lymph nodes. Combidex was compared to both the currently accepted methodology for evaluation of lymph nodes (i.e., nodal size) and a more subjective evaluation in which the individual reader used any criteria desired (Reader's Dx). The design of the trials compared unenhanced images (pre-dose) with Combidex enhanced images (post-dose), with histopathological confirmation of nodal status as the gold standard.

Additional evidence supporting the effectiveness and the clinical utility of Combidex in assisting in the differentiation of metastatic lymph nodes has been reported in the peer-reviewed literature including a study published in the New England Journal of Medicine.

The sponsor studied intravenous administration of Combidex by both bolus injection and by infusion following dilution in saline in the clinical trials leading up to the NDA submission. Adverse event rates related to a bolus injection led to a decision to withdraw the indication (liver and spleen imaging) involving this method of administration. A significant amount of additional data from post-NDA clinical trials using Combidex administered using the dilution and infusion method has been accumulated in the target patient population. The safety data demonstrate that administering Combidex by infusion following dilution in 100 ml saline over a period of approximately 30 minutes significantly reduces the incidence of adverse events, as well as facilitates prompt intervention, when appropriate, in treating events that may occur. Discontinuation of the infusion was often the only treatment required to manage adverse events.

Of particular importance, a lower rate of serious adverse was seen when Combidex was administered by infusion followed by dilution; there were 3/131 (2.3%) subjects with serious adverse events receiving the drug undiluted compared with 5/1930 (0.3%) subjects with serious events receiving the drug diluted and infused. The type of serious adverse events observed with dilution and infusion of Combidex is similar to the type of serious adverse events reported in the existing labeling for iodinated contrast agents used with CT however the rate of serious adverse events with Combidex is less than one third the rate in iodinated contrast package inserts. Radiologists are experienced in managing and treating these type of adverse events and the contrast agent will have warnings and precaution appropriate for contrast media and consistent with the FDA Class Labeling Guideline for Radiopaque Drugs[6] as can be seen in the proposed package insert for Combidex (refer to Appendix B).

Combidex addresses an unmet medical need for more accurate differentiation of metastatic from non-metastatic lymph nodes, thereby potentially allowing more appropriate and less

invasive treatment of patients with suspected cancer. Combidex enhanced MR imaging provides improved diagnostic accuracy and a lower risk of false nodal diagnosis. The adverse events observed are similar to those that occur with contrast media used with CT for nodal evaluation and are manageable with administration of Combidex by dilution and infusion. Given the significant morbidity associated with most cancer treatments, the potential benefits of the use of Combidex outweigh the risks in the intended population.

3 REGULATORY HISTORY OF COMBIDEX

Advanced Magnetics, Inc. has worked closely with the FDA's Division of Medical Imaging and Radiopharmaceutical Drug Products to ensure the development of Combidex reflected current policies with regard to the preclinical and clinical data requirements, and chemistry, manufacturing and controls for the contrast agent.

Table 1 provides a representative chronology of the ongoing FDA interactions involving the development of Combidex. Based on the ongoing interactions and agreements reached between the sponsor and the FDA in the development of this contrast agent, a large body of evidence supporting the safety and efficacy of Combidex has been developed.

Table 1: Combidex Regulatory Development Program

Activity	Date
Investigational New Drug Exemption Filed	February 1992
End of Phase II Meeting	December 1994
Meeting to discuss LN indication	July 1995
Phase III US-Based Study Protocol, Case Report Forms, and Statistical Analysis Plan Submitted to FDA for Review	August 1996
Meeting to discuss LN indication, statistical plan, blind read & blind read case report forms	June 1997
Phase III US-Based Study Protocol Revised Analysis Plan Submitted to FDA per FDA Request	July 1998
Meeting on the design and conduct of the blind read	September 1998
End-of-Phase III Meeting	June 1999
NDA Submission	December 1999
FDA Issuance of Approvable Letter	June 2000
Advanced Magnetics Response to Approvable Letter	September 2004

In December 1999, the original NDA was submitted which contained safety data for 947 subjects who had received Combidex in two patient populations for two distinct indications: imaging the liver/spleen and evaluation of lymph node disease. All of the patients for the lymph node indication were administered Combidex by dilution (50 or 100 ml saline) and slow infusion, but most of the patients enrolled in studies for imaging of the liver/spleen were administered Combidex by direct injection. Direct bolus injection was needed for liver/spleen imaging with Combidex to be viable. The sponsor has subsequently withdrawn the liver/spleen indication and the use of direct injection because both the rate of adverse events and the rate of serious adverse events were considerably higher with this method of administration than when the agent is diluted and administered by infusion.

Clinical studies have included pharmacokinetic and pharmacodynamic studies, dose ranging studies and Phase II and Phase III safety and efficacy studies. Clinical studies have been conducted in the US sponsored by Advanced Magnetics, Inc. and in the EU sponsored by Guerbet Laboratories.

Table 2 includes the studies submitted with the NDA to support the marketing of Combidex. The Phase III studies are identified as Protocols 38804-10, ALS-3-2-A, ALS-3-7-A, and ALS-3-10-A.

Table 2: Human Studies Included in the Combidex NDA (Phase III Pivotal Studies are Shaded)

Study Type	Protocol Number Location	Study Design
Phase III Studies	38804-10 US	Open-label, multicenter study in patients with highly suspected or confirmed cancer with possible metastasis to lymph nodes in head & neck, pelvis, breast, lung or abdomen
	ALS-3-2-A EU	Open-label, multicenter study in patients with squamous cell carcinoma of upper aerodigestive tract
	ALS-3-7-A EU	Open-labeled, multicenter study in patients with gynecologic or urologic cancer
	ALS-3-10-A EU	Open-label, multicenter study in patients with breast cancer
Dose-Ranging and PK Studies	38804-7 US	Open-label, Dose Range single-center study in normal volunteers
	38804-13 US	Open label, Dose Range, PK study in normal volunteers
Phase II Studies	38804-2, -3, -4 US	Open-label, multicenter, combined study in patients with confirmed extracranial head & neck cancers or known carcinoma of the pelvis, lung (Stage 1, 2, or 3A), or breast
	ALS-3-3-A (DC00293AC) EU	Open-label, multicenter study in patients with known carcinoma of the pelvis
	38804-9 US	Open-label, multicenter study in patients with confirmed head & neck, lung, breast or pelvic cancer

Pharmacokinetic and pharmacodynamic data from both nonclinical and clinical studies of Combidex are consistent with a three phase model of initial vascular distribution of the iron oxide crystals followed by phagocytosis or ingestion of the material primarily by the reticuloendothelial cells of the liver and spleen, with lesser amounts taken up by the lymph nodes. After dissolution the iron is incorporated into the normal body iron pool.

Combidex has a blood half life of approximately 25 to 30 hours in humans and is eventually incorporated into the elements of the reticuloendothelial system including lymph nodes. In the late phase of distribution (24 to 36 hours), the contrast agent allows imaging of lymph nodes. Non-metastatic lymph nodes (with macrophages present) phagocytose the contrast

agent resulting in decreased signal on post-contrast T2 or T2* MR images that gradually returns to pre-contrast levels over 3 to 10 days. Metastatic lymph nodes which have normal tissue displaced by tumor lacking macrophages, do not take up the contrast agent and hence show no change in signal on the post-contrast images. Combidex is dosed based on body weight and dose ranging studies identified a dose of 2.6 mg of iron per kilogram of body weight as the appropriate dose for evaluation in Phase III clinical trials.

The design, conduct, and analysis of the Phase III Combidex clinical trials are consistent with the FDA's Medical Imaging Guidance (2003). The agent has been developed for a disease or pathology detection or assessment indication. As such, the performance of Combidex was evaluated relative to the currently used methodology for image-based evaluation of lymph nodes, i.e., measurement of the nodes. Discussions with FDA resulted in the design of trials utilizing histopathological confirmation of nodal status as the gold standard for assessing the performance of both unenhanced size based image evaluation and Combidex enhanced image evaluation. The blinded image evaluation was designed with extensive input from FDA.

The Phase III clinical studies were designed to support a disease specific indication with histology as the gold standard. The proposed indication is: Combidex is for intravenous administration as a contrast agent for use with Magnetic Resonance Imaging (MRI). Combidex can assist in the differentiation of metastatic and non-metastatic lymph nodes in patients with confirmed primary cancer who are at risk for lymph node metastases. The information provided by Combidex should be considered in conjunction with other diagnostic information and lymph node findings from Combidex should be pathologically confirmed unless medically contraindicated. The demographic characteristics of the patients in the Phase III clinical studies are shown in the following table.

Table 3: Demographic Information for Evaluable Patients Phase III Clinical Trials

Characteristics	US Phase III Protocol 38804-10 (N=153)	EU Phase III Protocols -2-A/-7-A/-10-A (N=160)
Sex		
Male	86 (56%)	116 (73%)
Female	67 (44%)	44 (28%)
Race		
White	125 (82%)	160 (100%)
Black	15 (10%)	0 (0%)
Asian	3 (2%)	0 (0%)
Hispanic	8 (5%)	—
Other	2 (1%)	0 (0%)
Age (years)		
Mean (SD)	57.0 (13.46)	57.5 (10.38)
Range	25-87	35-84
<40	15 (10%)	5 (3%)
40-64	84 (55%)	117 (73%)
≥65	54 (35%)	38 (24%)
Body Region Imaged		
Head & Neck	35 (23%)	80 (50%)
Pelvis	39 (21%)	50 (31%)
Breast	23 (15%)	30 (19%)
Chest/Mediastinum	32 (21%)*	--
Abdomen	26 (17%)*	--

*Two patients underwent imaging of both abdomen and chest/mediastinum and are counted for each body region

The NDA was given a priority designation and in June 2000, FDA completed its review of the NDA and issued an "approvable letter" for the drug. Since the submission of the original NDA, complete safety and demographic data from an additional 1,114 subjects enrolled in clinical studies with Combidex have been provided. These data were submitted in the response to the FDA's approvable letter. Additionally, the response to the approvable letter included a study of 80 prostate cancer patients that was published in the June 2003 New England Journal of Medicine by Harisinhani et al. The findings of this study provide additional support for the safety and efficacy of Combidex.

4 EFFICACY OF COMBIDEX

4.1 Program Overview

- Phase I and II: A Phase I trial in 41 healthy volunteers showed the signal intensity of normal lymph nodes changed slightly at 4 hours and significantly at 24 hours after injection of a 1.7 mg Fe/kg dose. Phase II trials in 67 patients with cancer of the head and neck, lung, breast, and pelvis (Protocols 33804-2, -3, -4, and -9) confirmed the signal intensity of benign lymph nodes was substantially lower than that of metastatic nodes on post-dose images. Analysis of data from two dose-ranging studies (Protocols 38804-7 & 38804-13) in 60 subjects supported the dose of 2.6 mg Fe/kg and an imaging time of 24 to 36 hours for evaluation of lymph nodes. The results of these studies were confirmed in a study of patients with lung, pelvic and breast cancers undergoing lymph node examination for possible metastases. In all, over 100 subjects were studied in Phase II with safety and efficacy results that support the proposed indication.

- Phase III: Phase III studies in the US and the EU were designed to evaluate the ability of Combidex to differentiate metastatic from non-metastatic lymph nodes compared to unenhanced MR imaging using size criteria for diagnosis on a nodal level. They were consistent with respect to the patient population studied, the dose and administration of the contrast agent and the use of histological confirmation of disease as the gold standard. The US study evaluated lymph nodes in all anatomic regions. The three EU studies which evaluated lymph nodes in head and neck, pelvis and breast were pooled (per agreement with FDA) into one analysis of efficacy for the NDA. Sensitivity, specificity and accuracy of unenhanced MR and Combidex enhanced MR were compared on a nodal level using histopathology for the primary evaluation of efficacy. The use of size criteria on unenhanced imaging for diagnosis as the appropriate comparator was determined from a review of the literature on the use of anatomic imaging in differentiating metastatic from non-metastatic lymph nodes in all body regions, demonstrating the fact that size is the accepted standard of

practice in differentiating metastatic lymph nodes from benign nodes. The most common established criterion for abnormality is a lymph node greater than 1 cm. This is further discussed in Appendix D.

- Supportive Published Data: The sponsor has submitted a study of 80 prostate cancer patients that was published in the June 2003 issue of the New England Journal of Medicine. This study provides compelling additional evidence to support the effectiveness of Combidex in assisting in the anatomic image-based differentiation of metastatic lymph nodes and demonstrates the potential clinical utility of the contrast agent. The NEJM article and other recent publications showing the efficacy and clinical utility of Combidex are included in Appendix A.

- Integrated Analysis: An integrated analysis of the US, EU and the NEJM publication was undertaken to review the comparative imaging performance of Combidex in differentiation of metastatic from non-metastatic lymph nodes. Although there were differences in the efficacy results on the unenhanced image evaluations, the Combidex efficacy results were consistent and showed improved accuracy in the detection of metastatic lymph nodes in each of the studies. This review is included in this briefing document in Section 4.2.4.

- Clinical Utility and Patient Management: While the proposed indication for Combidex is for disease or pathology detection based on the improved accuracy of the agent over currently used methodology, additional information on clinical utility for the agent was collected in the clinical trials. This includes information supporting the impact of Combidex on patient staging and management. The data are reviewed in this briefing document in Sections 4.2.5 and 4.2.7.

4.2 US Phase III Study

4.2.1 US Protocol and Blind Read Development

The US Phase III clinical trial was designed to evaluate the use of Combidex in patients:

1) Who had highly suspected or confirmed cancer with possible metastasis to lymph nodes in at least one of the following body areas: head & neck, lung, breast, abdomen, pelvis; *and*
2) Had been identified by a surgeon or oncologist as needing to undergo surgery or needle biopsy within three weeks to evaluate nodal status; a*nd*
3) Had at least one lymph node visualized with unenhanced MR imaging.

