CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

Memorandum

Statistical Review and Evaluation

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To: STN # 103928/12

Date: July 1, 2004

Topic: Statistical Review

BLA: STN # 103928/12
Product: NeutroSpec®, Technetium Tc 99m Fanolesomab
Indication: Diagnosis of Appendicitis
Sponsor: Palatin

Summary

The clinical data reviewed in this BLA 103928 (Palatin, Technetium Tc 99m Fanolesomab) support the approval of the new drug to diagnose appendicitis in patients presenting with atypical signs and symptoms. This recommendation is based on a review of Technetium Tc 99m fanolesomab efficacy and safety in adult and pediatric patients above 5 years of age. The data were presented to the Advisory Committee (MIDAC) on July 10, 2000, and the Advisory Committee voted that the product was efficacious. The sponsor responded to FDA's Sept 25, 2000 CR Letter on September 30, 2003. This supplement contained no new efficacy data. The efficacy data were analyzed in the first submission and the analysis did not change.

The analyses were verified again. The results are consistent with the numbers used in the Package Insert.

The results are reproduced here for record purposes.

Brief Overview

The applicant submitted a Biologics License Application for Technetium Tc 99m fanolesomab kit for the preparation of Technetium Tc 99m fanolesomab for the diagnosis of appendicitis in patients with equivocal signs and symptoms.

Prior to the submission of the BLA the applicant had a pre-BLA meeting on May 20, 1999. In December 06, 1999, the applicant submitted a BLA with efficacy and safety data (study 97-003, 98-004) and additional safety data from a total of 14 other trials.

Technetium Tc 99m fanolesomab was evaluated for imaging efficacy and safety in two clinical trials in patients with equivocal signs and symptoms of appendicitis. Both the phase two (97-003), and phase three trials (98-004) were conducted under similar protocols. Both protocols sought to enroll patients with atypical signs and symptoms of appendicitis. The agreement between the blinded reader's diagnosis and the diagnosis from the institution (pathological) determined efficacy endpoints in similar fashion in both studies.

A total of 259 patients were studied in both phase 2 and phase 3 appendicitis trials. The incidence of appendicitis in the phase 2 and phase 3 study was 50% and 30% respectively.

The results of the above studies were reviewed by the agency and presented to a Medical Imaging Device Advisory Committee (MIDAC) on July 10, 2000. At that time, the MIDAC unanimously voted in favor of the adequacy of the data to support the safety and efficacy of the scan using Technetium Tc 99m fanolesomab.

This review summarizes the previous evaluation of the original BLA in addition to the review of new safety data from additional 84 patients that was provided in a follow-up submission on 11 February 2004, by Palatin, Inc. The overall safety data was obtained from 523 patients of which 259 were enrolled in the phase 2 and phase 3 appendicitis trials.

Efficacy

Efficacy was evaluated in 259 patients who participated in studies 97-003 (phase 2) and 98-004 (phase 3) for appendicitis. Both studies were designed to assess the efficacy of Tc 99m Technetium Tc 99m fanolesomab imaging for detection of acute appendicitis.

The performance of Technetium Tc 99m fanolesomab was based on the readings of the Technetium Tc 99m fanolesomab imaging by three experienced blinded nuclear medicine practitioners and the by the site investigators for the presence or absence of infection and, specifically, as "appendicitis" or "no appendicitis". The primary performance outcome measure was patient-based agreement rate between the blinded readers diagnosis and the final institutional diagnosis for appendicitis. For cases that underwent surgery, the surgical and pathology reports were the basis for the final diagnosis. In the event surgery was not performed, clinical follow up was obtained with in 2 weeks for the phase 3 and with in 4 weeks for the phase 2 study. Secondary performance outcome measures included patient-based rates of agreement of the individual site investigators assessments of the Tc 99m Technetium Tc 99m fanolesomab scans for the presence or absence of appendicitis compared with final institutional diagnosis.

Associated measures of sensitivity, specificity, negative and positive predictive value for blinded readers, site investigators and impact on clinical management as assessed by the comparison of the pre- and post-Technetium Tc 99m fanolesomab imaging questionnaires were obtained.

The primary efficacy analysis evaluated the performance of Technetium Tc 99m fanolesomab for diagnosis of acute appendicitis in both studies. The two clinical trials used the agreement rate as the primary efficacy outcome measure. Blinded reader evaluations are based on the individual reads of the three-blinded readers and their aggregate. The majority read (at least 2 out of 3 readers agreeing for an individual patient) determined the aggregate. The blinded reads were based on intent to treat (ITT) analysis.

The performance rates for the diagnosis of appendicitis by the blinded readers and by the clinical investigators are shown in the following Table.

