

	PANRETIN	PLACEBO
Assessment		(p=0.0003)
Patient's Subjective Assessment	47% (17/36)	11% (5/46)
Time to response, median (range)	28 ⁵¹ days	24 days
Time to progressive disease, median (range)	30 days	45 days
Duration of response, median (range)	64 days	57 days

One patient on panretin gel had a clinical complete response. Progressive disease as best response was 14% (5/36) on panretin and 35% (16/46) on placebo⁵².

The superiority of panretin over placebo was maintained after adjusting for age, gender, race, baseline aggregate area of index lesions, number of raised index lesions at baseline, baseline performance status, baseline CD4+ lymphocyte counts, and history of opportunity infections or other AIDS-related illnesses concurrent. The superiority of panretin over placebo was demonstrated with consideration of degree of prior anti-KS therapy, prior systemic anti-KS therapy, and prior topical/local anti-KS therapy. Responses were claimed in patients refractory to prior systemic anti-KS therapy and patients refractory to prior topical/local anti-KS therapy.

No patients died while on study drug. One vehicle patient died due to AIDS progression 4 days after removal from study.

Photographs were obtained for the purpose of providing supporting data for the primary endpoint of patient responses according to ACTG criteria. The change in appearance of KS lesions in the photographs which were intended only as a supporting data, generally followed the

⁵¹ This is a better time to response than the results in Study -503.

⁵² In Study -31, progressive disease as best response was 15% (20/134) on panretin and 23% (31/134) on placebo.

trend of responses according to ACTG criteria captured by the Investigators' index lesion assessments.

Eighty-seven percent (13/15) of the panretin responders were applying the gel twice a day at the time of their first response and best response.

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5.2.3 Safety Results

Most of the adverse events, which were determined to be clinically significant, occurred at the site of application of the topical agent. In this trial, study drug was applied to lesions twice a day in contrast to Study -31 in which study drug was applied four times a day. Forty-two percent (42%) of the panretin patients and 9% (4/46) vehicle patients had dose adjustments or discontinuations. Only 14% (5/36) of the panretin patients dose adjusted or discontinued therapy due to an adverse event in comparison to 7% (3/46) of the vehicle patients. Twenty-five percent (9/46) of the panretin patients and 4% (2/46) discontinued therapy due to personal reasons.

Adverse events @ the application site in blinded phase of Study -503 are illustrated in the table below.

Adverse event	Panretin gel, n=36	Vehicle gel, n=46
Rash	14% ⁵³	2%
Pain	0%	4%
Pruritus	3%	0%
Paresthesia	8%	2%
Edema	3%	0%

There was no statistical difference between the panretin gel and placebo for overall incidence of adverse events-- 94% (34/36) and 83% (38/46) (p=0.1), respectively⁵⁴. For Skin and Appendages body system, 67% (24/36) of panretin gel patients compared to 39% (18/46) of vehicle gel patients had at least one adverse events. The table below illustrates the incidence of adverse events at the application site plus incidence at the non-application site.

	PANRETIN, N=36	VEHICLE, N=46
Flu syndrome	3 (8.3%)	0
Headache	4 (11.1%)	1 (2.2%)
Constipation	2 (5.6%)	0
Paresthesia	4 (11.1%)	1 (2.2%)
Asthma	2 (5.6%)	0
Exfoliative dermatitis	3 (8.3%)	0
Dermatitis	3 (8.3%)	1 (2.2%)

⁵³ 75% in Study -31

⁵⁴ The proportions are almost identical as in Study -31 although study drug was applied less often in Study -503.

	PANRETIN, N=36	VEHICLE, N=46
fungoid		
Herpes simplex	4 (11.1%)	1 (2.2%)
Pruritis	3 (8.3%)	1 (2.2%)
Rash	13 (36.1%)	5 (10.9%)
Skin disorder	3 (8.3%)	0

There was no substantial difference in the overall incidence of potentially infection-related adverse events between treatment groups. The number of treatment emergent OIs/AIDS-related illness adverse events was 19% (7/36) for panretin and 13% (6/46) for vehicle. There was not a substantial difference in the overall incidence of potentially infection-related adverse events treatment groups, with 56% (20/36) of panretin patients and 46% (21/46) of vehicle patients (p=0.37).

