TAZORAL™ for the Treatment of Moderate to Very Severe Plaque Psoriasis

Briefing Document

Prepared by Allergan

for the

Dermatologic and Ophthalmic Drugs Advisory Committee

and Drug Safety and Risk Management Advisory Committee Meeting

12 July 2004

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Table of Contents

LIST OF IN-TEXT TABLES AND FIGURES

List of Abbreviations and Definition of Terms

AGN 190168	Allergan compound number for tazarotene
ALT (SGPT)	Alanine aminotransferase
AP	Alkaline phosphatase
AST (SGOT)	Aspartate aminotransferase
BMD	Bone mineral density
BUN	Blood urea nitrogen
CNS	Central nervous system
COSTART	Coding Symbols for a Thesaurus of Adverse Reaction Terms
CPK	Creatine phosphokinase (creatine kinase)
DXA	Dual x-ray absorptiometry
FDA	United States Food and Drug Administration
GGT	Gamma-glutamyl-transferase
HDL	High-density lipoproteins
ITT	Intent-to-treat
LDH	Lactate dehydrogenase
LDL	Low-density lipoproteins
LOCF	Last observation carried forward
NDA	New Drug Application (in the United States)
NHIS	National Health Interview Survey
OLA	Overall lesional assessment
PACT	Partnership to Promote Awareness and Compliance to Avoid Teratogenicity
PASI	Psoriasis Area and Severity Index
PPR	Pregnancy Prevention Registry
PUVA	Treatment with a psoralen followed by treatment with UVA
RAR	Retinoic acid receptor
RiskMAP	Risk Minimization Action Plan
RXR	Retinoid X receptor
SD	Standard deviation
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
T4	Thyroxine
TNF	Tumor necrosis factor
TPA	TAZORAL™ prescription authorization
TSH	Thyroid stimulating hormone
UVA	Ultraviolet light A

1.0 EXECUTIVE SUMMARY

TAZORAL™ is an oral retinoid that undergoes rapid hydrolysis in the blood to form tazarotenic acid. Tazarotenic acid binds with high affinity to and transactivates retinoic acid receptors (RARs) in a rank order of RARβ > RARγ >>> RARα, but does not bind to or transactivate retinoid X receptors (RXRs). The specificity of tazarotene for certain RAR receptors and lack of affinity for RXR receptors may account for the unique safety profile of tazarotene among available systemic retinoids for the treatment of psoriasis.

1.1 Indication

TAZORAL™ (tazarotene capsules) is indicated for the treatment of moderate to very severe plaque psoriasis. The recommended dosage is once daily administration of TAZORAL™ 4.5 mg with or without food.

1.2 Principal Findings

TAZORAL™ has been studied extensively in 1 dose-ranging phase 2 study and 4 phase 3 studies, including 2 randomized, double-blind, placebo-controlled studies. Generally, patients treated with TAZORAL™ 4.5 mg experienced a rapid onset of effect (within 2 weeks) and had clinically and statistically significant improvements in all measures of psoriasis which persisted for several weeks after treatment was completed. Few patients had serious adverse events or discontinued treatment because of adverse events. The adverse event profile of TAZORAL™ appears to offer some distinct safety advantages over other oral agents approved for psoriasis. The major findings from the TAZORAL™ clinical program are:

<u>Double-blind, Placebo-controlled Studies</u>

- TAZORAL™ rapidly improves the signs and symptoms of psoriasis. The incidence of a clinically relevant improvement (at least a 2-point decrease on the 6-point overall lesional assessment [OLA] score) was significantly greater in the TAZORAL™ group by the end of the second week of treatment and continued to improve for 4 weeks after completion of the 12-week treatment period. The maximum clinical response rate was 31.5% for TAZORAL™ versus 6.9% for placebo ($p < 0.001$). Similarly, the

proportion of patients with none or minimal disease (OLA score of 0 or 1) was also maximal 4 weeks after completion of treatment, with 21.8% of patients treated with TAZORAL™ achieving this criterion versus 3.7% treated with placebo ($p < 0.001$).

