

APPENDIX VI SYNOPSES OF INDIVIDUAL STUDIES

1. Phase 1-2 Evaluation of PANRETIN™ Gel in Patients with Cutaneous T-Cell Lymphoma (Mycosis Fungoides)

TITLE: Summary of PANRETIN™ Drug Substance Pharmacokinetics during Phase 1-2 Evaluation of PANRETIN™ Gel in Patients with Cutaneous T-cell Lymphoma (Mycosis Fungoides)

OBJECTIVES: The primary clinical objectives of the studies were to evaluate the safety, dose tolerance and potential efficacy of PANRETIN™ Gel applied topically to cutaneous T-cell lymphoma (mycosis fungoides). The pharmacokinetic objective of the studies was to evaluate systemic exposure following repeat topical application of PANRETIN™ Gel.

INVESTIGATORS AND STUDY SITES

Study L1057-94-03T:

Study L1057-94-05T:

Bio-analytical Investigator:

FORMULATIONS: 0.01%, 0.05% and 0.1% (w/w) PANRETIN™ Gel.

STUDY DESIGN: Treatment was initiated with the 0.01% gel or 0.05% gel (Study L1057-94-03T) or the 0.05% gel (Study L1057-94-05T) and was escalated in frequency or concentration every two weeks to 0.10% gel applied twice daily unless significant worsening of the cutaneous T-cell lymphoma plaques (by area or severity) or topical or systemic treatment-limiting toxicity including cutaneous reactions was observed. Provisions for dose reduction were included should the patients experience treatment-limiting intolerance or toxicity.

SUBJECT: Patients were adults diagnosed with histologically-confirmed cutaneous T-cell lymphoma (CTCL) with a maximum limit on body surface area involvement. Confirmation was made from skin biopsies showing mononuclear cell infiltration with some abnormal T-cell cytology and/or Pautrier's microabscesses in the epidermis. Patients had acceptable organ function and were sexually abstinent or used acceptable contraception methods. Pregnant or breast-feeding women, or patients with serious inter-current illness were excluded. Concomitant use of antipsoriatic or anticancer drugs was prohibited. Pharmacokinetic samples were obtained from a total of seven patients; two females (29%) and five males (71%). Patients had a mean age of 56.4 yr (median: 61; range: , a mean height of 174 cm (median: 172; range: and a mean weight of 86.7 kg (median: 82.8; range: Of the 7 patients enrolled, 6 were Caucasian (86%) and 1 was Black (14%).

ANALYTICAL METHODS:

SAMPLE COLLECTION: Single time point plasma samples were obtained from patients on Weeks 2 and 4 and every two to four weeks thereafter while patients remained on study. Samples were collected during office visits and the time of sampling and time of last gel application were recorded. Blood samples (10 mL) were collected in sodium heparin-containing tubes, centrifuged, and the plasma was removed and

placed in two equal aliquots in tubes. Tubes were stored at -20 °C or lower until shipped to Ligand Pharmaceuticals Inc.

RESULTS: A total of 107 plasma samples from 7 patients with cutaneous T-cell lymphoma lesions were analyzed. In all samples, plasma concentrations of PANRETIN™ drug substance and ATRA were below their respective LLQ values. Individual patient treatment areas ranged from . . . % BSA (median: 2%). Thus, even following extensive topical application of PANRETIN™ Gel, there was no quantifiable systemic exposure to PANRETIN™ drug substance. The lack of quantifiable systemic concentrations is consistent with previous observations following topical application of ATRA (tretinoin) and 13-*cis*-retinoic acid (isotretinoin).

CONCLUSIONS: Based on a plasma assay with lower limits of quantitation for PANRETIN™ drug substance and ATRA of . . . ng/mL and . . . ng/mL, respectively, there was no quantifiable systemic exposure to PANRETIN™ drug substance or ATRA following repeat topical application of PANRETIN™ Gel for the treatment of cutaneous T-cell lymphoma lesions.

COMMENTS: This study provided supportive data in patients with CTCL for the systemic exposure of 9-*cis*-retinoic acid in the patients with KS.

2. Phase 1-2 Evaluation of PANRETIN™ Gel in Patients with Cutaneous Kaposi's Sarcoma

TITLE: Summary of PANRETIN™ Drug Substance Pharmacokinetics during Phase 1-2 Evaluation of PANRETIN™ Gel in Patients with Cutaneous Kaposi's Sarcoma

OBJECTIVES: The primary clinical objectives of the studies were to evaluate the safety and cutaneous tolerance of PANRETIN™ Gel and to evaluate the anti-tumor effects of PANRETIN™ Gel applied topically to cutaneous KS lesions. The pharmacokinetic objective of the studies was to evaluate systemic exposure following repeat topical application of PANRETIN™ Gel.

