

4.2 RESULTS REPORTED BY THE SPONSOR

4.2.1 The Study Population

The study centers screened 375 patients. Two hundred sixty-eight of these patients (71%) were randomized to the clinical trial.

The median age of the enrolled patients was 39 years (range: 26-71). The racial composition was white (75%), Hispanic (16%), black (7%), and Asian or other (1.9%). Two patients were women. There was a borderline trend of more visceral disease in the placebo arm, 16% (21/134), compared to 8% (11/134) in the panretin arm ($p=0.09$). The following table provides additional demographic information on the two study arms.

	Panretin gel N=134	Vehicle gel N=134
Age, median (range)	38	40
Race		
White	105 (78.4%)	95 (70.9)
Black	9 (6.7%)	10 (7.5%)
Hispanic	18 (13.4%)	26 (19.4%)
Asian	1 (0.7%)	0 (0%)
Other	1 (0.7%)	3 (2.2%)
Sex	133 male	133 male
Karnofsky performance status, median	90	90
CD4+ lymph count, median	154	144
CD4+ count <200, %	54%	60%
CD4+ count <100, %	35%	37.3%
Duration of KS, median (mos.)	11.4	13.7
# of pts. with visceral KS	11	21 $p=.09$
% poor risk by TIS staging	73%	72%

¹³ Data is taken from Table 20, vol. 1.73, p.151. However, Table 28 does not appear to agree, i.e., 32% and 28% of patients at baseline randomized to panretin and vehicle, respectively, had no history of Ois/AIDS-related illnesses.

	Panretin gel N=134	Vehicle gel N=134
Hx of OI's or thrush ¹³	10%	8%
Patients with \geq 50 skin lesions	49 (36.6%)	40 (29.9%)
Number of index lesions Rx'ed, median (range)	6 (5-6)	6 (5-6)
Number raised, index 1-4 ¹⁴	# of pts. 55 (41%)	# of pts. 47 (35.1%)
5	23 (17.2%)	27 (20.1%)
6	56 (41.8%)	59 (44%)
Prior anti-KS Rx		
None	47 (35.1%)	46 (34.3%)
Systemic alone	21 (15.5%)	17 (12.7%)
Topical/local alone	39 (29.1%)	43 (32.1%)
Both systemic & topical/local	27 (20.1%)	28 (20.9%)
Prior antiretroviral Rx		
None	12 (9%)	15 (11.2%)
1 drug protease inhibitor (PI) not including PI	1 (0.7%)	3 (2.2%)
2 drugs including PI not including PI	1 (0.7%)	2 (1.5%)
9 (6.7%)	8 (6%)	
23 (23.9%)	17 (12.7%)	
>= 3 drugs including PI not including PI	80 (59.7%)	86 (64.2%)
8 (6%)	3 (2.2%)	

The foregoing table indicates that there was balance in the accrued patients to both study arms.

The 6 cutaneous KS lesions selected for study were to be representative of the patients' disease; at least 3 of the

¹⁴ Only 2 control patients had less than 3 raised lesions as required by protocol.

selected lesions were to be raised. The location of the panretin-treated index lesions was as follows: 46 lesions on the face, 12 on the hands, 20 on the neck, 195 on the forearms, 351 on the lower legs, 149, on the chest, and 35 on the back; the most frequent site treated was the lower legs. Of the 34 centers entering patients on this trial, only 12 centers selected lesions on face (i.e., an obvious site prone to social stigma) for panretin treatment; 6 additional centers could be added if neck lesions were included. At least 19% (273/1404) of panretin gel treated index lesions were on sun exposed anatomic areas (face, hands, neck, and forearms).

Patients were randomized, in a blinded fashion, to panretin gel (0.1%) versus placebo. The initial treatment was for 12 weeks; patients self-medicated themselves TID and escalated the frequency of application to QID as tolerated. The initial blinded treatment ended at the time of cross-over blinded therapy, open-label panretin gel, or withdrawal. Twenty-eight percent (28%) of panretin gel patients did not complete the initial blinded treatment phase. Twenty-four percent (24%) of vehicle gel patients did not complete the initial blinded treatment phase.

