which act through altering gene expression in the nucleus of the cell. The RXR receptors (RXRα, β and γ) have biological activity unique from that of the RARs. The RXRs act as effector proteins for the endogenous ligand, 9-*cis*-retinoic acid (9-*cis*-RA, alitretinoin), a retinoid pan-agonist that binds to and activates both the RAR and RXR families of receptors. When activated, the RXRs act as transcription factors that regulate processes such as cellular differentiation and proliferation, apoptosis, and insulin sensitization.

The RXRs are unique in the NR superfamily, in that they also have the ability to form heterodimers with numerous other members of the NR superfamily, including the RARs, the thyroid hormone receptor (TR), the peroxisome proliferator-activator receptor (PPAR), the vitamin D receptor (VDR), and a number of other NRs whose ligands have yet to be identified (orphan receptors), i.e., transcription factor NGFI-B, liver X receptor (LXR), pregnane X receptor (PXR), farnesoid X receptor (FXR) and RXR-interacting protein 14 orphan nuclear receptor (RIP14), among others. The ability of the RXRs to form heterodimers with various receptor partners that are important in cellular function and in physiology implies that the biological activities of RXR activators may encompass a greater diversity than those compounds that activate the RARs.

Bexarotene is a synthetic compound that exerts its biological action through selective binding and activation of the three RXRs (RXRα, β and γ). It binds with high affinity to the RXRs, demonstrating only weak binding to the RARs. These selective binding and transactivation properties distinguish it from other retinoids which either bind selectively to and activate the RARs (e.g., all-*trans*-retinoic acid [ATRA]), or which bind to and activate all six retinoid receptors (e.g., 9-*cis*-RA). By virtue of the selective interaction of bexarotene with the RXRs, bexarotene is thought to have the ability not only to modulate an overlapping, but in addition a distinct set of genetic responses when compared to ATRA.

Bexarotene is also a selective activator of RXR:NR heterodimers. Bexarotene produces only weak activation of the RXR:RARβ, RXR:RARγ, and RXR:VDR heterodimers at high concentrations (>1 μM), and fails to activate either RXR:RARα or RXR:TR. However, heterodimers of RXR:PPARα, RXR:PPARγ, RXR:NGFI-B, RXR:LXR and RXR:PXR are all transcriptionally activated by bexarotene.

Although the activity of bexarotene has not been explored in models of CTCL, studies have demonstrated that bexarotene inhibits the growth of tumor cells, and prevents the formation and causes regression of established mammary tumors in the rat. Bexarotene also induces adipocyte differentiation and acts as an insulin sensitizer in pre-adipocyte cells, by lowering hyperglycemia and hyperinsulinemia in rodent models of non-insulin dependent diabetes (NIDDM). The mechanism of action and the various pharmacological effects of bexarotene are discussed in detail in **Section 5.1.0.** of the NDA submission for Targretin® capsules **(NDA 21-055, Volume 10, pg. 120).**

6.3.2.2. Summary of Nonclinical ADME

The absorption, distribution, metabolism, and excretion of bexarotene have been studied in rats, mice, and dogs. Bexarotene has been administered to these species via topical application (rats), and by oral and/or intravenous (IV) administration. The results of these studies have been presented in detail in **Section 5A** of this submission and in **Section 5.3.0.** of the NDA submission for Targretin® capsules **(NDA 21-055, vol. 42, pg. 001).** A summary of the primary results and conclusions of these studies is presented below:

6.3.2.2.1. Pharmacokinetics following Topical Application

The pharmacokinetics of bexarotene following topical administration was examined in two studies in rats:

In a multiple dose study in male and female Sprague-Dawley rats (RR-845-94-008.a), bexarotene, in an ethanolic gel formulation (^{3}H-labeled bexarotene, 1.0% solution), was applied topically once daily at doses of approximately 120 mg/m^2 (20 mg/kg) to males and 150 mg/m^2 (25 mg/kg) to females (n=6/sex), for 7 days. Pharmacokinetic parameters are presented in **Table 6.3-B.**

Table 6.3-B. Pharmacokinetic Parameters in Male and Female Rats Following Daily Topical Administration of 1.0% Radiolabeled Bexarotene[(1)] for 7 Days (RR-845-94-008.a)

Sex	Dose (mg/m^2)[(1)]	C_{max} (ng/mL)	t_{max} (hr)	AUC_{0-24} (ng·hr/mL)
M	~120	332 ± 181	3.83 ± 4.54	3450 ± 1140
F	~150	55.7 ± 29.8	8.67 ± 13.3	846 ± 348

(1) Formulated as Lot 2LG-89A (1.0% active).
M: male, F: female

Bexarotene showed systemic absorption following topical application. Male rats exhibited increasing daily plasma bexarotene concentrations throughout the study (based on 6-hour monitoring data) and also exhibited greater plasma drug concentrations than female rats.

In another study (RR-815-94-008), bexarotene, in an ethanolic gel formulation (1.0% gel strength), was applied topically to male and female Sprague-Dawley rats once daily at doses of approximately 120 mg/m^2 (20 mg/kg) to males and 150 mg/m^2 (25 mg/kg) to females (n=4/sex), for 28 days. In this study, no overall sex differences were established in plasma concentrations, although in contrast to the 7-day study, a trend toward higher drug exposure was observed in females compared to males (**Table 6.3-C**).

Table 6.3-C. Plasma Bexarotene Concentrations in Male and Female Rats Following Daily Topical Administration of 1.0% Bexarotene[1] for 28 Days (RR-815-94-008)

Day of Sample	Time Point (hr)	Sex	Plasma Bexarotene Concentration Range (ng/mL)
1	6	M	BLQ – 246
		F	BLQ – 397
28	6	M	BLQ – 162
		F	BLQ – 288
	8	M	BLQ – 181
		F	BLQ – 223
	10	M	BLQ – 157
		F	BLQ – 517

[1] 1% Bexarotene formulated in ethanolic gel Lot 2LG-89A (1.0% active).
BLQ = Below Limit of Quantitation (150 ng/mL)
M: male, F: female

The metabolism and excretion of bexarotene following topical application was measured in rats in the 7-day multiple dose study (RR-845-94-008.a). Total feces and urine were collected at the end of each 24-hour period and assessed for radioactivity (^3H content). Radioactivity was present in each daily collection of fecal and urine samples. The radioactivity appearing in the excreta was mainly detected in the feces, with little measurable in urine. The total amount of radioactivity detected in the excreta indicated that a low percentage (<10%) of the applied dose was absorbed into the systemic circulation. Extracts of fecal samples from selected animals were analyzed for metabolites. Of 17 feces samples analyzed radio-chromatographically for metabolite content, 32% to 79% of the total radioactivity existed as bexarotene metabolites with the remainder being bexarotene. In summary, metabolism and excretion data from the 7-day topical pharmacokinetic study indicated that radioactivity from topically-applied radiolabeled bexarotene can be detected in excreta and is mainly contained in feces, as both parent compound and metabolites.

6.3.2.2.2. Pharmacokinetics following Oral and IV Administration

The oral and IV pharmacokinetics of bexarotene have been characterized primarily in Sprague-Dawley rats and in beagle dogs, the toxicology species used for bexarotene. The most pertinent conclusions drawn from the ADME studies conducted in these two species are summarized below:

- The general pharmacokinetics and metabolism of bexarotene are similar in the two species. Mean systemic pharmacokinetic parameters in rats and dogs are summarized in **Table 6.3-D**.

Table 6.3-D. Systemic Pharmacokinetic Parameters for Bexarotene in Sprague-Dawley Rats and Beagle Dogs After Single Intravenous Dose Administration (RR-845093-018.a and RR-845-93-022.a)

PK Parameter	Rat		Dog	
	Male	Female	Male	Female
$t_{1/2}$ (hr)	2.33±0.110	2.83±0.420	5.67±3.47	3.82±1.36
λ_z (hr^{-1})	0.299±0.0140	0.249±0.0395	0.172±0.112	0.206±0.083
CL (mL/min/kg)	16.4±4.39	8.47±0.563	2.78±0.817	3.65±0.90
V_{ss} (L/kg)	1.95±0.0379	1.31±0.0964	0.614±0.314	0.563±0.177

- Bexarotene is orally bioavailable, but bioavailability is dependent on formulation and bexarotene particle size.
- For Targretin® capsules (500 mg/m^2 dose), which contained micronized bexarotene in PEG, absolute bioavailability was 83.1% ± 16% in dogs.
- Absolute bioavailability of nonmicronized bexarotene (600 mg/m^2 dose in sesame oil) in rats was approximately 35%.
- Systemic drug exposure following single oral doses is generally dose-dependent, but is less than proportional to dose at high doses, for both rats and dogs.
- There are no consistent sex differences in bexarotene pharmacokinetics in the two species.
- Repeat dosing leads to induction of oral clearance and a resultant decrease in plasma drug concentrations. The magnitude of this induction of oral clearance is dependent on systemic drug exposure and the induction is generally greater in rats than in dogs.

- Bexarotene is highly protein-bound in plasma (≥99.9%) in rats and dogs.
- Bexarotene (and/or its metabolites) is widely distributed in the tissues of rats following oral dosing. Highest concentrations were measured in the gastrointestinal tract and in organs of elimination (liver, kidney). No substantial retention occurred in any tissue (< 1% radioactivity at 48 hrs).
- Primary oxidative Phase-I bexarotene metabolites in both the rat and the dog are 6- and 7-hydroxy-bexarotene and 6- and 7-oxo-bexarotene, respectively. 6-hydroxy-bexarotene is the major circulating metabolite of bexarotene in rats and dogs.
- Phase-II metabolites formed are products of the conjugation of parent compound and Phase-I metabolites with glucuronic acid, taurine and sulfate. Glucuronides are the most prevalent bexarotene metabolites in bile and feces, with glucuronides of the parent compound predominating in rats and glucuronides of the hydroxy metabolites predominating in dogs.
- Elimination of bexarotene and its metabolites is almost exclusively by the hepatobiliary route with subsequent fecal excretion, with ≤1% of the dose excreted in urine.

6.3.2.2.3. Comparison of Topical and Oral Bexarotene

The systemic exposure of bexarotene following oral administration and topical application was compared in the rat since pharmacokinetic parameters were determined using both routes for this test species.

In study number RR-845-98-007, bexarotene (micronized, in 10% PEG/aqueous CMC) was administered orally to male and female Sprague-Dawley rats at dose levels of 60, 180, and 600 mg/m^2 (10, 30, and 100 mg/kg, respectively) for 15 days. In study number RR-845-94-008.a, bexarotene (in ethanol/PEG, 137:60) was applied dermally to male and female Sprague-Dawley rats at dose levels of ~120 mg/m^2 (~20 mg/kg) and ~150 mg/m^2 (~25 mg/kg), respectively, for 7 days. These studies were chosen for comparison of pharmacokinetics since they represent the most similar exposure (in terms of days of dosing) for oral and topical bexarotene delivery routes. The $AUC_{0\text{-}24}$ values measured in male and female animals in both studies are shown in **Table 6.3-E.**

Table 6.3-E. **Dose-Normalized AUC_{0-24} Parameters in Male and Female Rats Following Daily Oral (Aqueous Suspension) Administration of 60, 180 or 600 mg/m^2 Bexarotene and Topical (1% Ethanolic Gel) Administration of 120 mg/m^2 Bexarotene to Male and Female Sprague-Dawley Rats**

Route	Sex	Dose (mg/m^2)	Dose-Normalized AUC_{0-24}	
			Treatment Day 7	Treatment Day 15
Oral*	M	60	-	491 ± 164
Dermal**		~120	173 ± 57	-
Oral*		180	-	262 ± 100
Oral*		600	-	155 ± 73
Oral*	F	60	-	552 ± 373
Dermal**		~150	34 ± 14	-
Oral*		180	-	363 ± 56
Oral*		600	-	286 ± 66

Values shown above are $AUC_{(0-24h)}$ (nM·hr/µmol/kg)

(1) 7= Multiple doses administered (on Days 1-7 and sampled on Day 7); 15 = Multiple doses administered (on Days 1-15 and sampled on Day 15).

*Study RR-845-98-007

**Study RR-845-94-008.a

The dose normalized systemic exposure of the male rat to bexarotene following dermal application is approximately one half that achieved after oral dosing. In female rats, the AUC_{0-24}/dose value measured following dermal application of 120 mg/m^2 (34 ± 14 nM·hr/µmol/kg) was much less than that measured following oral dosing at 60 mg/m^2 (552 ± 373 nM·hr/µmol/kg). Dose normalized systemic exposure of bexarotene to female rats following dermal application is low compared to that measured following oral administration.