INVESTIGATORS AND STUDY SITES:

Study L1057-94-01T:

Study L1057-94-02T:

Study L1057-94-04T:

Study L1057-94-07T:

Study L1057T-21:

Study L1057T-22:

Bio-analytical Investigators:

FORMULATIONS: 0.01%, 0.05% and 0.1% (w/w) PANRETIN™ Gel.

STUDY DESIGN: Patients were equally (1:1) randomized, using a sealed envelope system, to initial treatment with either 0.05% or 0.1% PANRETIN™ Gel. During the first two weeks, patients applied the treatment twice each day (BID) to the index KS lesion(s) to be treated. Starting with the second two-week

period, the patient was instructed to apply the treatment four times daily (QID). Patients initiating treatment with the 0.05% gel were to have subsequently escalated, every two weeks, to the 0.1% gel BID and 0.1% gel QID. Provisions were incorporated in the study to reduce the drug concentration and/or frequency of application should the patient experience treatment-limiting intolerance or toxicity.

SUBJECTS: Patients were confirmed serum HIV antibody positive with a diagnosis of KS and acceptable organ function and Karnofsky performance score. Pregnant or breast-feeding women, and patients with serious inter-current illness, were excluded. Patients had at least two cutaneous lesions to serve as control lesions and at least one other cutaneous lesion to serve as a treated index lesion(s). Plasma samples from a total of 94 male patients were assayed. These patients had a mean age of 38.7 years (range: a mean height of 177 cm (range: and a mean weight of 74.9 kg (range: Of the 94 patients evaluated, 76 were Caucasian (81%) and 18 (19%) were Hispanic.

ANALYTICAL METHODS:

SAMPLE COLLECTION: Single time point plasma samples were obtained from patients on Weeks 2 and 4 and every two to four weeks thereafter while patients remained on study. Samples were drawn during office visits and the time of sampling and time of last gel application were recorded. Blood samples (10 mL) were drawn in sodium heparin-containing tubes, centrifuged, and the plasma was removed and placed in two equal aliquots in tubes. Tubes were to be stored at -20 °C or lower until shipped to Ligand Pharmaceuticals Inc. Tubes were stored at -20 °C or lower until analysis.

RESULTS: A total of 483 plasma samples from 72 patients were analyzed with one of the two methods with a PANRETIN™ drug substance LLQ of ng/mL; 153 plasma samples from 22 patients were analyzed using the method with a PANRETIN™ drug substance LLQ of ng/mL.

PANRETIN™ drug substance concentrations were below the limit of quantitation in all samples analyzed with the analytical methods having LLQ values of ng/mL. In addition, plasma concentrations of ATRA and 4-oxo-9-cis-retinoic acid were less than their respective limits of quantitation: ng/mL and ng/mL. Using these assay methods, there was no quantifiable systemic exposure to PANRETIN™ drug substance, ATRA or 4-oxo-9-cis-retinoic acid following topical application of PANRETIN™ Gel.

PANRETIN™ drug substance was quantifiable in 26 of the 153 samples (17%) analyzed with the analytical method having LLQ of ng/mL. The highest observed PANRETIN™ drug substance concentration was ng/mL. Ten of 22 (45%) evaluated patients had quantifiable PANRETIN™ drug substance in at least 1 plasma sample. 4-oxo-9-cis-retinoic acid was not quantifiable in any of the 153 samples (LLQ: ng/mL). There did not appear to be any relationship between quantifiable PANRETIN™ drug substance concentrations and gel strength, time since application, frequency of application, or extent or duration of application suggesting that quantifiable concentrations may have been due, in whole or in part, to dietary or nutritional sources of this endogenous substance rather than exogenous application of 9-cis-retinoic acid.

CONCLUSIONS: Based on plasma assays with PANRETIN™ drug substance lower limits of quantitation (LLQ) of ng/mL or ng/mL, there was either no or minimal quantifiable systemic exposure to PANRETIN™ drug substance following repeat topical application of PANRETIN™ Gel for the treatment of

cutaneous Kaposi's sarcoma lesions. When quantifiable, PANRETIN™ drug substance concentrations did not appear to be correlated with PANRETIN™ Gel application, suggesting the ability to quantitate PANRETIN™ drug substance may have been related, in whole or in part, to dietary or nutritional sources of this endogenous hormone. There was no quantifiable exposure to the oxidative metabolite, 4-oxo-9-cis-retinoic acid (LLQ: ng/mL or ng/mL), or the isomeric metabolite, ATRA (LLQ: ng/mL).

COMMENTS: This study provide adequate information about the systemic exposure of 9-cis-retinoic acid. However, the samples for determining systemic exposure were obtained from the patients without dietary restrictions. Baseline samples were not available for any of the patients. These deficiencies weakened the conclusion that quantifiable concentrations of 9-cis-retinoic acid may be due, in whole or in part, to dietary or nutritional supplement sources of this endogenous substance rather than exogenous application of 9-cis-retinoic acid.