Patients received a single intravenous dose of Combidex based on body weight (2.6 mg Fe/kg). MRI examinations were performed within 14 days prior to drug administration and 24 to 36 hours after drug administration. Lymph node biopsy or surgery was performed within 3 weeks after drug administration. The presence or absence of lymph node metastases was determined by histopathologic analysis of the nodes. The primary efficacy endpoint was the ability of Combidex to differentiate metastatic from non-metastatic lymph nodes compared to unenhanced MR imaging using the established standard of size criteria with histolopathology as the standard.

The Phase III study design was rigorous in matching the lymph nodes seen on the MR images with nodes evaluated at pathology so that histological confirmation of nodal disease could be used as the gold standard in blinded readings of the images. In order to correlate the lymph nodes seen on the images with pathology the Investigators reviewed the nodal identifications with the surgeons prior to surgery either by providing the actual MR images as reference or by providing diagrams on which the nodes were drawn and labeled. Often the Investigator was present during the surgery to assist in labeling nodes for correlation.

The extent of surgery performed was based on the medical judgment of the patient's physician, who took into account the clinical history, physical examination results, and

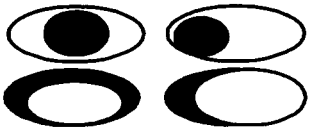
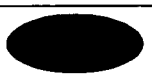
diagnostic imaging studies (excluding the Combidex enhanced MR images) for the patient. During surgery, the surgeon referred to the MR images and/or diagrams only to label the study nodes for the pathologist. The surgeon then placed each node or tissue specimen in a separate container to send to the pathologist. Each container with a study node (or nodal tissue sample in the case of needle biopsy) was labeled. Landmarks, size, and nodal configuration were also used to identify a node when it was excised. All nodes removed at surgery were examined histologically. If none of the lymph nodes, groups of nodes or coalescences visualized by the Investigators on both the pre- and post-dose MRI scans was sampled for histology, then the patient was considered not evaluable.

Because size is both the only objective criterion established in the medical literature and is the current standard of care in clinical practice, the blind read of the Phase III images was developed to test the efficacy of the contrast agent in differentiating metastatic from non-metastatic lymph nodes as compared to a pre-contrast evaluation based on nodal size. The blind read was also designed to test the performance of the guidelines showing nodal appearance with Combidex for inclusion of the diagrams in the package insert

The Blinded Readers evaluated the MR images without the nodes being identified on the images. This blind read design was mandated by the FDA's Division of Medical Imaging in order to minimize bias in the reading of lymph nodes. The blind readers were not involved with the clinical studies and were fully blinded to all patient history, clinical information and the results of other diagnostic tests. There were three separate blind readings: pre-dose, paired enhanced and unenhanced images, and post-contrast images only (post-dose only). Images were presented in a randomized manner to the blind readers. The Combidex paired and post alone blind read evaluations were conducted separately, at least two weeks apart, to minimize recall bias. For the post –contrast only blind read, the reader was instructed to use only the Combidex imaging guidelines to determine if a node was metastatic or non-metastatic.

The use of the Combidex Lymph Node Imaging Guidelines makes the reader more accurate and more consistent in the evaluation because it is an objective evaluation based on the normal physiological function of the lymph nodes (Table 4).

Table 4: Combidex Lymph Node Imaging Guidelines

#	Post-Dose	Description	Diagnosis
1		No blackening of node or node is hyperintense to surrounding tissue; heterogenous or homogenous architecture	Metastatic
2		Node has central high signal with darkening along the peripheral rim; heterogenous architecture	Metastatic
3		Partial darkening whereby more than 50% of the node has area of high signal intensity; heterogenous architecture	Metastatic
4		Less than 50% of node has high signal intensity; heterogenous architecture	Possibly Metastatic
5		Node having an overall dark signal other than a central or hilar area of fat seen on T1 sequence; heterogenous architecture	Non-metastatic*
6		Node having an overall dark signal with speckles of subtle granularities; homogenous architecture	Non-metastatic
7		Node having an overall dark signal intensity; homogenous architecture	Non-metastatic

*In the EU studies this did not appear as a separate category.

When the blinded evaluation of the unmarked images was completed, an independent radiologist (or adjudicator), who was not affiliated with the study, matched the nodes identified by the Blinded Readers with the nodes identified by the Investigators (nodal mapping). The nodal mapping permitted nodes sampled at surgery/biopsy with histology to be matched to those identified by the Blinded Readers.

This blind read was a rigorously designed and conducted test of the contrast agent in differentiating metastatic from non-metastatic lymph nodes. Blinded Readers were not provided any clinical information about the patient including medical history, physical exam results, laboratory data or the results of other imaging studies. Nodes were not identified for the readers on the images. Pre-contrast images were presented to the blind readers with all patient data obliterated and in a fully randomized manner; after the pre-contrast images were evaluated fully and committed to, the post-contrast image was added for the paired reading. After a time period of at least two weeks (to prevent recall bias), the post-contrast images were randomized and presented to the Blinded Readers for the post-contrast only reading.

The US Phase III clinical trial protocol and blinded readings were carefully developed with extensive input from the FDA's Division of Medical Imaging to support a disease specific indication of differentiation of metastatic from non-metastatic lymph nodes with histology as the gold standard.

4.2.1.1 US Phase III Efficacy Results

The Phase III Statistical Analysis Plan primary measure of efficacy was prospectively designed as the ability of Combidex to differentiate between metastatic and non-metastatic nodes. The specific primary statistical test was a McNemar's test of the ability of Combidex images as compared to pre-Combidex images to detect metastatic nodes (sensitivity). The diagnosis of metastatic nodes was based on pre-dose images as determined by size (nodes >10 mm were considered metastatic). Size was chosen as it is the generally recognized criterion of determining disease in lymph nodes as discussed in the overview to this section and in Appendix D; the 10 mm cutoff is the size most often cited in the literature and is used in clinical practice.

On a per node basis, it was prospectively assumed that Combidex enhanced imaging would result in 85% sensitivity, and that pre-Combidex images based on the 10 mm size threshold would result in 70% sensitivity (based on literature), and that a sample size of 97 nodes with

histologically documented metastasis would result in a significant ($p<0.05$) McNemar test with 80% power.

The primary efficacy measure in the Phase III clinical trial was prospectively stated as an improvement in sensitivity, on a nodal level, of Combidex enhanced MR images using signal intensity changes which were visually described in the Combidex Lymph Node Imaging Guideline when compared with results of unenhanced MR imaging using size where lymph nodes greater than 10 mm were considered metastatic and those less than 10 mm were considered non-metastatic.

In the blind reading, Combidex sensitivity was 85%, as expected, while the sensitivity using size criteria on the pre-dose images was 54%. The results of the blind read for the primary endpoint are shown in Table 5.

Table 5: Sensitivity, Specificity and Accuracy for Unenhanced and Combidex vs. Unenhanced Size Criteria on a Nodal Level

Evaluation		**N**	**Sensitivity**	**Specificity**	**Accuracy**
Pre-Dose MRI Dx (Size Criteria)	R1	173	54%	82%	69%
	R2	158	54%	81%	67%
	Mean	166	54%	82%	68%
Combidex Paired	R1	173	83%	76%	79%
	R2	157	83%	77%	80%
	Mean	165	83%	77%	80%
Combidex Post Alone	R1	169	85%	85%	85%
	R2	147	84%	84%	84%
	Mean	158	85%	85%	85%

R1=reader 1, R2=reader 2

The comparison of sensitivity and accuracy between the pre-dose and both the paired and post-dose only blinded readings yielded statistically significant improvements ($p<0.05$ McNemar's) in each case. It can be seen by these results that Combidex performed as

anticipated and that the prospective primary endpoint was met. Additionally, there was no statistically significant difference between the number of nodes seen on the pre-dose scans and the number seen on the post-dose images by the Blinded Readers.

The increase in the accuracy of differentiation of metastatic from non-metastatic lymph nodes demonstrated in the study results in a reduction of the number of incorrectly diagnosed lymph nodes as shown in Table 6.

Table 6: Average of Readers: True and False Positive and Negative Nodes: Combidex vs. Unenhanced Size Criteria

Evaluation	N	True Positive	True Negative	Correct	False Positive	False Negative	Incorrect
Pre-Dose MRI Dx	166	44	70	114	15	37	52
Combidex Paired	165	68	64	132	19	14	33
Combidex Post Alone	158	67	67	134	12	13	25

The data demonstrate that in the pre-contrast evaluations using the objective criteria of size, 31% (52/166) of the nodes were characterized incorrectly (false positive and false negative) compared with 20% (33/165) for the paired image evaluation and 16% (25/158) for the post alone evaluation.

The use of Combidex improves the accuracy of the imaging procedure from 68% to 85% and reduces the overall number of false diagnoses (both false positives and false negatives). The use of Combidex increases the reader's ability to correctly determine nodal status as metastatic or non-metastatic.

4.2.1.2 Patient Level Analyses

The improvement in accuracy observed at the nodal level also translated to fewer false diagnoses at the patient level. In addition, the post alone contrast evaluation in which only Combidex enhanced images were evaluated resulted in the lowest percentage of false diagnoses at the patient level. In this evaluation approximately one third of the pre-contrast

false patient diagnoses were eliminated. Table 7 shows the number of patients who were falsely diagnosed for each of the readings.

Table 7: Incidence of False Patient Diagnoses (FP + FN)
Combidec versus Pre-dose Size Criteria

Evaluation	Blind Reader 1	Blind Reader 2
Pre-Dose MRI Dx	30% (34/112)	32% (39/122)
Combidex Paired	25% (25/101)	23% (28/119)
Combidex Post Alone	20% (22/111)	21% (24/112)

There is reduced risk due to false diagnoses (false positives and false negatives), since Combidex enhanced MR has far fewer false diagnoses than unenhanced MR, both on a patient basis and a nodal basis. The impact of a false diagnosis is the same whether it is from a CECT, an ultrasound, an unenhanced MR or a Combidex enhanced MR – false diagnoses lead to potentially inappropriate treatment of the patient.

4.2.1.3 Reader's Diagnosis

Although diagnosis by size (MRI Dx) was the primary pre-dose efficacy comparator, the sponsor agreed to collect additional data for the pre-dose images based on an overall diagnosis using all information available to the reader (Reader's Dx) which was requested by the FDA's Division of Medical Imaging.

However, in the blind read, the Reader's Diagnosis involved asking the physician to make a subjective diagnosis of lymph node disease in the absence of any additional patient information. As such, the subjective Reader's Diagnosis in a blind reading bears little resemblance to the clinical practice of medicine and as discussed below resulted in a bias toward a positive nodal diagnosis. Even if one assumes that relying on size to evaluate images for nodal disease may be supplemented with additional patient-specific information to assist the skilled physician in making his or her best judgment, the Reader's Diagnosis in a blind reading does not represent how this would occur in clinical practice. Information such

as the tumor type, stage, grade, and proximity to the nodes being evaluated would all be considered as part of the decision making process in actual clinical practice but were no provided to the reader.

The average of the two blind reader's performance for differentiating malignant from non-malignant lymph nodes based on the gold standard of histology are presented in Table 8. The table provides the derived values of sensitivity, specificity and positive and negative predictive value and shows the unenhanced image evaluations using size criteria (MRI Dx) and the Reader's Dx.

Table 8: Average of Readers for the Two Pre-Dose Evaluations: - Sensitivity & PPV, Specificity & NPV, Nodal Level

Basis of Pre-Dose Evaluation	N	Sensitivity	PPV	Specificity	NPV
Pre-Dose MRI Dx	166	54%	74%	82%	65%
Pre-Dose Reader's Dx	166	91%	65%	51%	86%

The sensitivity and specificity of the two pre-dose evaluations were very different. When the blinded readers used objective size criteria (MRI Dx), sensitivity was low (54%) and specificity was high (82%). Subsequently when these blind readers were allowed to use any subjective criteria they wished (Reader's Dx) sensitivity was increased (from 54% to 91%) but only at the cost of substantially decreased specificity (from 82% to 51%).

Sensitivity is the number of nodes called positive out of the number of all real positive nodes on histology. PPV is the number of nodes that were correctly characterized as positive out of all those nodes called positive. The increase in pre-contrast sensitivity obtained for the Reader's Diagnosis was accompanied by a decrease in the PPV. This means the reader is getting higher sensitivity largely because he is calling a higher proportion of all nodes positive. In doing so the percent the reader is getting correct is dropping. The blind reader is incorrectly calling more nodes positive when he is allowed to be subjective about the reading. The subjective reader's diagnosis is biased towards calling more nodes metastatic,

sacrificing specificity (decreasing from 82% to 51%) for the sake of sensitivity (increasing to 91% from 54%). The same effect is observed with specificity. The readers in the Reader's Dx evaluation are calling too few of the true negatives correctly, so specificity is poor. The blind readers using the Readers Dx are over-diagnosing disease in this subjective assessment.

The unenhanced image evaluations result in high sensitivity (Reader's Dx) or high specificity (MRI Dx) but not both. The use of a subjective Reader's Diagnosis sacrifices specificity for the sake of sensitivity which ultimately does not improve the accuracy of the diagnosis. The two readings have the same accuracy (68% and 71%), but make different kinds of errors – the Reader's Diagnosis results in more false positives, the use of size (MRI Dx) results in more false negatives.

With Combidex enhanced imaging, specificity increases compared to the Reader's diagnosis and NPV stays high (82% and 85% Combidex paired and post only), meaning that the contrast agent is improving the ability of the radiologist to correctly identify normalcy (non-metastatic nodes) while the sensitivity increases relative to the MRI diagnosis based on nodal size. Table 9 presents a comparison of the pre-contrast evaluation based on the Reader's Diagnosis with Combidex in the same manner presented in Table 5 for the size based diagnosis.

Table 9: Sensitivity, Specificity and Accuracy for Combidex vs. Unenhanced Reader's Diagnosis on a Nodal Level

Evaluation		N	Sensitivity	Specificity	Accuracy
Pre-Dose Readers' Dx	R1	173	94%	38%	64%
	R2	158	88%	64%	77%
	Mean	166	91%	51%	71%
Combidex Paired	R1	173	83%	76%	79%
	R2	157	83%	77%	80%
	Mean	165	83%	77%	80%
Combidex Post Alone	R1	169	85%	85%	85%
	R2	147	84%	84%	84%
	Mean	158	85%	85%	85%

The Combidex paired image reading and the Combidex post only image reading both result in high sensitivity and high specificity, without a trade-off of one measure for the other. This results in an increase in overall accuracy from 71% to 85% for differentiation of metastatic from non-metastatic lymph nodes when compared to the Reader's Diagnosis.