- Over the 12-week treatment period, the percentage of patients with OLA scores indicating severe to very severe psoriasis decreased from 36% to 11% in the TAZORAL™ group and in the placebo group remained relatively unchanged, decreasing from 35% to 30%. The percentage of patients with improvement to scores representing mild or less were also greater in the TAZORAL™ group than the placebo group; 53% with TAZORAL™ vs 14% with placebo.

- Secondary endpoints (severity of plaque elevation, scaling and erythema, and percent of body surface area involved) also showed statistically and clinically significant differences between TAZORAL™ and placebo favoring TAZORAL™.

- According to the physician's global response to treatment, 53.8% of patients showed a treatment response of moderate (approximately 50% improvement) or better in the TAZORAL™ group versus 14.9% in the placebo group, and 33.5% of patients showed a treatment response of marked (approximately 75%) improvement or better in the TAZORAL™ group versus 8.9% in the placebo group.

- The efficacy of TAZORAL™ persisted 12 weeks after the 12-week treatment period. The peak effect for many efficacy variables, including the primary OLA evaluations, occurred 4 weeks after completion of treatment (week 16).

<u>All Studies</u>

- The efficacy of TAZORAL™ was sustained with continuous treatment for up to 1 year.

- TAZORAL™ was well-tolerated, rates of serious adverse events and discontinuations for adverse events were similar for TAZORAL™ and placebo-treated patients in the 2 placebo-controlled studies.

- Most adverse events were of mild severity and were typical of the adverse events associated with hypervitaminosis A. In the placebo-controlled studies the incidence of adverse events reported for hypertriglyceridemia, hypercholesterolemia, abnormal liver function tests, increased SGOT, increased SGPT, desquamation, eye dryness, alopecia, and nervous system were not different between the TAZORAL™ 4.5 mg and placebo groups.

- Based on normal reference ranges for laboratory data, there was a significantly higher incidence of elevated triglycerides in the TAZORAL™ group (22.8% TAZORAL™ vs 16.6% placebo). In the placebo group, there was a significantly higher incidence of elevated creatine phosphokinase (11.3% TAZORAL™ vs 19.9% placebo) alanine aminotransferase (ALT) (19.1% TAZORAL™ vs 25.3% placebo), and total bilirubin (0.9% TAZORAL™ vs 3.4% placebo).

- Treatment with TAZORAL™, unlike other retinoids, does not significantly increase the risk of hepatotoxicity, or alter lipid or thyroid function profiles, except for minimal elevations in triglycerides.

- In the 2 placebo-controlled trials there were no hyperostotic or ligamentous calcification effects, or bone mineral density changes. In the long-term studies, at 6 months and 1 year of treatment, there were small but statistically significant changes from baseline in median bone mineral density for total hip (-0.45% at 6 months and 1 year) and femoral neck (-0.92% and -0.29% at 6 months and 1 year, respectively), but not lumbar spine. At the 1-year time point only, a small percentage of patients showed radiographic changes (greater than 1 grade, on a 4-point scale) in ligamentous calcification and osteophyte formation in the cervical spine (5.2%) and plantar ankle (1.0%), but not in the dorsal ankle (0%). A larger percentage of patients showed smaller changes which are of unclear clinical significance (less than or equal to 1 grade, on a 4-point scale) in ligamentous calcification and osteophyte formation in the cervical spine (17.1%), plantar ankle (3.1%), and dorsal ankle (5.2%). These changes are consistent with the known effects of systemic retinoids.

- In contrast to other systemic retinoids, there was a very low incidence of ophthalmic adverse events. TAZORAL™ was not associated with any increased risk of vision impairment.

- At the proposed dose of 4.5 mg per day, TAZORAL™ neither inhibits nor induces cytochrome P450 enzymes and, therefore, is not expected to interact with other drugs.

- Like other systemic retinoids, tazarotene is teratogenic in animals. Because TAZORAL™ is a treatment option for women of child-bearing potential, a comprehensive risk-management program will be implemented.

- The half-life of tazarotene (7 to 12 hours) is much shorter than that of acitretin or its metabolite etretinate and the drug is not stored in fatty tissue. TAZORAL™-treated females of child-bearing potential should avoid pregnancy only for 1 month after the end of treatment compared with at least 3 years following treatment with acitretin. The short half-life also reduces the potential for teratogenicity in the event of unintended pregnancies after cessation of therapy.