In contrast to the relatively high systemic exposure observed in male rats, very little exposure was observed in humans after topical application of Targretin® gel. Ninety-three percent of bexarotene concentrations in plasma samples measured following topical application of the 1% gel at frequencies ranging from QOD to TID were below 5 ng/mL, and maximum plasma concentrations observed were only about 5% of mean C_{max} values obtained following oral dosing at the recommended dose of Targretin® capsules (300 mg/m^2 QD) (**Section 6.3.3.3.**). Morphologic and

physiologic differences between rat and human skin may account for the higher systemic exposure observed in rats following topical application of bexarotene.

6.3.3. ADME in Humans

This section provides data on the pharmacokinetic disposition of bexarotene in humans.

Section 6.3.3.1 summarizes the pharmacokinetic information available following topical application of Targretin® gel, including:

- The ability of bexarotene to penetrate into skin, studied in a pilot non-clinical study in human cadaver skin
- The strengths and compositions of the different gel formulations used in the clinical studies of Targretin® gel
- The topical pharmacokinetics of bexarotene from a Phase I-II clinical program in patients with CTCL (Studies L1069-94-04T, L1069T-11, and L1069T-12), a Phase III study in patients with CTCL (Study L1069T-25), and a Phase I-II clinical program in HIV-positive patients with KS (Studies L1069-94-03T, L1069T-07, L1069T-08, L1069T-13, and L1069T-15). These clinical data are presented separately by study or program, followed by a combined evaluation of data from all studies. These data demonstrate that:
    - Systemic exposure to bexarotene following topical application of Targretin® gel is low
    - The factors that affect levels of systemic exposure to bexarotene include surface area of treated lesions, CTCL stage, gel strength, and frequency of gel application. This is also discussed in further detail in **Section 6.3.5.**
    - No systemic bexarotene accumulation was observed in spite of long-term application of Targretin® gel
    - Demographic characteristics (age, gender, or race) do not have a statistically significant effect on bexarotene pharmacokinetics following topical application. This is also discussed in further detail in **Sections 6.3.6.1.** to **6.3.6.3.**

- Concomitantly administered CYP3A4 inhibitors or inducers do not show a statistical significant effect of on bexarotene pharmacokinetics following topical application, though an interaction with such drugs is theoretically possible. Concomitantly administered gemfibrozil has the potential to increase bexarotene concentrations. This is also discussed in further detail in **Section 6.3.7.1.**

Section 6.3.3.2. presents supportive pharmacokinetic data from oral administration of Targretin® capsules, obtained from clinical studies in patients with CTCL (Studies L1069-93-01, L1069-23, and L1069-24), patients with advanced cancers (Studies L1069-93-01, L1069-93-02, and L1069-94-02), patients with Type II diabetes mellitus (Study L1069DM-01), and healthy volunteers (Study L1069DM-01). The results from these studies that pertain to topical application are:

- Bexarotene exhibited linear kinetics up to single oral doses of 800 mg/m^2 and up to multiple doses of 230 mg/m^2 QD.
- Bexarotene was rapidly eliminated with an estimated half-life of 1 to 3 hours when determined over a 6-hour sampling interval, and an estimated half-life of 7 to 9 hours when determined over 24-hour sampling interval.
- Bexarotene showed minimal accumulation following multiple once-daily dosing.
- Bexarotene was primarily metabolized to the oxidative metabolites, 6- and 7-oxo-bexarotene and 6- and 7-hydroxy-bexarotene. The metabolism of bexarotene is also discussed in further detail in **Section 6.3.3.4.**
- Urinary excretion of bexarotene and its metabolites was minimal. The urinary excretion of bexarotene is also discussed in further detail in **Section 6.3.3.5.**
- Concomitantly administered gemfibrozil produced elevations in bexarotene concentrations. Concomitantly administered levothyroxine, atorvastatin or CYP3A4 inhibitors do not show a statistical significant effect of on bexarotene pharmacokinetics following oral administration. This is also discussed in further detail in **Section 6.3.7.2.**

Section 6.3.3.3 compares and contrasts bexarotene pharmacokinetics following topical versus oral administration. Systemic concentrations of bexarotene following topical application of Targretin® gel are compared to concentrations obtained at the recommended initial oral dose of Targretin® capsules.

Sections 6.3.3.4 and **6.3.3.5** provide information on the metabolism and excretion of bexarotene. Data on metabolism were obtained from a series of in vitro studies, and ex vivo studies conducted in conjunction with studies of Targretin® capsules (Studies L1069-93-01 and L1069-93-02). Data on excretion was obtained from a Phase II study in patients with Type II diabetes mellitus (Study L1069DM-01).

6.3.3.1. Bexarotene Pharmacokinetics following Topical Application of Targretin® Gel

The ability of bexarotene to penetrate into the skin following application of several solution-, gel-, or ointment-based formulations has been evaluated in a pilot study using human cadaver skin. This study assessed the ability of various bexarotene formulations to penetrate the skin layer. The results of this study are summarized below (**Section 6.3.3.1.1.**).

The formulation of Targretin® gel developed for topical application is a gelled solution (w/w) of bexarotene in a polyethylene glycol (PEG) 400 and dehydrated alcohol base. The various formulations and gel strengths used in the topical clinical studies and their gel strengths are detailed in **Section 6.3.3.1.2.**

The pharmacokinetics of bexarotene has been studied in patients with CTCL and KS following topical application of Targretin® gel. Single-time-point monitoring of bexarotene concentrations was conducted during a Phase I-II program evaluating the safety, tolerance and efficacy of Targretin® gel for the treatment of KS (Studies L1069-94-03T, L1069T-07, L1069T-08, L1069T-13, L1069T-15), during a Phase I-II

program evaluating the safety, tolerance and efficacy of Targretin® gel for the treatment of CTCL (Studies L1069-94-04T, L1069T-11, L1069T-12), and during a Phase III study evaluating the safety, tolerance and efficacy of Targretin® gel for the treatment of CTCL (Study L1069T-25). Bexarotene concentration data from each of these programs were evaluated and analyzed, to determine the pharmacokinetics of bexarotene following topical application. Two approaches for the analysis and interpretation of this sparse sample database were employed:

In the first approach, descriptive statistical measures were used to describe patient demographics and plasma bexarotene concentrations, and the demographics of patients with high plasma bexarotene concentration values were examined to identify characteristics that might be associated with higher plasma bexarotene concentrations. In this approach, no statistical analyses (other than descriptive statistics) were conducted on the plasma bexarotene concentrations. Results from these evaluations for each program (Phase I-II program in patients with CTCL, Phase III study in patients with CTCL, and Phase I-II program in patients with KS) are presented in **Sections 6.3.3.1.3.1.** to **6.3.3.1.3.3.** Additionally, an overall evaluation of bexarotene concentration data from all three programs is presented (**Section 6.3.3.1.3.4.**).

In the second approach, in order to enhance the possibility of detecting significant covariate effects on the pharmacokinetics of bexarotene and reduce potential bias, data from the Phase III study in patients with CTCL, from the Phase I-II program in patients in KS, and the Phase I-II program in patients with CTCL were pooled and subjected to population analyses. The purpose of these analyses was to determine if and how patient exposure to Targretin® gel, patient demographics and concomitant medications correlated with bexarotene plasma concentrations. The methodology and the results of the population analyses are summarized in **Section 6.3.3.1.3.4.**, and are further detailed in **Section 6.3.5.**

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6.3.3.1.3. Pharmacokinetics of Targretin® Gel in Patients with CTCL and KS

6.3.3.1.3.1. Plasma Bexarotene Concentrations Following Topical Application of Targretin® Gel in Phase I-II Studies in Patients with CTCL

Three Phase I-II open-label, multiple-dose, safety and dose-ranging trials (Studies L1069-94-04T, L1069T-11, and L1069T-12) of Targretin® gel were conducted in patients with CTCL (**RR-845-99-005**). The primary clinical objectives of these studies were to determine the safety, dose-tolerance and potential efficacy of bexarotene topical gel and vehicle in the treatment of CTCL. Patients were to have a confirmed diagnosis of CTCL involving up to 50% of body surface area and possess clinically adequate function of all organ systems. Although the characterization of bexarotene topical pharmacokinetics was not a primary objective, blood samples for determination of bexarotene plasma concentrations were obtained. Blood samples were collected pre-dose and every two to four weeks until Week 24 and every four weeks thereafter in order to determine bexarotene plasma concentrations.

Prior to protocol amendment, patients were started on 0.1% QD, and treatments were escalated in concentration and frequency every two weeks from 0.1% QD to 0.1% BID to 0.5% QD to 0.5% BID to 1% QD, and to 1% BID. This escalation of drug exposure was to be interrupted, modified or discontinued if a significant worsening of the cutaneous T-cell lymphoma plaques or treatment-limiting toxicities were observed. After protocol amendment, treatments escalated in frequency every one or two weeks from 1% gel every other day (QOD) to 1% every day (QD) to 1% twice daily (BID) to 1% three times daily (TID) to 1% four times daily (QID), as tolerated. In addition, the vehicle gel was to be applied to at least two lesions at the same frequency as the 1% gel, as tolerated. A total treatment duration of eight weeks was intended, but patients who reached and tolerated the treatment regimen of 1% gel QID were to be allowed to continue at this level of exposure at the discretion of the investigator.

A total of 67 patients participated in the studies, conducted at different study sites. Sixty-six of the 67 patients enrolled had blood samples collected for pharmacokinetic evaluation. Pharmacokinetic patients had a mean age of 57.6 years (median 60; range 30 – 87), a mean weight of 85.2 kg (median 83.8; range 50.4 - 162), a mean height of 172 cm (median 173; range 147 – 196), and a mean calculated total body surface area (BSA) of 2.02 m^2 (median 2.02; range 1.49 – 2.89). Thirty-six pharmacokinetic patients were male and 30 were female; and 56 patients were White, 8 were Black, and 2 were Asian.

Patients from the Phase I-II CTCL program were not graded according to TNM (Tumor, Node Metastases) staging, but were graded according to an alternate CTCL staging system. Consequently, the following algorithm was used to retrospectively convert staging of Phase I-II patients to TNM staging: Stage was IA, if CTCL stage was 1, and if the surface area of lesions was lower than 10% of total BSA; Stage was IB, if CTCL stage was 1, and if the surface area of lesions was 10% or higher than 10% of total BSA; and Stage was IIA, if CTCL stage was 2. Based on this staging, 42 pharmacokinetic patients were graded as Stage IA, 18 patients as Stage IB, and 6 patients as Stage IIA. Patients had lesions covering an average of 10.9% of their total BSA (median 5.0; range 0.1 – 50). Based on the definitions of disease stage, mean (± SD) treated BSA generally increased with increasing disease stage, being 3.6% ± 2.3% for Stage IA patients, 23.8% ± 12.8% for Stage IB patients, and 22.8% ± 17.9% for Stage IIA patients.

Patients were exposed to escalating frequencies of dosage and gel strengths (0.1, 0.5, and 1.0 %) during the course of the studies. On at least one occasion, 48 pharmacokinetic patients applied the 0.1% gel strength (QD and/or BID), 45 patients applied the 0.5% gel strength (QOD, QD, and/or BID), and 54 patients applied the 1% proposed marketed gel formulation (QOD, QD, BID, TID, and/or

QID). During the 1% gel application, blood samples were collected from eight patients who were receiving Targretin® gel QOD, 48 patients being treated QD, 38 patients being treated BID, 17 being treated TID, and one patient being treated QID.

A total of 965 blood samples (62 pre-dose and 903 post-dose samples) from 66 patients, representing a treatment duration of up to 135 weeks, were collected for determination of plasma bexarotene concentrations. Of the 965 samples, 963 samples were analyzed as two of the collected post-dose samples had insufficient volume for concentration determination. Forty-two of the 66 pharmacokinetic patients had at least one post-dose bexarotene concentration that was quantifiable.

Systemic concentrations of bexarotene were low following topical application of Targretin® gel. Of the 901 post-dose samples analyzed, 711 samples (79%) were found to have bexarotene concentration below the limit of quantification of the assay used for bexarotene determination (1 ng/mL). Of the 190 post-dose samples with quantifiable concentrations, 155 concentrations were <5 ng/mL, 15 concentrations were ≥5 ng/mL, but <10 ng/mL, 11 concentrations were ≥10 ng/mL, but <15 ng/mL, three concentrations were ≥15 ng/mL, but <20 ng/mL, and six concentrations were ≥20 ng/mL (**Figure 6.3-B**).

The highest plasma concentrations tended to be observed within 12 hr of gel application, and lower concentrations were generally observed at later time points. Plasma bexarotene concentrations as a function of time post-dose are summarized in **Table 6.3-G** and are plotted by gel strength in **Figure 6.3-C**. The time interval between last application of Targretin® gel and blood collection was available for 874 of the 963 assayed blood samples (90.8%). Only five of 86 blood samples collected at ≥48 hr post-dose exhibited quantifiable bexarotene concentrations, and these concentrations were generally low.

