PID	# NEW LESIONS	TIMING OF PROTEASE INHIBITOR (PI)	CD4-LYMPHO-CYTE @ BASELINE /UL	CD4-LYMPHOCYTE @ TIME OF RESPONSE CONFIRMATION /UL	TRIGLYCER-IDES @ BASELINE MG/DL	TRIGLYCER-IDES @ TIME OF RESPONSE CONFIRMATIO N MG/DL	COMMENTS
	Yes	Crixivan started 3 months prior to study	1370	500 CD4s decreasing; no contribution to response	290	324 slight increase in triglyceride; glucose normal	No PI effect
	No	None	248	225	391 Stable CD4s	317	No PI effect
	Either new lesions appearing and treated on back of right leg as early as 4 wks or lesions not mapped @ baseline						
	No	Unknown start date for crixivan	436	301 CD4s decreasing; no contribution to response this is nadir; CD4 slowly creeps back up	118	64 this is nadir; triglycerides slowly creep back up	No PI effect

PID	# NEW LESIONS	TIMING OF PROTEASE INHIBITOR (PI)	CD4-LYMPHO-CYTE @ BASELINE /UL	CD4-LYMPHOCYTE @ TIME OF RESPONSE CONFIRMATION /UL	TRIGLYCER-IDES @ BASELINE MG/DL	TRIGLYCER-IDES @ TIME OF RESPONSE CONFIRMATIO N MG/DL	COMMENTS
	Either new lesions on back of arms or not mapped @ baseline						
	New lesions on chest, right upper arm, left lower leg @ 18 wks						
	0	Saquinavir started 8 mos. Prior to on study	487	501 CD4s stable	144	291 Triglycerides doubled glucoses normal	No PI effect on response Maybe effect on response confirmation PI effect after response started
		Crixivan started 1 wk after response started; shrinkage of area started after PI changed		CD4 622 one month after confirmed response			Lesions start to disappear after crixivan started
	0	Saquinavir started 4 mos. Prior to on study	236	218	326	117 triglycerides lower	No PI effect
	Multiple new lesion @ 4 & 8 wks lower post. Legs	Crixivan started 1 mo. After on-study or 1 wk after response started					

PID	# NEW LESIONS	TIMING OF PROTEASE INHIBITOR (PI)	CD4-LYMPHO-CYTE @ BASELINE /UL	CD4-LYMPHOCYTE @ TIME OF RESPONSE CONFIRMATION /UL	TRIGLYCER-IDES @ BASELINE MG/DL	TRIGLYCER-IDES @ TIME OF RESPONSE CONFIRMATIO N MG/DL	COMMENTS
		Nelfinavir started 3 mo. After on-study					
		New lesions continue after crixivan					
		New lesions stop & start to disappear (lower post. Legs) after nelfinavir started					
	3	Norvir was started 3.25 mo. prior to on-study	433	369	378	306	No PI effect
	0	Norvir started 4 mo. prior to study	189	102	340	227	No PI effect
		Invirase started 6 months after response					

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	14	Crixivan started 5 mos. Prior to study	93	137	125	102	No PI effect
	Yes	None AZT + 3TC started 3 mos. prior to on-study	96	301 (no CD4s after this; 2 prior CD4s > 300) Why did CD4 go up 3-fold?	117	108	No PI effect but CD4 increased 3-fold; Ligand response: pt. Did not receive PIs prior to study or during the study
	Yes	Ritonavir started 3 mos. Prior to on-study	213	209	80	86	No PI effect
	0	Viracept started 1 - 1.5 months before study	108	25 CD4 decreased	194	157	No PI effect: CD4 decreased

PID	# NEW LESIONS	TIMING OF PROTEASE INHIBITOR (PI)	CD4-LYMPHO-CYTE @ BASELINE /UL	CD4-LYMPHOCYTE @ TIME OF RESPONSE CONFIRMATION /UL	TRIGLYCER-IDES @ BASELINE MG/DL	TRIGLYCER-IDES @ TIME OF RESPONSE CONFIRMATION MG/DL	COMMENTS
	0	Crixivan started 3 mos. prior to on-study	53	84	149	693 triglycerides triples (other levels < 300); glucoses normal	No PI effect
	0	Ritonavir started 3 mos. prior to on-study	695	666	298	435 Triglycerides increased	No PI effect
	0	Crixivan stable for 1 yr.	774	874	239	297	No PI effect
	Yes	Crixivan started on-study start date	235	472 CD4 doubled	311	417 Triglycerides increased	PI effect