1.3 Summary of Efficacy

The primary support for the efficacy of TAZORAL™ 4.5 mg for the treatment of moderate to very severe plaque psoriasis is provided by 2 phase 3 placebo-controlled studies (190168-048P and 190168-049P) in which patients were treated once daily for 12 weeks and followed for 12 weeks posttreatment. Supportive data comes from 2 open-label studies which provided data on treatment beyond 12 weeks. One study (190168-052P) enrolled patients who had an insufficient response to treatment in studies 190168-048P and 190168-049P.

These patients were treated with TAZORAL™ for 12 weeks and followed for 12 weeks posttreatment. In the second study (190168-050P) patients were treated with TAZORAL™ for up to 52 weeks and followed for 12 weeks posttreatment (See Table 5.1-1 for study design).

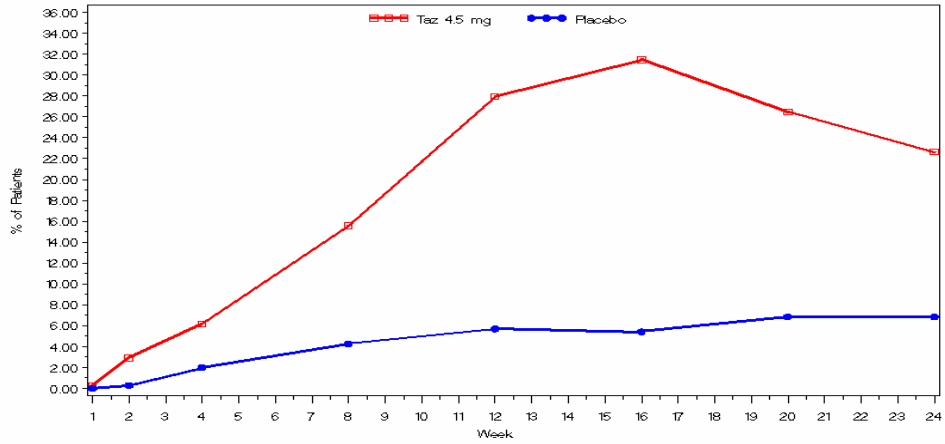
The basic eligibility criteria were the same for the 4 phase 3 studies. All patients had a diagnosis of moderate to very severe plaque psoriasis with a psoriatic involvement of at least 10% of body surface area. All TAZORAL™-treated patients received 4.5 mg once daily. These studies included 1189 patients (TAZORAL™ 831, placebo 358).

The primary efficacy variable was the 6-point OLA score, as agreed with the FDA. The OLA takes into account the most important features of psoriasis (primarily plaque elevation, while also taking into account scaling, and erythema) and is graded from 0 = none to 5 = very severe. The primary endpoint was the proportion of patients with at least a 2 grade decrease (improvement) in their OLA score. A 2-point decrease represents substantial clinical improvement and was defined as a clinical success. Secondary efficacy variables included an OLA score of none or minimal, severity of plaque elevation, erythema, and scaling (with severity scores of 0 = none to 4 = very severe), percentage of body surface area involved, and physician's overall global response to treatment (scored as 0 = completely cleared to 6 = condition worsened). Other efficacy variables included assessment of pruritus, scalp psoriasis, and nail psoriasis. (See Section 11.0 for scale details.)

