APPENDIX II BIOPHARMACEUTICS SUMMARY

TABLE 3.: Concentration Monitoring during Topical Studies

Study Number	Study Design	Route	Dose Form	Dose	Strength (% w/w)	Lot	Plant*/ Manufacture Date	Subject Number	IND # Submission Date	Applicant Conclusions
L1057-94-01T	Multiple-dose Safety, Tolerance, Efficacy and PK in patients with cutaneous KS	Topical	Gel	QD, BID, TID, QID	0.01 0.05 0.1	9402-001 9408-001 9402-002 9402-003 9408-004	2/15/94 8/16/94 2/17/94 2/22/94 8/18/94			No quantifiable systemic exposure to 9-*cis*-retinoic acid (LLQ: ng/mL) in 154 samples.
L1057-94-02T	Multiple-dose Safety, Tolerance, Efficacy and PK in patients with cutaneous KS	Topical	Gel	QD, BID, TID, QID	0.01 0.05 0.1	9407-001 9408-001 9402-003 9408-004	8/11/94 8/16/94 2/22/94 8/18/94			No quantifiable systemic exposure to 9-*cis*-retinoic acid (LLQ: ng/mL) in 127 samples.
L1057-94-03T	Multiple-dose Safety, Tolerance, Efficacy and PK in patients with CTCL	Topical	Gel	QD, BID, TID, QID	0.01 0.05 0.1	9402-001 9407-001 9402-002 9410-002 9402-003 9408-004	2/15/94 8/11/94 2/17/94 10/10/94 2/22/94 8/18/94			No quantifiable systemic exposure to 9-*cis*-retinoic acid (LLQ: ng/mL) in 91 samples.

* Plant =

LLQ = Lower Limit of quantitation.

Subject Number is number of subjects providing pharmacokinetic samples.

TABLE 3.: Concentration Monitoring during Topical Studies (cont.)

Study Number	Study Design	Route	Dose Form	Dose	Strength (% w/w)	Lot	Plant*/ Manufacture Date	Subject Number	IND # Submission Date	Applicant Conclusions
L1057-94-04T	Multiple-dose Safety, Tolerance, Efficacy and PK in patients with cutaneous KS	Topical	Gel	QD, BID, TID, QID	0.01 0.05 0.1	9407-001 9408-001 9408-004	8/11/94 8/16/94 8/18/94	[redacted]		No quantifiable systemic exposure to 9-*cis*-retinoic acid (LLQ: ng/mL) in 28 samples.
L1057-94-05T	Multiple-dose Safety, Tolerance, Efficacy and PK in patients with CTCL	Topical	Gel	QD, BID, TID, QID	0.01 0.05 0.1	9407-001 9408-001 9408-004	8/11/94 8/16/94 8/18/94	[redacted]		No quantifiable systemic exposure to 9-*cis*-retinoic acid (LLQ: ng/mL) in 16 samples.
L1057-94-07T	Multiple-dose Safety, Tolerance, Efficacy and PK in patients with cutaneous KS	Topical	Gel	QD, BID, TID, QID	0.01 0.05 0.1	9407-001 9408-001 9408-004	8/11/94 8/16/94 8/18/94	[redacted]		No quantifiable systemic exposure to 9-*cis*-retinoic acid (LLQ: ng/mL) in 6 samples.

* Plant =

LLQ = Limit of quantitation.

Subject Number is number of subjects providing pharmacokinetic samples.

TABLE 3: Concentration Monitoring during Topical Studies (cont.)

Study Number	Study Design	Route	Dose Form	Dose	Strength (% w/w)	Lot	Plant*/ Manufacture Date	Subject Number	IND # Submission Date	Applicant Conclusions
L1057T-21	Multiple-dose Safety, Tolerance, Efficacy and PK in patients with cutaneous KS	Topical	Gel	QD, BID, TID, QID	0.01 0.05 0.1	9407-001 9408-001 9408-004 9411-005	8/11/94 8/16/94 8/18/94 12/5/94	[redacted]		No quantifiable systemic exposure to 9-*cis*-retinoic acid (LLQ ng/mL) in 168 samples.
L1057T-22	Multiple-dose Safety, Tolerance, Efficacy and PK in patients with cutaneous KS	Topical	Gel	QD, BID, TID, QID	0.01 0.05 0.1	9407-001 9408-001 9408-004 9411-005	8/11/94 8/16/94 8/18/94 12/5/94	[redacted]		26 of 153 samples (17%) contain ng/mL 9-*cis*-retinoic acid; remaining samples ng/mL. No apparent correlation between 9-*cis*-retinoic acid quantitation and topical gel application.