PID	# NEW LESIONS	TIMING OF PROTEASE INHIBITOR (PI)	CD4-LYMPHO-CYTE @ BASELINE /UL	CD4-LYMPHOCYTE @ TIME OF RESPONSE CONFIRMATION /UL	TRIGLYCER-IDES @ BASELINE MG/DL	TRIGLYCER-IDES @ TIME OF RESPONSE CONFIRMATIO N MG/DL	COMMENTS
	Yes	Crixivan 5 months prior to on-study	191	224	362	276	no PI effect
	?	Saquinavir started 5 wks before start of study	83	95	299 Triglycerides decreased	192	No PI effect: CD4s stable
	?	Crixivan started 1 month before on-study	4.5	No data	96	286 one month after response confirmation	PI effect: inconclusive
	Yes	Ritonavir started 2 mos. Prior to entry on-study	253	706 increased CD4	289	354 Triglycerides increased	PI effect: CD4s increased @ time of response
	2	None	326	333	135	100	No PI effect; stable CD4

PID	# NEW LESIONS	TIMING OF PROTEASE INHIBITOR (PI)	CD4-LYMPHO-CYTE @ BASELINE /UL	CD4-LYMPHOCYTE @ TIME OF RESPONSE CONFIRMATION /UL	TRIGLYCER-IDES @ BASELINE MG/DL	TRIGLYCER-IDES @ TIME OF RESPONSE CONFIRMATIO N MG/DL	COMMENTS
	0	Indinavir started 17 wks after start of study and after response declared	219	206	76	88	No PI effect
	0	None	187	152	77	151 triglycerides doubled	No PI effect
	14	Saquinavir started five weeks before start of study	435	712 CD4 increased	120	97	PI effect; CD4 increased
		Only 5 instances of erythema out of a possibility of 90—> cannot see erythema in non-index lesions for determination of PI vs panretin effect; from lower post. Photos: non-index lesions not responding					

PID	# NEW LESIONS	TIMING OF PROTEASE INHIBITOR (PI)	CD4-LYMPHO-CYTE @ BASELINE /UL	CD4-LYMPHOCYTE @ TIME OF RESPONSE CONFIRMATION /UL	TRIGLYCER-IDES @ BASELINE MG/DL	TRIGLYCER-IDES @ TIME OF RESPONSE CONFIRMATIO N MG/DL	COMMENTS
	0	Crixivan started 23 wks after on-study	72	70	92	102	No PI effect
	0	None	338	351	103	129	No PI effect
	15	Saquinavir started 2 - 3 months before on-study	38	62	211	163	No PI effect on response Effect after crixivan started & response confirmed
		Crixivan started 1 wk after response confirmed					

PID	# NEW LESIONS	TIMING OF PROTEASE INHIBITOR (PI)	CD4-LYMPHO-CYTE @ BASELINE /UL	CD4-LYMPHOCYTE @ TIME OF RESPONSE CONFIRMATION /UL	TRIGLYCER-IDES @ BASELINE MG/DL	TRIGLYCER-IDES @ TIME OF RESPONSE CONFIRMATIO N MG/DL	COMMENTS
	Yes	Indinavir started 6 months after on-study	16	15	179	141	No PI effect
	0	Saquinavir started 3 mos. before study	199	191	70	85	No PI effect
	2	Indinavir started 6 months prior to study	901	848	191	175	No PI effect
	2	None	159	94	68	77	No PI effect
	None	Ritonavir started 5 wks after entry on-study	78	82	91	188 Triglycerides doubled	No PI effect??

PID	# NEW LESIONS	TIMING OF PROTEASE INHIBITOR (PI)	CD4-LYMPHO-CYTE @ BASELINE /UL	CD4-LYMPHOCYTE @ TIME OF RESPONSE CONFIRMATION /UL	TRIGLYCER-IDES @ BASELINE MG/DL	TRIGLYCER-IDES @ TIME OF RESPONSE CONFIRMATION MG/DL	COMMENTS
	2	None	677	491	182	124	No PI effect
	Yes	Saquanavir stopped 1 month before on study(started 2 mos. prior)	24	16	269	230	No PI effect
	Yes	Ritonavir started at start of study	217	210	192	193	No PI effect??
		Indinavir started @ wk 10					
	0	Ritonavir started 3 mos. prior to on-study; stopped after 3 mos. on-study	333	229	475	188	No PI effect

PID	# NEW LESIONS	TIMING OF PROTEASE INHIBITOR (PI)	CD4-LYMPHO-CYTE @ BASELINE /UL	CD4-LYMPHOCYTE @ TIME OF RESPONSE CONFIRMATION /UL	TRIGLYCER-IDES @ BASELINE MG/DL	TRIGLYCER-IDES @ TIME OF RESPONSE CONFIRMATION MG/DL	COMMENTS
	0	Indinavir started 6 mos. prior to on-study	76	167 CD4 doubled (& continued to steadily go up to 230); stavudine started 2 mos. prior to on-study	221	308 triglycerides increased	No PI effect?? Ligand states that PI not changed
	9	none	920	667	153	148	No PI effect
	Started interferon because of new lesions						
	7	indinavir started 6 wks before entry on study	130	242 CD4 increased	316	492 Triglycerides increased	PI effect