Fifteen patients crossed-over from the blinded vehicle to blinded panretin during the blinded phase (first 12 weeks). Eighty-five patients treated with vehicle during the blinded phase of the study were switched to open label panretin at the end of the blinded phase (first 12 weeks).

The following table summarizes the disposition of patients entered on both study arms.

Table 10. Disposition of Patients

Study Phase/Treatment	Number of Patients
Patients Screened	375
Patients Randomized	268
Patients Not Randomized(1)	107
Did Not Receive Any Treatment(2)	0
Patients Received Initial Blinded Treatment	268
Initial Blinded Treatment With PANRETIN Gel	134
Completed Initial Blinded Phase	96
Withdrawn Prior to Completing Initial Blinded Phase(3)	38
Cross-Over Blinded Phase	2
Open-label Phase After Cross-Over	1
Withdrawn After Cross-Over(7)	1
Open-label Phase Without Cross-Over	90
Withdrawn After Initial Blinded Phase(5)	4
Initial Blinded Treatment With VEHICLE Gel	134
Completed Initial Blinded Phase	102
Withdrawn Prior to Completing Initial Blinded Phase(4)	32
Cross-Over Blinded Phase	15
Open-label Phase After Cross-Over	8
Withdrawn After Cross-Over(8)	7
Open-label Phase Without Cross-Over	85
Withdrawn After Initial Blinded Phase(6)	2

The median duration of treatment with panretin was 112 days (range: 1 day to 71 wks). Eighty-five percent of the patients (200/234) treated with panretin achieved the QID frequency.

The following table summarizes the withdrawn patients entered on both study arms.

Table 11. Patients Withdrawn by Primary Reason for Withdrawal - Initial Blinded Phase (N=78)

Primary Reason for Withdrawal	% Pts. by Initial Blinded Phase Treatment(1)					
	All Patients(2)		PANRETIN Gel (N=42)		Vehicle Gel (N=34)	
	N	%	N	%	N	%
ES Disease Status						
Any Progressive Disease	15	19.7	7	16.7	8	23.5
PD - of Treated Index Lesions	4	5.3	1	2.4	3	8.8
PD - of Treated Non-Index Lesions	5	6.6	2	4.8	3	8.8
PD - of Untreated Lesions	13	17.1	7	16.7	6	17.6
Stable Disease of Treated Lesions	3	3.9	2	4.8	1	2.9
Partial Response of Treated Lesions	2	2.6	1	2.4	1	2.9
Clinical Complete Response of Treated Lesions	0	0.0	0	0.0	0	0.0
Non-Compliance						
Failure to Follow Dosing Regimen	0	0.0	0	0.0	0	0.0
Failure to Follow Appointment Schedule	9	11.8	7	16.7	2	5.9
Administrative						
Adverse Event	4	5.3	1	2.4	3	8.8
Withdraw Consent	9	11.8	5	11.9	4	11.8
Death	21	27.6	10	23.8	11	32.4
Lost to Follow-up	4	7.9	4	9.5	2	5.9
Study Blind Broken	7	9.2	5	11.9	2	5.9
	0	0.0	0	0.0	0	0.0
P-value(3)	0.7822					

4.2.2 Efficacy Results

Intent-to-treat analysis of ACTG response criteria (as applied to topical therapy) during the initial blinded 12 week period is depicted in the table below.

	PANRETIN	PLACEBO
Response index lesions)	76 47 ¹⁵ /134 (35.1%)	24/134 (17.9%) p = 0.002
Physician's Global Assessment (index + non-index lesions)	26/134 (19%)	5/134 (4%) p = 0.00014
Time to response, median (range)	34 days ¹⁶	33 days ¹⁷
Duration of response ¹⁸ , median (range)	55 days	57 days
Duration of treatment, median (range)	85.5 days	85 days

One patient on panretin gel had a clinical complete response. Progressive disease as best response was 15% (20/134) on panretin and 23% (31/134) on placebo.