* Plant =
LLQ = Limit of quantitation.
Subject Number is number of subjects providing pharmacokinetic samples.

TABLE 4.: Oral Studies with PANRETIN™ Capsules

Study Number	Study Design	Route	Dose Form	Strength	Lot	Plant*/ Manufacture Date	Dose	Subject Number	IND # Submission Date	Applicant Conclusions
L1057-93-01	Multiple-dose Safety, Tolerance, Efficacy and PK in patients with advanced cancer	Oral	Soft Gelatin Capsule	10 mg 25 mg	9312-001 9405-001 9312-002 9405-002	12/7/93 5/17/94 12/7/93 5/17/94	5 mg/m^2 QD 15 mg/m^2 QD 30 mg/m^2 QD 50 mg/m^2 QD 83 mg/m^2 QD 140 mg/m^2 QD 180 mg/m^2 QD 230 mg/m^2 QD 70 mg/m^2 BID			After single doses, C_{max} and AUC increase approximately dose-proportionally. After repeat dosing, evidence for induction of oral clearance at doses mg/m^2 (total daily dose). T½ values were approximately hours and independent of dose schedule. Little or no accumulation observed.

* Plant =

Subject Number is number of subjects providing pharmacokinetic profiles. One patient in the 5 mg/m^2 dose group was sampled, but did not contribute evaluable profiles.

TABLE 4: Oral Studies with PANRETIN™ Capsules (cont.)

Study Number	Study Design	Route	Dose Form	Strength	Lot	Plant*/ Manufacture Date	Dose	Subject Number	IND # Submission Date	Applicant Conclusions
L1057-93-02	Multiple-dose Safety, Tolerance, Efficacy and PK in patients with advanced cancer	Oral	Soft Gelatin Capsule	10 mg 25 mg	9312-001 9312-002 9405-002	12/7/93 12/7/93 5/17/94	5 mg/m^2 QD 15 mg/m^2 QD 30 mg/m^2 QD 50 mg/m^2 QD 83 mg/m^2 QD 140 mg/m^2 QD 50 mg/m^2 BID 60 mg/m^2 BID 70 mg/m^2 BID			After single doses, C_{max} and AUC increase approximately dose-proportionally. After repeat dosing, evidence for induction of oral clearance at doses mg/m^2 (total daily dose). T½ values were approximately hours and independent of dose schedule. Little or no accumulation observed.

* Plant

Subject Number is number of subjects providing pharmacokinetic profiles. One patient in the 5 mg/m^2 dose group was sampled, but did not contribute evaluable profiles.

TABLE 4: Oral Studies with PANRETIN™ Capsules (cont.)

Study Number	Study Design	Route	Dose Form	Strength	Lot	Plant*/ Manufacture Date	Dose	Subject Number	IND # Submission Date	Applicant Conclusions
AGN 192013/ ALRT1057-001	Multiple-dose Safety, Tolerance, Efficacy and PK in patients with severe plaque psoriasis.	Oral	Soft Gelatin Capsule	10 mg 25 mg	9412-003 9412-004	12/9/94 12/9/94	0.15 mg/kg QD 0.30 mg/kg QD 0.60 mg/kg QD 0.90 mg/kg QD 1.2 mg/kg QD 1.5 mg/kg QD			Pre-therapy 9-*cis*-retinoic acid concentrations ng/mL were observed in 29% of patients. Following single doses, 2-hour postdose 9-*cis*-retinoic acid concentrations increase with increasing dose. Following repeat dosing of doses mg/kg/day, 2-hour postdose 9-*cis*-retinoic acid concentrations appeared less than respective Day 1 values. 4-oxo-9-*cis*-Retinoic acid concentrations were approximately one-half those of parent.

* Plant =

** Original submission date.

Subject Number is number of subjects providing pharmacokinetic information. One patient enrolled in each of the 0.6 mg/kg and 1.5 mg/kg dose groups and 2 patients enrolled in each of the 0.9 mg/kg and 1.2 mg/kg dose groups did not provide evaluable postdose pharmacokinetic samples.