Table. Diagnostic Performance Of Technetium Tc 99m Fanolesomab

Evaluation	Performance Rates	
	Blinded Readers percentages (95%CI)	**Study Investigators** percentages (95%CI)
Sensitivity	75 (62, 85)	91 (80, 97)
Specificity	93 (87, 97)	86 (79, 91)
Accuracy	87 (82, 92)	87 (81, 91)
Positive Predictive Value	82 (69, 91)	74 (62, 84)
Negative Predictive Value	90 (84, 94)	96 (90, 99)

For blinded readers scintigraphy with technetium Tc 99m fanolesomab had a sensitivity of 75%, a specificity of 93% and an accuracy of 87% for a diagnosis of appendicitis. The positive predictive value and negative predictive value were 82% and 90%, respectively. For investigators at the clinical sites (site investigators), scintigraphy with technetium Tc 99m fanolesomab had a sensitivity of 91%, a specificity of 86% and accuracy of 87%. For the site investigators, the positive predictive value and negative predictive value were 74% and 96%, respectively.

Analyses by various demographic characteristics suggested that the performance of technetium in these subgroups was similar to that of the overall study population.

The above study results are supported by similar findings from the phase 2 trial that was conducted in 56 patients with equivocal signs and symptoms of appendicitis. The phase 2 study demonstrated that technetium Tc 99m fanolesomab had 89% sensitivity, 68% specificity, 73% PPV and 86% NPV as per the blinded reader assessments.

The details are given in the Appendix.

Safety

The safety information was obtained from 523 patients who received technetium Tc 99m fanolesomab in 14 trials. Four hundred seven (407) patients were enrolled in eleven studies

sponsored by Palatin Technologies, Inc. Of the 523 patients 259 participated in the phase 2 and phase 3 studies for appendicitis.

Patients ranged in age from 5.2 years to 91 years, with the median age of 35 years. Twenty-nine (5.5%) patients were between 5 and 11 years of age and 32 (6.1 %) were between 12 and 16 years. Sixty-four patients (12.2%) were 65 years of age or older. Two hundred seventy nine (53%) were female and 244 (47%) were male. There were 319 (61%) whites, 49 (9%) blacks, 98 (19 %) Hispanics, and 33 (6%) "other". For studies under Palatin INDs and for the appendicitis studies, the proportions of Caucasians patients were higher, 72% and 66%, respectively than other racial groups.

All patients received a single injection of Tc 99m Technetium Tc 99m fanolesomab, except for the 30 patients enrolled in Study 99-001, who received two injections of radioactively decayed Technetium Tc 99m fanolesomab to evaluate HAMA response. A total of 30 patients enrolled in Study 97-001 received a single injection of decayed Technetium Tc 99m fanolesomab to evaluate HAMA response.

The average antibody dose was 121 ug (range 32.5 ug to 250 ug). Excluding the patients who received decayed Technetium Tc 99m fanolesomab in studies 97-001 and 99-001, the radioactive dose ranged from 1.1 mCi to 33.0 mCi, with a mean of 15 mCi.

Thirty-seven of the 523 patients (7%) who received technetium Tc 99m fanolesomab reported a total of 49 adverse events (AEs). Of the 49 AEs reported, 4 (8%) were classified as severe: (pain, decrease in O2 saturation (68%) with chest pressure, sepsis and hypotension). Two of the 4 severe adverse events were serious adverse events and were accompanied by death. The four patients with severe adverse events are described below:

1) A 66-year-old man with diabetes mellitus and end stage renal disease, peritoneal dialysis catheter infection developed severe hypotension 7 hours after technetium Tc 99m fanolesomab injection and suffered cardiac and respiratory arrest. The cause of death was uncertain. The AE s were considered unrelated to the study drug by the investigators.

2) A 35 years old woman with diabetes mellitus, decubitus ulcer, sepsis, and respiratory failure received technetium Tc 99m fanolesomab injection for assessment of infection, continued to deteriorate and died 8 days later.

3) The third patient had a non-specified pain for 3 hours that started immediately after technetium Tc 99m fanolesomab injection.

4) An adult patient experienced chest pressure and decreased oxygen saturation 5 minutes post injection. The symptoms persisted for about 48 minutes. The patient required oxygen therapy and later recovered. These AE s were considered as possibly related to the study

drug by the investigator. The adverse events in this patient were initially classified as moderate by the investigator.

Thirty-five (71%) AEs were classified as mild in severity and 10 (20%) were moderate.

A total of 24 of the 49 AEs were considered possibly or probably related to the study drug and were experienced by sixteen (3%) of 523 patients. The events included 10 cases of flushing, 3 cases of dyspnea, 2 cases of chest pressure sensation, and single cases of nausea, injection site burning, injection site erythema, pO2 decrease, dizziness, headache, paresthesia, contusion and hot flushes.