The use of Combidex improves the accuracy of the imaging procedure (regardless of which pre-dose evaluation one uses) and reduces the overall number of false diagnoses (both false positives and false negatives). The use of Combidex increases the reader's ability to correctly determine nodal status of metastatic or non-metastatic and reduces the reader variability seen with the Reader's Diagnosis.

4.2.1.3.1 Consistency of the Combidex Efficacy Results

Significant differences in sensitivity and specificity were observed in the unenhanced evaluations based on whether a radiologist used size criteria alone (MRI Dx) or used the subjective Readers Dx. The inconsistencies in sensitivity and specificity of the two pre-dose evaluations as well as the greater variability between the Blind Readers with the use of the more subjective Readers Dx are shown in Table 10.

Table 10: Inconsistency of Unenhanced Efficacy Results

	Sensitivity	Specificity	Accuracy
Pre-Dose MRI Dx BR 1	54%	82%	69%
Pre-Dose MRI Dx BR 2	54%	81%	67%
Pre-Dose Readers Dx BR 1	94%	38%	64%
Pre-Dose Readers Dx BR 2	88%	64%	77%

The pre-dose evaluation based on size sacrifices sensitivity for specificity while the pre-dose evaluation based on the Reader's Dx sacrifices specificity for sensitivity. Inter-reader variability is the greatest for the Reader's diagnosis.

The post-contrast results are very consistent as shown in Table 11.

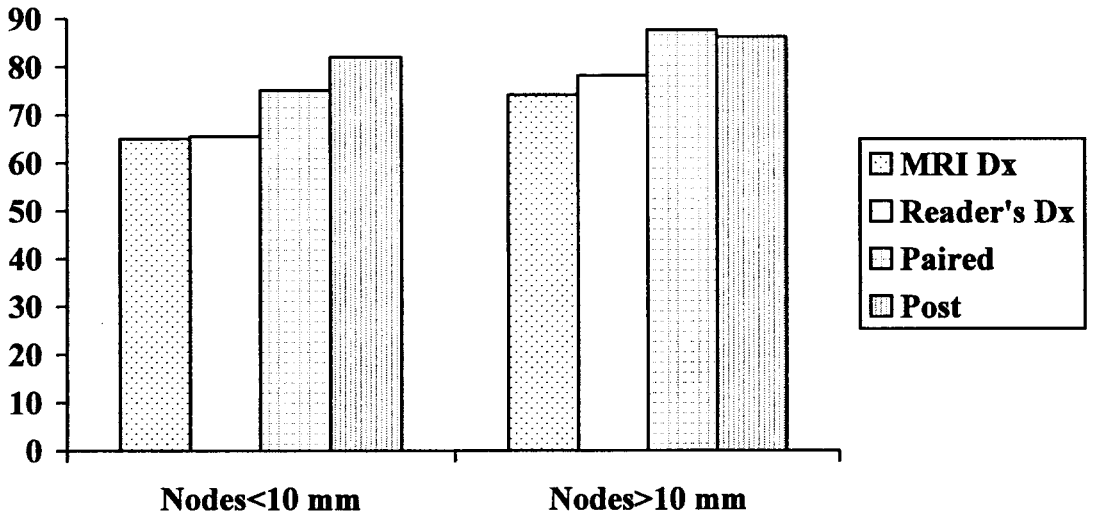
Table 11: Consistency of Combidex Efficacy Results

	Sensitivity	Specificity	Accuracy
Combidex Paired BR 1	83%	76%	79%
Combidex Paired BR 2	83%	77%	80%
Combidex Post only BR 1	85%	85%	85%
Combidex Post only BR 2	84%	84%	84%

The Combidex results are consistent with both high sensitivity and high specificity resulting in improved accuracy. The accuracy with Combidex enhanced imaging is improved over both of the pre-dose image evaluations.

Furthermore, the improvement in the accuracy of diagnosis with Combidex was observed in both enlarged and normal sized lymph nodes. The accuracy of Combidex enhanced images was greater than either of the two pre-dose evaluations in the blind read both for nodes greater than 10 mm and also for nodes less than 10 mm as seen in Figure 2.

Figure 2: Average Accuracy of Various Methods of Image Evaluation for Lymph Nodes Less Than and Greater than 10 mm



Regardless of the unenhanced evaluation used for comparison, the number of false diagnoses on a nodal level is reduced with Combidex enhanced imaging as shown in Table 12.

Table 12: Average of Readers: True and False Positive and Negative Nodes

Basis of Evaluation	N	True Positive	True Negative	Correct	False Positive	False Negative	Incorrect
Pre-Dose MRI Dx	166	44	70	114	15	37	52
Pre-Dose Reader's Dx	166	74	45	119	40	7	47
Combidex Paired	165	68	64	132	19	14	33
Combidex Post Alone	158	67	67	134	12	13	25

In the pre-contrast evaluations, using the objective criteria of size, 69% (114/166) of all nodes were correctly diagnosed whereas when the subjective Reader's diagnosis was employed 72% (119/166) of the same nodes were correctly diagnosed. The MRI Dx had more false negatives and the Reader's diagnosis had more false positives. In the Combidex Paired reading 80% (132/165) of the nodes were correctly diagnosed and in the Combidex Post - only readings 85% (134/158) of the nodes were correctly diagnosed.

The same effect can be seen on the patient level analysis, shown in Table 13. The use of Combidex enhanced imaging results in fewer false diagnoses on a patient level.

Table 13: Average of Readers: True and False Positive and Negative Patients

Basis of Evaluation	N	True Positive	True Negative	Correct	False Positive	False Negative	Incorrect
Pre-Dose MRI Dx	118	47	34	81	23	14	37
Pre-Dose Reader's Dx	118	55	23	78	34	6	40
Combidex Paired	111	50	34	84	18	9	27
Combidex Post Alone	110	50	39	89	11	10	21

The number of incorrectly diagnosed patients is reduced in the post-contrast evaluations with Combidex with the lowest levels obtained in the blinded read where only the Combidex enhanced images were evaluated. In the pre-contrast patient level analyses, the subjective Reader's Diagnoses performed slightly poorer than the size based evaluation. As discussed above, the subjective evaluation resulted in an increase in the number of false positives at the nodal level. At the patient level even one positive node results in an overall positive diagnosis for the patient. On the other hand, both post-contrast Combidex evaluations reduced the number of both false positives and false negatives as compared to the pre-contrast size based evaluation and reduced the number of false positives compared to the Reader's diagnosis.

4.2.1.4 Other Evaluations of Efficacy

4.2.1.4.1 ROC Curves

Receiver Operating Characteristic (ROC)[7] curves were generated for the size based pre-contrast reading using threshold values for metastasis of >5 mm, >10 mm, >15 mm and >20 mm, and for the post-contrast readings using the Combidex Imaging Guidelines as threshold values. A series of sensitivities and specificities were calculated from the Readers' responses, using those different thresholds for defining metastases and the ROC curves were constructed by plotting each sensitivity against one minus the corresponding specificity. The area under the curve (AUC) for the ROC analysis, which is a measure of the overall accuracy of a diagnostic procedure, was increased. The increases in AUC confirm the superiority of the paired and post-dose images over the pre-dose images for diagnosing malignant and non-malignant lymph nodes.

4.2.1.4.2 Quantitative Signal Intensity Measurement of Nodes

In order to quantify the effect of Combidex on the MR signal intensity of lymph nodes, quantitative signal intensity was measured for lymph nodes seen on both the pre- and post-dose images, for noise, and for muscle as a control tissue. The signal intensity decreases seen on the T2 and T2* sequences were much larger for non-metastatic nodes than for metastatic nodes, with the largest difference observed on T2* sequences (median change of -58% versus -15%).

4.2.2 EU Phase III Clinical Trials

4.2.2.1 Study Design and Justification

There were three separate Phase III studies with independent blind reads for each. The patient population, entry criteria, dose of Combidex and use of histology as the gold standard were the same in the European clinical trials as the US Phase III study. The EU studies used the patient as the primary endpoint, but collected data on a nodal and group level also. Because the sponsor and the FDA agreed the nodal level was the most appropriate primary

endpoint, the sponsor prospectively designed a data analysis to pool the results of the three studies and to present the pooled data on a nodal level in support of efficacy. This approach was reviewed and agreed upon with the FDA before the clinical trials were completed. The EU data were not available in advance of this decision; this was not a post-hoc analysis.

The European clinical studies enrolled patients scheduled to undergo surgery with lymphadenectomy (as did the US studies). Each of the three EU studies enrolled patients with a specific primary cancer: squamous cell carcinoma of the upper aerodigestive tract (head & neck, 80 patients), urologic or gynecologic tumors (50 patients), or breast cancer (30 patients). A major difference in the EU studies from those conducted in the United States was that the European sponsor (Guerbet Laboratories) initially decided that the exact correlation of nodes seen on the images with histology specimens could be reliably guaranteed only for nodes measuring at least 10 mm because of the resolution limits of the scanners at the time. In the largest Phase III study the protocol instructs that for pathology "Individual evaluation will be performed when anatomical mapping between MRI and surgery is considered reliable i.e. for lymph nodes having a small axis greater than 10 mm". Lymph nodes smaller than 10 mm were to be combined in anatomical groups and the diagnosis made on the entire group. As the studies progressed, the investigators recommended to Guerbet that smaller nodes be evaluated. At that point Guerbet allowed nodes less than 10 mm to be evaluated *if* the imaging sequences allowed. Consequently there was a significantly higher proportion of large (>10 mm) nodes evaluated in these studies than in the US studies (76% vs. 36%).

Similar to the US studies, the investigators reviewed the nodal identifications with the surgeons prior to surgery and provided the surgeons with images and/or diagrams to ensure the accuracy of the correlation of the nodes with pathology. In both the head and neck study and the breast cancer study the radiologist was in the operating room with the surgeon. After lymph node dissection the surgeon sent the sample to the pathologist with marks to identify the anatomic delineation of the nodal groups.

A blind reading of the images was conducted for each of the three studies. Readers were trained with images from studies that were not included in the reading. When the training was complete the blind readers evaluated the images which had been put in random order. The readers reviewed the pre-dose images first, then placed the post-dose images side-by-side with the pre-dose images for a paired review as done for the US blind read. In one study blind readers evaluated nodal groups rather than individual lymph nodes so the results of this study were not included in the pooled nodal analysis data. For each patient the readers were told which lymph node groups or levels had been removed to ensure that they evaluated only nodes for which histology was available. However the nodes were not marked on the images and the readers were blinded to patient medical history and all clinical information as well as the pathology results.

Two blinded readers evaluated the images from each of the studies independent of each other. In one study it became evident that one Blinded Reader did not use the specified study criteria provided to make his diagnosis. Because of this a third blind reader was added to this study.

The readers recorded the size of the node, signal intensity and architecture and also made a reader's diagnosis. The readers used the Combidex nodal imaging guideline shown previously for the diagnosis, although there were minor differences in recording.

In the analyses of sensitivity, specificity and accuracy, diagnoses of "metastatic" and "possibly metastatic" were combined as metastatic. The US and EU studies used the same classifications of disease based on nodal appearance.

4.2.2.2 EU Phase III Efficacy Results

The nodal level analysis of efficacy data from European clinical trials was conducted using the same criteria and rules as were used in the US studies.

Table 14 shows the efficacy data, on a nodal level, with histology as the gold standard that was obtained in the European clinical trials.

Table 14: Sensitivity, Specificity, Accuracy, Nodal Level, EU Studies

Nodal Basis		**Sensitivity**	**Specificity**	**Accuracy**
Pre-Dose MRI Dx	R1	93%	43%	81%
	R2	98%	46%	86%
	R3	71%	50%	64%
	Mean	87%	46%	77%
Pre-Dose Reader's Dx	R1	96%	36%	81%
	R2	98%	46%	86%
	R3	100%	50%	82%
	Mean	98%	44%	83%
Combidex Paired	R1	96%	92%	95%
	R2	93%	85%	91%
	R3	100%	60%	83%
	Mean	96%	79%	90%
Combidex Post Only	R1	83%	78%	80%
	R2	83%	86%	85%
	R3	82%	95%	92%
	Mean	83%	86%	86%

The sensitivity, specificity and accuracy of Combidex enhanced imaging in the EU Phase III clinical trials was comparable to that observed in the US Phase III study. As in the US Phase III study, the pre-dose evaluations exhibit the characteristic trade-off of sensitivity and specificity. In the EU Phase III study the pre-dose evaluation by size criteria resulting in high sensitivity and low specificity while in the US Phase III study the trade-off occurred in the opposite direction: low sensitivity and high specificity.

Because the pre-dose evaluation is based on size, the variability in these parameters occurs primarily as a result of differences in the size of the nodes evaluated in the studies. The sensitivity of the pre-dose MRI Dx using size criteria in the EU studies is high because the majority (76%) of the lymph nodes that were evaluated (those with histology) were greater than 10 mm. By definition, these nodes would have all been called positive using the size criteria of 10 mm in the sponsor's efficacy analysis. The sensitivity of the pre-dose image analysis using the subjective Reader's Diagnosis is also high, as was the case in the US blind reading. However, in both of these readings, the specificity is low. The two pre-dose readings have similar results with high sensitivity and low specificity. The resultant accuracy for the two pre-dose evaluations is similar at 77% and 83%. The effect of nodal size on the pre-dose imaging performance and a more thorough comparison of the results with Combidex across the studies is more extensively discussed in Section 4.3 of this document.

The use of Combidex results in both high sensitivity and high specificity, which provides overall improved accuracy. The accuracy of both the paired (90%) and post alone (86%) image readings with Combidex were better than the unenhanced blinded image readings. The use of Combidex not only is more accurate than unenhanced imaging but it improves the consistency between readers.

4.2.3 New England Journal of Medicine Publication

The sponsor submitted this important publication from a premier medical journal as additional support for the efficacy and clinical utility of Combidex in the diagnosis of metastatic lymph node disease (refer to Appendix A).