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5.3 FDA ASSESSMENT OF STUDY RESULTS

5.3.1 FDA Assessment of Study Conduct: Study -503

THE INTERIM ANALYSIS

Originally, Ligand had planned to submit, for their NDA package, a positive Phase 3 (Study -31) as their first pivotal trial plus the results from nine Phase 1-2 protocols⁵⁵ as their second pivotal trial. At a meeting between Ligand and FDA on May 8, 1997, the FDA disagreed with this proposal, i.e., nine Phase 1-2 trials as a second pivotal trial, for a number of reasons. First, the protocols were not designed as pivotal trials but as early exploratory studies at the individual investigator sites. During the early phase of the drug's development, the FDA had suggested that the Phase 1-2 protocols be coordinated as a multicenter protocol instead of separate protocols. Second, the nine protocols and their multiple amendments appeared to be a function of a learning curve experience with the topical ointment in KS patients. Third, pooling the data from the nine protocols would not be desirable because of the differences in the protocols. For example, initially, patients were required to have matched control and treated KS lesions. These lesions were to be as nearly identical as possible. This was later changed to provide for treatment of all KS lesions except for two control lesions. This change was without any requirement for comparability of treated and control lesions. Fourth, early cutaneous KS as described in these protocols was not life threatening. The FDA stated that its preference was for two Phase 3 studies as the basis for Ligand's NDA.

The planned accrual for Study -503 was 270 patients. The study was intended to complete enrollment in June 1998. In August 1997, the FDA learned from Ligand that the results from a planned interim analysis indicated early stopping of Study -503. The original intent of the planned interim analysis--if there was a large benefit for the active treatment--was to stop the trial early and submit the data to the European Regulatory Authorities for early Product Registration. The U.S. NDA for panretin is the first

⁵⁵ See "NON-PIVOTAL CLINICAL TRIALS: Kaposi's Sarcoma Trials" section of this review.

application filed worldwide.

For the interim analysis, 39 patients to each arm were planned for analysis, i.e. 78 patients⁵⁶. The study was stopped after 82 patients were accrued--36 panretin and 46 placebo.

This was problematic because originally, seventy-eight patients were to be evaluated--39 patients in each arm. This is not what was submitted in the NDA. Ligand stopped the study based on an analysis of 36 patients on panretin and 46 patients on placebo. It is unclear how this happened. An additional 52 patients were accrued--26 to each arm.

Per the protocol, the interim analysis should have been an evaluation of the first 39 patients accrued on panretin compared to the first 39 patients accrued on placebo. According to the protocol, parity in the comparison of the two group's analysis was driving the analysis and not the total number of patients accrued as suggested by Ligand (vol. 1.91, p. 034)⁵⁷. The protocol provided stoppage of the trial for "clear benefit for the active treatment" not "to minimize patient exposure to ineffective or toxic investigational treatments"⁵⁸.

Ligand provided the FDA a list of the total 134 patients enrolled in Study -503; they provided patient numbers, date entered, and response to therapy in the initial 12 week blinded period. The FDA sorted the patients by date entered. The results of sorting the patients provided useful information. It appears that a few of the patients in the second cohort of 52 patients overlap with the first cohort with regard to date on entry on study. The following two tables illustrate this. The first table shows the last five patients entered from the first 36 panretin patient cohort. The second table shows the first five patients entered from the second 26 panretin patient

⁵⁶ Although in the 82 patient interim analysis study report dated April 22, 1998, it was stated, "One interim analysis was to have been performed after 78 patients (36 [sic] patients per treatment group per treatment group)..." vol. 1.157, p. 128.

⁵⁷ "39 patients will be needed in each group for the interim analysis, i.e 78 patients in total"

⁵⁸ This is based on the claim that for the patient with limited disease that is not progressing rapidly, another alternative is a "wait-and-see," or "watchful waiting" strategy.

cohort.

The last 5 patients from the first cohort of panretin patients are shown in the table below.

Patient #	Date enrolled	criteria for ACTG response
	01/28/97	No
	01/28/97	No
	02/03/97	Area
	02/04/97	Area
	02/05/97	No

The first 5 patients from the second cohort of panretin patients⁵⁹ are shown in the table below.

Patient #	Date enrolled	criteria for ACTG response
	02/03/97	No
	02/19/97	No
	02/28/97	No
	03/04/97	No
	03/10/97	Area

⁵⁹ Note that sequential patients

were nonresponders.

The table below provides the interim analysis results as submitted to the NDA and the interim analyses if done per protocol (e.g., sequential 39 pts. per arm and the first sequential 78 pts.).