APPENDIX III IN VOVO STUDY DATA SUMMARY

TABLE 5. In Vivo Data Summary: Concentration Monitoring during Studies with PANRETIN™ Gel

Study Number	Route	Dose Form	Dose	Pts	Obs	Analyte	Observed Concentration Range (ng/mL)
L1057-94-01T	Topical	Gel	0.01%, 0.05%, 0.1% (w/w) gel applied QD, BID, TID, QID	20		9-*cis*-retinoic acid ATRA	
L1057-94-02T	Topical	Gel	0.01%, 0.05%, 0.1% (w/w) gel applied QD, BID, TID, QID	15		9-*cis*-retinoic acid ATRA	
L1057-94-03T	Topical	Gel	0.01%, 0.05%, 0.1% (w/w) gel applied QD, BID, TID, QID	6		9-*cis*-retinoic acid ATRA	
L1057-94-04T	Topical	Gel	0.01%, 0.05%, 0.1% (w/w) gel applied QD, BID, TID, QID	5		9-*cis*-retinoic acid ATRA	
L1057-94-05T	Topical	Gel	0.01%, 0.05%, 0.1% (w/w) gel applied QD, BID, TID, QID	1		9-*cis*-retinoic acid ATRA	
L1057-94-07T	Topical	Gel	0.01%, 0.05%, 0.1% (w/w) gel applied QD, BID, TID, QID	2		9-*cis*-retinoic acid 4-oxo- 9-*cis*-retinoic acid	
L1057T-21	Topical	Gel	0.01%, 0.05%, 0.1% (w/w) gel applied QD, BID, TID, QID	30		9-*cis*-retinoic acid ATRA	
L1057T-22	Topical	Gel	0.01%, 0.05%, 0.1% (w/w) gel applied QD, BID, TID, QID	22		9-*cis*-retinoic acid 4-oxo- 9-*cis*-retinoic acid	

Pts = Number of patients contributing pharmacokinetic samples.
Obs = Number individual plasma samples analyzed.

TABLE 6. In Vivo Data Summary: Pharmacokinetic Evaluations during Oral Studies with PANRETIN™ Capsules

Study Number	Route	Dose Form	Dose	Day	Pts	Obs	C_{max} (ng/mL)	t_{max} (hr)	$AUC_{(0-\infty)}$ (ng·hr/mL)	$t_{1/2}$ (hr)
L1057-93-01	Oral	Soft Gelatin Capsule	5 mg/m^2	1	3		ND	ND	ND	ND
			15 mg/m^2	1	3		77.1 ± 47.3	1.6 ± 0.5	185 ± 117	1.2 ± 0.1
			30 mg/m^2	1	5		138.0 ± 97.3	1.6 ± 0.5	308 ± 120	1.4 ± 0.2
			50 mg/m^2	1	1		281.3	2.0	785	1.4
			70 mg/m^2	1	4		258.6 ± 118.1	1.2 ± 0.5	831 ± 656	1.2 ± 0.3
			83 mg/m^2	1	3		198.1 ± 72.5	2.3 ± 1.5	601 ± 148	1.2 ± 0.1
			140 mg/m^2	1	7		340.2 ± 230.7	2.3 ± 0.8	1146 ± 962	1.3 ± 0.3[a]
			180 mg/m^2	1	6		528.5 ± 346.5	2.0 ± 0.0	1613 ± 738	1.4 ± 0.3
			230 mg/m^2	1	8		758.6 ± 362.0	2.0 ± 0.1	2445 ± 1400	1.2 ± 0.4
			5 mg/m^2 QD	>1	3		25.2	1.5	66	1.3[b]
			15 mg/m^2 QD	>1	3		43.8 ± 10.2	2.3 ± 0.9	127 ± 34	1.0 ± 0.4
			30 mg/m^2 QD	>1	5		96.9 ± 48.7	1.8 ± 1.0	224 ± 68	1.1 ± 0.3
			50 mg/m^2 QD	>1	1		169.3	1.0	347	1.1
			83 mg/m^2 QD	>1	3		174.6 ± 98.8	2.9 ± 2.0	513 ± 201	1.1 ± 0.2[a]
			140 mg/m^2 QD	>1	7		114.3 ± 119.3	2.6 ± 1.1	413 ± 408	1.3 ± 0.5[c]
			180 mg/m^2 QD	>1	3		143.9 ± 59.0	2.4 ± 1.3	477 ± 278	1.7 ± 0.2
			230 mg/m^2 QD	>1	4		201.3 ± 78.5	1.5 ± 0.5	619 ± 267	1.3 ± 0.5
			70 mg/m^2 BID	>1	1		175.7	2.0	404	0.9