3. Protocol L1057-93-01

TITLE: Pharmacokinetic Summary of the Clinical Study "Phase 1 Evaluation of Oral LGD1057 (9-cis-Retinoic Acid) in Patients with Advanced Cancer" (Protocol L1057-93-01)

OBJECTIVES: The primary objective of this study was to evaluate the tolerability, safety, potential toxicity, pharmacokinetics, and metabolic fate of 9-cis-retinoic acid (PANRETIN™ drug substance) following daily, oral dosing to patients with advanced cancer. The secondary objective was to evaluate the potential effectiveness of PANRETIN™ drug substance on clinical progression and outcome in patients with advanced cancer, categorized by type of cancer.

INVESTIGATORS AND STUDY SITES:

Bioanalytical Investigator:

FORMULATIONS: PANRETIN™ Capsules containing mg or mg were used in this study. The mg capsules (Lot # 9312-001 and Lot # 9405 001) had potencies of % and % of label claim, respectively, and the -mg capsules (Lot # 9312-002 and Lot # 9405-002) had potencies of % and % of label claim, respectively.

STUDY DESIGN: This was an open-label, uncontrolled, multiple-dose, dose-escalation, safety and efficacy evaluation study of oral PANRETIN™ Capsules administered once or twice daily to patients with proven, advanced cancer. The study was to have lasted 4 wk with an allowance to continue treatment in 4 wk increments. At least 3 patients were studied at each dose level until the maximum tolerated dose was determined.

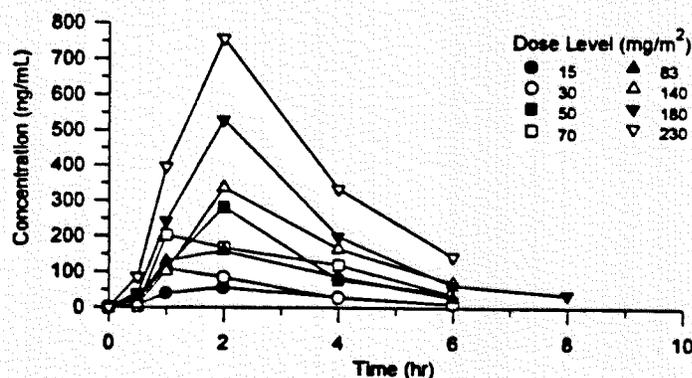
SUBJECTS: Patients had histologically confirmed advanced cancer, an ECOG performance status of 0, 1, or 2; and clinically adequate function of all organ systems. Patients were on stable doses of any drugs which could have affected hepatic drug metabolism or renal drug excretion, and initiation of such drugs was avoided during this study. Women of child-bearing potential were to have had a negative serum pregnancy test within 7 days prior to the initiation of treatment, and must have used an effective means of contraception for at least 4 wk prior to Day 1 and continued to use contraception throughout the study. Pregnant or lactating women were ineligible to participate in the study. The minimum age for enrollment was 18 yr. The 40 patients (27 men and 13 women) who provided pharmacokinetic information for this study had a mean ± SD (median, range) age and weight of 56 ± 11 (59, 27 to 71) yr and 164.6 ± 32.5 (166, 98.1 to 224.9) lb, respectively. Most patients were Caucasian (also 1 Asian, 1 Mediterranean, 1 Hispanic, and 2 Blacks). The first and last Day 1 doses were administered on

December 29, 1993, and October 9, 1995, respectively, and the last dose after which samples were collected for pharmacokinetic analysis for this study was administered on November 6, 1995.

ANALYTICAL METHODS:

SAMPLE COLLECTION AND PHARMACOKINETICS: After the first dose and after multiple doses (Days 15 and 29), serial blood samples (8 mL) were to be collected before dosing (0 hr) and 0.5, 1, 2, 4, and 6 hours postdose for the determination of PANRETIN™ drug substance and ATRA plasma concentrations. An additional blood sample was collected at 8 hours postdose for some patients. Standard noncompartmental methods were used to estimate pharmacokinetic parameters, including maximum observed plasma concentration (C_{max}), observed time to C_{max} (t_{max}), terminal elimination rate constant (λ_z), half-life ($t_{1/2}$), and area under the plasma concentration-time curve extrapolated to infinite time ($AUC_{0-\infty}$) for PANRETIN™ drug substance and ATRA.

RESULTS: PANRETIN™ drug substance concentrations were measurable at all dose levels, although single-dose data were unavailable for patients receiving 5 mg/m²/day due to insufficient volume for reanalysis after initial analysis by an unvalidated assay. There was a wide range of t_{max} values, but a t_{max} of 1 hour to 3 hours after both single and multiple oral doses was most common. Considerable interpatient variability in C_{max} and $AUC_{0-\infty}$ after single or multiple doses was observed, with coefficient of variation values often above 40%. After single doses, PANRETIN™ drug substance C_{max} and $AUC_{0-\infty}$ increased approximately dose-proportionally over the evaluable range of doses (mg/m² to mg/m²) administered in this study. PANRETIN™ drug substance mean concentration-time profiles after a single dose of mg/m² to mg/m² are shown below.