INTERIM ANALYSIS	PANRETIN	PLACEBO	COMMENT
Submitted Total #	36	46	
Submitted Responder #	15	3	
Submitted p-value	0.00027		Ligand's interim analysis significance level: Protocol = 0.005 Re-calculated = 0.00025 Lan-Zucker significance level: 0.00033
Per protocol & as pts. Were sequentially enrolled	39	39	
Submitted responder #	15	3	
Re-calculated p-value	0.00244		Lan-Zucker significance level: 0.00025
1 st 78 sequentially enrolled pts.	33	45	
Responder #	13	3	
Re-calculated p-value	0.00056		Lan-Zucker significance level: 0.00022

Based on the analyses in the above table, it appears that the interim analysis boundary was met only by the analysis submitted in the NDA. The other "per-protocol" analyses do not meet the interim analysis criteria for early stopping of the study.

The original interim stopping boundary specified in the protocol was 0.005 (O'Brien-Fleming, 2-sided test). This appears to be the case in Ligand's correspondence to the FDA on August 14, 1997 and from the FDA-Ligand meeting on October 14, 1997. At the October 1997 meeting the FDA was told that the interim analysis p-value of 0.00027 was strongly positive. According to the NDA study report for Study -503, in December 1997 Ligand ascertained that the protocol-specified significance level of 0.005 would apply if 50% of the total planned patients were enrolled and evaluable at the time of the interim analysis. The 82 patients included in the interim analysis represented approximately 30% of the planned 270 total patients. The re-calculated interim analysis p-value was 0.00025. Ligand informed the FDA of this in a meeting package dated December 23, 1997.

In response to the above information about the interim analysis, Ligand asked (Nov. 8, 1998) the following, "Based on the analyses conducted to date, does FDA believe that the study was stopped inappropriately and, as a result, cannot serve as a second pivotal study for the NDA?"

COMPARISON OF STUDY -503 WITH STUDY -31

It seems that submission of Study -503 as a "positive" pivotal trial for this NDA would be more difficult goal to achieve than Study -31 for the following reasons: 1. less frequent application of the study drug to patients, resulting in less frequent responses in the initial blinded phase; 2. because raised lesions were not required, a more rigorous response criteria, e.g., area reduction and disappearance of lesions, would be applied; and 3. stoppage of the study based on positive results in an interim analysis.

The entry criteria and evaluation of the study primary endpoint in Study -503 is not as rigorous as Study -31. In Study -31 a minimum of six (6) cutaneous KS lesions

including at least three (3) raised lesions were required for entry on study; a response could be scored by reduction in the height of lesions, reduction in area of lesions, and disappearance of lesions. In Study -503 at least 3 lesions were required for entry on study (raised lesions were not required); a response could be scored by, reduction in area of lesions, disappearance of lesions, and reduction in the height of lesions (only if raised lesions were selected). In Study -31 global photographs were required at evaluation points. Global photographs were not required in Study -503 and no investigator took global photographs in this study (Ligand response 10/15/98). Without global photographs, verification of the number of index lesions selected, treated, and evaluated during the study could not be ascertained. FDA verification of the physician subjective assessments of index and non-index lesions by the FDA was impossible.

In Study -31, patients applied the study drug three times daily; the frequency of application was increased according to protocol specifications to four times daily as tolerated, and was decreased to twice daily, once daily or every other day according to toxicity. In Study -503, patients applied the study drug two times daily or less.

SUMMARY TABLE OF DIFFERENCES BETWEEN THE TWO PIVOTAL TRIALS

	STUDY -31	STUDY -503
Eligibility: index lesions	≥ 6 (3 raised lesions)	≥ 3 (raised lesions not required)
Global photographs	Required	Not required
Gel application frequency	TID/QID	BID

THE DISEASE STUDIED

Panretin gel was reported in the NDA as an effective first-line treatment of the cutaneous lesions of AIDS-related KS. In the United States, daunoXome is indicated as a first line cytotoxic therapy for advanced HIV-associated Kaposi's sarcoma. Only one patient entered into Study -503 had received prior daunoXome therapy. Study site 101 (Boag)

had a history of an investigational trial with daunoXome but did not accrue patients who had received prior daunoXome⁶⁰.

In study -503, patients accrued were not restricted to patients with early, cutaneous-only KS but included patients with a wide ranging extent of cutaneous disease and prior therapy, as well as some patients with visceral KS. Information about the number total lesions and the total number of lesions treated with study drug was not required in this trial.