[a] N = 6.
[b] N = 1.
[c] N = 11.
Pts = Number of patients having pharmacokinetic samples drawn.
Obs = Number of observations contributing to parameter values.
ND = No data available.
SD = Not determined if number of observations <3.

TABLE 6. In Vivo Data Summary: Pharmacokinetic Evaluations during Oral Studies with PANRETIN™ Capsules (cont.)

Study Number	Route	Dose Form	Dose	Day	Pts	Obs	C_{max} (ng/mL)	t_{max} (hr)	$AUC_{(0-\infty)}$ (ng·hr/mL)	$T_{½}$ (hr)
L1057-93-02	Oral	Soft Gelatin Capsule	5 mg/m^2	1	3		32.0	2.5	73	0.9
			15 mg/m^2	1	3		48.4	1.0	145	1.7
			30 mg/m^2	1	3		61.9 ± 11.0	2.4 ± 1.6	218 ± 36	1.8[a]
			50 mg/m^2	1	9		171.0 ± 92.5	3.2 ± 2.0	456 ± 155	1.3 ± 0.1
			60 mg/m^2	1	4		191.2 ± 99.8	2.1 ± 0.2	560 ± 269	1.1 ± 0.1
			70 mg/m^2	1	5		298.9 ± 150.5	1.9 ± 0.4	704 ± 245	1.2 ± 0.2
			83 mg/m^2	1	8		282.1 ± 169.1	2.5 ± 1.5	744 ± 363	1.3 ± 0.4
			140 mg/m^2	1	6		497.5 ± 142.0	2.4 ± 0.8	1744 ± 480	1.5 ± 0.3
			5 mg/m^2 QD	>1	2		45.6	1.5	77	0.8
			15 mg/m^2 QD	>1	3		58.2 ± 11.6	1.5 ± 0.6	126 ± 39	1.1 ± 0.2
			30 mg/m^2 QD	>1	3		ND	ND	ND	ND
			50 mg/m^2 QD	>1	3		194.2 ± 108.5	1.7 ± 0.6	463 ± 188	1.2 ± 0.1
			83 mg/m^2 QD	>1	6		185.5 ± 125.1	2.0 ± 0.0	502 ± 255	1.2 ± 0.3
			140 mg/m^2 QD	>1	3		184.5 ± 181.4	2.7 ± 1.2	547 ± 429	1.2 ± 0.4
			50 mg/m^2 BID	>1	6		32.7 ± 19.1	2.1 ± 1.6	110 ± 41	1.6 ± 0.5
			60 mg/m^2 BID	>1	2		125.2	3.0	302	1.1
			70 mg/m^2 BID	>1	3		87.9 ± 82.4	1.8 ± 0.6	177 ± 120	1.1 ± 0.1

[a] Number of observations = 2.
Pts = Number of patients having pharmacokinetic samples drawn.
Obs = Number of observations contributing to parameter values.
ND = No data available.

TABLE 7. In Vivo Data Summary: Concentration Monitoring during Oral Studies with PANRETIN™ Capsules

Study Number	Route	Dose Form	Dose	Day	N	2-Hour Postdose 9-*cis*-Retinoic Acid Concentration (ng/mL)	2-Hour Postdose 4-oxo-9-*cis*-Retinoic Acid Concentration (ng/mL)
AGN 192013/ ALRT1057-001	Oral	Soft Gelatin Capsules	0.15 mg/kg QD	0	5		
			0.30 mg/kg QD	0	5		
			0.60 mg/kg QD	0	9		
			0.90 mg/kg QD	0	8		
			1.2 mg/kg QD	0	9		
			1.5 mg/kg QD	0	8		
			0.15 mg/kg QD	28	3		
			0.30 mg/kg QD	28	4		
			0.60 mg/kg QD	28	5		
			0.90 mg/kg QD	28	7		
			1.2 mg/kg QD	28	6		
			1.5 mg/kg QD	28	7		
			0.15 mg/kg QD	56	4		
			0.30 mg/kg QD	56	3		
			0.60 mg/kg QD	56	6		
			0.90 mg/kg QD	56	8		
			1.2 mg/kg QD	56	6		
			1.5 mg/kg QD	56	7		

Study Day 0 = First day of dosing.