PID	# NEW LESIONS	TIMING OF PROTEASE INHIBITOR (PI)	CD4-LYMPHO-CYTE @ BASELINE /UL	CD4-LYMPHOCYTE @ TIME OF RESPONSE CONFIRMATION /UL	TRIGLYCER-IDES @ BASELINE MG/DL	TRIGLYCER-IDES @ TIME OF RESPONSE CONFIRMATIO N MG/DL	COMMENTS
	?	indinavir started 11 days prior to on study	466	405	241	88 triglycerides decreased	No PI effect
	Yes	crixivan started 3 mos. prior to study	175	103	211	117	No PI effect
	Yes	invirase started 5 months after response started	150	37 CD4 decreased	78	100	No PI effect
	2	indinavir started 6 wks before study	357	311	198	151	No PI effect?
	0	Invirase started 5 months prior to on-study	12	18	266	433 Triglycerides increased	No PI effect

PID	# NEW LESIONS	TIMING OF PROTEASE INHIBITOR (PI)	CD4-LYMPHO-CYTE @ BASELINE /UL	CD4-LYMPHOCYTE @ TIME OF RESPONSE CONFIRMATION /UL	TRIGLYCER-IDES @ BASELINE MG/DL	TRIGLYCER-IDES @ TIME OF RESPONSE CONFIRMATION MG/DL	COMMENTS
	New lesions on right leg @4.7 wks						
	0	Crixivan started 5 mos. prior to on-study	145	79 CD4 decreased	356	120 triglycerides decreased	No PI effect
	New lesions on neck @ 17 wks; most of lesions in upper anterior photo gone						
	0	Viracept started < 1 month prior to on study	142	143	569	520	No PI effect
	0	Nelvinavir started 1 mo. Prior to on-study	264	589 CD4 doubled	174	178	PI effect

GENERAL RESPONSE EVALUATION

According to Ligand's evaluation of the response data, the pattern of response to panretin and vehicle were comparable. For panretin, 70% of the responders had reduction in the height of the index lesion alone as the criteria for response; for the vehicle responders, 75% of the patients met these criteria. For panretin, 30% of the responders had index lesion area reduction alone or in combination with height reduction as the criteria for response; for the vehicle responders, 26% of the responders met these criteria. The table below illustrates the data.

ACTG RESPONSE CRITERIA	PANRETIN 47 RESPONDERS	VEHICLE 24 RESPONDERS
Plaque to macule	27 (57%)	14 (58%)
Nodule reduced	4 (9%)	3 (13%)
Nodule reduced + plaque to macule	2 (4%)	1 (4%)
Area	1 (2%)	2 (8%)
Area + plaque to macule	12 (26%)	3 (13%)
Area + nodule reduced	1 (2%)	
Area + nodule reduced + plaque to macule		1 (4%)

In a given responder, panretin and the vehicle gel were efficient in flattening raised lesions. The following table demonstrates the high proportion of index lesions, which became flat in responders. Between 76% to 96% of raised lesions--selected as index lesions--became flat in a panretin responder. Between 56% and 89% of raised lesions--selected as index lesions--became flat in a vehicle responder.

RESPONDERS: EFFICIENT FLATTENING OF RAISED LESIONS

LESION I.D. #	PANRETIN # FLATTENED/# RAISED @ BASELINE (%)	VEHICLE # FLATTENED/# RAISED @ BASELINE (%)
1	38/43 (88%)	15/19 (80%)
2	43/45 (96%)	17/22 (77%)
3	32/42 (76%)	15/20 (75%)
4	29/34 (85%)	13/16 (81%)
5	28/30 (93%)	10/18 (56%)
6	21/26 (81%)	16/18 (89%)

However, the nonresponders did not fare as well. Sixty panretin nonresponders did not have one index lesions become flat. Fifteen panretin nonresponders had at least 1 raised index

lesion become flat. Five panretin nonresponder had raised lesions become flat but an increase in area of the lesions intervened. Ninety-four vehicle nonresponders did not have one index lesions become flat. Twelve vehicle nonresponders had at least 1 raised index lesion become flat. One vehicle nonresponder had raised lesions become flat but an increase in area of the lesions intervened.