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⁶⁰ Uthayakumar S et al. Randomized cross-over comparison of liposomal daunorubicin versus observation for early Kaposi's sarcoma. AIDS 1996, 10:515-519. Dr. Boag was one of the investigators in this study.

5.3.2 FDA Assessment of Efficacy

THE SECOND PIVOTAL TRIAL: Study -503

THE RESPONDERS AND THE STUDY SITES

Six centers out of 17 produced responders. Eleven centers had no responders with accruals of 1 (4 centers), 2 (1), 3 (3), 4 (2)⁶¹, and 10 (1)⁶². Over 50% of the panretin responders were reported from one site in Australia⁶³; 87% of the panretin responders were reported outside the United States. The table below illustrates the distribution of responders at the study sites.

	INVESTIGATOR	PANREITIN	CONTROL
London, UK	Boag	4/4	0/4
Darlinghurst NSW, Australia	Bodsworth	8/14	1/14
Prahran VIC, Australia	Spelman	1/2	0/3
Boston Univ Med Ctr, Boston, MA	Cooley	1/1	0/2
Maitland, FL	Goodgame	N/A	1/1
Los Angeles, LA	Ruane	1/2	1/2

KAPOSI'S SARCOMA AND THE RESPONDERS

Information about the number total lesions and the total number of lesions treated with study drug was not required in Study -503. Three panretin responders had oral/visceral KS; one vehicle responder had oral/visceral KS. Three panretin responders had cutaneous KS symptoms at baseline; none of the vehicle responders had symptoms at baseline. Five panretin responders had received prior anti-KS therapy. Only one of the panretin responders had progressive disease to prior systemic therapy. This patient had progressive disease to thalidomide; in the discrepancy section of the CRF, it was stated "Thalidomide was not for Kaposi's Sarcoma". One vehicle responder had

⁶¹ Milliken, Donnell

⁶² Bloch

⁶³ Five FDA responders were at this site.

received prior anti-KS therapy; this patient had responded to doxil. The following two tables illustrate this baseline data for the panretin arm and the vehicle arm.

PANRETIN RESPONDERS

PID	PRIOR KS RX (BEST RESPONSE) ⁶⁴	VISCERAL LESION	SYMPTOMS RELATED TO MUCOCUTANEOUS KS
	Radiotherapy (MR)	None	no symptoms
	Thalidomide (SD)		
	None	None	no symptoms
	Vinblastine (PR, MR)	None	no symptoms
	Vinblastine (SD) Thalidomide (PD)	None	no symptoms
	last thalidomide: 3 wks prior to on-study protocol violation		
	None	None	no symptoms
	None	Hard palate	Symptoms of patches of KS on hard palate, eye, foot, back, & arms
	None	None	no symptoms
	None	None	no symptoms

⁶⁴ Partial response = PR; minimal = MR; stable = SD; progressive disease (PD); unknown = ?

PID	PRIOR KS RX (BEST RESPONSE) ⁶⁴	VISCERAL LESION	SYMPTOMS RELATED TO MUCOCUTANOUS KS
	None	None	no symptoms
	None	None	pruritus Lesion, A
	None	None	no symptoms
	None	Hard palate	no symptoms
	BV (PR) Vinblastine (?)	None	no symptoms
	VP-16 (PR) Taxol (PR)	Palate Gingiva esophagus	no symptoms
	None	None	L & R arm pruritus

VEHICLE RESPONDERS

PID	Prior KS Rx (BEST RESPONSE)	Visceral lesion	Symptoms related to mucocutaneous KS
	None	none	no symptoms
	None	Base of tongue	no symptoms
	Doxil (PR)	None	no symptoms

PROTEASE INHIBITORS AND KAPOSI'S SARCOMA

As discussed in the FDA's assessment of Study -31, an event or events in the patients may have triggered the physicians to add, change, or adjust the protease inhibitor therapy.

The table below examines the influence of protease inhibitors on Kaposi's sarcoma in this study. New lesions were not required to be recorded. CD4-lymphocyte counts, at baseline and at response confirmation, were assessed for immune function changes that may occur with effective protease inhibitor therapy. Triglyceride levels were looked at because of the association of elevation of triglycerides and protease inhibitors.