TALBE 8. In Vivo Data Summary: Oral Studies with 9-*cis*-Retinoic Acid

Study Number	Route	Dose Form	Dose	Day	N	Analyte[a]	C_{max} (ng/mL)	t_{max} (hr)	$AUC_{(0-\infty)}$ (ng·hr/mL)	$T_{½}$ (hr)
Non-Ligand Sponsored Study 1	Oral	Soft Gelatin Capsule	5 mg	1	6	9cRA	24.7	3.2	49.2	–
						4-oxo9cRA	–	–	–	–
						ATRA	–	–	–	–
						4-oxo -ATRA	–	–	–	–
						13-*cis*RA	–	–	–	–
			15 mg	1	6	9cRA	56.6	3.0	161.5	–
						4-oxo9cRA	24.0	4.6	58.5	–
						ATRA	3.0	5.3	–	–
						4-oxo -ATRA	18.4	5.7	–	–
						13-*cis*RA	–	–	–	–
			40 mg	1	6	9cRA	146.2	4.0	374.2	1.9
						4-oxo9cRA	60.4	3.8	154.3	–
						ATRA	8.3	3.4	–	–
						4-oxo -ATRA	–	–	–	–
						13-*cis*RA	26.5	3.4	–	–
			80 mg	1	6	9cRA	355.7	3.0	1076.1	1.9
						4-oxo9cRA	240.0	2.8	755.2	–
						ATRA	11.8	2.5	25.8	–
						4-oxo -ATRA	10.4	3.2	–	–
						13-*cis*RA	28.6	2.8	15.7	–
			150 mg	1	6	9cRA	587.2	3.0	1671.7	1.6
						4-oxo9cRA	484.6	3.7	1599.1	–
						ATRA	23.9	3.2	54.7	–
						4-oxo -ATRA	19.4	3.6	65.3	–
						13-*cis*RA	40.0	3.5	30.5	–

[a] 9cRA = 9-*cis*-retinoic acid; 4-oxo9cRA= 4-oxo-9-*cis*-retinoic acid; ATRA= all-*trans*-retinoic acid; 4-oxo -ATRA= 4-oxo-all-*trans*-retinoic acid; 13-*cis*RA= 13-*cis*-retinoic acid.

– = Not reported or not determined.

Non-Ligand Sponsored Study 1: Weber C. and Dumont E. J Clin Pharmacol 37:566-574, 1997.

AUC values for metabolites are AUC from Time zero to time of last detectable concentration, $t_{½}$ values for metabolites not determined.

TALBE 8. In Vivo Data Summary: Oral Studies with 9-*cis*-Retinoic Acid (cont.)

Study Number	Route	Dose Form	Dose	Day	N	C_{max} (ng/mL)	t_{max} (hr)	$AUC_{(0-\infty)}$ (ng·hr/mL)	T½ (hr)
Non-Ligand Sponsored Study 2	Oral	Soft Gelatin Capsule	10 mg/m^2 BID	1	3	60.4	6.1	165.1	–
				22	2	28.5	3.6	83.5	–
			15 mg/m^2 BID	1	3	59.5	1.1	128.4	–
				22	3	54.8	3.1	133.2	–
			22.5 mg/m^2 BID	1	3	161.1	2.1	415.5	–
				22	3	33.4	1.1	81.9	–
			33.8 mg/m^2 BID	1	4	247.6	2.7	733.7	–
				22	3	60.7	4.0	207.5	–
			50.5 mg/m^2 BID	1	6	283	2.0	882.6	–
				22		–	–	–	–
			75.9 mg/m^2 BID	1	3	409.4	4.0	1483.8	–
				22		–	–	–	–

– = Not reported or not determined.
t_{max} values are medians.