Mean PANRETIN™ Drug Substance Plasma Concentrations After a Single Oral Dose of 15 mg/m² to 230 mg/m² PANRETIN™ Capsules (n=1 to 8)

C_{max} and $AUC_{0-\infty}$ values after multiple daily doses of mg/m² to mg/m² PANRETIN™ Capsules were not consistently different from those observed after the first dose. Although many patients receiving mg/m² had lower C_{max} and $AUC_{0-\infty}$ values on Day 15 compared to those on Day 1, most patients who had at least two assessments after multiple doses had multiple-dose values that were similar to those

after a single dose on at least one occasion. However, as shown in the table below, following repeat daily doses of mg/m^2 to mg/m^2 , mean C_{max} and $\text{AUC}_{0-\infty}$ values were substantially lower than those observed after the first dose, suggesting induction of PANRETIN™ drug substance oral clearance at these higher dose levels.

Mean (\pm SD) PANRETIN™ Drug Substance Pharmacokinetic Parameters after Single and Multiple Daily Oral Doses of PANRETIN™ Capsules to Patients with Advanced Cancer (Protocol L1057-93-01)

Dose Level (mg/m^2)	Dose Number ^a	N	Parameter			
			t_{max} (hr)	C_{max} (ng/mL)	$\text{AUC}_{0-\infty}$ (ng·hr/mL)	$t_{1/2}$ ^b (hr)
5	S	0	ND	ND	ND	ND
	M	2	1.5	25.2	66	1.3
15	S	3	1.6 (0.5)	77.1 (47.3)	185 (117)	1.2 (0.1)
	M	5	2.3 (0.9)	43.8 (10.2)	127 (34)	1.0 (0.4)
30	S	5	1.6 (0.5)	138.0 (97.3)	308 (120)	1.4 (0.2)
	M	9	1.8 (1.0)	96.9 (48.7)	224 (68)	1.1 (0.3)
50	S	1	2.0	281.3	785	1.4
	M	2	1.0	169.3	347	1.1
70 ^c	S	4	1.2 (0.5)	258.6 (118.1)	831 (656)	1.2 (0.3)
	M	2	2.0	175.7	404	0.9
83	S	3	2.3 (1.5)	198.1 (72.5)	601 (148)	1.2 (0.1)
	M	8	2.9 (2.0)	174.6 (98.8)	513 (201)	1.1 (0.2)
140	S	7	2.3 (0.8)	340.2 (230.7)	1146 (962)	1.3 (0.3)
	M	12	2.6 (1.1)	114.3 (119.3)	413 (408)	1.3 (0.5)
180	S	6	2.0 (0.0)	528.5 (346.5)	1613 (738)	1.4 (0.3)
	M	5	1.3 (0.7)	143.9 (59.0)	477 (278)	1.7 (0.2)
230	S	8	2.0 (0.1)	758.6 (362.0)	2445 (1400)	1.2 (0.4)
	M	7	1.5 (0.5)	201.3 (78.5)	619 (267)	1.3 (0.5)

^a S = single dose (Day 1); M = multiple doses (at least 10 days of dosing).

^b $t_{1/2}$ values could not be calculated for all patients; n=1 for dose level 5 mg/m^2 , n=6 for multiple doses of 83 mg/m^2 , n=6 and 11 for single and multiple doses of 140 mg/m^2 , respectively.

^c Patients received 70 mg/m^2 twice daily ($140 \text{ mg/m}^2/\text{day}$).

ND = Not determined; incomplete or insufficient data for determination.

SD is not presented if $n \leq 2$.

In contrast, mean $t_{1/2}$ values were consistently about 1.2 hours for all dose levels, and the values after single doses did not appear to be different from those after multiple doses, suggesting minimal change in systemic clearance with multiple dosing. While detectable predose PANRETIN™ drug substance concentrations were often observed following multiple doses of mg/m^2 , these concentrations were minimal (mean concentrations of $\leq 6 \text{ ng/mL}$), suggesting essentially no accumulation of PANRETIN™ drug substance after multiple doses of up to mg/m^2 administered once daily (maximum predose

concentration of ng/mL) or mg/m² administered twice daily (maximum predose concentration of ng/mL). Also, two patients receiving mg/m² PANRETIN™ Capsules had no apparent accumulation after multiple doses for 73 and 78 days. In general, ATRA concentrations were below the LLQ following all but the two highest doses, and the pharmacokinetics of this metabolite were not assessed. ATRA concentrations of the 0-hour and 6-hour samples were almost uniformly below the LLQ at all doses, suggesting rapid clearance of any ATRA that may have been formed. In addition, for many chromatograms, a peak was observed corresponding to the 9-cis-retinoic acid metabolite 4-oxo-9-cis-retinoic acid (LG100182).