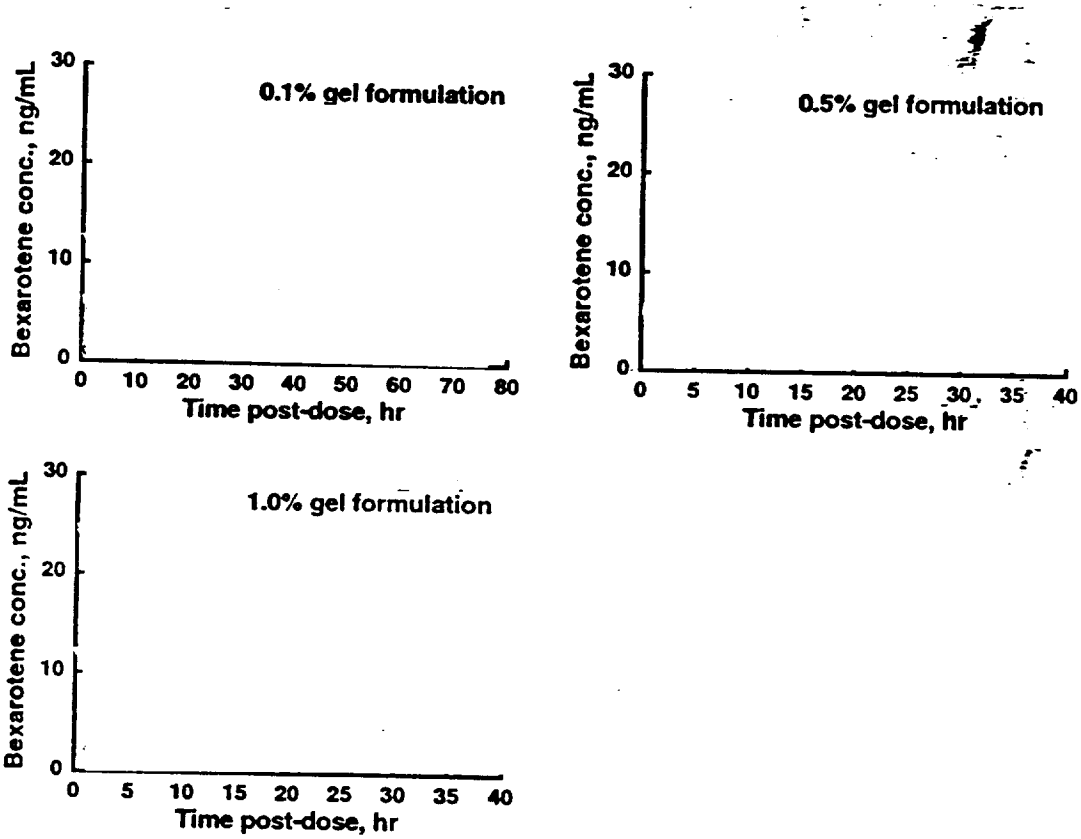
Table 6.3-G. Distribution of Bexarotene Plasma Concentrations per Time Interval in Patients Participating in the Phase I-II CTCL Program (Studies L1069-94-04T, L1069T-11, and L1069T-12)

Time post-dose	Number of Samples	N (%) Quantifiable Samples [1]	Bexarotene Concentration (ng/mL)		
			Mean ± SD	Median	Range
Pre-dose	62	0	0	0	N/A
T < 4 hr	166	41 (24.7)	1.02 ± 3.20	0	0 – 23.52
4 ≤ T < 8 hr	243	74 (30.5)	1.10 ± 2.86	0	0 – 24.04
8 ≤ T < 12 hr	113	25 (22.1)	1.19 ± 3.51	0	0 – 24.17
12 ≤ T < 16 hr	138	22 (15.9)	0.514 ± 1.819	0	0 – 13.65
16 ≤ T < 20 hr	73	10 (13.7)	0.256 ± 0.745	0	0 – 4.24
20 ≤ T < 24 hr	10	2 (20.0)	0.894 ± 2.362	0	0 – 7.49
24 ≤ T < 48 hr	43	4 (9.3)	0.567 ± 2.243	0	0 – 11.14
48 ≤ T < 72 hr	10	1 (10.0)	0.713 ± 2.255	0	0 – 7.13
72 ≤ T < 96 hr	6	0	0	0	N/A
T ≥ 96 hr	70	4 (5.7)	0.494 ± 3.348	0	0 – 27.78
Total Post-dose	872	183 (21.0%)	0.842 ± 2.778	0	0 – 27.78

[1] Percentage based on the number of samples within each time interval.

Notes: Table entries are the number of samples collected within each time interval that have complete dosing and sampling information. Twenty-nine samples taken post-dose (after Week 1) did not have complete dosing and sampling information to calculate a post-dose time. Additionally, two samples that had insufficient volume for bexarotene determination are not included in this table.

Figure 6.3-C. Pooled Plasma Bexarotene Concentrations Obtained from Post-Dose Samples Collected in the Phase I-II CTCL Program (Studies L1069-94-04T, L1069T-11, and L1069T-12)



Notes: Only plasma bexarotene concentrations measured in samples with known post-dose and gel formulation strength values are displayed in the figure. Bexarotene concentrations obtained in four samples collected more than 96 hr after Targretin® gel application are not plotted in the figure.

Only three patients (in Study L1069T-11) had bexarotene concentrations ≥20 ng/mL in the Phase I-II CTCL studies: One patient (Patient 611; 46-year-old White male) had a bexarotene concentration of 27.78 ng/mL at Week 88, which, based on dosing data available, appeared to be measured at 137 hours post last dose. Except for a low concentration of 1.39 ng/mL at Week 4, this patient had no quantifiable concentrations in the 25 samples collected prior to the Week 88 reading. Furthermore, bexarotene concentrations in six samples collected in the six months following this measurement were not quantifiable. Patient 611 did not take any potential concomitant medications that could have altered the pharmacokinetics of

bexarotene. Due to uncertainty about the accurate recording of the date and time of the last dosing for this sample, it was excluded from the population pharmacokinetic analyses. Patient 620 (36-year-old Black female) had a concentration of 20.9 ng/mL at Week 92, measured 2.7 hours from last dose. Bexarotene concentrations in 24 samples collected prior to Week 92 for this patient did not exceed 9 ng/mL and this patient was not taking any concomitant medications that could potentially interact with bexarotene. Patient 625 (49-year-old White male) had three concentrations above 20 ng/mL (Week 36, 21.6 ng/mL; Week 56, 23.52 ng/mL; and Week 60, 24.17 ng/mL) for blood samples drawn within 10 hours from last dose. This patient showed relatively high concentrations throughout the study (mean 10.74 ng/mL), relative to the <5 ng/mL concentrations observed for other patients. He was documented as having taken gemfibrozil throughout the duration of the study, which may have contributed to the higher concentrations seen. Though the highest concentrations observed in the Phase I-II CTCL program was measured in these patients, these plasma concentrations were only about 2 - 3% of mean C_{max} values obtained following oral dosing at the intended dose of Targretin® capsules (300 mg/m^2 QD) for treatment of CTCL.

Several patients took systemic concomitant medications with Targretin® gel that were considered to have the potential to affect the pharmacokinetics of bexarotene (CYP3A4 inducers or inhibitors, or gemfibrozil; **Section 6.3.7.**). Thirteen patients took a concomitant medication known to be an inhibitor of CYP3A4, and three patients took concomitant gemfibrozil during the time of pharmacokinetic blood sampling in the Phase I-II CTCL studies. The CYP3A4 inhibitors taken by patients included erythromycin, fluconazole, omeprazole, ketoconazole, clarithromycin, paroxetine, and sertraline. No patient took a CYP3A4 inducer concurrently with blood sampling. In the majority of the patients who took CYP3A4 inhibitors, the associated bexarotene concentration was below the lower quantitation limit. Only three of 65 samples (4.6%) had a quantifiable bexarotene plasma concentration when concomitant CYP3A4 inhibitors were being taken and, in all three cases, prior and posterior concentrations (also during concomitant administration of CYP3A4-

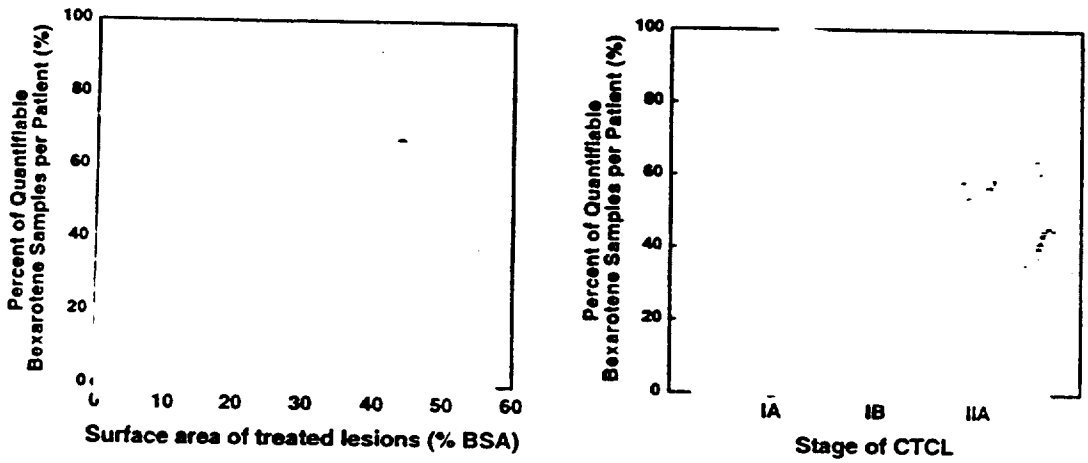
inhibitors) did not achieve quantifiable bexarotene levels. Therefore, concomitant administration of CYP3A4 inhibitors did not appear to increase bexarotene concentrations following application of Targretin® gel.

Three patients (Patient 609 and 625 in Study L1069T-11, and Patient 612 in Study L1069T-12) took gemfibrozil in concomitance with Targretin® gel. Patient 609 took gemfibrozil (600 mg BID PO) during a large part of the study (Week 6 to 64 and Week 88 to 132) to control hyperlipidemia. While on gemfibrozil, bexarotene concentrations in this patient did not exceed 3.5 ng/mL and more than half of the concentrations measured were below LLQ. Patient 612 was taking gemfibrozil (300 mg BID PO) at enrollment and continued on this medication throughout the study. Of the two blood samples taken within 24 hours of dosing, both had quantifiable bexarotene concentrations (2.15 and 2.51 ng/mL). Only one patient (Patient 625), who took gemfibrozil (600 mg BID PO) throughout the study (74 weeks), had elevated bexarotene levels relative to other patients (average of 11 ng/mL, range of BLQ-24.17 ng/mL, of which 89% of samples [17/19] were above LLQ). However, this effect was not observed in the other patients on concomitant gemfibrozil.

The influence of various demographic, disease, dosing, and baseline laboratory covariates, and systemically administered concomitant medications on bexarotene pharmacokinetics was examined in a cross-study population pharmacokinetic analysis, performed on pooled single-time-point concentration data from patients with CTCL and KS. The methodology and results of these analyses are discussed in detail in **Section 6.3.5** of this submission. Briefly, the results indicated that bexarotene plasma concentrations correlated positively with surface area of treated lesions (which correlates with CTCL stage), gel strength used, and the frequency of application. These results are in agreement with results of the evaluation of bexarotene concentration data in this Phase I-II program, which showed an increase in the percent of quantifiable bexarotene concentrations >1 ng/mL per patient, with

increasing surface area of treated lesions or advancing stage of CTCL (**Figure 6.3-D**).

Figure 6.3-D. Distribution of Samples with Bexarotene Plasma Concentrations Above 1 ng/mL (expressed as % per patient) as a Function of Surface Area of Treated Lesions and CTCL Stage in Patients Participating in the Phase I-II CTCL Program (Protocols L1069-94-04T, L1069T-11, and L1069T-12)



Notes: The line in the left panel is the linear regression line through the plotted data. Horizontal lines in the right panel are the mean percentages of samples with measurable concentrations for each CTCL stage.

6.3.3.1.3.2. Plasma Bexarotene Concentrations Following Topical Application of Targretin® Gel in a Phase III Study in Patients with CTCL

A Phase III trial (Study L1069T-25) of Targretin® gel 1% was conducted in patients with refractory or persistent early stage CTCL (**RR-845-99-004**). Patients were to have had a biopsy-confirmed diagnosis of CTCL (Stage IA, IB, or IIA); be refractory to, intolerant to, or have reached a response plateau for at least six months on at least two specified prior therapies; have a Karnofsky performance score ≥ 60; be free of serious concurrent illness; and possess clinically adequate function of all organ systems. The primary (clinical) objective of this study was to evaluate the safety, tolerability and efficacy (anti-tumor effects) of Targretin® gel 1% applied topically to cutaneous CTCL lesions. The secondary (pharmacokinetic) objective of

this study was to evaluate the systemic exposure and the pharmacokinetics of bexarotene following repeat application of Targretin® gel 1%.