Non-Ligand Sponsored Study 2: Kurie, J.M., Lee, J.S., Griffin, T., Lippman, S.M., Drum, P., Thomas, M.P., Weber, C., Bader, M., Massimini, G. Hong, W.K. Clin Cancer Res 2, 287-293, 1996.

APPENDIX IV *IN VIVO* ANALYTICAL METHODS SUMMARY

Clinical Study Supported	Type of Biological Fluid	Method	Analyte	Lower Limit of Quantitation	Standard Curve Range	Analytical Report Reference
L1057-94-01T	Plasma		9-*cis*-retinoic acid ATRA	ng/mL ng/mL	ng/mL ng/mL	RR 845-94-012
L1057-94-02T	Plasma		9-*cis*-retinoic acid ATRA	ng/mL ng/mL	ng/mL ng/mL	RR 845-94-012
L1057-94-03T	Plasma		9-*cis*-retinoic acid ATRA	ng/mL ng/mL	ng/mL ng/mL	RR 845-94-012
L1057-94-04T	Plasma		9-*cis*-retinoic acid ATRA	ng/mL ng/mL	ng/mL ng/mL	RR 845-94-012
L1057-94-05T	Plasma		9-*cis*-retinoic acid ATRA	ng/mL ng/mL	ng/mL ng/mL	RR 845-94-012
L1057-94-07T	Plasma		9-*cis*-retinoic acid 4-oxo-9-*cis*-retinoic acid	ng/mL ng/mL	ng/mL ng/mL	RR 845-94-012
L1057T-21	Plasma		9-*cis*-retinoic acid ATRA	ng/mL ng/mL	ng/mL ng/mL	RR 845-94-012
L1057T-22	Plasma		9-*cis*-retinoic acid 4-oxo-9-*cis*-retinoic acid	ng/mL ng/mL	ng/mL ng/mL	RR 845-97-015
L1057-93-01	Plasma		9-*cis*-retinoic acid ATRA	ng/mL ng/mL	ng/mL ng/mL	RR 845-94-012
L1057-93-02	Plasma		9-*cis*-retinoic acid ATRA	ng/mL ng/mL	ng/mL ng/mL	RR 845-94-012
AGN 192013/ ALRT1057-001	Plasma		9-*cis*-retinoic acid 4-oxo-9-*cis*-retinoic acid	ng/mL ng/mL	ng/mL ng/mL	RR 845-97-014

ATRA = All-*trans*-retinoic acid.

APPENDIX V. FORMUATIONS USED IN CLINICAL TRIALS

Only the 0.1% gel was designated for use in Phase 3 clinical studies, L1057T-31, ALRT1057- 503/504. The formulation was as follows:

Component	Percentage (w/w)
Dehydrated Alcohol, USP	
Polyethylene Glycol 400, NF	
Hydroxypropylcellulose, NF	
Butylated Hydroxytoluene, NF	
LGD1057	

* 5% overage of labeled LGD1057 amount retained until experience with manufacture at a large scale was obtained.

PANRETIN™ Gel Phase 1-2 Formulations

Ingredients [%w/w]	0.01% Gel	0.05% Gel	0.1% Gel
Dehydrated Alcohol, USP			
Polyethylene Glycol 400, USP			
Hydroxypropylcellulose, NF			
Butylated Hydroxytoluene, NF			
LGD1057[1]			

[1] Initially, a 5% overage of the labeled amount of LGD1057 was used until it could be demonstrated that the drug product could be consistently manufactured to label claim

0.01% Gel used in Phase 1-2 Studies L1057-94-01T, L1057-94-02T, L1057-94-03T, L1057-94-04T, L1057-94-05T, L1057-94-07T, L1057T-21, L1057T-22, L1057T-24, L1057T-25, and L1057T-30.

0.05% Gel used in Phase 1-2 Studies L1057-9-01T, L1057-94-02T, L1057-94-03T, L1057-94-04T, L1057-94-05T, L1057-94-07T, L1057T-21, L1057T-22, L1057T-24, L1057T-25, and L1057T-30.

0.1% Gel used in Phase 1-2 Studies L1057-94-01T, L1057-94-02T, L1057-94-03T, L1057-94-04T, L1057-94-05T, L1057-94-07T, L1057T-21, L1057T-22, L1057T-24, L1057T-25, and L1057T-