CONCLUSIONS: Oral administration of PANRETIN™ Capsules resulted in quantifiable systemic exposure to PANRETIN™ drug substance at all dose levels mg/m²/day to mg/m²/day). After single doses, C_{max} and AUC_{0-∞} increased approximately dose-proportionally. The pharmacokinetics after multiple doses suggested induction of PANRETIN™ drug substance oral clearance at the higher dose levels (once daily doses of mg/m²). In contrast, mean t_{1/2} values were consistently about 1.2 hours for all dose levels irrespective of dose regimen or frequency. There was little or no accumulation of PANRETIN™ drug substance at any dose level. In general, ATRA concentrations were below ng/mL after daily doses of mg/m² PANRETIN™ Capsules, and 4-oxo-9-cis-retinoic acid was detected in many samples.

COMMENTS: This study provided pharmacokinetics of oral formulation of PANRETIN™ and was reviewed only as supportive data to the systemic exposure of 9-cis-retinoic acid from topical gel formulation. It was demonstrated that the elimination was rapid and the lack of accumulation was observed following repeat oral administration of 9-cis-retinoic acid. This was consistent with the very low or undetectable 9-cis-retinoic acid concentrations found after topical application of 9-cis-retinoic acid in patients.

4. Protocol L1057-93-02

TITLE: Pharmacokinetic Summary of the Clinical Study "Phase 1-2a Evaluation of Oral LGD1057 (9-cis-Retinoic Acid) in Patients with Advanced Cancer" (Protocol L1057-93-02)

OBJECTIVES: The primary objective of this study was to evaluate the tolerability, safety, potential toxicity, pharmacokinetics, and metabolic fate of 9-cis-retinoic acid (PANRETIN™ drug substance) following daily oral dosing to patients with advanced cancer. The secondary objective was to evaluate the potential effectiveness of PANRETIN™ drug substance on clinical progression and outcome in patients with advanced cancer, categorized by type of cancer.

INVESTIGATORS AND STUDY SITES:

Bioanalytical Investigator:

FORMULATIONS: PANRETIN™ Capsules containing mg or mg LGD1057 were used in this study. The mg capsules (Lot 9312-001) had a potency of % of label claim, and the -mg capsules (Lots 9312-002 and 9405-002) had potencies of % and % of label claim, respectively.

STUDY DESIGN: This was an open-label, uncontrolled, multiple-dose, dose-escalation, safety and efficacy evaluation study of oral PANRETIN™ Capsules administered once or twice daily to patients with proven, advanced cancer. The study lasted four weeks with an allowance to continue treatment in four

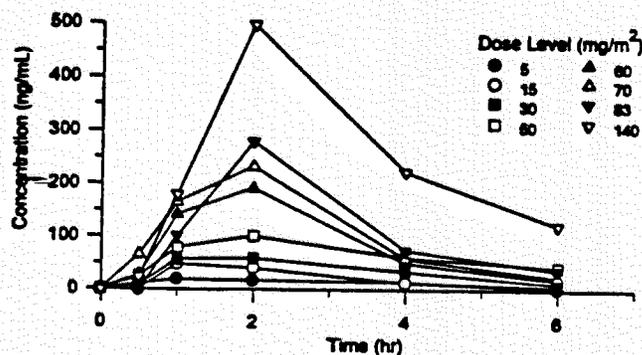
week increments. At least three patients were studied at each dose level until the maximum tolerated dose was determined.

SUBJECTS: Patients had histologically confirmed advanced cancer, an ECOG performance status of 0, 1, or 2; and clinically adequate function of all organ systems. Patients were on stable doses of any drugs which could have affected hepatic drug metabolism or renal drug excretion, and initiation of such drugs was avoided during this study. Women of child-bearing potential had a negative serum pregnancy test within seven days prior to the initiation of treatment, and must have used an effective means of contraception for at least four weeks prior to Day 1 and continued to use contraception throughout the study. Pregnant or lactating women were ineligible to participate in the study. The minimum age for enrollment was 18 years. The 41 patients (17 men and 24 women) who provided pharmacokinetic information for this study had a mean \pm SD (median, range) age and weight of 58 ± 12 (60, 21 to 83) yr and 158.2 ± 39.6 (162, 74.0 to 230.5) lb, respectively. Most patients were Caucasian (also 1 Asian, 2 Lebanese, 2 Indian, 3 Filipino, and 4 Blacks). The first and last Day 1 doses were administered on January 6, 1994, and July 5, 1995, respectively, and the last dose after which samples were collected for pharmacokinetic analysis for this study was administered on July 20, 1995.

ANALYTICAL METHODS:

SAMPLE COLLECTION AND PHARMACOKINETICS: On Day 1 and Day 15 and later, serial blood samples (8 mL) were collected before dosing (0 hr) and 0.5, 1, 2, 4, and 6 hours postdose for the determination of PANRETIN™ drug substance and ATRA plasma concentrations. Standard noncompartmental methods were used to estimate pharmacokinetic parameters, including maximum observed plasma concentration (C_{max}), observed time to C_{max} (t_{max}), terminal elimination rate constant (λ_z), half-life ($t_{1/2}$), and area under the plasma concentration-time curve extrapolated to infinite time ($AUC_{0-\infty}$) for PANRETIN™ drug substance and ATRA.