The most frequently reported AE was flushing, experienced by 10 patients (1.9%). Dyspnea was reported by 5 (1.0%) patients. Dizziness and paresthesia were reported in 3 patients (0.6%) each. Nausea, chest pressure, pain, nasopharyngitis, headache, hypotension and syncope were reported in 2 patients (0.4%) each. Action was taken for 5 AE s (dizziness; weakness; syncope; chest pressure and decrease in pO2; each involved a change in body position (place to supine position) to resolve the event. All AEs had resolved by the end of the study period.

Time of onset ranged from immediately post-injection to 4.5 days post- injection and duration ranged from 1 minute to 4 hours in cases where onset and duration were specified (excluding LT-006-02, subject 1012 who had a pre-existing condition of sepsis).

For 441 patients, changes in vital signs were evaluated at 5 minutes, 30 minutes and 1-hour post injection. Statistically significant decreases in systolic and diastolic blood pressures were noted following injection, and a statistically significant decrease in pulse rate was noted at 1-hour post-injection. However, the changes were small and not clinically significant.

Clinical laboratory parameters were measured and evaluated for changes from baseline in four studies. A total of 7 clinically significant changes in laboratory parameters were reported in 4 of the 284 patients (1.4%). The only clinically significant changes in laboratory parameters that were possibly attributed to technetium Tc 99m fanolesomab were elevations in AST and LDH in one subject after a second injection. These elevated liver enzymes returned to baseline without treatment; clinical and laboratory follow-up revealed no cause, so the investigator was unable to exclude the possibility of relationship to the injection of technetium Tc 99m fanolesomab.

For the phase 3 appendicitis study and the phase 2 osteomyelitis study, statistically significant shifts downward in laboratory parameters were noted at 2 hours post-injection for WBC, neutrophils, hemoglobin, total protein and BUN.

Considering other clinical laboratory parameters for which post-injection values shifted in one direction or the other for at least 10 patients, there was a tendency to shift downward for Hct (28

of 39 shifts) and RBCs (15 of 24 shifts). There was a tendency to shift upward for lymphocytes (19 of 29 shifts) and for monocytes (17 of 22 shifts).

The highest incidence of shifts occurred for neutrophils and WBCs. Twenty-six of 188 patients (14 %) and 28 of 151 patients (21%) in Studies 98-004 and 98-005 combined demonstrated a negative shift at 2 hours post- Technetium Tc 99m fanolesomab administration in WBCs and neutrophils, respectively. WBC and granulocyte counts demonstrated partial recovery by 4 hours post injection. The shifts in the other laboratory parameters (hemoglobin, total protein and BUN) were not believed to be related to study drug.

None of the 54 patients having HAMA assays before and after a single injection of technetium Tc 99m fanolesomab had a positive HAMA response at any time point. Five (16.7%) of the 30 patients who received two injections of technetium Tc 99m fanolesomab exhibited positive HAMA responses. Two of the five patients had marginal responses and three had moderate responses. None of the responses were considered strong (greater than 1000 ng/mL).

In summary, technetium Tc 99m fanolesomab has an acceptable safety profile in all studied populations, including the pediatric, adult and geriatric populations, for use according to the proposed indication. Further studies will be needed to demonstrate activity and safety in a neutropenic population.

Appendix

Table 1: LeuTech, Palatin Technologies, Inc.
Sponsor's Analysis of Evaluable Patients

TRUTH – STUDY # 98-004 N = 200 (N = 182 for onsite reader)											
Readers		Blinded Reader 1		Blinded Reader 2		Blinded Reader 3		Aggregate Readers		On Site Reader	
		+	-	+	-	+	-	+	-	+	-
Dx : Scan Results	+	48	17	39	14	45	8	44	10	49	18
	-	11	124	20	127	14	133	15	131	5	110
	Total	59	141	59	141	59	141	59	141	54	128
Sensitivity (%)		81		66		76		75		91	
95% CI		(69-90)		(53-78)		(63-86)		(62-85)		(80-97)	
Specificity (%)		88		90		94		93		86	
95% CI		(81-93)		(84-94)		(89-98)		(87-97)		(79-91)	
Accuracy (%)		86		83		89		88		87	
95% CI		(80-90)		(77-88)		(84-93)		(82-92)		(81-91)	
PPV (%)		74		74		85		81		74	
95% CI		(61-84)		(60-85)		(72-93)		(69-91)		(62-84)	
NPV (%)		92		87		90		90		96	
95% CI		(86-96)		(80-91)		(85-95)		(84-94)		(90-99)	

Conclusions:

Assumes the population prevalence rate is approximately same as seen in the sample, i.e., approximately 30%.