4.2.3.1 NEJM Blind Read Design

The publication presents the results of a blinded reading of images from 80 prostate cancer patients. The blind reading was conducted independently from both the US sponsor Advanced Magnetics and the European sponsor Guerbet Laboratories. Images were obtained from patients enrolled in two clinical trials, one in the US at Massachusetts General Hospital

sponsored by Advanced Magnetics and one in the Netherlands sponsored by Guerbet. The studies incoluded patients with a resectable prostate cancer as determined by conventional imaging methods, digital rectal examination, an ultrasound-guided sextant core biopsy, and measurement of serum prostate specific antigen levels.

The radiologists in the two clinical studies worked with the surgeons to accurately match the nodes seen on the images with those evaluated by the pathologist. These investigators provided the surgeon for each patient with a schematic drawing (Netherlands) or a 3D reconstruction of the pelvic anatomy (MGH, example shown in Figure 3 of the article), identifying all of the nodes in relation to the iliac vessels to ensure optimal correlation of the nodes visualized on the images with those removed at open or laparoscopic surgery for prostatectomy with conventional nodal sampling.

At removal, nodes were placed on a grid identifying their location and orientation and then were sent for histopathological analysis by two independent pathologists with no knowledge of the imaging results.

4.2.3.2 Blind Reading

The images from qualifying patients were taken in equal numbers from each study site in enrollment order. Qualifying patients for this blind reading were patients with biopsy proven prostate cancer for whom histological evaluation of lymph nodes was obtained. Consecutive patients who met these criteria were included in the evaluation to minimize bias in patient or image selection. All patient images provided in this fashion were read, none were excluded. The patient identification was stripped from the data file prior to analysis and the nodes were given an arbitrary number for the analysis.

The Blinded Readers were board-certified abdominal radiologists who were not involved in the clinical conduct of the trial and were unfamiliar with both the patient history and the clinical conduct of the trials. They were trained on images from Phase III studies and on images from other malignancies. None of the images used for training were included in the

blind read. Images were provided to the readers on an electronic work station, plain film was not used. The images were blinded and prepared for the reading by an individual independent from the clinical trial and the blind read. To ensure the protection of confidential patient information the images were de-identified. Images were stripped of all identifying information except the pulse sequences. It could not be determined which site produced the images.

Blind Readers were blinded to all demographic and clinical information except to the knowledge that the patients had prostate cancer. They were not provided any information on PSA level, clinical stage, or Gleason score. The nodes were not marked on the images. All sequences (T2, T2* and T1 for each patient) of the images were presented on computer workstations independently to each reader at each reading session. The unenhanced images alone were read in a session separated by approximately two weeks from a reading of the pre-dose and post-dose images combined.

The following information was collected in the blind read: A consecutively assigned patient number, Node ID, Size of Node, Diagnosis 1-5 (see below), Diagnosis benign or malignant. After all the images had been read the data was transferred from the original record sheets to 2 x 2 tables.

On the pre-contrast images, nodes were diagnosed as malignant if the short-axis diameter was elongated and exceeded 10 mm or was rounded and exceeded 8 mm. On the post-contrast images, nodes were considered malignant if they met one of the following criteria: 1) decrease in signal intensity of less than 30% on T2 FSE or T2 GRE; 2) heterogeneous (mottled) signal, discrete focal defects, or both; or 3) a central area of hyperintensity (excluding fatty hilum) with peripheral decrease in signal intensity. The readers were aware of the Combidex Nodal Imaging Guidelines (see page 26) used in the Phase III clinical trials and these were used in training the blind readers. The readers were also asked to assign one of five confidence levels to each node on a scale that ranged from 1 (definitely malignant) to

5 (definitely benign) so that ROC analysis could be performed. Objective signal intensity of the nodes was also measured.

After the blind read was performed, a different radiologist, who was not involved in the blind read, correlated the nodes as identified by the blind readers with those having histological results.

4.2.3.3 NEJM Study Efficacy Results

In 80 patients with biopsy proven prostate cancer for whom histological evaluation of lymph nodes was obtained, 334 lymph nodes with direct MRI-histopathology correlation were evaluated. The histology results by size are shown in Table 15.

Table 15: Characteristics of the Evaluated Nodes, NEJM Publication

Characteristic	Total N	Metastatic N	% Metastatic
Short axis diameter <5 mm	125	17	13.6%
Short axis diameter 5–10 mm	185	28	15.1%
Short axis diameter >10 mm	24	18	75.0%
Total	334	63	18.9%

It is important to note that the vast majority of nodes evaluated in this study (93%) were less than 10 mm. Improvements in the MR imaging procedures since the original US and EU Phase III studies conducted from 1996 to 1998 now allow the identification of smaller nodes than when the Phase III clinical studies submitted in the NDA were conducted. This allows a greater number of small nodes to be evaluated.

In all, 33 (41%) of the 80 patients had 63 histologically proven metastatic nodes. Of these 63 metastatic nodes, 45 (71.4%) did not meet the established imaging criterion for malignancy in pelvic nodes and would therefore be falsely diagnosed as negative on all the clinically accepted imaging procedures.

On a nodal basis, 90.5% of the metastatic nodes were correctly identified (90.5% sensitivity) with Combidex imaging, compared to 35% pre-dose. This difference was highly statistically significant ($p<0.001$). Additionally, on both the patient and nodal basis specificity, accuracy, PPV and NPV all increased post-contrast to the mid or high nineties. The calculated values for sensitivity, specificity, accuracy, PPV and NPV are shown in Table 16.

Table 16: Sensitivity, Specificity, Accuracy, and Positive and Negative Predictive Values of MRI Alone and MRI with Combidex, NEJM Study

Variable	MRI Alone	MRI with Combidex	P Value
Results per patient (n=80)			
Sensitivity (%)	45.4	100	<0.001
Specificity (%)	78.7	95.7	<0.05
Accuracy (%)	65.0	97.5	<0.001
Positive predictive value (%)	60.0	94.2	
Negative predictive value (%)	67.2	100	
Results per individual lymph nodes of all sizes (n=334)			
Sensitivity (%)	35.4	90.5	<0.001
Specificity (%)	90.4	97.8	<0.001
Accuracy (%)	76.3	97.3	<0.001
Positive predictive value (%)	55.9	95.0	
Negative predictive value (%)	80.3	97.8	
Results for nodes with a short-axis diameter of 5–10 mm (n=185)			
Sensitivity (%)	28.5	96.4	<0.001
Specificity (%)	87.2	99.3	<0.001
Accuracy (%)	78.3	98.9	<0.001
Positive predictive value (%)	28.5	96.4	
Negative predictive value (%)	87.2	99.3	
Results for nodes with a short-axis diameter of <5 mm (=125)			
Sensitivity (%)	0	41.1	<0.05
Specificity (%)	100	98.1	
Accuracy (%)	86.4	90.4	
Positive predictive value (%)	NA*	77.7	
Negative predictive value (%)	86.4	91.3	

The table shows the improvement with Combidex enhanced imaging both on a patient level and on a nodal level. Additionally, for the nodal analysis the efficacy data is broken down by nodal size. The sensitivity of Combidex enhanced imaging is statistically significantly improved on a patient level and on a nodal level. The accuracy on a patient level, as well as, for lymph nodes of all sizes and for lymph nodes 5-10 mm was also statistically significantly improved with Combidex.

On a patient basis, all 33 (100%) of the patients with metastases were correctly identified with Combidex imaging (100% sensitivity), compared to less than half (15/33 patients, 45%) pre-contrast. At the same time the positive predictive value for the Combidex images was greatly increased over that obtained pre-contrast (94.2% vs. 60.0%). This indicates that the increase in sensitivity observed for the Combidex images did not occur as a result of the fact that a higher percentage of all nodes were called positive post-contrast. In addition, for the 47 patients without metastases, 45 were correctly identified with Combidex imaging (specificity 95.7%), compared to 37 patients (78.7%) pre-contrast. Notably, negative predictive value on a patient basis was 100% – all of the patients identified as node-negative were correctly identified, whereas only 65% of those so identified on unenhanced imaging were actually negative.

4.2.4 Integrated Analysis of the US, EU and NEJM Studies

The imaging performance of Combidex in differentiating metastatic from non-metastatic lymph nodes was prospectively evaluated by comparison of pre-and post-contrast imaging results using histopathology as the gold standard in three large studies; the US Phase III study, the EU Phase III study and the blinded read results published in the New England Journal of Medicine (NEJM). In each case, the defined clinical setting was the same (i.e., patients with a known or suspected primary cancer scheduled for surgery or biopsy to evaluate nodal status), the dose of Combidex administered was the same (2.6 mg/kg), and efficacy results compared to pre-dose evaluations using size criteria were obtained via an

independent blinded read of unmarked images using pathology as the gold standard for the evaluation of efficacy.

The basic data including intent to treat (ITT) enrollment and evaluable numbers, demographics, patient population and node sizes evaluated are shown in Table 17.

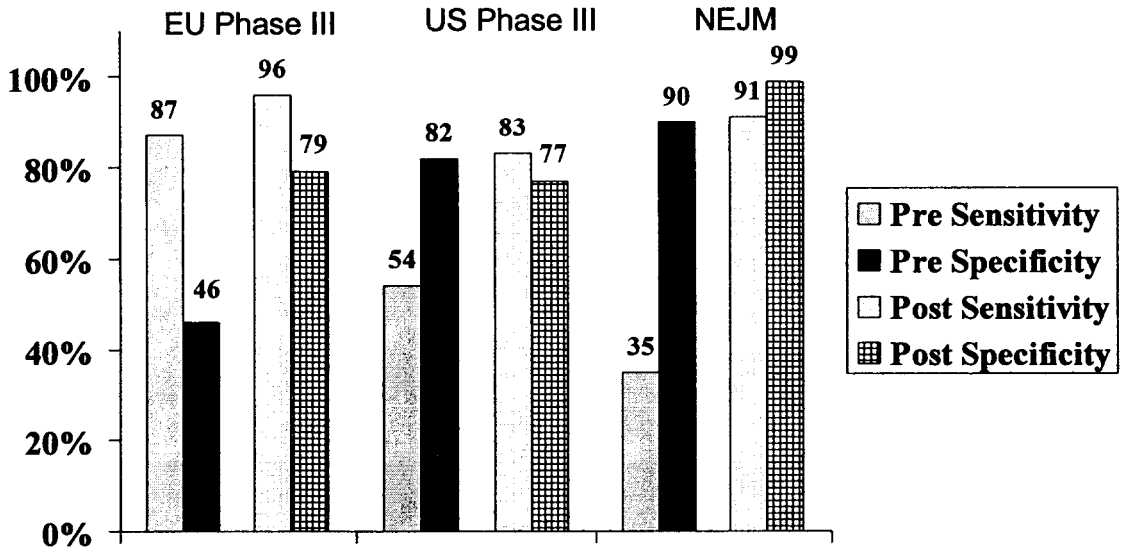
Table 17: Number of Patients and Nodes Evaluated US, EU, NEJM

Study	US Phase III	European Phase III	NEJM
Number of ITT Patients	156	181	80
Evaluable Patients	153	160	80
Male/Female	85/67	126/55	80/0
Mean Age	57	58	64
Primary Cancer	All sites	Head & Neck, Pelvic, Breast	Prostate
Number of evaluable nodes with histology	166	273	334
Percent of Nodes >10 mm	36%	76%	7%
Percent of Nodes <10 mm	64%	24%	93%
Percent of Patients with metastatic lymph nodes	49%	55%	41%
Study dates	1996 to 1998	1996 to 1998	1999 to 2002

This section reviews and compares the imaging findings, both pre- and post-contrast among and between the US Phase III study, the EU Phase III study and the blinded read results published in the NEJM. Although each of these studies found the Combidex enhanced evaluations more accurate in differentiating metastatic from non-metastatic nodes, examination of the imaging performance characteristics (i.e., sensitivity and specificity) underlying the increase in accuracy reveals an apparent inconsistency between the European Phase III study and the other two (Figure 3). In both the US Phase III study and the NEJM blinded read results the post-contrast evaluations resulted in large increases in sensitivity and smaller changes in specificity as compared to the pre-contrast results. However, in the European Phase III study the sensitivity exhibited only minor changes between the pre- and

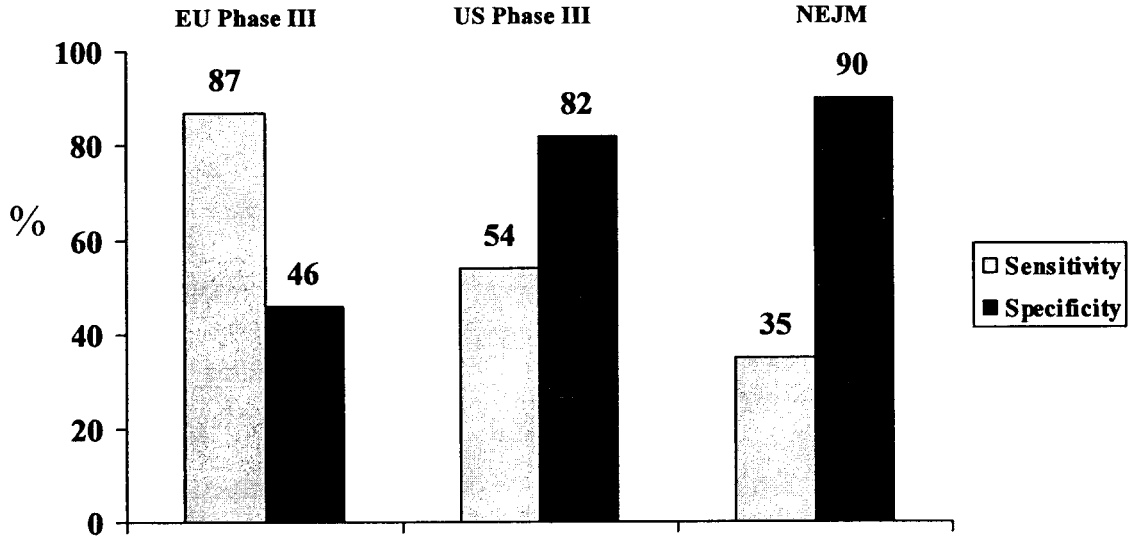
post-contrast evaluations, while specificity showed a large increase. These data also demonstrate that the "inconsistencies" between studies occurred primarily in the pre-contrast evaluations. While pre-contrast sensitivities and specificities varied by two to three fold across the studies, the post-contrast results were much more consistent.

