Questions for MIDAC: BLA # 99-1407
July 10, 2000

1 Characterization of pre-test probability of disease is important for several reasons: a) a test should be evaluated in patients in whom the diagnosis is equivocal; b) a test may perform differently in patients with different probabilities of disease; and c) results may require different interpretation in patients with different pre-test probabilities of disease.

In the phase 3 study under consideration, entry required some suspicion of appendicitis but one or more atypical features.

In future studies of aytpical appendicitis, should entry criteria be based principally on physician uncertainty or atypical features? If the latter, please comment on which combination of atypical features would be most useful.

2. Safety data following LeuTech administration are available on approximately 400 patients (all studies, including ongoing, and for other indications). Of these, approximately 250 comprise the experience in the appendicitis setting. The most frequently reported adverse event in all studies was vasodilatation, which was mild to moderate and did not require intervention. There have been no serious adverse events attributed to the administration of LeuTech. If LeuTech were to lead to serious adverse events in 1 out of 100 patients treated, there is an 8% chance that an event would not be detected in a study of 250 patients. If LeuTech were to result in serious events in as little as 1 in 1000 patients treated, there is an 80% chance that an event would not be detected in a sample size of 250 patients. Estimates of the incidence of appendicitis in the United States are as high as 1 in 500 per year (approximately 600,000 cases per year). Of these, up to 1/3, or approximately 200,000 cases/year, present with atypical signs and symptoms and could potentially be imaged with LeuTech.

Please comment on the adequacy of the safety database given the potential for use of this product in a large patient population.

3 The data regarding repeat administration of LeuTech are limited. Since repeat use of a protein product can lead to safety concerns and/or loss of efficacy resulting from antibody formation, if approved, LeuTech would be labeled as a one time administration. However, repeat imaging could be useful for patients who have recurrent abdominal pain atypical for appendicitis. Of 30 normal volunteers enrolled in a readministration study, 5 developed a human anti-mouse antibody (HAMA) response with redministration. None of the 5 had "high" antibody titres (defined by the sponsor as > 1000 ng/ml) and no patient experienced adverse events related to the second administration.

If licensed, should the sponsor be required to generate additional data on repeat imaging as a phase 4 commitment? If so, can these data can all be generated in normal volunteers, or should some data also be generated in patients?

4 The Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use (February 28, 1997) recommends "the off site image should be the basis of the definitive analysis of imaging performance in the phase 3 clinical trial." "Off site image interpretation should be performed in as 'blinded' a fashion as possible." In this phase 3 trial, the off site readers were only provided with demographic information (age, sex, weight, height) for each patient. In such a manner one can ensure that the accuracy of reads is influenced by information in the scans, not by other predictive factors such as leukocytosis or physical findings. In actual use, scans may be interpreted in the context of other information.

In addition to the offsite (blinded) and onsite interpretations, is there a value in having offsite physicians read scans after being supplied with clinical information (e.g., presenting signs and symptoms) and/or results of other diagnostic tests?

5 For patients who present with atypical signs and symptoms of appendicitis, there is a need for agents that can assist physicians in diagnosing or ruling out appendicitis. In certain subpopulations, especially, women with pelvic inflammatory disease and young children, this need is especially great because other illnesses can confound the diagnosis. Women with coexisting PID were excluded from the phase 3 studies. Forty - eight patients (19 %) were between 10-17 years of age, with 15 (6%) between 5 and 9 years of age, and N= 10 (5%) were > age 65.

a. Has the sponsor gathered sufficient data in pediatric and geriatric populations such that, if licensed, the indicated population will be all patients who present with atypical signs and symptoms, without age restriction?

b. If licensed, should the sponsor be required as a phase 4 commitment to generate data on LeuTech in patient populations, such as women with coexisting PID, patients with other concurrent infections, pediatric patients?

6 The phase 3 trial performance data for the aggregate blinded reads, based on the surgeon's pre-scan likelihood estimates, are as follows:

Surgeon's Pre-scan Likelihood Estimate (N)	Incidence of Appendicitis			Sensi-tivity	Speci-ficity
	total	If scan + (PPV)	If scan – (100%-NPV)		
0-19% (22)	0%	-	-	-	100%
20-39% (61)	15%	86%	6%	67%	98%
40-59% (65)	25%	67%	8%	75%	88%
60-79% (44)	61%	86%	33%	74%	82%
80-100% (8)	88%	100%	50%	86%	100%
20-79% (170)	31%	79%	11%	73%	92%

Please comment on whether these data support the ability of LeuTech to aid in the diagnosis of appendicitis. Please comment specifically on its utility to rule in appendicitis and to rule out appendicitis in patients with various levels of pre-test likelihoods.

7 The sponsor developed a questionnaire for surgeons designed to evaluate the utility of LeuTech. The surgeons filled out the questionnaire prior to obtaining the LeuTech scan. The surgeons ranked the likelihood of appendicitis, indication for other tests, and patient disposition. After the LeuTech scan results, with instructions to assume the scan result is accurate, the surgeons again filled out the same questionnaire. The shifts in patient management, as reflected by changes in the responses on the questionnaire, were recorded. The shifts in patient management are shown below:

Distribution Of Intended Clinical Management Phase 3 Study			
FINAL DIAGNOSIS	MANAGEMENT		
		Pre-scan	Post-scan
Acute Appendicitis	Send Home	5	2
	Admit for Observation	29	4
	Surgery	21	49
No Acute Appendicitis	Send Home	38	78
	Admit for Observation	84	43
	Surgery	12	13

Is this approach useful for assessing clinical utility? Do the data generated by the questionnaire support the clinical utility of LeuTech?

8 If licensed, the sponsor will institute a training program for the end users. Ideally, the training program following licensure should be identical to or very similar to the training program utilized in the phase 3 trial. The instructions given to both the Phase 3 and blinded readers in the training program were as follows: " read for highest sensitivity and negative predictive value", " read with mindset of being afraid to miss the diagnosis of appendicitis ".

Please comment on the on the potential impact of these instructions to the readers in this clinical setting. Is this type of instruction appropriate for a training program?