There is no significant difference from Reader to Reader except that the sensitivity of the blinded reader 2 is significantly lower than the sensitivity of the onsite reader (non-overlapping 95% confidence interval).

Clinical Dx: The analysis of the clinical assessment of appendicitis before the administration of LeuTech agent (e.g., physical Dx, X-rays, other scans (CT), etc.) is being done. This will help us in evaluating the supplemental value of the agent in diagnosing appendicitis. The sensitivity could be as low as 53% with 95% confidence. The specificity is good, i.e., LeuTech appears to help in ruling out appendicitis in patients who do not have appendicitis but do have equivocal signs and symptoms.

There appears to be beneficial shifts in intended patient management post-scan versus pre-scan.

There were 203 patients in this study. Duration of imaging for one patient was insufficient for efficacy evaluation (however, efficacy evaluations were provided in the data). Two other patients were lost to follow-up. The sponsor's results are based on 200 evaluable patients for blinded readers and 182 evaluable for onsite readers. There was a violation of sponsor's own algorithm in treating aggregate values which were assigned a Dx based on consensus/majority of the blinded readers' Dx.

Patient #	Truth	Dx corresponding to blinded reader 1	2	3	Dx for Aggregate Reader per Sponsor	Dx Onsite Reader	Truth (sponsor) Missing due to	**Intent-to-treat Analysis** Dx Aggregate
A14	+	+	+	+	Missing		+	Lost to f/u
D07	-	-	-	-	Missing		-	Lost to f/u
E09	-	-	-	-	Missing		+	Inadequate takeup (+)

A correct analysis is intent-to-treat analysis with lost to follow-up patients assigned as having no appendicitis (conservative), and their LeuTech blinded & onsite readers Dx are provided.

Table 2: – LeuTech, Palatin Technologies, Inc.
Intent-to-treat Analysis

TRUTH – STUDY # 98-004 N = 203											
Readers		Blinded Reader 1		Blinded Reader 2		Blinded Reader 3		Aggregate Readers		On Site Reader	
		+	-	+	-	+	-	+	-	+	-
Dx : Scan Results	+	48	18	39	15	45	9	44	11	54	20
	-	12	125	21	128	15	134	16	132	6	123
	Total	60	143	60	143	60	143	60	143	60	143
Sensitivity (%)		80		65		75		73		90	
95% CI		(68-89)		(52-71)		(62-85)		(60-84)		(79-96)	
Specificity (%)		87		90		94		92		86	
95% CI		(81-92)		(83-94)		(88-97)		(87-96)		(79-91)	
Accuracy (%)		85		82		88		87		87	
95% CI		(80-90)		(76-87)		(83-92)		(81-91)		(82-91)	
PPV (%)		73		72		83		80		73	
95% CI		(60-83)		(58-84)		(71-92)		(67-90)		(61-83)	
NPV (%)		91		86		90		89		95	
95% CI		(85-95)		(79-91)		(84-94)		(83-94)		(90-98)	

Conclusions:

The Intent-to-Treat analysis includes all patients. The overall conclusions are similar to the evaluable patient population. One difference is that the estimates of sensitivity, specificity, PPV, NPV and accuracy are lower in this ITT analysis.

Table 3: BLA 99-1407 – LeuTech, Palatin Technologies, Inc.
Analysis after deleting two lost to follow-up patients

TRUTH – STUDY # 98-004 N = 201											
Readers		Blinded Reader 1		Blinded Reader 2		Blinded Reader 3		Aggregate Readers		On Site Reader	
		+	-	+	-	+	-	+	-	+	-
Dx : Scan Results	+	48	17	39	14	45	8	44	10	54	19
	-	12	124	21	127	15	133	16	131	6	122
	Total	60	141	60	141	60	141	60	141	60	141
Sensitivity (%)		80		65		75		73		90	
95% CI		(68-89)		(52-71)		(62-85)		(60-84)		(79-96)	
Specificity (%)		88		90		94		93		87	
95% CI		(81-93)		(84-94)		(89-98)		(87-97)		(80-92)	
Accuracy (%)		86		83		89		87		88	
95% CI		(80-90)		(77-88)		(83-93)		(82-91)		(82-92)	
PPV (%)		74		74		85		81		74	
95% CI		(61-84)		(60-85)		(72-93)		(69-91)		(62-84)	
NPV (%)		91		86		90		89		95	
95% CI		(85-95)		(79-91)		(84-94)		(83-94)		(90-98)	

Conclusions:

This analysis includes all patients except for the two lost to follow-up patients. The overall conclusions are similar to the evaluable patient population. One difference is that the estimates of sensitivity, specificity, PPV, NPV and accuracy are lower in this analysis. The analysis of the evaluable patient population is most favorable to the sponsor.