Figure 3: Pre- and Post-Contrast Sensitivity and Specificity



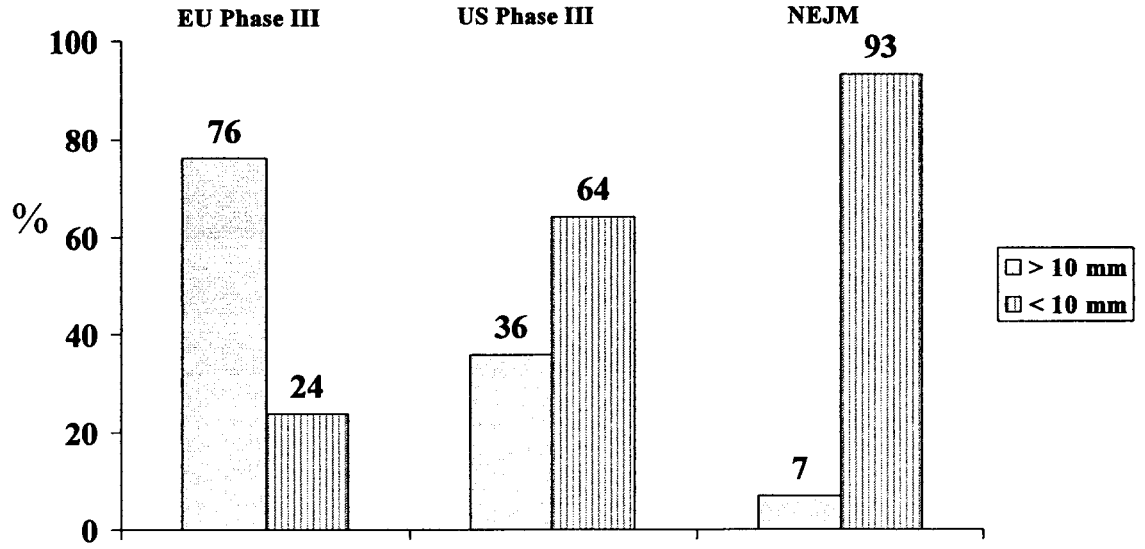
Examination of the pre-contrast results for the European Phase III study, the US Phase III study and the NEJM blinded read (left to right respectively in Figure 4) reveals a trade-off of decreasing sensitivity for increasing specificity. This trade-off between sensitivity and specificity is an inherent characteristic of the use of size based criteria to differentiate between metastatic and non-metastatic lymph as seen in the literature review presented in Appendix D of this submission.

Figure 4: Pre-Contrast Sensitivity and Specificity



Since the inconsistencies between studies involved the size based pre-contrast evaluations, each of the studies was examined with respect to the size distribution of the nodes evaluated in the blinded reads. Figure 5 shows the distribution of nodal sizes in these studies categorized on the basis of whether nodes were greater or less than 10 mm, the cut-off for nodal positivity in the pre-contrast evaluation.

Figure 5: Distribution of Nodal Sizes in the Studies



There is a decreasing percentage of nodes larger than 10 mm as one moves from the European Phase III study (where three fourths of the nodes were larger than 10 mm), to the US Phase III study (where only one third of the nodes were larger than 10 mm), to the NEJM study (where only 7% of the nodes were larger than 10 mm).

These trends in the size of the nodes evaluated in the pre-contrast blinded reads are consistent with the sensitivity and specificity findings described above. For instance, in the European Phase III study where the majority of the nodes evaluated were >10 mm one would expect that the sensitivity would be high in the pre-contrast evaluation because the use of size based criteria results in all of these large nodes being called positive. For example, if all the nodes were >10 mm the sensitivity of the pre-contrast evaluation would by definition be 100% because all of those nodes would be called positive. The trade-off for this high sensitivity occurs in specificity. Because many enlarged nodes are not metastatic one would expect that in a population of predominantly large nodes the pre-contrast specificity would be low. That is exactly what was observed in the European Phase III study.

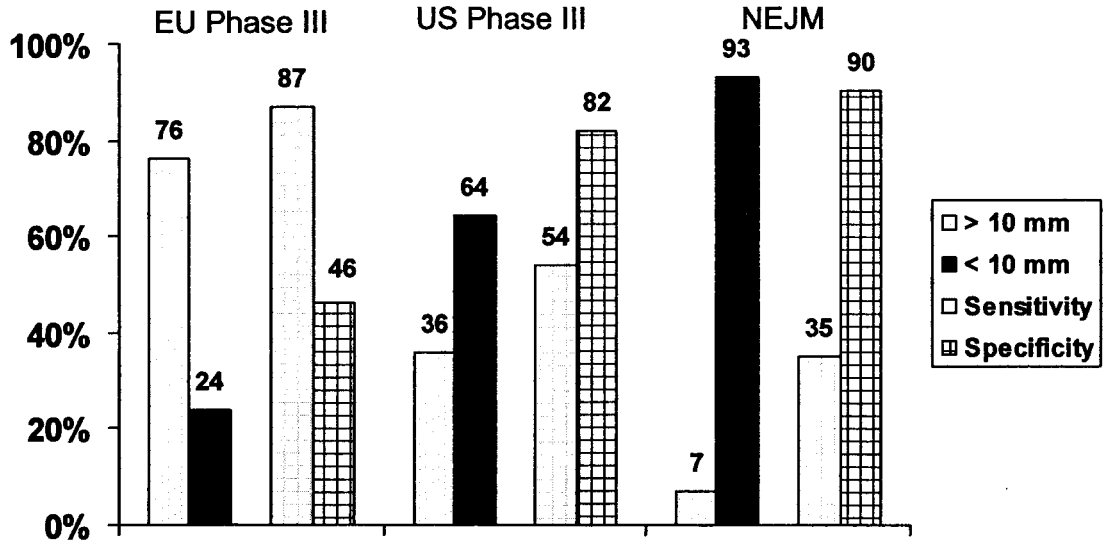
The opposite end of this trend can be seen in the results of the NEJM blinded read where almost all of the nodes (93%) evaluated were smaller than 10 mm. The size based pre-contrast criteria forces all of these small nodes to be called negative. Under such circumstances, one would expect the pre-contrast specificity to be high. This is exactly what was observed. The pre-contrast specificity in the NEJM blinded read was the highest of all the studies. Again, the trade-off for this high specificity occurs in sensitivity. Because some of the small nodes are metastatic and small nodes make up almost all of those examined in the study one would expect the size based pre-contrast sensitivity to be low. The NEJM blinded read had the lowest pre-contrast sensitivity (35%) of all the studies.

The US Phase III study in which the distribution of nodal sizes was intermediate between the EU Phase III study and the NEJM blinded read yielded both sensitivity and specificity results that were likewise intermediate between the other two studies. The relationship between pre-

contrast sensitivity and the percentage of nodes >10 mm and likewise pre-contrast specificity and the percentage of nodes <10 mm is demonstrated in Figure 6.

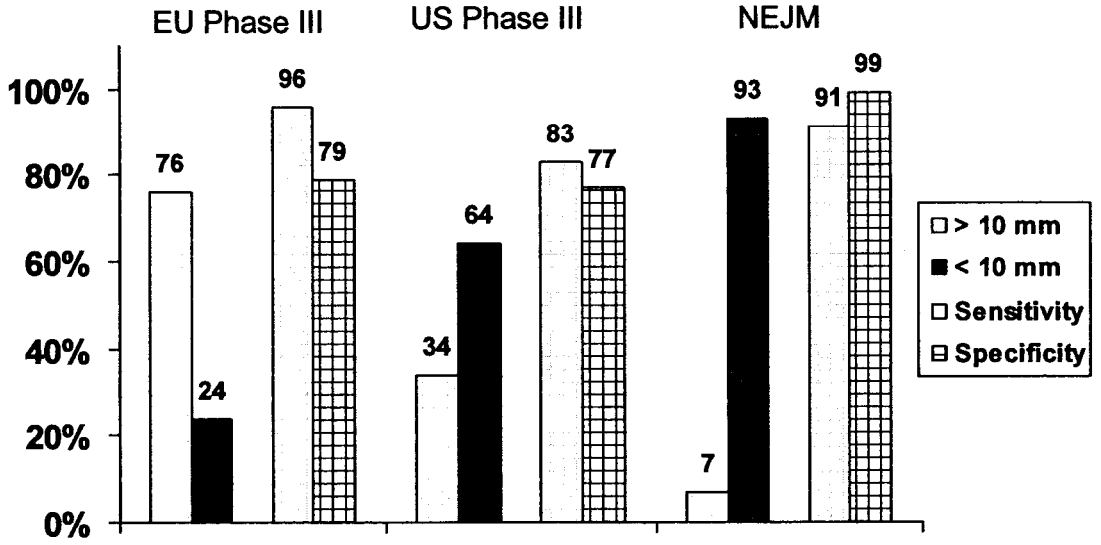
The downward trend in the percentage of nodes >10 mm (open bars) is accompanied by a similar downward trend in pre-contrast sensitivity (light cross-hatch bars). Likewise, the upward trend in the percentage of nodes <10 mm (solid bars) is accompanied by a similar upward trend in pre-contrast specificity (dark cross-hatch bars). Thus the characteristic trade-off of sensitivity for specificity inherent in the use of size based criteria to differentiate metastatic from non-metastatic lymph nodes is shown in these data.

Figure 6: Nodal Size and Pre-Contrast Sensitivity and Specificity



By way of comparison, in the post-contrast blinded evaluations the observed values of both sensitivity and specificity were uniformly high and not influenced by trends in the distribution of nodal sizes Figure 7. Thus the use of Combidex resulted in high levels of both sensitivity and specificity without the trade-off of one for the other.

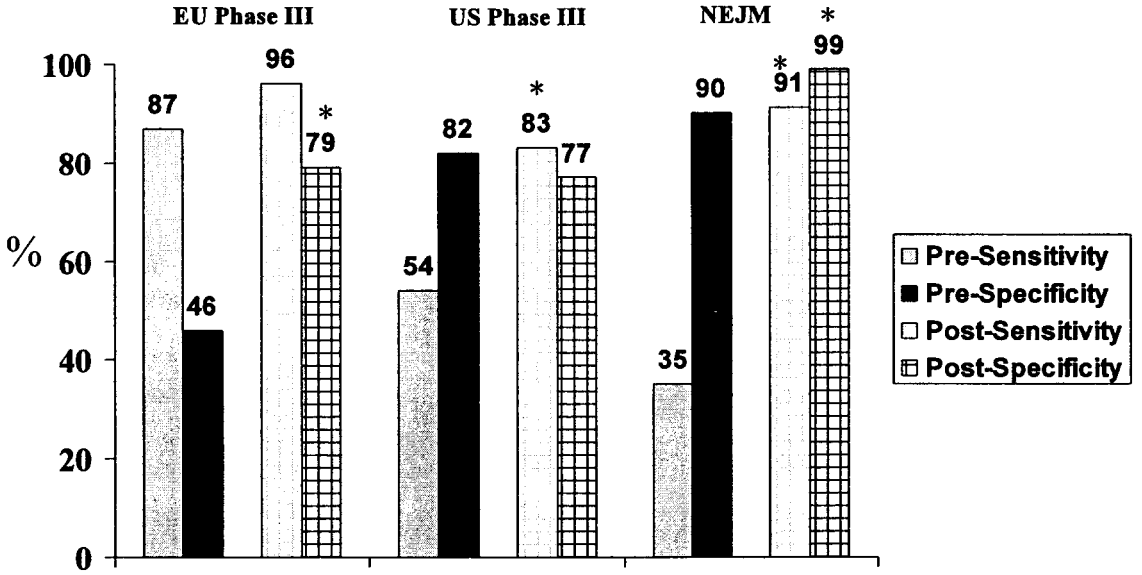
Figure 7: Nodal Size and Post-Contrast Sensitivity and Specificity



These studies, collectively and individually demonstrate the benefits of the use of Combidex in differentiating metastatic from non-metastatic lymph nodes. Accuracy is consistently improved in the post-contrast evaluation regardless of whether the nodes being evaluated are predominantly large nodes (such as in the EU Phase III study) or small nodes (such as in the US Phase III study or the NEJM blinded read). As compared to size based pre-contrast evaluations, the underlying imaging parameter (i.e., sensitivity or specificity) whose increase results in this improvement in accuracy is largely dependent on the size of the nodes being evaluated. This occurs as a result of the trade-offs between sensitivity and specificity inherent in the use of size based criteria. Thus, in studies where most of the nodes evaluated are large (such as the EU Phase III study) use of Combidex results in an increase in specificity as compared to the pre-contrast findings whereas in studies where most of the nodes are small (such as the US Phase III study and the NEJM blinded read) it is sensitivity in which the largest increases are observed as a result of the use of Combidex. Figure 8

shows the improvements in post-contrast sensitivity and specificity based on prospective analyses carried out for each study.

Figure 8: Improvements in Post-Contrast Sensitivity and Specificity



* Statistically significant improvement from pre-contrast result

4.2.4.1 Patient Level Results

At the patient level, the two different pre-contrast readings gave similar accuracy in both the US and EU studies as shown in Table 18. Accuracy was improved in all cases with the use of Combidex.

Table 18: Patient Level Analysis: Accuracy of Diagnosis

Reading	US Phase III	European Phase III	NEJM Study
Pre Size	69%	71%	65%
Pre Reader	66%	72%	
Paired	76%*	75%*	98%@
Post	80%@*		

Results are the average of the blind readers.
@p<0.05 vs. Size Dx, *p<0.05 vs Reader's Dx for at least one reader.

Table 19 shows the number of patients falsely diagnosed as positive or negative. On a patient basis in all three studies the number of false diagnoses was reduced.