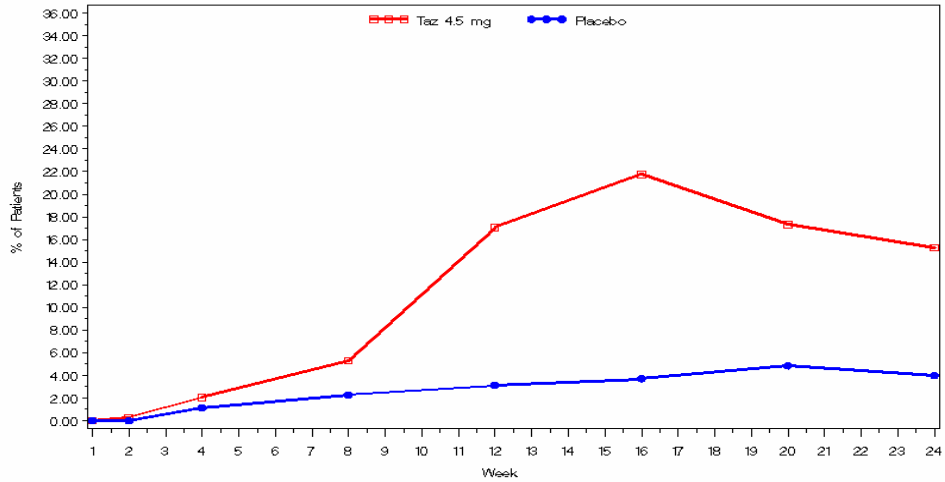
In the 2 double-blind, placebo-controlled studies, the proportion of patients with at least a 2-grade decrease from baseline in their OLA score was significantly greater in the TAZORAL™ group compared with the placebo group from week 2 through week 24 ($p \leq 0.008$; Figure 1.2-1). The proportion of patients with an OLA score of minimal or none was significantly greater in the TAZORAL™ group compared with the placebo group from week 8 through week 24 ($p \leq 0.035$; Figure 1.2-1). The highest proportion of TAZORAL™ patients with at least a 2-grade decrease in their OLA score (31.5%) and an OLA score of none or minimal (21.8%) occurred at week 16, 4 weeks after treatment was completed.

Figure 1.2-1 Overall Lesional Assessment; Studies 190168-048P and 190168-049P Combined

Percentage of Patients with at Least a 2-Grade Decrease from Baseline in OLA Score



Percentage of Patients with an OLA Score of Minimal or None



In the 2 double-blind placebo-controlled studies there was a statistically significant and consistently greater improvement in plaque elevation in the TAZORAL™ group from week 1 through 24, in erythema from week 8 through 24, and in scaling from week 2 through 24.

The decreases in mean percentage of body surface involved were significantly greater in the TAZORAL™ group than in the placebo group from week 8 through week 24 ($p < 0.001$). In the TAZORAL™ group, the mean decrease from baseline peaked at week 16 (8.8%), 4

weeks after treatment was completed, and was 8.2% at week 24. In the placebo group, mean changes from baseline ranged from 0.0% to –1.0%.

Efficacy was maintained throughout 52 weeks of treatment in study 190168-050P. The magnitude of the changes from baseline for the various efficacy variables were comparable to the magnitude of the changes in the 2 double-blind, placebo-controlled studies. Improvement in all efficacy variables increased over time and reached a plateau that was maintained throughout the treatment period. The maximum improvement was observed at week 12 for plaque elevation, week 16 for scaling, week 20 for erythema, week 32 for proportion of patients with OLA score of minimal or none and mean percentage body surface involvement, and week 36 for proportion of patients with at least a 2-grade decrease in OLA. For all efficacy variables, the values remained close to the peak levels throughout the remainder of the treatment period. In addition, efficacy was maintained throughout the 12-week posttreatment period.

Patients who had not responded to TAZORAL™ treatment in either of the 2 double-blind, placebo-controlled studies were found to respond during their second 12 weeks of receiving TAZORAL™ in study 190168-052P. In these patients, the highest proportion with at least a 2-grade decrease in OLA score was 24.6% at week 20 of the study (8 weeks after stopping 24 weeks of treatment) and the highest proportion with an OLA score of minimal or none was 18.3% at week 16 (4 weeks after stopping 24 weeks of treatment).

1.4 Summary of Safety

The safety of TAZORAL™ is based on data from 5 studies (1 phase 2, 4 phase 3) of patients with moderate to very severe plaque psoriasis; 987 treated with TAZORAL™, 383 treated with placebo. These studies included 831 treated with TAZORAL™ 4.5 mg/day. Of these patients, 640 were treated for ≥ 12 weeks, 261 were treated for ≥ 24 weeks, and 153 completed 48 weeks. In addition, supporting safety data come from 2 phase 2 studies of patients with nodular acne (223 treated with TAZORAL™ up to 6.0 mg/day for up to 24 weeks, 54 treated with placebo), 1 phase 1 studies of 34 patients with cancer refractory to conventional therapy (treated with TAZORAL™ up to 33.6 mg/day for up to 12 weeks), and

12 bioavailability/ pharmacokinetic studies (449 patients) in healthy volunteers. The total number of patients treated with TAZORAL™ in all studies was 1693; 437 were treated with placebo.