Two panretin responders were not receiving protease inhibitors. Eight panretin responders started protease inhibitors greater than 2 months prior to entry on study. Two panretin responders had a change in protease inhibitors before a response was declared or during the period when the response was being confirmed; one panretin responder had protease started and then discontinued within 2 weeks due to toxicity. Only two panretin responders had a change in protease inhibitor therapy within a two month period prior to entry on-study. A determination of a protease inhibitor effect was inconclusive in four patients because required follow up CD4-counts were not available⁶⁵; three of these patients started protease inhibitor therapy greater than two months prior to on-study and one patient was not receiving protease inhibitor. There were no definite panretin responders who the FDA believed also had a protease inhibitor effect on their KS disease. The FDA did not disqualify responders based on the change in protease inhibitors.

CD4+-lymphocyte counts were required at 12 weeks. In Study -503 39% (32/82) were not available in the NDA database (Ligand response to queries, dated 10/15/98). Four of the 15 responders to panretin gel did not have the week 12 CD4+-lymphocyte counts done; one of 3 responders to vehicle gel did not have 12 week CD4+-lymphocyte counts done.

⁶⁵ CD4+-lymphocyte counts were required at 12 weeks. In Study -503 39% (32/82) were not available in the NDA database (Ligand response to queries, dated 10/15/98). Four of the 15 responders to panretin gel did not have the week 12 CD4+-lymphocyte counts done; one of 3 responders to vehicle gel did not have 12 week CD4+-lymphocyte counts done.

PANRETIN RESPONDERS: PROTEASE INHIBITOR REVIEW

PID	TIMING OF PROTEASE INHIBITOR (PI)	CD4-LYMPHOCYTE COUNT @ BASELINE /UL	CD4-LYMPHOCYTE COUNT @ TIME OF RESPONSE CONFIRMATION /UL	TRIGLYCERIDES @ BASELINE MG/DL	TRIGLYCERIDES @ TIME OF RESPONSE CONFIRMATION MG/DL	COMMENTS
	Saquinavir and ritonavir started 13 wks. Prior to on-study	114	135	363	644	No PI effect
	Indinavir started 5 mos. prior to on-study	144	Ligand: not done at 12 wks	358	584	PI effect INCONCLUSIVE No CD4s done @ 12 wk
			No other CD4s done—protocol violation		Done @ 4 wks	No biochemistry or CD4 done @ wk 12—protocol violation
	Indinavir started 6 mos. prior to on-study	190	Ligand: not done	378	Not done	PI effect: INCONCLUSIVE No other CD4s done
						No biochemistry or CD4 done @ wk 12—protocol violation
	None	96	Ligand: not done	306	85 Done @ wk 8	PI effect: INCONCLUSIVE No other CD4s done
	Saquinavir started 11 mos. prior to on-study	35	66	275	Not done	No PI new lesions appearing
	Ritonavir started 1 wk after on-study					
	None	130	80	132	115	No PI effect
						New KS lesions on right leg @ wk 8

PID	TIMING OF PROTEASE INHIBITOR (PI)	CD4-LYMPHOCYTE COUNT @ BASELINE /UL	CD4-LYMPHOCYTE COUNT @ TIME OF RESPONSE CONFIRMATION /UL	TRIGLYCERIDES @ BASELINE MG/DL	TRIGLYCERIDES @ TIME OF RESPONSE CONFIRMATION MG/DL	COMMENTS
	Saquinavir started 5 mos. prior to on-study	333	480 CD4 increased	129	176	No PI effect Ligand: no change in protease inhibitors during study
	Saquinavir started 11 mos. on-study	105	113	113	89	No PI effect
	Saquinavir started 7 mos. on-study	486	282	395	98	No PI effect
	Indinavir started 1 wk after on-study; d/c'ed after 2 wks because of rash	110	71	261	160	No PI effect
	Saquinavir started 9 mos. prior to on-study	208	285	465	328	No PI effect
	Ritonavir started 1 mo. Prior to on-study					
	Saquinavir started 4 mos. prior to on-study	127	152	78	324	No PI effect??
	Ritonavir started 6 wks after on-study					
	Ritonavir & saquinavir started 3 mos. prior to on study	478	549 CD4 increased	252	234	No PI effect? Ligand: no change in protease inhibitors during study.
	Norvir started 8 mos. prior to on-study	160	170	986	1305	No PI effect
	Indinavir started 3 mos. prior to on-study	39	Ligand; not done	500	372	PI effect: INCONCLUSIVE No other CD4s done