Ninety panretin and eighty-five vehicle patients entered the open-label panretin phase. Among the 85 vehicle patients who entered the open label panretin phase, 25 or 29% responded.

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, concurrent antiretroviral therapy, concurrent illnesses. More first and best responses were reported in patients applying panretin QID.

¹⁵ Includes one clinical complete response.

¹⁶ Among the 4 vehicle treated patients who progressed and then crossed-over to panretin, the time to onset of response was 25 days. Among the 60 panretin responders (initial blind plus open-label treatment), the median time to onset for response for the patients randomized to panretin was 63 days.

¹⁷ Among the 25 panretin responders who started on vehicle and then were treated with open-label panretin, the median time to onset of response was 56 days (vol. 1.73, p. 197).

¹⁸ Defined as the onset of first confirmed response to relapse, PD, or censor date.

The superiority of panretin persisted after consideration of prior anti-KS therapy, prior systemic anti-KS therapy, and prior topical/local anti-KS therapy. Ninety-three patients had received at least one prior systemic therapy. There were 27 and 28 patients who were unresponsive to at least one systemic therapy, randomized to panretin and placebo, respectively. The response rates were 30% (8/27) for panretin and 18% (5/28) for vehicle.

There were 21 and 23 patients, who failed to respond to at least one prior systemic therapy, enrolled on panretin and vehicle, respectively. During the initial blinded phase 38% (8/21) and 13% (3/23) patients responded while on panretin and vehicle, respectively. Among the panretin responders reported, there were patients refractory to the following prior systemic anti-KS therapies: interferon, n=3; bleomycin, n=2; liposomal doxorubicin, vincristine, tretinoin, liarozole, and IM 862 nasal spray, n=1 each.

Eighty-five patients who received vehicle initially were switched to panretin gel. The response rate in this group of patients was 29% (25/85)¹⁹.

Only 2 panretin gel patients crossed-over to the other therapy during the blinded phase; neither of the two patients met the response criteria or the progressive disease criteria after cross-over. Fifteen patients randomized to vehicle crossed-over to the other therapy during the blinded phase; 27% (4/15) of these patients had a partial response to panretin.

The panretin group had a trend toward lighter color lesions than the vehicle gel group (p=0.66).

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

Four patients initially randomized to panretin died during the study; seven patients initially randomized to vehicle

¹⁹ Among the 85 patients initially treated with vehicle, 22 or 26% responded.

died during the study. The median time to death was 78 days (range for the panretin arm and 98 days (range for the vehicle arm. During the initial blinded study four patients died while on panretin and five died while on vehicle. Two other patients died during open-label panretin. One additional patient died after database closure during panretin open-label.

Quality of life questionnaires were utilized in this study. Five percent (14/268) of the patients did not complete the complete quality of life questionnaire at baseline. One hundred seventy-nine patients completed 12 weeks of therapy and eighty-nine patients did not complete 12 weeks of the initial blinded therapy. A substantial difference in the nine question composite for QOL favored panretin over vehicle when the 12-week completers and the non-completers were compared ($p=0.0002$ and $p=0.0161$, respectively). Three questions were most affected by topical therapy using a mixed model for longitudinal data analysis: 1. Level of satisfaction with physical appearance with respect to KS lesions being treated ($p=0.0004$); 2. Change in KS lesions compared to before participation in the study ($p \leq 0.0001$); and 3. Overall level of satisfaction with the study drug treatment ($p=0.0001$). There was no substantial change detected for feelings overall, physically, emotionally, personal life, and lesions' interference with work and social activities.

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4.2.3 Safety results

The common panretin gel-related adverse events at the application site during all phases of the study included rash (66%), pain (30%), pruritus (12%), exfoliative dermatitis (9%), skin disorder (9%), and edema (5%). Ninety-nine percent (223/225) of the adverse events occurred at the site of panretin application.