In the 2 double-blind, placebo-controlled studies, during the treatment period the overall adverse event rates, and the incidence of cheilitis, dry skin, headache, arthralgia, myalgia, back pain, joint disorder, nasal dryness, rash, foot pain, hyperglycemia, and dermatitis were significantly higher ($p \leq 0.05$) for TAZORAL™ 4.5 mg compared with placebo. Most of these adverse events are typical of the adverse events associated with hypervitaminosis A. The most common adverse events were cheilitis (65.5% TAZORAL™, 16.8% placebo), headache (18.7% TAZORAL™, 12.0% placebo), arthralgia (17.5% TAZORAL™, 7.3% placebo), myalgia (14.7% TAZORAL™, 8.4% placebo), and dry skin (23.6% TAZORAL™, 14.8% placebo). During the posttreatment period, only the incidence of cheilitis (48.4% TAZORAL™ 4.5 mg, 16.1% placebo), and emotional lability (0.5% TAZORAL™ 4.5 mg, 4.6% placebo) were significantly different for the 2 treatment groups.

In the 2 double-blind, placebo-controlled studies, there were no remarkable differences between TAZORAL™ 4.5 mg and placebo in the incidence of serious adverse events (0.9% TAZORAL™ 4.5 mg, 2.8% placebo) or discontinuations due to adverse events (5.2% TAZORAL™ 4.5 mg, 4.5% placebo). As expected, in the long-term study (190168-050P) rates of serious adverse events (8.7%) and discontinuations due to adverse events (18.3%) were higher than the rates in the shorter-term studies.

The analyses of the changes from the screening visit in laboratory test values showed that TAZORAL™ 4.5 mg, unlike other oral retinoids, does not significantly increase the risk of hepatotoxicity nor does it alter the lipid or thyroid function profiles, except possibly for a minimal elevation in triglycerides. In the placebo-controlled trials, the incidence of triglyceride levels above 250 mg/dL was 30.9% in the TAZORAL™ group vs 23.6% in the placebo group ($p < 0.05$). However, there was no statistically significant difference between the groups for triglyceride levels above 500 mg/dL (TAZORAL™ 2.6% vs placebo 2.0%). In the 1-year clinical trial, significant elevations in triglycerides were seen in no more than 2.5% of patients at any time during treatment, and almost all were detected within 2 months

of beginning therapy. Given the clinical data, it may be reasonable to monitor patients with known hypertriglyceridemia or patients at high risk for hypertriglyceridemia.

In the phase 3 studies, ligament calcification and osteophyte formation was evaluated using x-rays of the cervical spine and both ankles. Bone mineral density was assessed by DXA scans. There were small but statistically significant changes from baseline in median bone mineral density for total hip (-0.45% at 6 months and 1 year) and femoral neck (-0.92% and -0.29% at 6 months and 1 year, respectively), but not lumbar spine. At the 1-year time point only, a small percentage of patients showed radiographic changes (greater than 1 grade, on a 4-point scale) in ligamentous calcification and osteophyte formation in the cervical spine (5.2%), plantar ankle (4.1%), but not in the dorsal ankle. These changes are consistent with the known effects of systemic retinoids.

In the 1-year study, the proportion of patients with alkaline phosphatase values that were above the upper-limit of normal increased from 0.8% at week 4 to 18.6% at week 56 and then declined to 8.8% at week 64. However, none of the increases were more than 100% above the upper-limit of normal. The clinical significance of these changes is unknown, but may represent a modest effect of TAZORAL™ on bone metabolism. There were no clinically meaningful changes in ALT, AST, GGT, or bilirubin to suggest the alkaline phosphatase changes represent a hepatotoxic effect.