Table 19: Patient Level Analyses: Total Number of False Diagnoses

		Pre-Dose (MRI Dx)	Pre-Dose (Readers Dx)	Combidex Paired	Combidex Post-Dose
US (n=112)	BR1	34	45	25	22
	BR2	39	35	28	24
Europe (n=160)	BR1	52	51	35	
	BR2	46	42	31	
NEJM (n=80)		28		2	

The evaluation of false diagnoses on a patient basis indicates that in all three studies the number of false positive diagnoses was reduced substantially. Overall, far more patients were correctly diagnosed on the post-contrast reads.

4.2.5 Clinical Utility of the Use of Combidex

The proposed indication for Combidex is for differentiation of metastatic from non-metastatic lymph nodes. This indication is supported by the data from clinical studies of the agent, where Combidex was found to improve the sensitivity, specificity and accuracy of differentiating metastatic from non-metastatic lymph nodes as compared to the currently accepted methodology used in clinical practice (size based determination).

Although nodal staging and patient management were not primary endpoints and are not intended for inclusion in the indication, these data were collected in the blind readings and further demonstrate the clinical benefit of using Combidex including an improvement in clinical nodal staging and reduced risk due to false diagnoses. Additional support for the clinical utility of Combidex comes from the published literature. Copies of recent publications in peer reviewed journals are included in Appendix C.

4.2.6 Nodal Staging

Nodal staging information was prospectively collected in the US Phase III clinical trial by comparing the agreement between clinical nodal stage (based solely on MR imaging) and the eventual pathologic nodal stage according to the twelve categories in the American Joint Committee on Cancer (AJCC)[3].

Categories used for the radiologist/oncologist staging included:

1. NX: cannot be assessed
2. N0: no disease
3. N1: generally one node: subcategories for some cancers
4. N1a
5. N1b
6. N1c
7. N2: generally one big node or two nodes: subcategories for some cancers
8. N2a
9. N2b
10. N2c
11. N3: generally multiple large nodes
12. Other: usually distant metastases

As shown by the data in Table 20, the clinical nodal stage was correct in a significantly higher proportion of patients when the Blinded Readers evaluated Combidex enhanced images compared with their evaluations of the pre-dose images.

Table 20: Percent of Patients with Agreement in Clinical & Pathologic Nodal Staging

Blinded Reading	Compare Accuracy of Staging Patients With:	Pre-Dose	Post-contrast: paired or alone	P-Value
1	Pre-Dose and Paired	23% (25/108)	34% (37/108)	0.017
	Pre-Dose and Post-Dose	24% (24/100)	45% (45/100)	<0.001
2	Pre-Dose and Paired	33% (39/118)	46% (54/118)	0.020
	Pre-Dose and Post-Dose	34% (35/104)	49% (51/104)	0.023

It should be noted that clinical nodal staging by the radiologist/oncologist teams was done blinded – without any knowledge of the patient's medical history or primary disease – and thus shows the ability of the contrast agent alone to assist in clinical nodal staging.

To simplify the analysis, the twelve AJCC[3] nodal staging categories can be collapsed into three categories of diseased (N+), not diseased (N0), and unknown (Nx). When the blinded reader results are collapsed to these three categories and compared with the histology, the results shown in Table 21 are obtained.

Table 21: Nodal Staging Categorized as Diseased, Not Diseased, or Unknown

PRE-DOSE			
	Reader 1	**Reader 2**	**Average**
Correct	33% (32/97)	51% (59/115)	43% (91/212)
Incorrect	13% (13/97)	42% (48/115)	29% (61/212)
(NX or Other)	54% (52/97)	7% (8/115)	28% (60/212)
COMBIDEX PAIRED			
	Reader 1	**Reader 2**	**Average**
Correct	51% (52/101)	68% (77/114)	60% (129/215)
Incorrect	18% (18/101)	25% (29/114)	22% (47/215)
(NX or Other)	31% (31/101)	7% (8/114)	18% (38/215)
COMBIDEX POST ONLY			
	Reader 1	**Reader 2**	**Average**
Correct	62% (61/98)	69% (73/106)	66% (134/204)
Incorrect	10% (10/98)	25% (26/106)	18% (36/204)
(NX or Other)	27% (27/98)	7% (7/106)	17% (34/204)

The use of Combidex increased the percentage of patients who are correctly identified as having nodal disease, improved the consistency of the results between the two readers and significantly decreased the number of patients for whom nodal staging could not be determined on unenhanced images. In this nodal staging evaluation, the Combidex post only image reading again produced the highest percentage of correct results.

The clinical nodal stage assigned on the basis of the MRI results was correct in a significantly higher proportion of patients when the blinded team evaluated Combidex images, compared to their evaluations of pre-dose images. This was true for both blinded

readings whether the comparison was between pre-dose and paired results or between pre-dose and post-dose results. Comparing the pre-dose and post-dose results demonstrates that nearly twice as many patients were staged correctly with Combidex than were correctly staged with unenhanced MRI or CT. This result is important because clinical nodal staging is used in the initial planning of treatment of patients before pathological nodal staging is performed.

The percentage of patients where the clinical stage agreed exactly with the eventual pathologic staging rose from 23-34% to 45-49%, depending on the reader. In all cases the improvements were statistically significant. When categorized as diseased, not diseased and unknown, both the number of incorrectly staged patients and the number of patients who could not be staged decreased substantially. Correctly staged patients increased from 33-54% to 62-69%, depending on the reader. Readers indicated that the information provided by the contrast images would most often change treatment planning or surgical status.

Table 22 compares the pathologic stage with the paired and post-dose MRI stage for two specific subgroups of patients with changes in blinded staging. These subgroups were chosen because they represent patients whose treatment or prognosis could have been changed by the Combidex results, specifically those for whom the nodal stage was unclear based on pre-dose images, and for those whose diagnosis was changed from metastatic to not metastatic based on Combidex images.

Table 22: Patient-Level Analysis: Comparison of Clinical Nodal Stage and Pathologic Nodal Stage for Subgroups of Patients with Changed Diagnoses due to Combidex

Subgroup Based on Clinical Nodal Staging Results	No. (%) for Whom Paired or Post Combidex Stage Matched Pathologic Stage	
	Blinded Reading 1	Blinded Reading 2
Pre NX → Paired N0-N3	58% (14/24)	50% (1/2)
Pre NX → Post N0-N3	57% (16/28)	67% (2/3)
Pre not N0 → Paired N0	70% (14/20)	80% (24/30)
Pre not N0 → Post N0	72% (18/25)	73% (24/33)

When the nodal stage could not be assigned based on the pre-dose images but could be assigned based on either the Combidex paired or post-dose images, the Combidex-assigned stage of N0 to N3 was confirmed at surgery/biopsy in 50% to 67% of the cases. For these patients, the benefits would include improved accuracy in planning surgery, biopsy or non-surgical interventions - all of which are now planned based on clinical staging using less accurate anatomic imaging without Combidex. On a patient basis, approximately 16-25% were assigned a clinical nodal stage of N0 based on the paired or post-dose evaluations, but had been assigned a different node positive stage based on the pre-dose evaluation. Among these patients, 70% to 80% had no nodal metastases at surgery/biopsy.

The Combidex images provided clinical nodal staging information that the pre-dose images did not for 62-64% of the patients evaluated. Table 23 summarizes the types of information provided.

Table 23: Clinical Nodal Staging of Patients:
Types of Additional Clinical Nodal Staging Information Provided by Combidex Images

Information Provided*	Blinded Reader 1 (N=77)	Blinded Reader 2 (N=87)
Suspect regional involvement	12 (16%)	19 (22%)
No regional nodal involvement suspected	14 (18%)	5 (6%)
Identify increased number of nodes suspected for metastases	16 (21%)	15 (17%)
Identify decreased number of nodes suspected for metastases	26 (34%)	46 (53%)
Assist in determining extent of nodal disease	18 (23%)	36 (41%)
Other	32 (42%)	0 (0%)

* For a given patient, the reader may have indicated that more than one category applied.

For both readers, the Combidex images frequently provided information identifying increased or decreased numbers of nodes suspected for metastases and assisted in determining the extent of nodal disease. For Blinded Reader 1, the type of information provided was most often classified as "other." This included increased confidence in the presence of metastases, increased confidence in the presence of non-metastatic lymph nodes or decreased suspicion of metastases, and visualization of benign lymph nodes.

4.2.7 Patient Management

The sponsor is not seeking a patient management indication and this was not a primary efficacy endpoint in any of the studies. This information is provided because it shows how more accurate nodal differentiation may play a role in patient care.

The results of the US Phase III blinded staging evaluation can be used to extrapolate the effects on patient management by using the accuracy in detection of disease data on a patient basis. The increased number of correctly diagnosed patients per thousand compared to the

unenhanced image evaluations using either size or the Reader's Diagnosis can be derived and is shown in Table 24.

Table 24: Increased Number of Correctly Diagnosed Patients per Thousand with Combidex Enhanced MRI

			Number of New Correct Diagnoses with Combidex per 1,000 patients	
	Comparator		**Paired Reading**	**Post Only Reading**
Pre Combidex	Reader 1	MRI (Size) Dx	56	105
		Reader (Subjective) DX	154	204
	Reader 2	MRI (Size) Dx	85	106
		Reader (Subjective) DX	52	73

No matter which unenhanced evaluation is used, the use of Combidex results in more correct and fewer false patient diagnoses. The use of Combidex, depending on the pre-contrast evaluation used as a basis of comparison, would increase the number of correct patient diagnoses per thousand for between 56 and 204 patients for Blind Reader 1 and between 52 and 106 patients for Blind Reader 2.

If Combidex enhanced images indicate the presence of a metastatic node where none had been previously suspected, the planned nodal sampling could be extended. In fact, this occurred in the two EU studies in which the results of Combidex imaging were allowed to be used to influence surgery and in the NEJM study where 11% of the patients had the surgical field extended to retrieve skip metastases.

Evaluation of nodes on Combidex enhanced images decreases the number of both false positive and false negative findings. This improvement in the ability to differentiate lymph node metastases from benign lymph nodes will have numerous benefits for patients who are undergoing cancer staging to determine treatment and prognosis. Readers indicated that the information provided by the contrast images would most often change treatment planning or surgical status. On an individual patient basis, approximately one of every six patients for

Blinded Reader 1 and one of every four patients for Blinded Reader 2 were assigned a clinical nodal stage of N0 based on the paired or post-dose evaluations, but had been assigned a different stage based on the pre-dose evaluation. Among these patients, 70% to 80% had no nodal metastases at surgery/biopsy. A patient whose cancer has not spread to the regional lymph nodes may be a candidate for curative surgery (e.g., with prostate cancer or bladder cancer) or may be spared unnecessary surgery or radiation therapy of the lymph nodes (e.g., breast cancer or head and neck cancers).

For both the EU and NEJM studies, certain changes in patient management occurred as a result of the Combidex enhanced images. (Changes in patient management based on Combidex results were not permitted in the US study). In the European studies where such changes were permitted, the surgical procedure was modified in 12 cases out of 130. In eight cases the change involved extending the surgical field to encompass nodes or nodal groups that the Combidex enhanced images indicated as metastatic. In four cases, the groups had been planned for surgery, but the Combidex images allowed identification of specific suspicious nodes within the group.

In the study published in the NEJM, 80 patients were scheduled for radical prostatectomy with standard bilateral obturator lymph node sampling. After the Combidex imaging, five patients were sent instead for CT guided biopsy of non-enlarged solitary nodes deemed metastatic; when these specific nodes were confirmed metastatic, the status of these patients was changed to non-surgical. In another nine patients, again because of nodes deemed suspicious on Combidex imaging, the surgical field was extended to sample nodes outside of the usual surgical field and metastatic foci (skip metastases) were confirmed.

Radical prostatectomy with lymph node dissection is an invasive technique, with significant morbidity and a mortality rate of approximately 0.25%. In this study, 6% of the patients were converted from surgical to non-surgical status, eliminating their risk of complications from surgery. Another 11% had their lymph node dissection extended to sample nodes outside the normal surgical field resulting in more accurate pathologic staging. The more

accurate information provided by Combidex enhanced MRI helped make better treatment decisions in 18% of the patients.

4.3 Summary of Efficacy

The imaging performance of Combidex in differentiating metastatic from non-metastatic lymph nodes was prospectively evaluated in three large studies; the US Phase III study, the EU Phase III study and the blinded read results published in the NEJM. In each of these studies the ability to differentiate metastatic from non-metastatic lymph nodes was improved for the post-contrast images as compared to that obtained pre-contrast.

There was a clear trend among studies with a decreasing percentage of nodes larger than 10 mm as one moves from the European Phase III to the US Phase III to the NEJM publication. These trends in the size of the nodes are responsible for the differences between studies in the pre-contrast sensitivity and specificity findings. In studies where most of the nodes evaluated were large in size (i.e. greater than 10 mm), the use of Combidex resulted in an increase in specificity whereas in studies where most of the nodes were small in size, it was the sensitivity which increased as a result of the use of Combidex.

The Combidex enhanced MR images provided *both* high sensitivity and high specificity in all three studies. The high sensitivity and specificity result in improved accuracy. Accuracy was similar with the Combidex post-dose images only (85-86%) and the paired images (80-90%). This improvement in accuracy was seen across all studies. Combidex enhanced imaging improved the accuracy in differentiating metastatic lymph nodes from non-metastatic nodes with MRI regardless of whether a reader used the clinically established size criteria or employed a subjective assessment such as the Reader's diagnosis.

A product such as Combidex has the potential to make a significant impact—both from an economic and a patient management standpoint—by increasing the ability of radiologists and oncologists to diagnose and stage metastatic disease non-invasively regardless of the anatomical site.