RESULTS: PANRETIN™ drug substance concentrations were measurable at all dose levels. There was a wide range of t_{max} values, but a t_{max} of 1 hour to 3 hours after both single and multiple oral doses was most common. Considerable interpatient variability in C_{max} and $AUC_{0-\infty}$ after single or multiple doses was observed, with coefficient of variation values often above 40%. After single doses, PANRETIN™ drug substance C_{max} and $AUC_{0-\infty}$ increased approximately dose-proportionally over the range of doses administered in this study (mg/m² to mg/m²). PANRETIN™ drug substance mean concentration-time profiles after a single dose of mg/m² to mg/m² are shown below.



Mean PANRETIN™ Drug Substance Plasma Concentrations After a Single Oral Dose of 5 mg/m² to 140 mg/m² PANRETIN™ Capsules (n=2 to 9)

C_{max} and AUC_{0-∞} values after multiple once-daily doses of 5 mg/m² to 50 mg/m² PANRETIN™ drug substance were not consistently different from those observed after the first dose. Multiple once-daily doses of 83 mg/m² PANRETIN™ drug substance appeared to result in lower mean concentrations than those after the first dose, although the differences were not substantial. Clearly, following repeat daily doses of ≥100 mg/m²/day (both as single daily dose or combined total dose), mean C_{max} and AUC_{0-∞} values were consistently lower than those observed after the first dose, suggesting induction of PANRETIN™ drug substance oral clearance at the higher total daily dose levels.

Mean (±SD) PANRETIN™ Drug Substance Pharmacokinetic Parameters after Single and Multiple Daily Oral Doses of PANRETIN™ Capsules to Patients with Advanced Cancer (Protocol L1057-93-02)

Dose Level (mg/m ²)	Dose Number ^b	N	Parameter			
			t _{max} (hr)	C _{max} (ng/mL)	AUC _{0-∞} (ng·hr/mL)	t _{1/2} ^a (hr)
5	S	2	2.5	32.0	73	0.9
	M	2	1.5	45.6	77	0.8
15	S	2	1.0	48.4	145	1.7
	M	4	1.5 (0.6)	58.2 (11.6)	126 (39)	1.1 (0.2)
30	S	3	2.4 (1.6)	61.9 (11.0)	218 (36)	1.8
	M	2	ND	ND	ND	ND
50	S	9	3.2 (2.0)	171.0 (92.5)	456 (155)	1.3 (0.1)
	M	3	1.7 (0.6)	194.2 (108.5)	463 (188)	1.2 (0.1)
	MBID ^c	6	2.1 (1.6)	32.7 (19.1)	110 (41)	1.6 (0.5)
60	S	4	2.1 (0.2)	191.2 (99.8)	560 (269)	1.1 (0.1)
	MBID ^c	2	3.0	125.2	302	1.1
70	S	5	1.9 (0.4)	298.9 (150.5)	704 (245)	1.2 (0.2)
	MBID ^c	3	1.8 (0.6)	87.9 (82.4)	177 (120)	1.1 (0.1)
83	S	8	2.5 (1.5)	282.1 (169.1)	744 (363)	1.3 (0.4)
	M	6	2.0 (0.0)	185.5 (125.1)	502 (255)	1.2 (0.3)
140	S	6	2.4 (0.8)	497.5 (142.0)	1744 (480)	1.5 (0.3)
	M	3	2.7 (1.2)	184.5 (181.4)	547 (429)	1.2 (0.4)

- a $t_{1/2}$ values could not be calculated for all patients; n=3 for dose level 15 mg/m², multiple doses, n=2 for dose level 30 mg/m², n=7 and 5 for single and multiple twice-daily doses of 50 mg/m², respectively, and n=7 and 5 for single and multiple doses of 83 mg/m², respectively.
 - b S = Single dose (Day 1); M = multiple once-daily doses (at least 14 days of dosing).
 - c MBID = Patients received doses twice daily for total daily doses of 100, 120, or 140 mg/m²/day.
- ND = Not determined; incomplete or insufficient data for determination.

In contrast, mean $t_{1/2}$ values were consistently about 1.3 hours for all dose levels, and the values after single doses did not seem to be different from those after multiple doses, suggesting minimal change in systemic clearance with multiple dosing. While detectable predose PANRETIN™ drug substance concentrations were often observed following multiple doses of mg/m²/day, these concentrations were minimal, suggesting essentially no accumulation of PANRETIN™ drug substance after multiple doses of up to mg/m²/day administered once daily (maximum predose concentration of ng/mL) or mg/m² to mg/m² administered twice daily (maximum predose concentration of ng/mL). In general, ATRA concentrations were below the LLQ following all doses, and the pharmacokinetics of this metabolite were not assessed. In addition, for many chromatograms, a peak was observed corresponding to the 9-*cis*-retinoic acid metabolite 4-oxo-9-*cis*-retinoic acid (concentrations were not quantified).