Patients began treatment with Targretin® gel 1% applied topically once every other day (QOD). The frequency of application was escalated at one week intervals to once daily (QD), then twice daily (BID), then three times daily (TID) and then four times daily (QID), as tolerated. The frequency of application could be adjusted for toxicity. Treatment was intended for a minimum of 16 weeks. Treatment could be continued beyond 16 weeks for any patient as long as the study remained open and active, the investigator believed the treatment to be of potential benefit to the patient, and no unacceptable toxicity occurred. Although all lesions were to be treated, up to five lesions, representative of the overall extent of cutaneous disease, were to be selected as index lesions. Patients were evaluated at pretreatment (within 14 days of initiation of therapy), baseline (Day 1), every two weeks until Week 4, and every four weeks thereafter for the duration of treatment. A follow-up evaluation was to be performed at least four weeks after discontinuation of therapy.

A total of 50 patients participated in the study, of which thirty-eight patients had single-time-point blood samples collected for pharmacokinetic evaluation. Most of the pharmacokinetic patients were graded Stage IA (n=21) or IB (n=15), with one patient each graded as IIA and IIB. In pharmacokinetic patients, an average of 7.7 lesions (median 8; range 2 - 16), covering an average of 15.8% of the total BSA (median 8.5; range 0.9 – 90), were treated with Targretin® gel. In general, mean (±SD) treated BSA increased with increasing disease stage, being 4.4% ± 3.9% for Stage IA patients, and 28.2% ± 25.3% for Stage IB patients. The body surface area of treated lesions was 50.0% for the single Stage IIA patient, and 14.0% for the single Stage IIB patient. Patients had a mean age of 61.3 years (median 63; range 13 – 85), a mean weight of 82.1 kg (median 79; range 41.8 – 145.9), a mean height of 171 cm (median 170; range 150 – 193), and a mean calculated total body surface area (BSA) of 1.97 m^2 (median 1.96; range 1.33 - 2.67). Eighteen pharmacokinetic patients were male and 20 were female, and 30 patients were White and 8 were

Black. Blood samples were collected at predose (Day 1), Week 2, Week 4, and every four weeks thereafter for the duration of treatment. Plasma concentrations of bexarotene were determined using an [redacted] **(Section 6.3.8.2.)**.

A total of 301 blood samples, representing a treatment duration of up to 100 weeks, were obtained from 38 patients at 17 study sites for the determination of plasma bexarotene concentrations. All 38 patients received the 1% gel formulation. Patients were exposed to escalating frequencies of dosage during the course of the study. Blood samples were collected from 11 patients while receiving Targretin® gel QOD, 23 patients while treated QD, 20 patients while treated BID, 22 patients while treated TID, and 21 patients while treated QID. Thirty-five of the 38 pharmacokinetic patients had at least one bexarotene concentration that was quantifiable. Of the 301 samples collected, 34 samples were collected prior to Targretin® gel application, and 267 samples were collected post-dose. The time interval between last application of Targretin® gel and blood collection was available for 240 of the 267 post-dose blood samples.

The highest plasma concentrations tended to be observed within 12 hr of gel application, and lower concentrations were generally observed at later time points. Blood collection occurred within 24 hr of the last gel application for 195 of the 240 samples (81.3%), of which the majority of samples were obtained over a time period of 0-8 hours following dosing (n=131), where concentrations would be expected to be maximum **(Table 6.3-H** and **Figure 6.3-E)**.

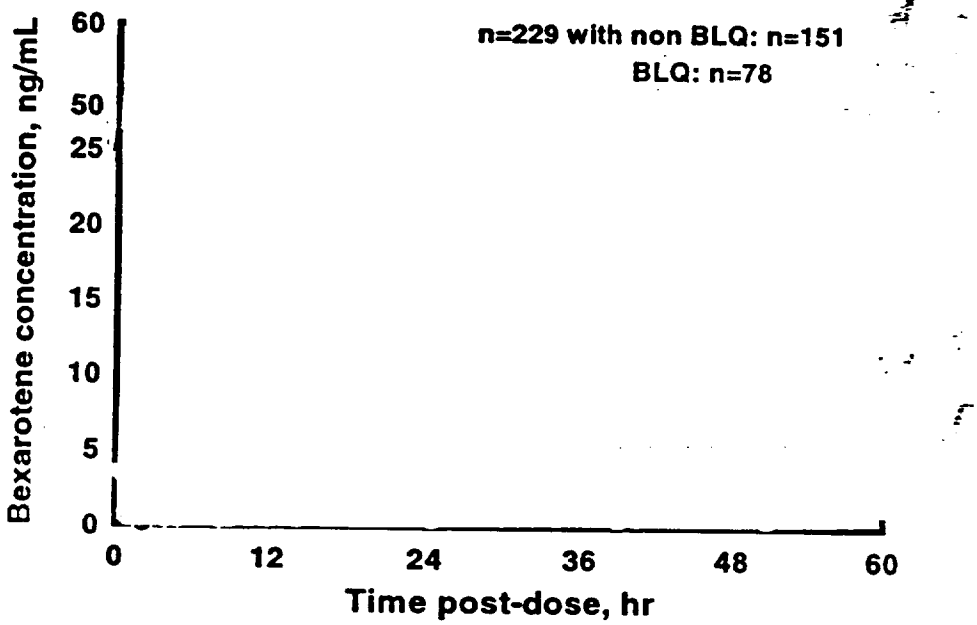
Table 6.3-H. Distribution of Bexarotene Plasma Concentrations per Time Interval in Patients Participating in Study L1069T-25

Time post-dose	Number of Samples	N (%) Quantifiable Samples [1]	Bexarotene Concentration (ng/mL)		
			Mean ± SD	Median	Range
Pre-dose	34	6 (17.7%)	0.168 ± 0.399	0	0 – 1.460
T < 4 hr	90	55 (61.1%)	2.10 ± 3.59	0.865	0 – 21.600
4 ≤ T < 8 hr	41	28 (68.3%)	4.05 ± 9.07	1.15	0 – 54.900
8 ≤ T < 12 hr	20	17 (85.0%)	1.65 ± 1.61	1.10	0 – 6.150
12 ≤ T < 16 hr	28	24 (85.7%)	2.53 ± 3.17	1.39	0 – 11.983
16 ≤ T < 20 hr	9	4 (44.4%)	1.21 ± 1.55	0	0 – 3.794
20 ≤ T < 24 hr	7	3 (42.9%)	0.814 ± 1.099	0	0 – 2.504
24 ≤ T < 48 hr	29	18 (62.1%)	1.32 ± 1.92	0.739	0 – 8.985
48 ≤ T < 72 hr	3	2 (66.7%)	0.595 ± 0.582	0.621	0 – 1.164
72 ≤ T < 96 hr	2	0 (0.0%)	0	0	N/A
T ≥ 96 hr	11	5 (45.5%)	0.899 ± 1.256	0	0 – 4.004
Total Post-dose	240	156 (65.0%)	2.19 ± 4.64	0.899	0 – 54.900

[1] Percentage based on the number of samples (n) within each time interval.

Note: Table entries are the number of samples collected within each time interval that have complete dosing and sampling information.

Figure 6.3-E. Pooled Plasma Bexarotene Concentrations Obtained from Samples Collected in Patients Participating in Study L1069T-25

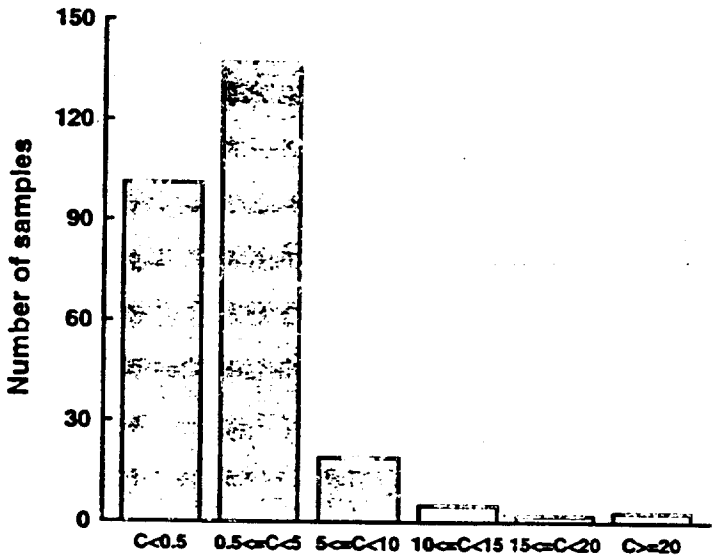


Note: Only plasma bexarotene concentrations measured in samples with known post-dose values are displayed in the figure. Any bexarotene concentrations obtained in the 11 plasma samples collected more than 96 hr after Targretin® gel application were not evaluated in the population analysis and are not plotted in this figure.

Systemic concentrations of bexarotene were low following topical application of Targretin® gel. Of the 267 post-dose blood samples collected, 101 samples (38%) had concentrations below the assay lower limit of quantitation (<0.5 ng/mL) and 166 samples (62%) had quantifiable plasma concentrations. Of the 166 post-dose samples with quantifiable concentrations, 137 concentrations were <5 ng/mL, 19 were ≥5 ng/mL but <10 ng/mL, five were ≥10 ng/mL but <15 ng/mL, two were ≥15 ng/mL but <20 ng/mL, and three were higher than 20 ng/mL (**Figure 6.3-F**).

As evidenced by the generally low and sporadically-detectable plasma bexarotene concentrations, bexarotene showed minimal accumulation despite long-term application of gel for up to 100 weeks, over a lesion area that covered up to 90% of total body surface area.

Figure 6.3-F. Distribution of the Bexarotene Plasma Concentrations in Samples Collected from Patients Participating in Study L1069T-25



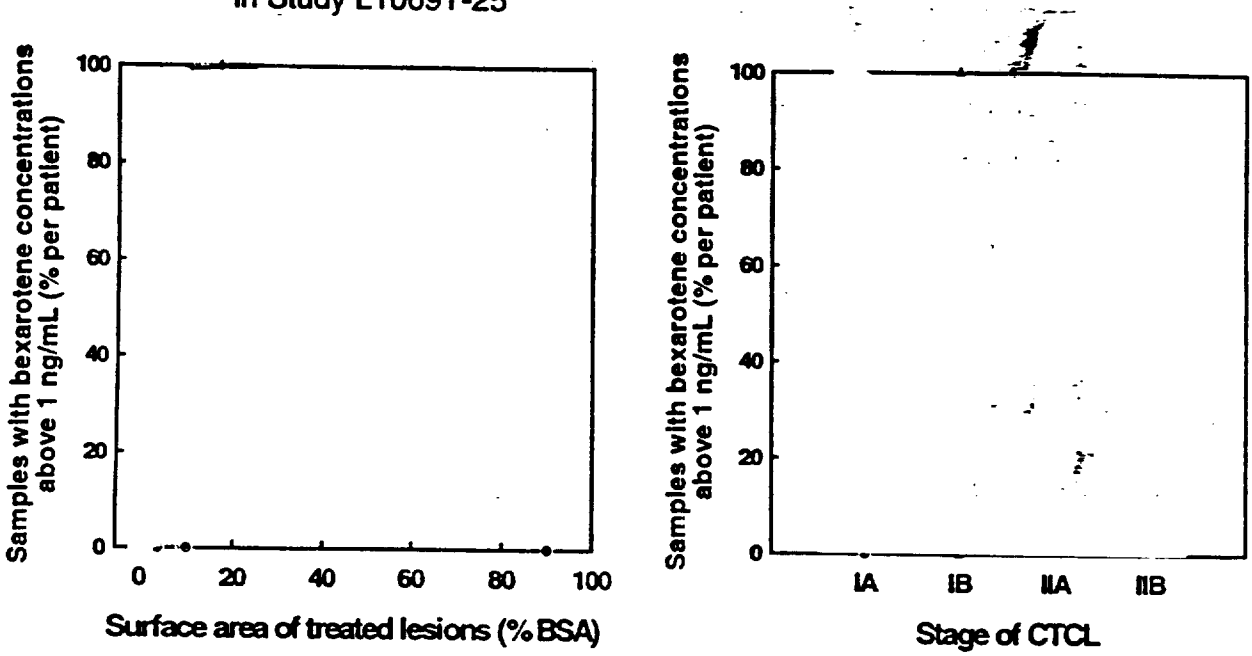
While the majority of plasma bexarotene concentrations were low, a few higher concentrations of bexarotene were observed. All three of the samples with concentrations over 20 ng/mL (21.6, 47.1, and 54.9 ng/mL) were observed in one patient (Patient 744) with Stage IB CTCL, who had treated lesions over 45% of her total body surface area. This patient started applying Targretin® gel TID as early as Week 4, and apparently applied an inordinately large amount of Targretin® gel 1% over the course of the study, as evidenced by the large number of gel tubes dispensed to this patient (90 tubes were dispensed to this patient at Week 16, the study period during which the high concentrations were observed, compared to a maximum of 17 tubes to other patients at any study visit). This patient is considered to be uncharacteristic of the population to be treated, in terms of both usage and

exposure. These plasma concentrations were only about 4 - 5% of mean C_{max} values obtained following oral dosing (300 mg/m^2 QD) with Targretin® capsules at the initial recommended dose for treatment of CTCL.