Based on the neuropsychiatric evaluations performed in the phase 3 studies, there was no evidence that treatment with TAZORAL™ 4.5 mg increased the risk of depression. There were no reported cases of suicide or attempted suicide.

Ophthalmological evaluations (visual acuity, biomicroscopy, vitreous pathology, optic disk, night vision, ERG [electroretinogram]) in the phase 3 studies did not indicate that patients treated with TAZORAL™ 4.5 mg are at greater risk of vision impairment than patients treated with placebo, or that there is an increased risk of vision impairment with treatment for up to 1 year.

1.5 Risk Management Plan

The TAZORAL™ risk management program or PACT™ (Partnership to Promote Awareness and Compliance to Avoid Teratogenicity) is a new risk minimization action plan designed specifically for TAZORAL™ and patients with moderate-to-very severe plaque psoriasis. It considers that moderate-to-very severe psoriasis is primarily a disease of adults (the average age is >45 years) and is a chronic, lifelong disease, often requiring many years of therapy. PACT™ goes beyond many other risk management programs in that it incorporates insights gained from recent FDA advisory committee meetings on other programs, as well as the FDA's recent draft guidances on risk management, including but not limited to:

- Mandatory registration and certification of physicians and pharmacies
- A mandatory pregnancy prevention registry (PPR) of females of childbearing potential with required, regular system interactions aimed at minimizing the risk of pregnancy, including monthly laboratory-confirmed pregnancy tests
- The ability to monitor and track the exposed pregnancy rate, as well as a number of other health outcomes; systems compliance and failure; and knowledge and understanding metrics in order to effectively and regularly evaluate program success and enable targeted improvements when needed.
- A method for assessing physician and pharmacy compliance with the system that avoids the potential limitations of a pharmacy audit and allows analysis of over 90% of the prescriptions written.
- A preprinted TAZORAL™ prescription authorization (TPA) form with predominantly displayed information on risks (see Section 11.2 of this Briefing Document); critical components of the PACT™ program must also be completed on this form, including an unambiguously defined patient qualification date
- Restricted access; a 1-month supply with no refills for females of childbearing potential; a 1 month supply with no more than 2 refills for other patients; and built-in mechanisms to prevent dispensing of drug to pregnant women. All prescriptions must be filled within 7 days of the qualification date
- Enhanced targeted education for all patients
- A formal, protocol-driven, pregnancy-exposure registry for women who experience a pregnancy while taking TAZORAL™ that collects data on both pregnancy outcome and reasons for program failure (ie, root-cause analysis)

- An enhanced ability to allow controlled access to TAZORAL™ that allows patients to achieve maximum benefit while at the same time providing maximum protection against the risk of teratogenicity

Details on the goals, objectives, tools, and logistics of the program are provided in Section 8.0 of this Briefing Document.

1.6 Conclusion

TAZORAL™ offer a significant new, safe, and effective treatment for patients with moderate to very severe plaque psoriasis.

2.0 OVERVIEW

2.1 Pharmacological Class

Tazarotene inhibits cell proliferation, regulates epithelial cell differentiation, and down-regulates inflammatory markers (Camisa, 1994; Esgleyes-Ribot et al, 1994). These pharmacological effects are the basis for using tazarotene in the treatment of psoriasis.

Tazarotene and tazarotenic acid, the free acid metabolite of tazarotene, belong to a class of retinoids called acetylenic retinoids. Tazarotene itself does not bind to retinoic acid receptors (RARs), but rather undergoes rapid hydrolysis in the blood to form tazarotenic acid. Tazarotenic acid binds with high affinity to and transactivates the RARs according to the following rank order: RARβ > RARγ >>> RARα. It is important to note that neither tazarotene nor tazarotenic acid bind to or transactivate retinoid X receptors (RXRs). This specificity for certain RARs (primarily RARβ and RARγ) and lack of affinity for RXRs may account for tazarotene's unique efficacy and safety profile among the currently available systemic retinoids.

2.2 Indication

TAZORAL™ (tazarotene capsules) is indicated for the treatment of moderate to very severe plaque psoriasis. The recommended dosage is once daily administration of TAZORAL™ 4.5 mg with or without food.