CONCLUSIONS: Oral administration of PANRETIN™ Capsules resulted in quantifiable systemic exposure to PANRETIN™ drug substance at all dose levels mg/m²/day to mg/m²/day). After single doses, increases in C_{max} and $AUC_{0-\infty}$ were proportional to the dose. The pharmacokinetics after multiple doses suggest induction of PANRETIN™ drug substance oral clearance at the higher total daily dose levels (doses of mg/m²/day). In contrast, mean $t_{1/2}$ values were consistently about 1.3 hours for all dose levels irrespective of dose regimen or frequency. There was little or no accumulation of PANRETIN™ drug substance at any dose level examined in this study. In general, ATRA concentrations were below ng/mL, and 4-oxo-9-*cis*-retinoic acid was detected in many samples, although concentrations were not quantified.

COMMENTS: This study provided same supportive information as the study in synopsis 4. Please refer to the Comment for that study.

5. Study AGN 192013/ALRT1057-001

TITLE: Pharmacokinetic Analysis of Plasma 9-*cis*-Retinoic Acid and 4-oxo-9-*cis*-Retinoic Acid Concentrations from Study AGN 192013/ALRT1057-001, Titled "A Multicenter, Open Label, Dose-Response Pilot Safety and Efficacy Study of AGN 192013/ALRT1057 in Patients with Severe Plaque Psoriasis"

OBJECTIVES: The primary clinical objective of the study was to evaluate the safety, efficacy and dose-response of AGN 192013/LGD1057 in patients with severe plaque psoriasis. The pharmacokinetic objective of the study was to evaluate predose and 2-hour postdose plasma concentrations of LGD1057 (9-*cis*-retinoic acid) and 4-oxo-9-*cis*-retinoic acid at three separate occasions (Days 0, 28 and 56) during the study.

INVESTIGATORS AND STUDY SITES:

Bio-Analytical Investigator:

FORMULATIONS: soft gelatin capsules containing - mg LGD1057 (Lot 9142-003; Assay: % [1/31/97]) or mg LGD1057 (Lot 9412-004; Assay: % [1/31/97]) supplied by Ligand Pharmaceuticals Inc.

STUDY DESIGN: The study design was a multicenter, open-label, dose-response study designed to assess the safety and efficacy of LGD1057 in doses ranging from mg/kg to mg/kg administered once daily with the morning meal for up to 56 days in patients with severe plaque psoriasis. Administered doses were calculated by rounding to the nearest dose attainable using whole mg and/or mg capsules. Dose escalation in new patients was dependent upon the successful completion of previous dose panels by earlier patients. Intra-patient dose escalation was not allowed. On pharmacokinetic sampling days, doses were administered with 250 mL of a liquid dietary supplement (Ensure® Plus) or a morning meal.

SUBJECT: Patients were adults diagnosed with severe plaque psoriasis involving greater than 20% of body surface area and a minimal overall plaque elevation score of moderate. Patients had acceptable organ system function. Female patients were postmenopausal or surgically sterile. Pregnant or breast-feeding women, and patients with serious intercurrent illness were excluded. Concomitant use of anti-psoriatic medications was prohibited. A total of 50 patients were enrolled in the study; nine female (18%) and 41 male (82%) patients. Patients had a mean age of 45.6 years (median: 45; range:), a mean height of 68.9 inches (median: 69; range:) and a mean weight of 90.9 kilograms (median: 90; range:). Of the 50 patients enrolled, 41 were Caucasian (82%), one was Black (2%), three were Hispanic (6%), four were Asian (8%) and one (2%) was categorized as "Other".

ANALYTICAL METHODS:

SAMPLE COLLECTION: Predose and 2-hour postdose plasma samples were obtained from patients on Study Days 0 (first day of dosing), 28 and 56. Blood samples (10 mL) were collected in sodium heparin-containing tubes, centrifuged, and the plasma removed and placed in two equal aliquots in tubes. Tubes were stored at -20°C or lower until shipped to Drug Studies Unit for analysis.

RESULTS: A total of 223 plasma samples from 48 patients with severe plaque psoriasis were obtained for this pharmacokinetic analysis.

9-*cis*-retinoic acid was present at concentrations exceeding ng/mL in (29%) evaluable Day 0 predose (prior to therapy) samples. 9-*cis*-Retinoic acid concentrations could not be accurately quantitated in six samples of the 13 Day 0 predose samples due to unacceptable performance of the lowest calibration standard ng/mL) for the respective analytical runs for these samples. However, the chromatographic peak height ratios observed for these samples indicated the 9-*cis*-retinoic acid concentration in these samples was between ng/mL (LLQ for the validated assay) and ng/mL (LLQ for the specific analytical runs). The highest observed Day 0 predose 9-*cis*-retinoic acid

concentration in the seven samples which could be accurately quantitated was ng/mL (mean: 0.493; range ng/mL). The metabolite 4-oxo-9-cis-retinoic acid was only observed in one of 45 evaluable Day 0 predose samples ng/mL; the 9-cis-retinoic acid concentration in this single sample was less than ng/mL.