Based on limited data, no apparent relationship was observed between administration of concomitant CYP3A4 inducers or inhibitors and bexarotene concentrations. Three patients took an inhibitor of CYP3A4, including clarithromycin (Patient 741 for two courses of 11 and 25 days), fluconazole (Patient 891 for three days), and metronidazole (Patient 621 for 13 days). Plasma bexarotene concentrations in these patients were not elevated relative to concentrations in patients not receiving concomitant CYP3A4 inhibitors. Patient 622 took two inducers of CYP3A4 during the duration of the study (carbamazepine and phenytoin). No patient took gemfibrozil concomitantly with Targretin® gel. CYP3A4 inducers and inhibitors, and gemfibrozil are medications that are considered to have the potential to affect the pharmacokinetics of bexarotene with Targretin® gel when administered systemically (**Section 6.3.7.**).

The influence of various demographic, disease, dosing, and baseline laboratory covariates, and systemically administered concomitant medications on bexarotene pharmacokinetics was examined in a cross-study population pharmacokinetic analysis, performed on pooled single-time-point concentration data from patients with CTCL and KS. The methodology and results of these analyses are discussed in detail in **Section 6.3.5.** of this submission. Briefly, the results indicated that bexarotene plasma concentrations correlated with surface area of treated lesions (which correlates with CTCL stage), gel strength used, and the frequency of application. These results are in agreement with results of the evaluation of bexarotene concentration data in this Phase III study, which showed an increase in the percent of quantifiable bexarotene concentrations >1 ng/mL per patient, with increasing surface area of treated lesions or advancing stage of CTCL (**Figure 6.3-G**).

Figure 6.3-G. Distribution of Samples with Bexarotene Plasma Concentration above 1 ng/mL (expressed as % per patient) as a Function Surface Area of Treated Lesions and CTCL Stage in Patients Participating in Study L1069T-25



Notes: Horizontal lines in the right panel are the mean percentages of samples with measurable concentrations for each CTCL stage.

6.3.3.1.3.3. Plasma Bexarotene Concentrations Following Topical Application of Targretin® Gel in Phase I-II Studies in Patients with KS

Five Phase I-II open-label, controlled, multiple-dose trials (Studies L1069-94-03T, L1069T-07, L1069T-08, L1069T-13, and L1069T-15) of Targretin® gel (0.5% or 1%, applied QD, BID, TID, or QID) were conducted in HIV-positive patients with AIDS-related cutaneous KS (**RR-845-99-006**). The primary clinical objectives of these studies were to determine the safety, cutaneous tolerance and efficacy (anti-tumor effects) of bexarotene topical gel in the treatment of cutaneous lesions of KS. Patients were to have a biopsy-proven diagnosis of KS and confirmed serum HIV antibody; a Karnofsky score ≥ 60; acceptable organ function and no concurrent serious active infections. As a secondary objective, blood samples were obtained for characterization of bexarotene topical pharmacokinetics.

Patients were equally (1:1) randomized to treatment with either the 0.5% or 1% (w/w) Targretin® gel topical formulation. Clinical evaluation of topical Targretin® gel was to be performed on 'index' KS lesions using each patient's baseline evaluation for comparison, as well as two lesions that remained untreated (control lesions), over a 16-week period. The initial treatment period was four weeks. During the first two weeks, the patients were to be instructed to apply the treatment twice each day (BID) to the index KS lesions to be treated. Starting with, but not until, the second 2-week period, patients were to be instructed to apply the treatment four times each day (QID). Patients were to continue treatment in 4-week increments if treatment was judged by the investigator to be of clinical benefit to the patient and no unacceptable toxicity was manifested. Additionally, QD and TID regimens and escalation of gel strength were available options for escalation or reduction of dosing frequency, depending on individual patient tolerance. Each study was planned to treat up to 36 patients. Blood samples were collected at the end of two and four weeks of therapy (Days 15 and 29) and every two to four weeks thereafter for patients who continued beyond the initial four weeks of treatment.

A total of 78 male patients participated in the studies, conducted at different study sites, of which 45 patients had blood samples collected for pharmacokinetic evaluation. Pharmacokinetic patients had an average of 4.7 lesions (median 4; range 1-10) treated with Targretin® gel, which covered an average of 0.2% of their total BSA (median 0.1; range 0.01 – 1.4). Patients had a mean age of 40.7 years (median 40; range 23 – 53), a mean weight of 73.4 kg (median 71.6; range 54.5 – 95.7), a mean height of 178 cm (median 178; range 163 – 191), and a mean calculated total body surface area (BSA) of 1.91 m^2 (median 1.89; range 1.62 – 2.24). Forty-one patients were White, 1 was Black, and 3 were Asian. Plasma bexarotene concentrations were determined by(

The

The 45 patients who had blood collected were exposed to escalating frequencies of dosage and gel strengths. Twenty-two patients applied the 0.5% strength formulation gel, and 37 patients received the 1% strength formulation gel over the course of the studies. Blood samples were collected from 11 patients while receiving Targretin® gel QOD, 23 patients while treated QD, 20 patients while treated BID, 22 patients while treated TID, and 21 patients while treated QID.

Bexarotene showed no or minimal systemic exposure and accumulation despite long-term application of Targretin® gel for up to 80 weeks. A total of 303 post-dose blood samples, collected from 45 patients, were assayed for bexarotene plasma concentrations, of which 297 samples (98%) had a bexarotene concentration below the assay limit of quantification (LLQ of 1 ng/mL). Of the 6 quantifiable samples, all were obtained from one patient (patient 605, Study L1069T-13), and concentrations in these samples were lower than 10 ng/mL (

The time of blood collection relative to the last application of Targretin® gel was available for 284 of the 303 blood samples (93.7%) (**Table 6.3-I**). Blood collection occurred within 24 hr of the last gel application for 266 of the 284 samples (93.7%). A total of 18 blood samples were drawn more than 24 hr post-dose, all of which had bexarotene plasma concentrations below the limit of quantification.

Table 6.3-I. Distribution of Bexarotene Plasma Concentrations per Time Interval in Patients with AIDS-Related KS Participating in Studies L1069-94-03T, L1069T-07, L1069T-08, L1069T-13, and L1069T-15

Time post-dose	Number of Samples	N (%) Quantifiable Samples [1]	Bexarotene Concentration (ng/mL)		
			Mean ± SD	Median	Range
Pre-dose	0	0 (0.0%)	N/A	N/A	N/A
T < 4 hr	144	5 (3.5%)	0.106 ± 0.704	0	0 – 7.44
4 ≤ T < 8 hr	36	1 (2.8%)	0.0497 ± 0.298	0	0 – 1.79
8 ≤ T < 12 hr	39	0 (0.0%)	0	0	N/A
12 ≤ T < 16 hr	26	0 (0.0%)	0	0	N/A
16 ≤ T < 20 hr	18	0 (0.0%)	0	0	N/A
20 ≤ T < 24 hr	3	0 (0.0%)	0	0	N/A
24 ≤ T < 48 hr	1	0 (0.0%)	0	0	N/A
48 ≤ T < 72 hr	2	0 (0.0%)	0	0	N/A
72 ≤ T < 96 hr	4	0 (0.0%)	0	0	N/A
T ≥ 96 hr	11	0 (0.0%)	0	0	N/A
Total Post-dose	284	6 (2.1%)	0.0600 ± 0.5139	0	

[1] Percentage based on the number of samples within each time interval.
N/A – not applicable

Patient 605 (Study L1069T-13), in whom the six quantifiable concentrations were measured, was a 36 year old White male of average height (180 cm) and weight (69.3 kg), who received Targretin® gel 0.5% up to week 6 (BID followed by TID) and then switched to 1% gel for the remainder of the study (BID followed by TID). In comparison to the mean number of lesions treated in the Phase I-II KS program (4.69 ± 2.66), Patient 605 treated a total of eight lesions which covered 0.09% of his total BSA (compared to a mean total treated BSA of 0.21% in the Phase I-II KS program). The patient was compliant with prescribed Targretin® gel therapy, and took the following concomitant medications of interest systemically during the study: one CYP3A4 inhibitor (fluconazole) and one CYP3A4 inducer (rifabutin) throughout the course of the study, one CYP3A4 inhibitor (indinavir) from Week 6 through the end of the study, and one CYP3A4 inhibitor (nefazadone) from Week 16 through the end of the study. The six quantifiable concentrations obtained from this patient were measured within 1.5 to 4.3 hours post-dose. One concentration (1.6 ng/mL) was measured 1.5 hours following administration of the 0.5% gel strength, and the remaining measurable concentrations were observed following application of the 1%

gel strength, with the highest plasma concentration (7.4 ng/mL) being observed 1.5 hours following application of the 1% gel strength. The reason why this single patient in the KS program had quantifiable concentrations could not be determined.

No apparent relationship was observed between administration of concomitant CYP3A4 inducers, CYP3A4 inhibitors, or gemfibrozil and bexarotene concentrations. Thirty-four patients were reported to have taken at least at least one such medication systemically, in concomitance with Targretin® gel at some time during the study. Of these 34 patients, 27 patients took at least one CYP3A4 inhibitor, 11 patients took at least one CYP3A4 inducer, and one patient took gemfibrozil. Four patients took a combination of both CYP3A4 inducers and inhibitors. Despite the large number of patients on concomitant medications (27 patients [60%] on CYP3A4 inhibitors), the majority of plasma concentrations (98%) were not quantifiable, indicating that drug-drug interactions are unlikely.

The influence of various demographic, disease, dosing, and baseline laboratory covariates, and systemically administered concomitant medications on bexarotene pharmacokinetics was examined in a cross-study population pharmacokinetic analysis, performed on pooled single-time-point concentration data from patients with CTCL and KS. The methodology and results of these analyses are discussed in detail in **Section 6.3.5** of this submission. Briefly, the results indicated that bexarotene plasma concentrations correlated with surface area of treated lesions, gel strength used, and the frequency of application. The results of the population analyses are consistent with results of the evaluation of individual bexarotene concentration data in this Phase I-II KS program.

6.3.3.1.3.4. Plasma Bexarotene Concentrations Following Topical Application of Targretin® Gel – Combined Assessment of Data from Studies in Patients with CTCL and KS

Data from the Phase I-II studies in patients with CTCL (Studies L1069-94-04T, L1069T-11, and L1069T-12), the Phase III study in patients with CTCL (Study L1069T-25), and the Phase I-II studies in patients with KS (Studies L1069-94-03T, L1069T-07, L1069T-08, L1069T-13, and L1069T-15) were pooled and subjected to cross-study statistical and pharmacokinetic population analyses. The pooled database included pharmacokinetic data from 149 patients. Demographic and baseline characteristics of patients in this database and the results of the population analyses are discussed in detail in **Section 6.3.5.** However, the results of these population analyses as well as a descriptive evaluation of individual bexarotene concentration data in the pooled database are summarized below.

Systemic concentrations of bexarotene were low following topical application of Targretin® gel. Plasma bexarotene concentrations were quantifiable in only 362 (24.6%) of the 1471 post-dose blood samples collected and assayed in these 149 pharmacokinetic patients across all gel strengths, and 297 of the 362 (82%) post-dose plasma samples had bexarotene concentrations lower than 5 ng/mL. When bexarotene concentrations were evaluated for Targretin® gel 1% alone (from the Phase I-II CTCL program and Phase III CTCL study), plasma bexarotene concentrations were quantifiable in only 300 (37.2%) of the 807 post-dose blood samples collected and assayed. Of the 300 post-dose plasma samples with quantifiable concentrations, 245 had bexarotene concentrations lower than 5 ng/mL, 28 were ≥5 ng/mL but <10 ng/mL, 13 were ≥10 ng/mL but <15 ng/mL, five were ≥15 ng/mL but <20 ng/mL, and only nine were higher than 20 ng/mL.

The magnitude of bexarotene plasma concentrations appeared to depend, at least in part, on the strength of Targretin® gel applied. Most of the non-quantifiable post-dose plasma concentrations were encountered in the Phase I-II KS and CTCL programs, in which patients were exposed to the lower Targretin® gel strengths of

0.1% and 0.5%, and in which a less sensitive assay was used (LLQ was 1 ng/mL in the Phase I-II KS and CTCL programs, relative to an LLQ of 0.5 ng/mL in the Phase III study). In the Phase III L1069T-25 study in which Targretin® gel 1% was used exclusively, 46.1% of samples had post-dose concentrations >1 ng/mL compared to 21.1% of samples in the Phase I-II CTCL program and 2.0% in the Phase I-II KS program).