2.3 Pathophysiology of Psoriasis

Psoriasis is a polygenic, chronic, immune-mediated skin disorder with a significant impact on patients' quality of life. It affects more than 4.5 million Americans. Skin lesions are characterized by well-demarcated red plaques with thick micaceous scales, which are a reflection of underlying hyperkeratosis, parakeratosis, acanthosis with long rete ridges, tortuous dilated blood vessels extending high into the dermal papillae, and an infiltrate typically composed of lymphocytes and neutrophils. The histologic findings are derived from abnormal epidermal proliferation and differentiation as well as immune system alterations. In normal skin, keratinocytes mature and are shed approximately every 28 days. In psoriasis, the time for this cycle is reduced to 3 to 6 days. Approaches to the treatment of psoriasis include reducing the hyperproliferation of keratinocytes, effecting their differentiation, reducing inflammation, and modulating the cellular immune system (van de Kerkhof, 2003).

Psoriasis tends to flare for weeks or months, with intermittent periods of remission. According to a 1979 report published by the National Center for Health Statistics (NCHS) on the prevalence of psoriasis, over 2/3 of psoriasis patients are aged 45 to 74 years.

Psoriatic plaques commonly occur on knees, elbows, trunk, and scalp. There is often considerable discomfort caused by fissured skin and itching. In some cases, there may be pitting, ridging, and discoloration of fingernails and toenails. Psoriatic arthritis accompanies psoriasis in about 10% to 30% of patients. For many patients, the psychological impact of the disease is quite severe. Patients report dissatisfaction with current therapies, suggesting there is a significant unmet need in the treatment of this condition (Mayo Clinic, 2002; National Psoriasis Foundation, 2003).

2.4 Scientific Rationale for Development

Allergan decided to develop an oral formulation of tazarotene since it is effective in psoriasis when applied topically, is rapidly metabolized and excreted, and has high specificity for ß and ? retinoic acid receptors (RARs) with little binding affinity for RARa and none for RXR. These features led to the hypothesis that tazarotene could be an effective oral therapy for

psoriasis and could prove to be a safer alternative than other oral systemic retinoids and some other systemic treatments for psoriasis.

Naturally occurring retinoids, such as all-trans retinoic acid, 13-cis-retinoic acid, 9-cis-retinoic acid, and other metabolites, are essential for normal epithelial cell proliferation and differentiation, and embryo fetal development. They also play a critical role in several physiological processes, including vision, formation of lipids, and bone metabolism. The retinoids, all-trans-retinoic acid and 13-cis-retinoic acid, are in use as drugs for the treatment of skin disease. All-trans-retinoic acid is available as Retin-A for the treatment of acne; as Renova for use as an adjunctive agent for use in the mitigation (palliation) of fine wrinkles, mottled hyperpigmentation, and tactile roughness of facial skin in patients who do not achieve such palliation using comprehensive skin care and sun avoidance programs alone; and as Vesanoid for the induction of remission in patients with acute promyelocytic leukemia. 13-cis-retinoic acid is available as Accutane for the treatment of severe recalcitrant nodular acne. All-trans-retinoic acid and its stereoisomers, 13-cis-retinoic acid and 9-cis-retinoic acid, are the natural ligands for the RARs, whereas RXRs are activated by the natural ligand 9-cis retinoic acid. Because the isomers are readily interconverted from one to another, each can activate both RAR and RXR receptors either directly or indirectly. This feature may be important in explaining some crucial differences between tazarotene and other retinoids. Retinoids may have many different clinical effects depending on which receptor subtypes are activated. For example, "traditional" retinoid side effects, such as effects on lipids, liver, epistaxis, and eye irritation and dryness, may be associated with either RARα and/or RXR receptors. Tazarotenic acid may be less likely to cause these side effects as it binds minimally to RARα receptors and does not bind at all to RXR receptors.

Synthetic retinoids include etretinate (Tigason for the treatment of psoriasis, no longer marketed in the United States) and acitretin (Soriatane for the treatment of severe psoriasis in adults). Both acitretin and etretinate can activate all the RAR-subtypes, that is RARa, ß, and ?. It is unknown whether acitretin or its metabolites, including etretinate, can activate RXR. Bexarotene (Targretin for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least 1 prior systemic therapy) selectively binds and activates retinoid X receptor subtypes (RXRa, RXRß, and RXR?). As well as

forming homodimers (RXR with RXR), RXRs can form heterodimers with various other receptor partners including RARs, vitamin D receptor, thyroid receptor, and peroxisome proliferator activator receptors (PPARs).