Index lesions selected for study were distributed as follows: face (26 pts; median # of lesions: 1, [range:), hands (13 pts; median: 1, , neck (19 pts; median: 1, forearms (117 pts; median: 1, lower legs (156 pts; median: 2, chest (88 pts; median: 2, , back (32 pts; median: 1, , other (236 pts; median: 3, .

There were 12 panretin patients with facial lesions selected as index lesions Six patients were panretin responders; 10 out of 11 lesions (in the responding pts.) responded to panretin. There were 14 vehicle patients with facial lesions selected as index lesions. Four patients were vehicle responders; 5 out of 5 lesions (in the responding pts.) responded to vehicle. Although complete information on the location of the facial index lesions was not readily available for the nonresponders, evaluation of all the index lesions in the nonresponders suggested that few of these facial lesions responded.

FDA REVIEW OF THE LIGAND REPORTED PANRETIN RESPONDERS

The FDA reviewed primarily the panretin responders in Study -31. In the interests of a "Priority Review" as requested by Ligand, the placebo patients, as reviewed by the Ligand, were assumed to be correct; also to best evaluate the placebo arm, the nonresponders would also require review[35].

The primary efficacy endpoint was KS cutaneous tumor response during the 12-week initial blinded phase of the study. The review concentrated on this time period.

A. Per Protocol Review of Index Lesions

The FDA reviewed Listing 33 (Response Chronology–Initial Blinded Treatment) and ACCESS Database (response data tabulation on

[35] Post completion of the "DRAFT REVIEW", these assessments were performed and the results entered in the EFFICACY SUMMARY table.

index lesions [height, area]), using the per protocol modified ACTG tumor response criteria.

FDA disagreed with one Ligand panretin responders. The table below comments on this patient.

PID	COMMENTS
	3 raised lesions: 1 became flat, 6 became nodular or a grade not specified in CRF ? (6 lesions scored as 3 which is not part of height scale on CRF) 1 raised lesion became flat then raised @ next visit

B. Cosmetically Beneficial Panretin Responses Based on Photographs

The FDA determination of cosmetically beneficial tumor responses in panretin patients, who were reported by Ligand to have tumor responses based on the modified ACTG criteria, was based primarily on the photographs. The assessment described in the following Table included cosmetically beneficial tumor responses either in the blinded phase of the study or the continuation phase of the study in patients initially randomized to the panretin arm of the study. Cosmetically beneficial response assessments were also determined during the initial 12 week blinded phase of the study for panretin and placebo patients who were reported by Ligand to have tumor responses based on the modified ACTG criteria. These were recorded in the Efficacy Summary Table.

In assessing the photographs for beneficial response, the FDA looked for a 50% improvement in appearance from baseline, considering the KS lesion and dermal toxicity at the lesion site. 50% of the index lesions were required to improve in appearance. For the blinded phase analysis (12 wks) if the response started by 12 weeks, the response confirmation could occur after 12 weeks. The improvement was to be maintained 3-4 weeks.

The FDA assessment also included comments on other aspects of the tumor response evaluation. Specifically, the FDA reviewed: 1. Listing 33: Response Chronology–Initial Blinded Treatment; 2. ACCESS Database: a. concurrent medications, especially protease

inhibitors, b. CD4-lymphocyte counts @ baseline and @ response confirmation, c. glucose @ baseline and @ response confirmation, d. triglycerides @ baseline and @ response confirmation, e. overall Quality of Life @ baseline and @ response confirmation, f. with respect to KS lesions treated, overall satisfaction with study drug treatment @ response confirmation, g. Physician's Global Assessment Assessment (treated index and non-index lesions) @ response confirmation, h. response data tabulation on index lesions (height, area, erythema); 3. photographs (index lesions and globals), especially a comparison of baseline and @ response confirmation; and 4. Case Report Forms, on a limited basis, for clarification of points of interest.

The FDA had comments about most of the panretin responders. These included: 1. poor photographic evidence of response (24 pts.); 2. flattening of lesions associated with erythema & edema of the skin surrounding the KS lesion (16 pts.); 3. protease inhibitor effect on the primary response or confounding the duration of response (8 pts.); 4. incorrect or mislabeled photos (7 pts.); 5. no baseline photos (6 pts.); 6. missing follow up photos (5 pts.); 7. flat lesions becoming raised or area of lesions increasing prior to response confirmed (5 pts.); 8. new lesions (6 pts.); 9. Not all lesions mapped @ baseline or more lesions Rx'ed than reported (2 pts); and 10. 1 pt. each: wrong lesion Rx'ed, index lesions not representative of disease, erythema not accurately scored, unable to find lesion @ baseline, and non-index treated lesions not responding.

Among the 47 panretin responders reported by Ligand, the FDA believed that 23 patients had beneficial responses.