The highest plasma concentrations tended to be observed within 12 hr of gel application, with lower concentrations generally observed at later timepoints. For samples where the time interval between the last application of Targretin® gel and blood collection was available (1398 of 1569 [89.1%] samples, across all gel strengths), blood collection generally occurred within 24 hr of the last application of Targretin® gel (1206 of 1398 samples; 86.3%). The majority of samples were obtained during the time period 0-8 hr, where concentrations would be expected to be maximal (n=721).

Minimal accumulation of bexarotene was observed despite long-term application of gel for up to 135 weeks over a lesion area of up to 90% of total body surface area. Ninety-six percent of bexarotene concentrations, measured across all gel strengths, were below 5 ng/mL. Additionally, of a total of 92 samples collected at late time points (from 96 hrs up to 28 days post dose), 83 had bexarotene plasma concentrations below the limit of quantification, indicating a lack of drug accumulation. The remaining nine plasma samples had low bexarotene levels that averaged 4.94 ± 8.63 ng/mL (median = 1.54 ng/mL).

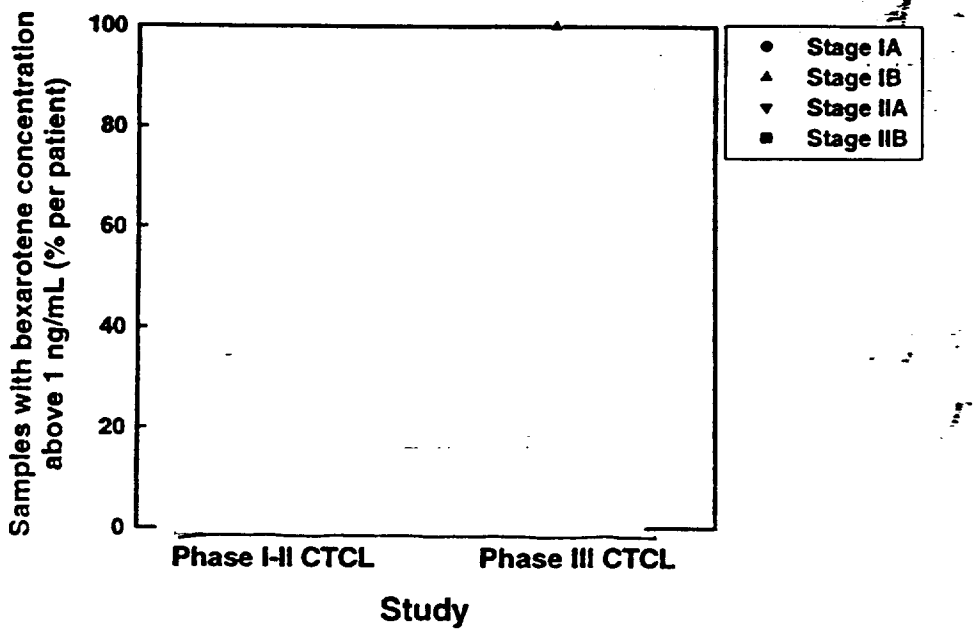
A total of 54 out of the 149 pharmacokinetic patients were reported to have taken at least one medication of interest (CYP3A4 inhibitors or inducers, or gemfibrozil) concomitantly with Targretin® gel. CYP3A4 inducers and inhibitors, and gemfibrozil are medications that are considered to have the potential to affect the pharmacokinetics of bexarotene with Targretin® gel when administered systemically (Section 6.3.7.). Of the 54 patients, 43 patients took at least one CYP3A4 inhibitor,

12 patients took at least one CYP3A4 inducer, and four patients took gemfibrozil. No apparent relationship was observed between administration of concomitant CYP3A4 inducers or inhibitors and bexarotene concentrations. However, bexarotene plasma concentrations were elevated in one of the four patients on concomitant gemfibrozil (Patient 625, Study L1069T-11, bexarotene concentration range of BLQ-24.17 ng/mL, of which 89% [17/19] of samples were above LLQ).

The influence of various demographic, disease, dosing, and baseline laboratory covariates, and systemically administered concomitant medications on bexarotene pharmacokinetics was examined in a cross-study population pharmacokinetic analysis, performed on pooled single-time-point concentration data from patients with CTCL and KS. Covariates studied included demographic variables (age, gender, and ethnic origin), disease variables (such as disease population, surface area of treated lesions, and stage of CTCL), dosing covariates (such as gel strength and application frequency), baseline laboratory covariates (including renal clearance and liver function tests), and concomitant medications with the potential to affect bexarotene pharmacokinetics (CYP3A4 inducers or inhibitors, and gemfibrozil). Model-independent statistical analysis (multivariate stepwise linear regression and linear mixed effects modeling) and non-linear mixed effects modeling (NONMEM) were used to examine the effect of these covariates on bexarotene concentrations or pharmacokinetics.

Results of the population analyses indicated that bexarotene plasma concentrations obtained following application of Targretin® gel were positively correlated with the body surface area of treated lesions (which correlates with CTCL stage), strength of gel applied, and gel application frequency. These results were in agreement with results of the descriptive evaluation of individual bexarotene concentration data in the pooled database, which showed an increase in the percent of quantifiable bexarotene concentrations >1 ng/mL per patient, with increasing surface area of treated lesions or advancing stage of CTCL (**Figure 6.3-H**).

Figure 6.3-H. Distribution of Samples with Bexarotene Plasma Concentration above 1 ng/mL (expressed as % per patient) as a Function of Study and CTCL Stage in Patients Participating in Phase I-II CTCL Program (Studies L1069-94-04T, L1069T-11, and L1069T-12), and Phase III CTCL Study (Study L1069T-25)



Note: The thick horizontal lines are the mean percentages of samples with measurable concentrations within each program; thin horizontal lines are the mean percentage of samples with measurable concentrations within each study and for each CTCL stage.

Results of the population analysis also showed no significant effects of demographics (age, gender, or ethnic origin) or CYP3A4 inhibitors or inducers on bexarotene pharmacokinetics. Additionally, no clinically meaningful correlation was found between laboratory measures of renal (serum creatinine and renal clearance) and liver function (ALT, AST, bilirubin, alkaline phosphatase, and total protein) and bexarotene pharmacokinetics.

6.3.3.1.4. Request for Waiver of Requirement for Bioavailability Study for Targretin® Gel

Targretin® gel is intended for topical application and is a solution of bexarotene in dehydrated alcohol, USP/NF, and polyethylene glycol 400 (PEG400), USP/NF, to which a gelling agent, hydroxypropyl cellulose, USP/NF, is added to increase viscosity and form a gel.

As discussed and agreed with the FDA at the [redacted] Clinical Meeting held on 21 July 1999 and documented in the meeting minutes (Question 10), Targretin® gel is eligible for a waiver of the requirement for evidence of in vivo bioavailability or bioequivalence, since the drug product is "a solution for application to the skin" and its bioavailability is considered to be self-evident [CFR 320.22 (b) (3) (i)]. Consequently, Ligand hereby requests a waiver from the conduct of a bioavailability study requested in CFR 320.25 (d) (1) (i).

As also discussed and agreed at the [redacted] Clinical Meeting held on 21 July 1999 (Question 10), Ligand is submitting data in this NDA review and submission that meet the requirements of CFR 320.25 (d) (1) (ii) by describing the pharmacokinetics of the active drug ingredient.

6.3.3.1.5. Overall Summary of Bexarotene Topical Absorption and Pharmacokinetics

The topical pharmacokinetics of bexarotene has been characterized in a non-clinical study in human cadaver skin and in several clinical studies utilizing Targretin® gel. Bexarotene concentration data obtained from sparse blood sampling in a Phase I-II program in patients with CTCL, a Phase III study in patients with CTCL, and a Phase I-II program in patients with AIDS-related KS were pooled and evaluated using descriptive statistical methods, and separately using cross-study population analyses. The results of the descriptive and population evaluations are summarized below.

Targretin® gel shows good penetration into the skin. In a non-clinical study utilizing human cadaver skin, a total of 25.3% of drug was recovered in the epidermis, dermis, and stratum corneum.

Systemic exposure to bexarotene following application of Targretin® gel is low. Plasma bexarotene concentrations, measured primarily within 24 hours of dosing, were generally very low (<5 ng/mL) and only sporadically quantifiable. Concentrations were quantifiable in only 300 (37.2%) of the 807 post-dose blood samples collected and assayed for patients treated with Targretin gel 1% in the Phase I-II CTCL program and the Phase III CTCL study. Of the 300 post-dose plasma samples with quantifiable concentrations, 245 had bexarotene concentrations lower than 5 ng/mL, 28 were ≥5 ng/mL but <10 ng/mL, 13 were ≥10 ng/mL but <15 ng/mL, five were ≥15 ng/mL but <20 ng/mL, and only nine were higher than 20 ng/mL. The highest concentrations (47.1 and 54.9 ng/mL) measured across all studies were obtained in one patient in the Phase III study, who is believed to have applied an inordinately large amount of Targretin® gel 1% during the course of the study (90 tubes of gel dispensed to this patient at one visit, compared to a maximum of 17 tubes in other patients at any study visit). Following topical application, the highest plasma were observed within 12 hr of Targretin® gel application, with generally lower concentrations at later time points.

Accumulation of bexarotene following topical application is minimal. Despite long-term application of Targretin® gel (0.1%, 0.5%, or 1% gel strengths for up to 135 weeks) over up to 90% of body surface area in CTCL patients, the large majority of blood samples had non-quantifiable (<1 ng/mL) or generally sporadic low (<5 ng/mL) plasma bexarotene concentrations.

Systemic concentrations of bexarotene achieved following topical application are related to the extent of topical exposure to Targretin® gel. Results of population analyses of pooled data from the Targretin® gel studies demonstrated that higher bexarotene plasma concentrations were obtained in patients who treated a larger surface area of lesions (which correlated with CTCL stage), in patients who utilized a higher gel strength, and in patients who applied Targretin® gel more frequently. These results were in agreement with results of a descriptive evaluation of bexarotene concentration data in the pooled database, which showed an increase in the percent of quantifiable bexarotene concentrations (>1 ng/mL) in patients, with increasing surface area of treated lesions or advancing stage of CTCL. The correlation between plasma concentrations and gel strength applied was also evident in the observation that the largest percentage of quantifiable bexarotene concentrations were observed in the Phase III L1069T-25 study (46.1% had post-dose concentrations >1 ng/mL in Study L1069T-25 compared to 21.1% in the Phase I-II CTCL program and 2.0% in the Phase I-II KS program), in which Targretin® gel 1% was used exclusively.

Demographic characteristics (age, gender, and ethnic origin) did not have a significant effect on bexarotene pharmacokinetics. No formal studies have been conducted to evaluate the effect of renal or hepatic dysfunction on bexarotene pharmacokinetics. However, no correlation was found between measures of renal function (creatinine clearance) or liver function (liver function tests) and bexarotene pharmacokinetics, for patients in the Targretin® gel studies.

No formal studies have been conducted to evaluate drug interactions with Targretin® gel. While no evidence for an interaction with concomitantly administered CYP3A4 inhibitors was observed in the Targretin® gel studies, CYP3A4 inhibitors could theoretically lead to an increase in plasma bexarotene concentrations. Only limited data were available on concomitantly administered gemfibrozil. However, bexarotene plasma concentrations appeared elevated (concentrations up to

24.17 ng/mL) in one patient applying Targretin® gel who was on concomitant gemfibrozil.

6.3.3.2. Bexarotene Pharmacokinetics following Oral Administration of Targretin® Capsules

The following sections provide information on the pharmacokinetics of bexarotene following oral dosing with Targretin® capsules. Data from the Targretin® capsule studies, which are considered to be supportive to this NDA submission, have been previously submitted in their entirety in NDA 21-055 and are therefore only summarized in the following sections.

This summary of oral pharmacokinetics focuses on data obtained from the use of Targretin® capsules containing micronized bexarotene. Early in clinical development, clinical studies were initiated using a Targretin® capsule formulation (SG-1) containing nonmicronized bexarotene. However, formulations containing micronized bexarotene (SG-2, SG-3, SG-4, SG-5, and SG-6) were subsequently developed in order to enhance the content uniformity of Targretin® capsules. Studies in beagle dogs demonstrated that micronization also produced an increase in oral bioavailability. Consequently, Targretin® capsules containing micronized bexarotene were introduced into the clinical studies at a dosage level that took the anticipated enhancement in bioavailability into account. Therefore, although pharmacokinetic evaluations were conducted with both micronized and nonmicronized Targretin® capsule formulations, the majority of pharmacokinetic data was obtained with micronized bexarotene.