Most of the adverse events, which were determined to be clinically significant, occurred at the site of application of the topical agent.

Adverse events with incidence > 5% @ application site in Study -31; number of patients represent both initial blinded treatment plus blinded cross-over patients.

Adverse event	Panretin gel, n=149 ²⁰	Vehicle gel, n=136 ²¹
Rash	75%	12%
Pain	34%	7%
Pruritus	13%	4%
Exfoliative dermatitis	9%	2%
Skin disorder	9%	0%
Paresthesia	4%	1%
Edema	7%	3%

In the overall studies of panretin gel 0.1%, the incidence of drug-related adverse events was not clearly related to frequency of application of panretin. For example, rash was reported in patients 35%, 52%, 29%, and 30% of the time who applied the topical agent QID, TID, BID, and QD, respectively. Pruritus, exfoliative dermatitis, dry skin, and edema did not appear to increase in incidence with frequency of application of panretin.

Panretin gel was well tolerated over a treatment duration for patients during the initial blinded phase of 12.2 weeks (range: . . . weeks). The median time on study for all phases of 15.9 weeks (range: 1 day to 71 weeks).

There were only 2 serious adverse events related to panretin—both in the same patient . . . The patient

²⁰ Includes patients who crossed-over from vehicle gel to panretin.

²¹ Includes patients who crossed-over from panretin to vehicle.

developed cellulitis and then had a (+) blood culture after scratching a pruritic KS lesion under treatment with panretin; the patient recovered. The incidence of withdrawal from study was similar for both panretin and placebo, i.e., 31% (42/134) and 25% (34/134), respectively. The reasons for withdrawal included: withdrawal of consent (28%), any KS progressive disease (20%), failure to follow appointment schedule (12%), adverse event (12%), lost to follow-up (9%), and death (8%). During the initial blinded phase, fifteen patients on panretin had grade 3 dermal toxicity (erythema + edema + vesiculation) and one patient on panretin had grade 2 dermal toxicity (erythema + possible edema). During the open-label phase of the study, three percent (6/184) of patients developed grade 3 dermal toxicity (erythema plus edema + vesiculation).

There was a difference between the panretin gel and placebo for overall incidence of adverse events—90% (121/134) and 78% (104/134) ($p=0.0047$), respectively. For Skin and Appendages body system, 81% (109/134) of panretin gel patients compared to 35% (47/134) of vehicle gel patients had at least one adverse events ($p=0.0001$). The nonapplication site incidence of adverse events was not substantially different between the two treatment groups for any COSTART 5 body system.

There was no substantial difference in overall incidence of potentially infection-related adverse events with 31% (41/134) in both treatment arms experiencing at least one event. The number of treatment emergent OIs/AIDS-related adverse events was evenly divided between the two initial blinded treatment groups during the blinded phase of the study prior to cross-over, i.e., 9 events in each arm.

4.3 FDA ASSESSMENT OF STUDY RESULTS

4.3.1 FDA Assessment of Study Conduct: Study -31

THE DISEASE STUDIED

The patient population in Study -31 is patients who have never been treated for KS and for patients who have had one or more prior treatments. The primary endpoint is ACTG response. The secondary efficacy endpoint analyses included physician global assessment, and quality of life measures.

In initial discussions with the FDA, Ligand indicated that the patient population would be patients with early cutaneous KS not severe enough to merit treatment with systemic agents. However, 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. In a Ligand meeting package (dated 11/20/95), the FDA was told that the patient benefits included: 1. rapid flattening of raised lesions; 2. CCR of some lesions; 3. improvement in color; 4. a safe option for treatment at early stage of disease, prior to systemic therapy; 5. a very low-risk therapy with minimal toxicity even with long-term application; 6. a self-administered and self-adjusted treatment.