In the clinical trials conducted in the US and Europe, the Blinded Readings showed that:

- Evaluation of Combidex images alone (post-dose evaluation) or in conjunction with pre-dose images (paired evaluation) provided high sensitivity, specificity, and accuracy for diagnosing lymph node metastases from head and neck, lung, breast, abdomen, and pelvic carcinoma.
- Results were better and more consistent with Combidex images than with pre-dose images, whether the pre-dose diagnosis was based on lymph node size (MRI Dx) or on all information available to the Readers on the images (Readers Dx).
- Use of Combidex reduced the number of false positive and false negative results obtained when evaluating lymph nodes with MRI. Pre-dose images alone produced either higher numbers of false positives or higher numbers of false negatives than did Combidex images.
- Improvements in imaging performance, clinical staging and consistency between readers were greatest for the post-contrast only blinded readings with the only images available being those obtained with Combidex.
- Review of MR images obtained after administration of Combidex improved the accuracy of clinical nodal staging (compared with pre-dose images) in a statistically significant manner and provided additional information to the reader in approximately two thirds of the cases.

It is important to keep in mind that, as part of the inclusion criteria for these studies, each patient had a primary tumor and was scheduled for surgery or biopsy to evaluate potential metastatic involvement. However, of those who ultimately underwent surgery or biopsy, only about half had histologically confirmed lymph node metastases. This demonstrates the short-comings of current imaging procedures for diagnosing nodal involvement and for nodal staging. Based on histories and the results of other diagnostic tests in use today, about half of the patients with suspected spread of disease to the lymph nodes may be undergoing invasive

procedures that could prove unnecessary or have the potential for modification to more limited surgery (e.g., neck or axillary dissections). Imaging procedures are currently used routinely in a large number of patients, but the results are variable, depending on the criteria used for diagnosing metastases.

In summary, while some endpoints were different, the clinical trials performed in the US and Europe yielded data that supports the use of Combidex in the differentiation of metastatic from non-metastatic lymph nodes. The study published in the New England Journal of Medicine, as well as other published literature, also supports the proposed indication and the clinical utility of the agent.

5 COMBIDEX SAFETY

5.1 Introduction

The original NDA submission contained safety data for 947 subjects who had received Combidex in two patient populations for two distinct indications: imaging the liver/spleen and evaluation of lymph node disease. Most of liver/spleen patients were administered Combidex by direct undiluted injection (n=131). The use of direct injection (and the imaging liver/spleen indication) was abandoned because both the rate of adverse events and the rate of serious events is considerably higher with this method of administration. When the agent is diluted and administered by infusion, the adverse event rates are substantially reduced.

Since the original NDA filing the sponsor has accumulated a significant amount of additional safety data in 1114 patients from clinical trials where Combidex was administered using dilution and infusion. The break down by method of administration is shown in Table 25.

Table 25. Total Exposure by Method of Administration.

Method of Administration	Number
Total number of patients	2061
Undiluted administration, all doses	131
Diluted, all doses and dilutions	1930
Diluted in 50 ml of saline, all doses	364
Diluted in 100 ml of saline, all doses	1566
Proposed dose and method: 2.6 mg Fe/kg, diluted in 100 ml of saline	1236

The current safety database demonstrates that administering Combidex by infusion following dilution in 100 ml saline over a period of approximately 30 minutes not only significantly reduces the incidence of adverse events, but it also facilitates prompt intervention, when appropriate, in treating those adverse events that may occur. In many cases if a patient had an adverse event, merely discontinuing the infusion was the only treatment required. The rate of serious adverse events is also reduced with dilution and infusion of the agent.

5.2 Common Adverse Events

The most frequent adverse events associated with Combidex at the proposed dose of 2.6 mg/Fe kg using dilution in 100 ml normal saline and infusion over 30 minutes are vasodilation (3.4%), rash (3.0%), back pain (2.4%) and pruritus (2.2%).

Table 26 shows the adverse events that occurred in greater than 0.5% of the 1236 subjects who received Combidex at a dose of 2.6 mg Fe/kg (the dose for the lymph node indication) diluted in 100 ml saline and infused over 30 minutes.

Table 26: Adverse Events with 100 ml Dilution in ≥0.5% of the subjects at a dose of 2.6 mg Fe/kg: Proposed Dose and Method of Administration

Adverse Event	N = 1236
Vasodilation	3.4%
Rash	3.0%
Back pain	2.4%
Pruritus	2.2%
Urticaria	1.7%
Dyspnea	1.3%
Nausea	1.2%
Chest pain	1.1%
Pain	0.8%
Sweating	0.7%
Headache	0.6%
Patients with any AE	15.8%

5.3 Effect of Method of Administration on Adverse Events

This section reviews the impact of administration using dilution and infusion on adverse events including data from the NDA and from clinical trials that have been ongoing since the NDA was submitted. The review includes the impact of dilution and infusion on pain related events, hypotension, hypersensitivity events and how dilution and infusion reduces the number of events and allows for management of those events that do occur.

In clinical trials conducted since the original NDA it has been seen that administering Combidex by infusion over a period of approximately 30 minutes following dilution in 100 ml saline not only significantly reduces the incidence of adverse events, but it also facilitates prompt intervention, when appropriate, in treating those adverse events that may occur. In many cases if a patient had an adverse event, merely discontinuing the infusion was the only treatment required.

Overall, the incidence of adverse events was markedly reduced from 30.0% for all patients receiving a bolus injection to 14.2% in patients when the contrast agent was administered by infusion following dilution in 100 ml of saline.

Administration of Combidex by infusion following dilution significantly reduces the incidence of a variety of adverse events as shown in the tables contained in this discussion. The effect of the use of dilution and infusion on the overall adverse event rate is shown below in Table 27. The rate of adverse events is greatest when the drug is given rapidly by direct injection and decreases with dilution in 50 ml of normal saline and is slowly infused over 15 minutes and is further decreased with dilution in 100 ml of normal saline and infusion over 30 minutes.

Table 27: Effect of Method of Administration on the Overall Incidence of AEs at all doses

Bolus Injection (N=131)	Dilution in 50 ml and slow infusion (N = 364)	Diluted in 100 ml and slow infusion (N = 1566)
30.0%	17.6%	14.2%

The most frequent adverse event reported following the administration of Combidex, vasodilation, was reduced from an incidence rate of 11.4% in patients who received the agent by bolus injection to a rate of 3.4% when it was diluted in 100 ml saline and infused.

Not only is the overall rate of adverse events reduced using dilution and infusion but there are also fewer serious adverse events when Combidex is administered in this manner. There were 3/131 (2.3%) patients with serious adverse events who received the drug by direct bolus injection as compared with 5/1,930 (0.3%) which were classified as serious by the investigator when Combidex was administered diluted and infused (either 50 or 100 ml). The type and rate of serious adverse events observed with dilution and infusion of Combidex is similar to the type and less than the rate of serious adverse events (>1%) reported in the existing labeling for iodinated contrast agents used with CT.

5.4 Effect of Dilution and Infusion on Pain Related Adverse Events

As shown by data submitted in the original NDA and confirmed by additional data obtained in ongoing clinical studies, the incidence of pain related events was significantly higher in

patients who received the agent by bolus injection (used for the abandoned liver/spleen indication) than in patients where the agent was first diluted in normal saline and then infused. This is shown in Table 31.

Table 28: Effect of Method of Administration on Incidence of Pain-Related AEs at All Doses

Term	Bolus Injection N = 131	50 ml Dilution N = 364	100 ml Dilution N = 1566
Back pain	4.6%	3.3%	2.5%
Chest pain	3.8%	1.4%	1.2%
Abdominal pain	3.8%	1.4%	1.0%
Pain	2.3%	2.2%	0.8%

In approximately half of these subjects the onset of pain was within 15 minutes of the start of the drug administration and resolved within 30 minutes. The majority of pain related events were mild or moderate in intensity.

5.5 Immediate Hypersensitivity Reactions

For this NDA review the FDA has provided an operational definition for an immediate hypersensitivity reaction as follows:

Any subjects who presented within 3 hours post Combidex administration with the following symptom(s):

1. One or more symptoms under column A OR
2. Dyspnea and any other symptom under column B

A Terms	**B Terms**
Urticaria	Dyspnea
Facial edema/swelling	AND any of the following terms:
Laryngeal edema	Syncope
Allergic reaction	Hypotension
Rash	Vasodilation/flushing
Pruritus	
Asthma	
Generalized edema	

Table 29 shows the rates of immediate hypersensitivity reactions.

Table 29: Patients with Immediate Hypersensitivity Reactions

	Total (N=2061) N (%)	At proposed dose and administration (N=1236) N (%)
Hypersensitivity reaction	101 (4.9%)	61 (4.9%)
Classified as serious	4 (0.2%)	2 (0.16%)

Although the rate of immediate hypersensitivity events was not different due to the method of administration, the use of dilution and infusion facilitated managing the events. Nineteen of these subjects had the infusion stopped and four of the nineteen had the infusion resumed and completed. Sixty two of the 101 subjects with an immediate hypersensitivity reaction received treatment with either antihistamines or steroids except for one case of asthma that was treated with an inhaler.

5.6 Anaphylactoid/Anaphylactic Reactions

The FDA noted that signs and symptoms of "anaphylactoid" reactions were associated with the administration of Combidex. There are two clarifications that are important to make regarding "anaphylactoid" reactions associated with Combidex:

1. The mechanism of these "anaphylactoid" reactions to iron based parenterals such as Combidex appears to be direct mediator releasing effects of iron and is not based on classical type I anaphylaxis mechanisms involving IgE. This is important when discussing dose effects.

   Mechanistically, *anaphylaxis* has been defined as "a systemic immediate hypersensitivity caused by the rapid, IgE-mediated immune release of potent mediators from tissue mast cells and peripheral blood basophils." In contrast, *anaphylactoid reactions* are "those clinical events caused by mediator release from mast cells and basophils by non-IgE-mediated triggering events."

Examples of hypersensitivity inducing agents include IgE sensitizers such as hymenoptera venom and penicillin. Following sensitization to these agents, exposure to even minute amounts of antigen may result in anaphylaxis. Examples of direct releasers of mast cell mediators include ciprofloxacin, vancomycin and radiocontrast agents. A critical issue and distinction between these two mechanisms and groups of agents is that for the direct releasers of mast cell mediators, total dose and rate of exposure are directly related to the severity of the reaction.

A detailed discussion, with references, of the mechanistic and clinical characteristics of hypersensitivity reactions with particular emphasis on the types and manifestations of such reactions when observed in response to contrast agents and parenteral iron agents can be found in Appendix E.

2. Hypotension alone (in the absence of other adverse events) has been observed following administration of a variety of parenteral iron agents (such as sodium ferric gluconate and iron sucrose injection) used for the treatment of anemia. When it occurs it is typically without other hypersensitivity symptoms and is self-limited. It may be a direct vasodilalatory effect, and as noted in approved labeling for currently marketed products, is not an allergic phenomenon. It is reported in labeling to be associated with rapid administration of iron. The package insert for ferric gluconate injection states, "Hypotensive reactions are not associated with signs of hypersensitivity and have usually resolved within one or two hours."

This is also true of reactions that were reported following administration of Combidex that were classified as hypotension as is shown on the tables that follow in this section. (See iron therapy package inserts and related material in Appendix F).

5.7 "Anaphylactoid" Adverse Events

For this NDA review the FDA has defined an anaphylactic/anaphylactoid reaction as any subject who had an immediate hypersensitivity reaction regardless of severity, necessity for clinical intervention, or clinical significance as previously defined that involved two or more specified body systems, as follows:

Respiratory System: dyspnea, laryngeal edema and asthma

Cardiovascular System: syncope and hypotension

Skin: urticaria, rash, pruritus, facial edema/swelling, vasodilation/flushing and generalized edema.

The incidence of events that met this definition is shown in Table 30. All but one of the respiratory symptoms were dyspnea. The onset time of dyspnea was rapid, from ten seconds to 19 minutes after starting the infusion, and the duration was less than one hour.

Table 30: Incidence of Anaphylactoid/Anaphylactic Adverse Events

	Total, N=2061 N (%)	**At proposed dose and administration (N=1236)**
All	14 (0.7%)	11 (0.9%)
Respiratory & skin	13 (0.6%)	10 (0.8%)
Respiratory & cardiovascular	1(0.05%)	1 (0.09%)
Classified as serious	4 (0.2%)	2 (0.16%)

Almost all of the incidents of dyspnea were managed by stopping the infusion. Thirteen of the 14 patients had the infusion discontinued; seven of these had no other treatment. In four of the patients the infusion was restarted and completed with no further symptoms. The most common treatments for those patients who received pharmacological intervention were antihistamines or steroids.

5.8 Hypotension

Hypotension has been observed following administration of a variety of parenteral iron agents (such as sodium ferric gluconate and iron sucrose injection). When it occurs it is typically without other symptoms and does not require treatment as was the case with the events reported with Combidex. Hypotensive reactions reported with rapid administration of iron are not associated with signs of hypersensitivity and are usually resolved within one or two hours. (See parenteral iron therapy package inserts in Appendix F). For this reason, the sponsor has included this separate analysis and discussion of the reports of hypotension in patients administered Combidex.

As discussed above, for direct releasers of mast cell mediators in general and iron based parenterals in particular, the rate of exposure is related to the incidence and severity of symptoms. This effect was also observed in clinical trials of Combidex during which patients who received a bolus administration experienced a higher incidence of hypotension than did patients who received the agent by slow infusion following dilution as shown in Table 31.

Table 31: Incidence of Hypotension: bolus vs. diluted

Bolus Injection, N=131 N (%)	50 ml Dilution, N=364 N (%)	100 ml Dilution, N=1566 N (%)
3 (2.3%)	0	8 (0.5%)

Although the investigators called the events hypotension many of these patients did not have clinically meaningful hypotension. The lowest blood pressure recorded in any patient was 90/60 and only one patient received treatment of any kind. In the eight patients who were reported by the investigators to have experienced hypotension following administration of Combidex following dilution and infusion, none of the events were considered serious and six were self-limiting (requiring no treatment) and occurred without any other symptoms. In four of the eight patients (50%) the event was managed by stopping the infusion.

Hypotension alone has been observed following administration of a variety of parenteral iron agents (such as sodium ferric gluconate and iron sucrose injection). When it occurs it is typically without other symptoms and is self-limited. It may be a direct vasodilatory effect, and, as noted in labeling, is not an allergic phenomenon. This is true for the events which were called hypotension in the Combidex clinical trials using dilution and infusion.