The pharmacokinetics of orally administered bexarotene were characterized in clinical studies in patients with advanced cancers, patients with advanced head and neck cancer, patients with Type II diabetes mellitus, patients with CTCL, and normal volunteers who had been administered Targretin® capsules. The data demonstrate

that the pharmacokinetics of bexarotene after a single oral dose were essentially dose-proportional over an 18 mg/m^2 to 800 mg/m^2 dose range. Following repeat dosing, mean C_{max} and AUC_{0-6} values were similar to respective single-dose values at most dose levels <230 mg/m^2 QD, but at dose levels ≥230 mg/m^2 QD, values were lower than respective values following single-dose administration in many patients, suggestive of an induction of bexarotene oral clearance at these higher dose levels. However, plasma concentrations in some patients at dose levels as high as 1000 mg/m^2 QD did not change with repeat dosing, indicating that there was not a clear relationship between the reduction in plasma concentrations and dose level.

Bexarotene was eliminated relatively rapidly from the body following oral administration. This is evident in the estimates of half-life of bexarotene, which ranged from approximately 1 to 3 hours when determined over a 6-hour sampling interval, and approximately 7 to 9 hours when determined over a 24-hour sampling interval. Consistent with its rapid elimination, minimal accumulation of bexarotene was observed with repeat dosing, even after up to 520 days on study. Additionally, predose concentrations of bexarotene following multiple dosing were low (approximately 4-6% of C_{max}).

The pharmacokinetics of bexarotene in patients with CTCL were found to be similar to the pharmacokinetics observed in patients with advanced cancers other than CTCL.

The metabolism and renal excretion of bexarotene following oral dosing are detailed in **Sections 6.3.3.4. and 6.3.3.5.**, respectively. The primary metabolites of bexarotene observed in plasma following oral dosing were the oxidative metabolites, 6- and 7-hydroxy-bexarotene and 6- and 7-oxo-bexarotene. Urinary excretion of bexarotene or its metabolites was minimal. No detectable bexarotene (LLQ of 10 ng/mL) or 6- or 7-oxo-bexarotene was observed, and only trace quantities of 6- or 7-hydroxy-bexarotene were found in urine. Consequently, while a mass-balance

study was not done, bexarotene is believed to be primarily excreted through hepatobiliary mechanisms.

The effect of concomitant medications on bexarotene pharmacokinetics following oral dosing is further detailed in **Section 6.3.7.2.** Of the concomitant medications evaluated (levothyroxine, atorvastatin, gemfibrozil, CYP3A4 inhibitors [azole antifungals and macrolide antibiotics]), only gemfibrozil was observed to produce elevations in bexarotene plasma concentrations.

6.3.3.2.1. Oral Pharmacokinetics in Patients with Advanced Cancers

The oral pharmacokinetics of bexarotene were evaluated during one Phase I and two Phase I-II studies in patients with advanced cancers. Two of the studies (L1069-93-01 and L1069-93-02) employed repeat once-daily dosing of bexarotene, while one study (L1069-94-02) in a limited number of patients employed repeat twice-daily dosing of bexarotene. Pharmacokinetic results of each of these studies are presented below. Additionally, data from the two studies that employed repeat once-daily dosing (Studies L1069-93-01 and L1069-93-02) were combined to present an overall evaluation of bexarotene pharmacokinetics in an oncology patient population. Data from the study using twice-daily dosing (Study L1069-94-02) were not included in this combined assessment due to the limited number of patients and the different dosing regimen.

Study L1069-93-01 was a Phase I open-label, uncontrolled, multiple-dose, dose-escalation, safety and efficacy evaluation study of oral Targretin® capsules administered once daily to patients with proven, advanced cancers **(RR-845-98-010.a, NDA 21-055, Section 6.7.1).** A treatment duration of 4 weeks was intended, with an allowance to continue treatment in 4-week increments if clinically indicated. Targretin® capsules were administered with food or a liquid dietary supplement. Doses of 5, 20, and 40 mg/m^2 of the nonmicronized formulation and doses of 18, 50, 140, 300, and 400 mg/m^2 of the micronized formulation were

administered once daily and serial blood samples were collected on Days 1, 15, and 29, up to 6 hours post-dose, for the determination of plasma bexarotene concentrations. On pharmacokinetic sampling days, doses were administered with 250 mL of a liquid dietary supplement following a fast of at least 8-hour duration. Of the 52 patients enrolled in the study, 27 had pharmacokinetic evaluations, 10 of whom received the nonmicronized formulation and 17 of whom received the micronized formulation. These 15 (56%) men and 12 (44%) women had a mean ± SD (median, range) age of 54 ± 12 (54, 25 to 73) yr and mean ± SD (median, range) weight of 159 ± 31 (150, 114 to 224) lb. The race distribution for patients with pharmacokinetic evaluations was 23 White (85%), two Asian (7%), one Black (4%), and one categorized as Other (4%). The following summary of pharmacokinetics pertains to subjects who received the micronized formulation only.

Bexarotene C_{max} and AUC_{0-6} values following either single-dose or repeat daily-dose administration increased approximately dose-proportionally over an 18 mg/m^2 to 400 mg/m^2 dose range (**Table 6.3-J**). Mean single-dose and repeat daily-dose plasma bexarotene concentration-time profiles are shown in **Figure 6.3-I** and **Figure 6.3-J**, respectively. Interpatient variability in C_{max} and AUC_{0-6} after a single dose was relatively low, with coefficient of variation values ranging from 10% to 52%. For all patients, t_{max} values ranged between 1 and 4 hours after either a single dose or multiple doses. After multiple, once-daily doses, bexarotene C_{max} and AUC_{0-6} values were not consistently different from those observed after the first dose, suggesting no change in bexarotene oral clearance with multiple dosing at any dose level in this study.

Mean bexarotene $t_{1/2}$ values after single doses were similar to $t_{1/2}$ values observed after multiple doses. Although the terminal elimination phase was insufficiently defined for many of the patients, the overall harmonic mean $t_{1/2}$ was 1.4 hours based on values after single and multiple doses of all dose levels of the micronized formulation. When measurable, predose concentrations were only a small percentage of the subsequent C_{max} (overall mean of 6%), indicating little

accumulation of bexarotene after multiple doses of up to 400 mg/m^2 administered once daily.

Table 6.3-J. Mean (SD) Bexarotene Pharmacokinetic Parameters After a Single Dose and After Multiple Daily Oral Doses of Targretin® Capsules (Micronized Formulation) to Patients With Advanced Cancers (Study L1069-93-01)

Dose (mg/m^2)	Regimen[1]	N Obs	Parameter				
			t_{max} (hr)	C_{max} (ng/mL)	C_0 (ng/mL)	AUC_{0-6} (ng·hr/mL)	$t_{1/2}$[2] (hr)
18	S	3	3.3 (1.2)	67 (15)	NA	232 (102)	1.0 -
	M	6	2.3 (1.4)	89 (38)	0	266 (99)	1.2 (0.4)
50	S	3	1.7 (0.6)	308 (121)	NA	1010 (527)	1.9 (0.8)
	M	6	2.1 (1.1)	248 (77)	5 (4)	771 (257)	1.4 (0.5)
140	S	3	2.0 (0.0)	516 (53)	NA	1701 (175)	1.6 (0.4)
	M	5	2.8 (1.1)	324 (159)	14 (12)	1175 (585)	1.9 (0.7)
300	S	4	2.3 (1.3)	791 (124)	NA	2826 (327)	2.2 (0.9)
	M	6	2.7 (1.0)	1111 (261)	15 (5)	3213 (677)	1.8 (0.6)
400	S	3	3.4 (1.2)	2404 (855)	NA	8127 (2798)	2.5 -
	M	5	3.2 (1.1)	1930 (957)	88 (89)	7322 (4655)	1.8 (0.1)

(1) S = Single dose (Day 1); M = Multiple once-daily doses (Day 15 or 29).

(2) $t_{1/2}$ values could not be calculated for all profiles; N=2 for dose level 18 mg/m^2, single dose; N=4 for dose level 140 mg/m^2, multiple doses; N=5 for dose level 300 mg/m^2, multiple doses; and N=2 and 4 for single and multiple doses of 400 mg/m^2, respectively. Standard deviation values are not reported for N=2 or less.

N Obs. = Number of observations.

NA = Not applicable.

- = Not calculated.

Figure 6.3-I. Mean (N=3 or 4) Bexarotene Plasma Concentrations (Logarithmic Ordinate) After Single Oral Doses of 18 mg/m^2 to 400 mg/m^2 Targretin® Capsules (Micronized Formulation) (Study L1069-93-01)

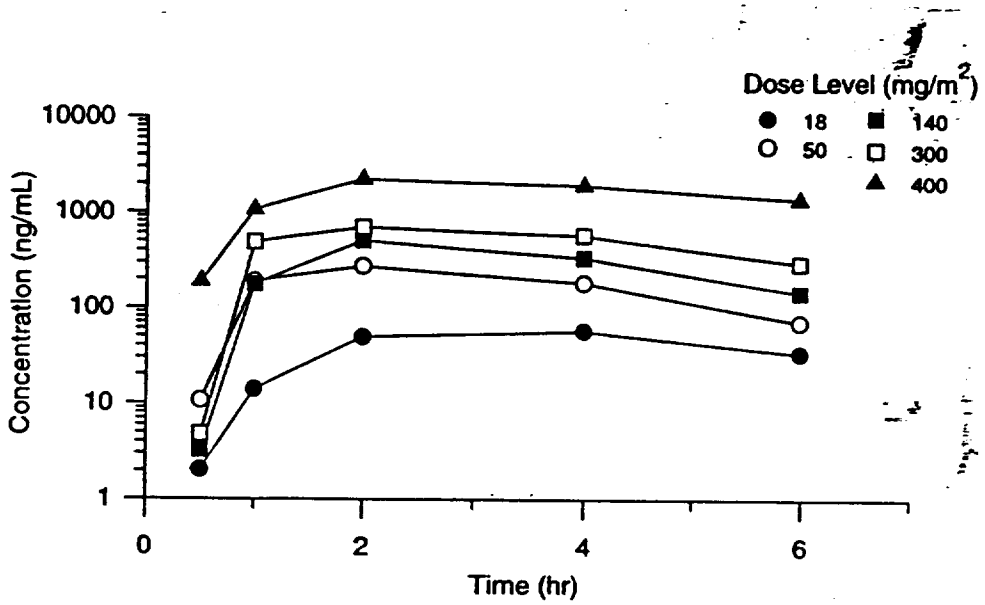
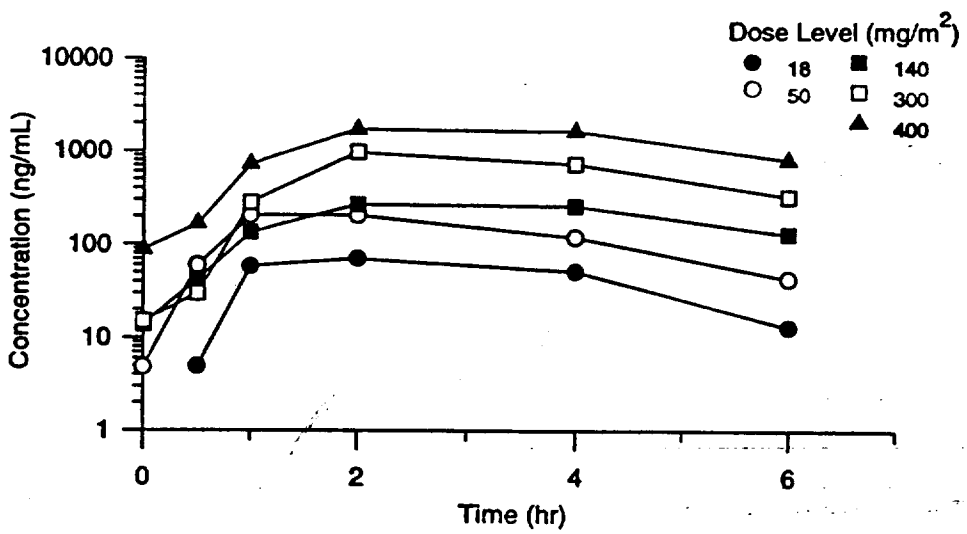


Figure 6.3-J. Mean (N=5 or 6) Bexarotene Plasma Concentrations (Logarithmic Ordinate) After Multiple Oral Doses of 18 mg/m^2 to 400 mg/m^2 Targretin® Capsules (Micronized Formulation) (Study L1069-93-01)



The metabolic fate of bexarotene was also assessed in this study and the data are presented in greater detail in **Section 6.3.3.4.1.2.** Briefly, the predominant metabolite peaks observed [redacted] were 6- and 7-hydroxy-bexarotene and 6- and 7-oxo-bexarotene. Using selected plasma samples from patients in this study, [redacted] suggested that exposure to some of the oxidative metabolites could be similar to, or somewhat greater than, that to bexarotene. Because the binding of bexarotene metabolites to human retinoid receptors is weak, and the potency of oxidative metabolites in a human retinoid receptor transactivation assay is low, the contribution of metabolites to the clinical retinoid receptor activity of bexarotene is probably insignificant.