Mean (\pm SD) Day 0 2-hour postdose 9-cis-retinoic acid concentrations increased from ng/mL following a mg/kg dose to ng/mL following a mg/kg dose. Similarly, mean (\pm SD) 2-hour postdose 4-oxo-9-cis-retinoic acid concentrations increased from ng/mL following a mg/kg dose to ng/mL following a mg/kg dose. Day 28 and Day 56 2-hour postdose 9-cis-retinoic acid concentrations were similar to Day 0 values at dose levels up to mg/kg. However, at doses mg/kg, 2-hour postdose concentrations following repeat dosing were less than respective Day 0 values. Similar reductions in concentrations following repeat dosing were also observed with 4-oxo-9-cis-retinoic acid at these dose levels. In most instances, mean repeat dose predose 9-cis-retinoic acid and 4-oxo-9-cis-retinoic acid concentrations were % of respective 2-hour postdose values, indicating negligible accumulation over the course of the study.

Mean \pm SD (N) 2-Hour Postdose Plasma 9-cis-Retinoic Acid and 4-oxo-9-cis-Retinoic Acid Concentrations Following Single (Day 0) or Repeat (Days 28, 56) Daily Dose Administration of PANRETIN™ Capsules to Patients with Severe Plaque Psoriasis

PANRETIN™ Capsule Dose (mg/kg/day)	9-cis-Retinoic Acid Concentration (ng/mL)		
	Day 0	Day 28	Day 56
	0.15	21.4 \pm 16.2 (5)	18.3 \pm 21.9 (3)
0.30	37.1 \pm 15.3 (5)	21.6 \pm 11.9 (4)	25.0 \pm 15.3 (3)
0.60	82.4 \pm 37.1 (9)	89.8 \pm 47.8 (5)	78.8 \pm 57.6 (6)
0.90	142 \pm 82 (8)	100 \pm 59 (7)	87.7 \pm 45.5 (8)
1.2	152 \pm 83 (9)	42.8 \pm 14.9 (6)	75.6 \pm 43.2 (6)
1.5	426 \pm 262 (8)	236 \pm 92 (7)	175 \pm 130 (7)
	4-oxo-9-cis-Retinoic Acid Concentration (ng/mL)		
	Day 0	Day 28	Day 56
0.15	7.62 \pm 4.15 (5)	7.76 \pm 8.49 (3)	7.28 \pm 6.41 (4)
0.30	19.0 \pm 10.8 (5)	10.6 \pm 5.9 (4)	12.7 \pm 12.8 (3)
0.60	39.9 \pm 23.3 (9)	37.8 \pm 25.8 (5)	33.3 \pm 27.0 (6)
0.90	78.3 \pm 37.1 (8)	47.6 \pm 33.8 (7)	47.3 \pm 32.3 (8)
1.2	122 \pm 86 (9)	33.7 \pm 12.8 (6)	65.5 \pm 64.2 (6)
1.5	194 \pm 124 (8)	119 \pm 79 (7)	70.9 \pm 54.1 (7)

CONCLUSIONS: Based on a plasma assay with lower limits of quantitation for 9-cis-retinoic acid and 4-oxo-9-cis-retinoic acid of ng/mL and ng/mL, respectively, up to 29% percent of patients with psoriasis have pretreatment 9-cis-retinoic acid concentrations equal to or greater than ng/mL. Following single oral dose treatment with 9-cis-retinoic acid, 2-hour postdose plasma 9-cis-retinoic acid and 4-oxo-9-cis-retinoic acid concentrations increase with increasing dose over a mg/kg to mg/kg dose range. Following repeat daily dosing, 2-hour postdose 9-cis-retinoic acid and 4-oxo-9-cis-retinoic acid concentrations were similar to single dose values at doses up to mg/kg, but were less than single dose values at doses mg/kg. At all dose levels, over all sampling periods, 4-oxo-9-cis-retinoic acid concentrations were approximately one-half plasma 9-cis-retinoic acid concentrations.

COMMENTS: This study evaluated predose and 2-hour postdose plasma concentrations of 9-cis-retinoic acid and 4-oxo-9-cis-retinoic acid at three separate occasions (Days 0, 28 and 56) after oral

administration of LGD1057 (9-*cis*-retinoic acid) capsule in patients with severe plaque psoriasis. Since more sensitive assay was used with LLQ of ng/mL, the predose concentrations of 9-*cis*-retinoic acid were available in certain samples. These predose concentration evaluations made it possible to compare with the concentrations after application of topical gel.

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