The incidence and severity of hypotension can be controlled by administering Combidex using dilution and infusion.

5.9 Serious Adverse Events

Not only is the overall rate of adverse events reduced using dilution and infusion but there are also fewer serious adverse events when Combidex is administered in this manner. There were 3/131 (2.3%) patients with serious adverse events who received the drug undiluted as compared with 5/1930 (0.3%) which were classified as serious by the investigator when Combidex was administered diluted and infused These latter events with Combidex administered by infusion following dilution are described here:

> A 65 year old female who received a dose of 2.6 mg Fe/kg diluted in 100 ml experienced cough in the first 5 seconds lasting 5 minutes, dyspnea in the first 10 seconds lasting 10 minutes and hypotension lasting 2 minutes. The infusion was discontinued and she was treated with IV antihistamines. She vomited 90 minutes later. There was no respiratory compromise or prolonged hypotension. (Study ALS-3-15-A, #3003)

> A 63 year old female who received a dose of 2.6 mg Fe/kg diluted in 100 ml experienced vasovagal faint and flush 5 minutes after starting the infusion lasting 30 minutes. The infusion was discontinued. She was treated with IV fluids only. Blood pressure was not recorded. (Study ALS-3-31-A, #7026)

A 23 year old male who received 1.7 mg Fe/kg diluted in 100 ml reported dyspnea, chest pain, back pain, hypertension and tachycardia. The duration of the events was from 13 minutes to 2 hours. The patient received no treatment for the events and completed the MR imaging procedure. This patient's medical history was significant for dysphasia, osteochondroma, itching of the lower extremities and nightly fevers. The patient presented with symptoms of increasing dyspnea on exertion which had been persistent for six months prior to enrollment in the study. (Study 38804-5, #106)

A 42 year old female who received a dose of 2.6 mg Fe/kg diluted in 100 ml reported dyspnea, coughing and abdominal pain 45 minutes after the start of the infusion. The infusion was discontinued temporarily, restarted and completed. The patient was given hydrocortisone, albuterol and oxygen. The symptoms lasted for one hour and then resolved. (Study ALS-3-31-A, #7227)

A 48 year old male with a history of lung cancer and a significant medical history of respiratory illness, COPD, who received a dose of 2.6 mg Fe/kg diluted in 100 ml had dyspnea, sweat and flushing 5 seconds after the start of the infusion that lasted for 10 minutes. The infusion of Combidex discontinued and the patient was given methylprednisolone for the events. (Study ALS-3-33-A, #5008)

The rate of serious adverse events when Combidex is administered by dilution and infusion is significantly lower (0.3%) than with direct injection (2.3%). The rate of serious adverse events with diluted administration of Combidex is lower than that in the current labeling for iodinated contrast agents used with CT such as Iohexol® (1.1% serious adverse reactions) and Oxilan® (1.5% serious adverse reactions) which are currently used in anatomic imaging for evaluation of lymph node disease. (See iodinated contrast package inserts in Appendix G).

Diluting Combidex and infusing it reduces the overall number of adverse events and the number of serious adverse events. Dilution also allows the trained physician the opportunity to better manage any events that may occur. Radiologists are trained in managing these

events, such as those that occur with iodinated contrast. The package insert specifies the use of 100 ml dilution and slow infusion over 30 minutes for the administration of Combidex.

There was one patient who died following administration of Combidex. This patient was a liver patient who received a bolus injection. The patient was a 70 year old male with underlying hypertension, atrial fibrillation, CVA, diabetes, and metastatic colon cancer who received a bolus injection over 1 - 2 minutes for liver imaging. The patient experienced hypotension and then cardiac arrest. Only oxygen was administered at the site; epinephrine and atropine were administered only after the patient was transferred from the MRI unit to an emergency room. Appropriate treatment for hypotension and respiratory arrest was much delayed and undoubtedly contributed to the fatal outcome.

This type of event can and does occur with all contrast agents and current labeling notes that these agents be given in a setting where necessary personnel and equipment are present to treat such reactions. The FDA Diagnostic I.V. Radiopaque Drugs Class Labeling Guideline[6] states that:

> "Diagnostic procedures which involve the use of radiopaque diagnostic agents should be carried out under the direction of personnel with the prerequisite training and with a thorough knowledge of the particular procedure to be performed. Appropriate facilities should be available for coping with any complication of the procedure, as well as for emergency treatment of severe reactions to the contrast agent itself. After parenteral administration of a radiopaque agent, competent personnel and emergency facilities should be available for at least 30 to 60 minutes since severe delayed reactions have occurred. The possibility of an idiosyncratic reaction in susceptible patients should always be considered. The susceptible population includes patients with a history of a previous reaction to a contrast media, patients with a known sensitivity to iodine per se, and patients with a known clinical hypersensitivity; bronchial asthma, hay fever, and food allergies."

The current standard class labeling for the Warnings Section of contrast media also contains information regarding possible severe reactions.

It is noteworthy that no reactions even approaching this degree of severity occurred with administration by infusion following dilution in saline used for lymph node evaluation as now proposed for the product and that it is likely that prodromal signs and symptoms of lesser severity would occur with the administration of the dilute dosing allowing for discontinuation of the infusion if necessary.

5.10 Summary of Safety

Combidex can be safely administered by slow infusion over a period of approximately 30 minutes following dilution in 100 ml of normal saline. This method of administration minimizes adverse events and allows management of adverse events that may occur by stopping the infusion. The rate of serious adverse events is less than a third of the rates experienced with iodinated contrast agents currently used with CT.

6 RISK BENEFIT DISCUSSION

The Combidex NDA was given a priority review as there is no imaging agent currently approved for differentiating metastatic from non-metastatic lymph nodes. Combidex meets an unmet medical need and the improvement in accuracy of differentiating metastatic from non-metastatic lymph nodes with Combidex results in improvement of nodal staging.

Anatomic imaging is presently used for clinical nodal staging as shown in consensus guidelines including the American College of Radiology (ACR) Appropriateness Criteria[1], the National Comprehensive Cancer Network (NCCN) Practice Guidelines[2] and the American Joint Committee on Cancer Staging Manual[3]. Evaluation of lymph nodes with anatomic imaging, including CT, MRI and ultrasound currently relies primarily on the size of the lymph node to determine whether or not it is metastatic. A review of the current recommendations for anatomic imaging in clinical nodal staging of various cancers is

provided in Appendix H including verbatim excerpts from the various monographs for each cancer. These practice guidelines were chosen for their wide availability; other similar guidelines are available.

Typically when a radiologist uses size as the criteria, nodes that are greater than 10 mm are considered metastatic. The problem with using nodal size criteria is that large nodes can be non-metastatic and small nodes can be metastatic. This leads to low sensitivity and high specificity, with a high number of false negative diagnoses. Reducing the size cut off for a metastatic node classifies more nodes as metastatic and increasing the sensitivity while decreasing the specificity – the false negatives are reduced at the cost of increased false positives.

Some radiologists use more subjective criteria in addition to size for nodal differentiation. The problem with using subjective nodal characteristics is that they are based on individual experience and can neither be generalized nor validated. The use of this approach in clinical trials of Combidex resulted in a bias towards high sensitivity at the cost of low specificity. As recognized by the Agency in the Medical Imaging Guidance document, subjective image assessments can be difficult to validate and replicate.
The shortcomings of current imaging procedures for diagnosing nodal metastasis were demonstrated very clearly during the clinical trials of Combidex. Whether one uses size criteria or an overall interpretation or reader's diagnosis, current imaging techniques have high sensitivity *or* high specificity, *but not both*, which results in overall poor to moderate accuracy.

The results of the US and EU and the NEJM multicenter studies showed that Combidex provided consistently high sensitivity, specificity and accuracy in differentiating metastatic from non-metastatic lymph nodes. Combidex reduced the number of both false positive and false negative diagnoses when evaluating lymph node status and significantly improved the accuracy of clinical nodal staging.

There are several important factors in the assessment of the balance of risks and benefits of a contrast agent such as Combidex. The Medical Imaging Draft Guidance notes that potential risks include both the risks related to the administration of the drug and the risks of incorrect diagnostic information.

6.1 Risks Related to the Administration of Combidex

The additional risk of using Combidex when anatomic imaging is used for lymph node evaluation in cancer patients is that a serious adverse event will occur that would not have occurred with contrast enhanced CT or unenhanced MR (the current methods of anatomic imaging used for lymph node evaluation). Analysis of the original NDA database of 947 patients and additional safety data from over 1,000 patients enrolled in clinical trials conducted since the initial NDA filing demonstrates that this risk can be moderated by patient selection (e.g. history of allergy), drug administration (slow infusion following dilution which not only reduces the frequency of adverse events but also facilitates monitoring), and physician education.

The use of dilution and infusion of Combidex has been shown to reduce the overall rate of adverse events, and decrease the number of serious adverse events. It also allows the clinician to better manage events. The rate of serious adverse events in iodinated contrast agent labeling used for CT such as ioxilan or iohexol is over 1.0%, substantially greater than the 0.3% rate for observed Combidex when administered using dilution and slow infusion. Radiologists are trained and equipped to manage adverse reactions from contrast agents.

The risks of administering Combidex by dilution and infusion include:

- An overall adverse event rate of 15.2%. The overall adverse event rate is not unusual for a parenterally administered contrast agent. The majority of adverse events occur during the infusion and are of short duration.

- A serious adverse event rate of 0.3%. This is less than one third of the serious adverse event rate reported in the package inserts for iodinated contrast agents used for CT, which is the most common current anatomic imaging technique used in this patient population

- Risk of rare serious, life threatening anaphylactic events. This risk is identified in the labeling of all current contrast agents in standard wording in a bold warning in the Precautions section of the package insert. Radiologists are trained in the possibility of these events when they use contrast agents.

There is an increased risk of adverse events if the drug is administered by direct injection. This is addressed in the revised proposed package insert and in physician education.

The Medical Imaging Guidance states that the risk due to false diagnoses with the use of a contrast agent must also be considered when evaluating risk. False diagnoses of lymph node status can lead to either under-treatment or over-treatment of the patient. For example, a patient with metastatic nodes falsely diagnosed as negative may have surgery (with its attendant morbidity and mortality) potentially curative for local disease, but not for node positive disease. A patient without metastatic disease falsely diagnosed as having it may be denied potentially curative surgery or might be given more extensive radiation therapy (with accompanying morbidity) than required. The impact of a false diagnosis is the same regardless of the technology used to reach the diagnosis–CT or MR, enhanced or not. Combidex enhanced MR reduces the risk due to false diagnoses.

6.2 Benefits of Combidex for Detection of Lymph Node Disease

The National Cancer Institute estimates that approximately 8.2 million Americans living today have a history of cancer. In 2002, the American Cancer Society estimated that 1.3 million new cases of cancer would be diagnosed and more than half a million patients will die of their cancers. Today, cancer patients are being managed more aggressively than ever with new drugs, radiation therapy and surgery.

Combidex fills an unmet medical need as there is no other FDA approved non invasive method that accurately differentiates metastatic from non-metastatic lymph nodes. The current standard practice of evaluating lymph nodes using size has poor accuracy resulting from low sensitivity in small nodes and low specificity in enlarged nodes.
The benefits of Combidex enhanced MR imaging include:

- Improved diagnostic accuracy on a nodal level and a lower risk of false nodal diagnoses.
- Increased numbers of correctly diagnosed patients.
- Increased accuracy in clinical nodal staging
- More appropriate patient management as demonstrated in each of the efficacy studies.
- More appropriate treatment planning.

Lymph node status is one important part of clinical cancer staging. In virtually all cancer treatment algorithms for both newly diagnosed cancer and for recurrent disease, the presence and number of metastatic nodes is an important factor in planning the most appropriate and effective course of therapy. Nodal evaluation is done to determine if the primary cancer has metastasized to regional lymph nodes because for many types of cancer (i.e., breast, prostate, head and neck), a primary mode of metastasis is to the lymph nodes. Determination of lymph node status is critical to developing the most appropriate treatment plan for an individual patient.

The patient management results obtained in Phase III demonstrated several benefits that could be derived from the use of Combidex in MRI of lymph nodes from any body region. First, the images obtained after Combidex administration provided clinical nodal staging information that the pre-dose images did not for a majority of the patients (62% to 64%). The types of additional information provided by the Combidex images were most often;

1) Identifying increased or decreased numbers of suspected metastatic nodes,
2) Assisting in determination of the extent of nodal disease, and
3) Increasing confidence in the differentiation of metastatic and non-metastatic nodes.

All of this information is useful, in conjunction with all of the other clinical information available, in developing the most appropriate treatment plan for an individual patient. If Combidex images indicate the presence of a metastatic node where none had been previously suspected, the planned nodal sampling can be extended. (In fact, this occurred in the two European studies and in the NEJM study.) On the other hand, the finding of isolated nodal involvement on Combidex images could suggest a confirming needle biopsy be done and in some cases obviate the need for surgery, as occurred in the NEJM study.

7 REFERENCES

1) Martin TA, Quiroz FA, Rand SD, Kahn CE. Applicability of American College of Radiology Appropriateness criteria in a general internal medicine clinic. Am J. Roentgenol. 1999 Jul;173(1):9-11.

2) National Comprehensive Cancer Network. Practice guidelines in Oncology. Nov 1, 2003.

3) Green FL. American Joint Committee on Cancer, and American Cancer Society. American Joint Committee on Cancer staging manual. 6th Edition, p. xiv, New York: Springer-Verlag; 2002.

4) Harisinghani MG, Baretsz J, Hahn PF, Deserno M, Tabatabaei S, Hulsbergen van de Kaa, C, de la Rosette J, Wessleder R. Noninvasive Detection of Clinically Occult Lymph-Node Metastases in Prostate Cancer. N Engl J Med 2003;348:2491-9.

5) FDA Guidance for Industry: Developing Medical Imaging Drug and Biological Products (2003).

6) FDA Diagnostic IV Radiopaque Human Prescription Drugs Class Labeling Guideline

7) Obuchowski, NA, Receiver Operating Characteristic Curves and Their Use in Radiology, Radiology, 2003; 229:3-8