L1069-93-02 was a Phase I-IIa open-label, uncontrolled, multiple-dose, dose-escalation, safety and efficacy evaluation study of oral Targretin® capsules administered once daily to patients with proven, advanced cancers **(RR-845-98-015.a, NDA 21-055, Section 6.7.2).** A treatment duration of 4 weeks was intended, with an allowance to continue treatment in 4-week increments if clinically indicated. Targretin® capsules were administered with food or a liquid dietary supplement. Doses of 5, 10, 20, 30, 45, and 75 mg/m^2 of the nonmicronized formulation and doses of 21, 50, 83, 140, 230, 380, 500, 650, 800, and 1000 mg/m^2 of the micronized formulation were administered once daily and serial blood samples were collected on Days 1 and 15, up to 6 hours post-dose, for the determination of plasma bexarotene concentrations. On pharmacokinetic sampling days, doses were administered with 250 mL of a liquid dietary supplement.

Of the 60 patients who had pharmacokinetic evaluations, 18 received the nonmicronized formulation, and 43 received the micronized formulation. One patient initially received the nonmicronized formulation and was switched to the micronized formulation on Day 334. These 31 (52%) men and 29 (48%) women had a mean ± SD (median, range) age of 60 ± 13 (63, 27 to 80) yr and mean ± SD (median, range) weight of 161 ± 36 (154, 103 to 260) lb. Most patients (N=45) were White (75%). There were also 11 Blacks (18%), one Hispanic (2%), one Asian (2%),

and two categorized as Other (3%). The following summary of pharmacokinetics pertains to subjects who received the micronized formulation only.

Mean single-dose and repeat daily-dose plasma bexarotene concentration-time profiles are shown in **Figure 6.3-K** and **Figure 6.3-L**, respectively. In general, interpatient variability in C_{max} and AUC_{0-6} after a single dose was relatively high, particularly for doses of 500 mg/m^2 or more. Single-dose bexarotene C_{max} and AUC_{0-6} values increased approximately dose-proportionally over a 21 mg/m^2 to 800 mg/m^2 dose range (**Table 6.3-K**). Increases in bexarotene mean C_{max} and AUC_{0-6} values after a dose of 1000 mg/m^2 were somewhat less than proportional to the dose, but the interpatient variability values were substantial for both parameters. The values for t_{max} were typically 2 to 3 hours after either a single dose or multiple doses.

Figure 6.3-K. Mean (N=3 to 6) Bexarotene Plasma Concentrations (Logarithmic Ordinate) After a Single Oral Dose of 21 mg/m^2 to 1000 mg/m^2 Targretin® Capsules (Micronized Formulation) (Study L1069-93-02)

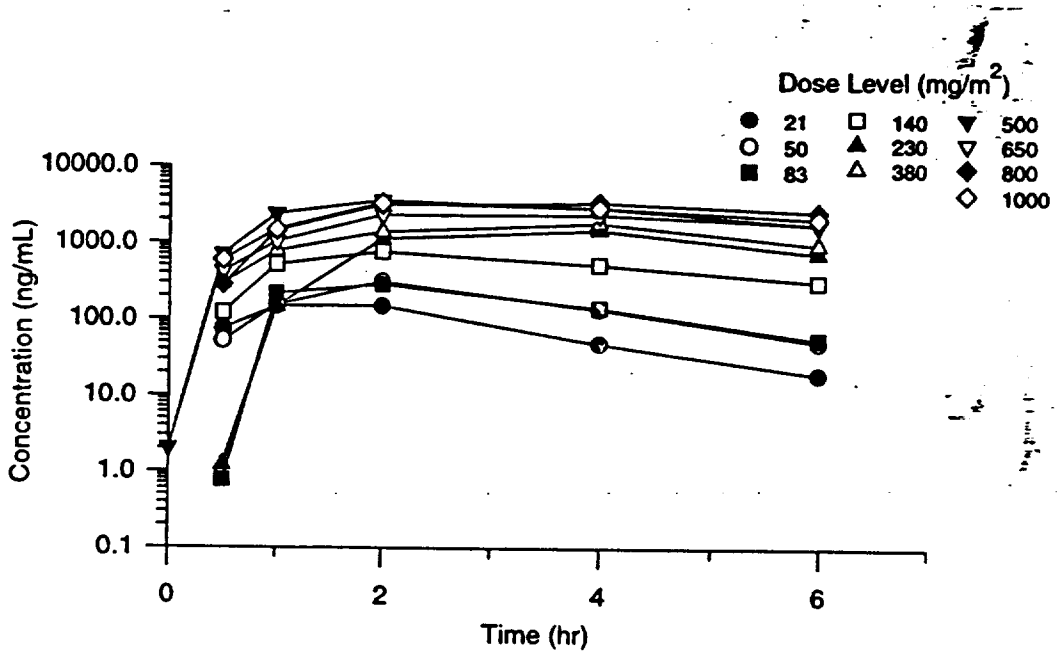


Figure 6.3-L. Mean (N=3 to 5) Bexarotene Plasma Concentrations (Logarithmic Ordinate) After Multiple Oral Doses of 21 mg/m^2 to 1000 mg/m^2 Targretin® Capsules (Micronized Formulation) (Study L1069-93-02)

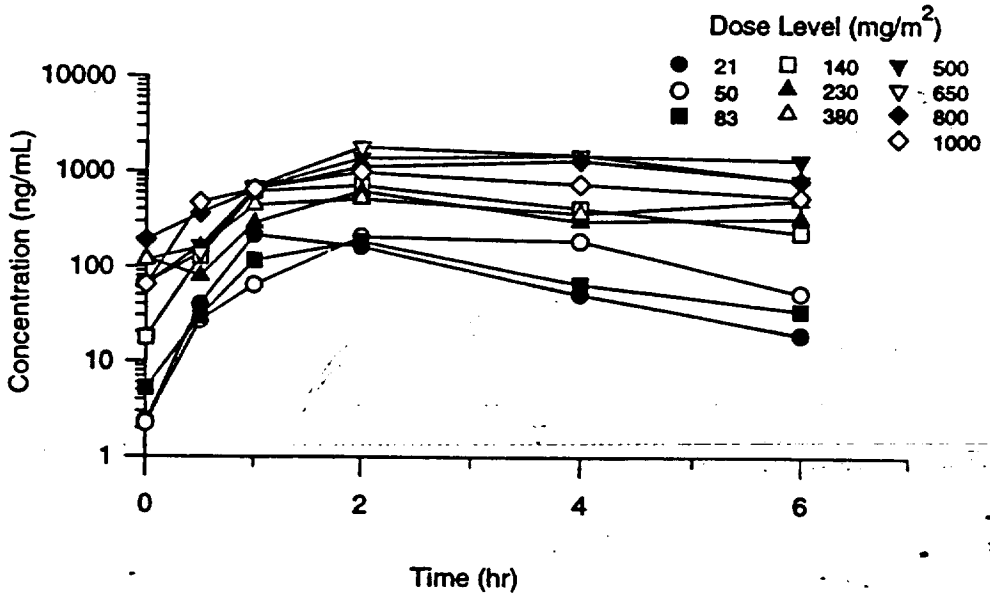


Table 6.3-K. Mean (SD) Bexarotene Pharmacokinetic Parameters After Single or Multiple Daily Oral Doses of Targretin® Capsules (Micronized Formulation) to Patients With Advanced Cancers (Study L1069-93-02)

Dose (mg/m^2)	Regimen[1]	N Pts.	N Obs.	Parameter				
				t_{max} (hr)	C_{max} (ng/mL)	C_0 (ng/mL)	AUC_{0-t} (ng·hr/mL)	$t_{1/2}$[2] (hr)
21	S	3	3	1.3 (0.6)	183 (90)	NA	498 (260)	1.5 (0.2)
	M	3	3	1.3 (0.6)	189 (58)	2 (2)	514 (153)	1.5 (0.4)
50	S	3	3	2.0 (0.0)	317 (86)	NA	946 (171)	1.4 (0.3)
	M	3	3	2.7 (1.3)	214 (110)	2 (1)	824 (396)	1.2 (0.4)
83	S	3	3	1.4 (0.6)	320 (153)	NA	948 (494)	1.4 (0.2)
	M	3	4	2.0 (0.1)	186 (99)	5 (3)	546 (211)	2.3 (0.5)
140	S	4	4	2.6 (1.0)	858 (468)	NA	3010 (1228)	2.7 (0.9)
	M	3	3	1.4 (0.6)	754 (256)	14 (8)	2666 (1128)	2.8 (1.2)
230	S	4	4	3.0 (1.2)	1640 (1068)	NA	5586 (3544)	2.1 (0.5)
	M	5	4[3]	3.5 (1.9)	760 (575)	45 (64)	2325 (1623)	1.3 -
380	S	5	5	3.8 (1.1)	1959 (1215)	NA	7657 (4789)	2.9 (1.8)
	M	4	4	2.9 (2.3)	850 (550)	117 (173)	2528 (1268)	2.0 (0.8)
500	S	4	4	2.6 (0.9)	3744 (2429)	NA	15496 (9044)	3.4 (2.5)
	M	4	4	4.1 (1.6)	1648 (794)	66 (44)	6997 (4084)	3.5 -
650	S	6	6	3.2 (1.1)	2792 (1696)	NA	11310 (6646)	2.3 (0.6)
	M	5	5	3.3 (1.5)	2065 (1710)	66 (58)	7232 (5808)	1.7 (0.4)
800	S	6	6	3.1 (1.8)	4138 (2570)	NA	15900 (10486)	3.6 (0.9)
	M	5	5	4.3 (1.3)	1531 (576)	192 (240)	5926 (1707)	1.8 (0.6)
1000	S	6	6	3.1 (1.6)	3647 (2605)	NA	14746 (12023)	2.9 (0.8)
	M	4	4	3.4 (2.2)	1196 (222)	64 (30)	4299 (841)	2.7 (1.3)

[1] S = Single dose (Day 1); M = Multiple once-daily doses (most samples collected on Day 15).

[2] $t_{1/2}$ values could not be calculated for all patients; N=2 for dose levels 230 mg/m^2 and 500 mg/m^2, multiple doses; N=3 for dose levels 380 mg/m^2 and 1000 mg/m^2, multiple doses; N=4 for dose level 650 mg/m^2, single and multiple doses; and N=4 for dose levels 800 mg/m^2 and 1000 mg/m^2, single dose.

[3] There were five observations for C_0.

N Pts. = Number of patients.

N Obs. = Number of observations.

NA = Not applicable.

- = Not calculated.

Measurable concentrations were achieved for the entire 24-hour dosing interval following once-daily multiple dosing. However, predose concentrations were only a small percentage of the subsequent C_{max} (overall mean of 6%), indicating little accumulation of bexarotene after multiple doses of up to 1000 mg/m^2 administered once daily. Additionally, plasma bexarotene concentrations were low in predose samples collected for some patients after long-term multiple dosing (233 to

520 days), suggesting that there is minimal accumulation of bexarotene even after long-term repeat daily dosing.

Although interpatient variability was high, at dose levels of 230 mg/m^2 and greater, mean bexarotene C_{max} and AUC_{0-6} values tended to be lower after multiple dosing compared to those after a single dose (**Table 6.3-K**). Repeat-dose administration of doses >650 mg/m^2 did not result in mean AUC_{0-6} values greater than that observed at the 650 mg/m^2 dose level, suggesting a dose-dependent induction of oral clearance of bexarotene. However, some individual patients receiving doses up to 1000 mg/m^2 did not have a reduction in bexarotene concentrations with repeated daily dosing, indicating that relationship of this effect to the dose level was not consistent.

Although the terminal elimination phase was insufficiently defined for most of the patients, the overall harmonic mean $t_{1/2}$ was 1.9 hours based on values after single and multiple doses. Bexarotene mean $t_{1/2}$ values after single doses did not appear to be different from those after multiple doses. Despite the apparent induction of oral clearance of bexarotene in some patients, there was no corresponding change in half-life values, possibly because the terminal elimination phase may not have been reached within the relatively short 6-hour sampling periods used in the studies.

The metabolic fate of bexarotene was also assessed in this study and the data are presented in greater detail in **Section 6.3.3.4.1.2.** Briefly, the predominant metabolite peaks observed [redacted] were 6- and 7-hydroxy-bexarotene and 6- and 7-oxo-bexarotene. Using selected plasma samples from patients in this study, [redacted] suggested that exposure to some of the oxidative metabolites could be similar to, or somewhat greater than, that to bexarotene. Because the binding of bexarotene metabolites to human retinoid receptors is weak, and the potency of oxidative metabolites in a human retinoid receptor transactivation assay is low, the contribution of metabolites to the clinical retinoid receptor activity of bexarotene is probably insignificant.