PHOTOGRAPHIC EVIDENCE OF EFFICACY

The FDA had indicated to Ligand that photographic evidence would be very helpful in their review of the NDA and that FDA would depend on this information. Ligand responded that they had taken this into account and had provided a uniform photographic system to all sites in their Phase 3 study²². Ligand outlined for their investigators very meticulous procedures for the required photography of patients' treated index lesions. These procedures included: 1. the same image size for the lesion on the slide; 2. the same orientation of the lesion on the slide; 3. the lesion in the very center of the slide; 4. a sharp focus on the lesion; 5. the label at the very top of the

²² Ligand Meeting Minutes, FDA-Ligand meeting held 5/8/97 (dated 6/4/97)

slide; and 6. the label to contain the correct information. All rolls of film were sent to

In support of these procedures, Ligand had sent a memo to their study coordinators of study -31 stating, "Photography of the patient's index lesions is very important documentation of the patient's response to treatment in this phase 3 study"²³. In the Phase 3 study reports, Ligand stated that photographs were obtained for the purpose of providing supporting data for the primary efficacy endpoint of patient responses according to ACTG. Ligand has observed that the change in appearance of KS lesions in the photographs generally follows the trend of response which was captured in the investigator lesion assessments of area in the CRFs²⁴. According to Ligand, the change in appearance of KS lesions in the photographs which were intended only as supporting data, generally followed the trend of responses according to ACTG criteria captured by the Investigators' index lesion assessments.

However, Ligand continued by stating that the quality of photographs could vary from lesion to lesion and from visit to visit, depending on the skill and care of the photographer. Ligand believed that photographs could not be expected to achieve the same full appreciation of KS lesions as provided by direct, hands-on clinical observation. The reasons for this included: 1. the two-dimensional aspect of the photographic medium; 2. reflected light producing artifact obscuring parts of lesions; 3. the inability of photographs to adequately capture lesion height; 4. the frequent lack of photographs at termination or follow-up visits in these studies; 5. occasional erythema at the treatment site; 6. potential partial blurring of lesions margins; and 7. the difficulty in distinguishing the lesion margins in photographs of patients with darker skin tones²⁵.

The above commentary was different than the understanding the FDA had. During the FDA-Ligand pre-NDA meeting the longest question from Ligand to the FDA concerned the photographs. Also, during the pre-NDA process, Ligand provided the FDA with training in the use of electronic software, containing their photographs. During an end-of-Phase 2 meeting between FDA and Ligand for another product for KS, Ligand provided a portfolio of photographs to support their

²³ Dated 5/17/96; vol. 1.294, p. 318.

²⁴ vol. 1.73, p. 287-288

²⁵ vol 1.73, p. 287.

meeting package. That photographic evidence would be a problem in supporting the efficacy of panretin was first and only mentioned in the current NDA.

IN-STUDY KAPOSI'S SARCOMA BIOPSIES

In response to an inquiry about the mechanism of action of panretin, biopsies on treated lesions were mentioned. Ligand stated that there was anecdotal information of KS clearing from biopsies but that there was no formal plan in the protocol for this type of evaluation²⁶. According to the protocol for Study -31, an optional procedure, KS tumor biopsies (of selected KS lesions in patients before, during and after study drug treatment) could be obtained. KS tumor biopsies were to be limited to supplemental treated (non-index) lesions. One purpose of these biopsies was to evaluate the cellular response to topical ALRT1057 treatment. If a biopsy sample of the patient's KS tumor was obtained, laboratory studies were to be performed on tissue derived from that biopsy sample. Very few KS biopsies were performed on-study. The results while on panretin were provided in the NDA. The ACCESS database and adverse event database showed that there might be other patients who had KS biopsies performed while on study but data was not submitted to the NDA²⁷.

In view of the responses reported in the vehicle treated arm (response rate: 18%), biopsies of panretin treated lesions and vehicle treated lesions would have provided important histologic information about the mechanism of action of panretin.

ULTRASOUND EVALUATION OF RESPONSE IN KAPOSI'S SARCOMA

According to the protocol for Study -31, an optional procedure, ultrasound measurement of selected KS index lesions were to be obtained from selected patients before, during and after study drug treatment. The purpose of the ultrasound evaluation was to provide an additional objective measure of tumor depth/volume change in response to study drug treatment. No ultrasound (except from Center 054) results while on panretin were provided in the NDA. The ACCESS database confirmed that patients

²⁶ Ligand Meeting Minutes, meeting held 5/8/97 (dated 6/4/97).

²⁷ ACCESS: panretin pts.: ; vehicle pt.: . Adverse event: panretin pt at least 2 biopsy sites infected.

did have the procedure performed²⁸. Ligand stated that clinical experience with ultrasound for assessment of cutaneous KS was limited and little was known about the validity of ultrasound as a possible tool for the evaluation of KS lesions. In a June 1998 commentary, one KS investigator stated that the use of sonograms to measure changes in the volume of cutaneous KS nodules could increase the precision of KS response assessment²⁹.

A cursory review of the thickness and vascular area assessments @ Center 054 by ultrasound compared to the investigator's assessments of height and area suggests little correlation between these two techniques (vol. 1.73, p. 290). It is unknown whether this is a function of ultrasound as a poor evaluator of response or whether panretin responses cannot be confirmed with ultrasound.

DIVISION OF SCIENTIFIC INVESTIGATION CONCERNS

The audit of the study sites revealed

DSI recommended that the data from this site not be used until it was verified by Ligand (Memo: G. Turner to A. Chapman, 11/18/98).

The cases in question were
None of these cases were responders. Therefore, these cases did not impact on the efficacy results, i.e. the response rate by the modified ACTG criteria.

²⁸ The ACCESS database also indicated that patient had an ultrasound performed during week 8.

²⁹ Known SE. The Little et al article reviewed. Oncology 1998; 12:883-884.

Fifteen centers had no responders; accruals of: 1 (6 centers), 2 (3), 3 (2), 4 (1)³⁰, 5 (1)³¹, 7 (1)³², and 16 (1)³³.

KAPOSI'S SARCOMA AND THE PANRETIN RESPONDERS

One hundred and ten patients entered Study -31 had 20 or less KS lesions. Most of the patients had less than 50 cutaneous KS lesions. Eighty-nine patients had 50 or more lesions; 14 of these patients had visceral lesions (4 GI, 4 oral, 1 lung, 1 BM, 1 right leg?, 2 lung + palate, 1 colon/small intestines + rectum. Among the panretin responders, 14 responders had greater than 50 cutaneous lesions; 28 responders had less than 20 lesions; and 5 had between 21 and 50 lesions. Six panretin responders had oral/visceral KS. Six panretin responders treated only six lesions; all the patients had more than six total lesions except for one patient. Fifteen panretin responders treated > 6 lesions and almost all the lesions except for one patient. Four patients treated all (estimated) their lesions plus new lesions that developed during therapy. For 22 panretin responders, it is known that the 6 index lesions were treated with panretin; it is unknown how many total lesions were treated.

The table below tabulates in the panretin responders the number of total lesions at baseline and the number of lesions treated during the trial.

PID	# TOTAL LESIONS	# LESIONS TREATED
	25	Estimated 25 + new lesions as they developed
	38	38
	21	21
	16	Estimated 16 + new lesions as they developed
	>50 + palate	6?
	10	6?
	18	6?
	10	6
	>50	6?

³⁰ Anderson

³¹ Duvic

³² Brosgart

³³ Wagner

PID	# TOTAL LESIONS	# LESIONS TREATED
	10	14
	6	6
	6	6?
	7	6?
	9	6
	>50	6
	14	14
	>50	50
	14	14
	13	13
	15	15
	6	?
	10	?
	>50	>50
	>50	?
	18	18
	9	?
	>50 + esophagus	75
	27	6
	10	?
	>50	?
	10	?
	>50	50 -100 on lower left leg
	8	7
	14 + palate	13
	>50 + lung/palate	20
	11 + colon	?
	>50	?
	11	11
	9	?
	9	?
	33	33

PID	# TOTAL LESIONS	# LESIONS TREATED
	15	6
		pt. treated > 6 lesions (by global photos)
	>50	?
	6	?
	>50 + palate	?
	>50	?
	7	?

There were 22 patients (11 patients on each arm) entered on Study -31 whose best response to prior systemic therapy was progressive disease. Four panretin responders had progressive disease as their best response to prior systemic therapy (agents: tretinoin [1 pt], alpha-interferon [2 pts], intron A [1 pt], and liarozole [1 pt]). Two vehicle responders had progressive disease as their best response (agent: interferon [2 pt]). Four panretin patients with progressive disease to prior systemic chemotherapy (doxil, adriamycin, bleo/velban, vincristine) did not respond to panretin. Three vehicle patients with progressive disease to prior systemic chemotherapy (doxil [2], vincristine/velb) did not respond to vehicle gel.

PROTEASE INHIBITORS AND KAPOSI'S SARCOMA

An event or events in the patients may have triggered the physicians to add, change, or adjust the protease inhibitor therapy. These events could include: 1. plasma HIV RNA level changes; 2. drug failure; 3. drug toxicity; 4. low or declining CD4-lymphocyte counts; 5. OI's or other AIDS-related illnesses; 6. new KS lesions; 7. publication of anecdotes, describing the effect of protease inhibitors in KS; 8. FDA approval of new protease inhibitors; 9. and 10. patient demand.

The table below examines the influence of protease inhibitors on Kaposi's sarcoma. New lesions were assessed. Since plasma HIV RNA data was not required in the protocol, CD4-lymphocyte counts, at baseline and at response confirmation, were assessed for immune function³⁴ changes that may occur with effective protease inhibitor therapy. Triglyceride levels were looked at

³⁴ It is understood that failure of CD4+ lymphocytes to increase in late stages of HIV disease may be due to irreversible damage to the regenerative capacity of the immune system.

because of the association of elevation of triglycerides and protease inhibitors. Also there was the remote possibility of significant absorption of panretin and the known triglyceride elevating effect of systemic panretin.

In the total patient population, 131 patients (131/268 or 49%) developed new lesions since baseline. There were 22 panretin responders (22/47 or 47%) with new lesions during the trial. There were 16 patients with no new lesions recorded during the trial. There were four patients recorded as unknown with regard to new lesions. There were five panretin patients recorded as not having new lesions but there was evidence in the global photographs that new lesions were appearing.

Nine panretin responders were not receiving protease inhibitors. Seventeen patients started protease inhibitors greater than 2 months prior to entry on study; for one patient the start date of the protease inhibitor was unknown. Four panretin responders had a change in their protease inhibitor beyond the 12 week initial blinded phase. Four responders had a change in protease inhibitors before a response was declared or during the period when the response was being confirmed. Only twelve responders had a change in protease inhibitor therapy within a two month period prior to entry on-study. The FDA did not disqualify these responders based on the change in protease inhibitors. For five of these responders, there did appear to be a protease inhibitor effect that could have affected KS response.

PANRETIN RESPONDERS: PROTEASE INHIBITOR REVIEW

PID	# NEW LESIONS	TIMING OF PROTEASE INHIBITOR (PI)	CD4-LYMPHO-CYTE @ BASELINE /UL	CD4-LYMPHOCYTE @ TIME OF RESPONSE CONFIRMATION /UL	TRIGLYCERIDES @ BASELINE MG/DL	TRIGLYCERIDES @ TIME OF RESPONSE CONFIRMATION MG/DL	COMMENTS
	11	Viracept started @ mo. 4 on study	57	32 no response of CD4 to PI and probably no effect on response with viracept, CD4 changed from a trend of decreasing to one of increasing and doubling; i.e., CD4 144 after started of viracept	160	127	No PI effect on response Maybe an effect on duration of response