Because all currently available retinoids for systemic use (all-trans-retinoic acid, 13-cis-retinoic acid, acitretin, and bexarotene) can activate all RAR-subtypes and in some instances RXR either directly or indirectly, while tazarotene has a much more selective binding and activation profile (RARß, and ? primarily with little propensity to activate RARa and none for RXR), there is a good possibility of a more selective and thus improved adverse event profile with oral tazarotene. Additionally, the relatively short half-life (7 to 12 hours) of tazarotenic acid (the major active metabolite of tazarotene) means that the drug is cleared from the body within a few days. This may be contrasted with the long-term storage in body fat that occurs with etretinate, a metabolite of acitretin that can be formed in the presence of alcohol. This is of major concern for females of childbearing potential, who currently are obliged to avoid pregnancy for 3 years following the end of treatment with acitretin. Thus, tazarotene possesses a clear advantage in this regard, since women who wish to become pregnant will not face an unusually long washout period.

2.5 Other Non-retinoid, Systemic, Psoriasis Treatments

The current nonretinoid systemic treatments for psoriasis include the use of cyclosporine, methotrexate, and methoxsalen (together with UVA). All are associated with significant toxicities. Recently, several biologics were approved for the treatment of psoriasis, including alefacept (Amevive), which interferes with lymphocyte activation and reduces pathogenic T-cells; efalizumab (Raptiva), which inhibits T-cell activation, and etanercept (Enbrel), which blocks inflammatory cytokines. Because these products modulate the immune system, there are concerns about their safety with long-term use. Some of the problems associated with the current nonretinoid systemic treatments for psoriasis and the recently approved biologics, based on their product labeling, are discussed below.

Neoral (cyclosporine) is indicated “for the treatment of adult, nonimmunocompromised patients with severe (ie, extensive and/or disabling), recalcitrant, plaque psoriasis who have

failed to respond to at least 1 systemic therapy (eg, PUVA, retinoids, or methotrexate) or in patients for whom other systemic therapies are contraindicated, or cannot be tolerated. While rebound rarely occurs, most patients will experience relapse with Neoral as with other therapies upon cessation of treatment." The principal adverse reactions associated with the use of cyclosporine in patients with psoriasis are renal dysfunction, headache, hypertension, hypertriglyceridemia, hirsutism/hypertrichosis, paresthesia or hyperesthesia, influenza-like symptoms, nausea/vomiting, diarrhea, abdominal discomfort, lethargy, and musculoskeletal or joint pain. Labeling notes that the frequency and severity of serum creatinine elevations increase with the dose and duration of cyclosporine therapy and may result in irreversible renal damage without dose reduction or discontinuation.

Methotrexate is indicated "in the symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy, but only when the diagnosis has been established, as by biopsy and/or after dermatologic consultation." The prescribing information indicates that it "has the potential for serious toxicity. Toxic effects may be related in frequency and severity to dose or frequency of administration but have been seen at all doses. Because they can occur at any time during therapy, it is necessary to follow patients on methotrexate closely." Methotrexate use most notably carries the risk of hepatic fibrosis and cirrhosis, which are not always evident on liver function tests. Other more rare, but potentially life-threatening adverse effects include pancytopenia, lymphoproliferative disorders, and acute pneumonitis.

Photochemotherapy (methoxsalen with long wave UVA radiation) is indicated "for the symptomatic control of severe, recalcitrant, disabling psoriasis not adequately responsive to other forms of therapy and when the diagnosis has been supported by biopsy. Because of the possibilities of ocular damage, aging of the skin, and skin cancer (including melanoma), the patient should be fully informed by the physician of the risks inherent in this therapy.

Amevive (alefacept) is indicated "for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy". Because of the effects on lymphocytes, there are concerns about malignancies and infections. The most serious adverse reactions were lymphopenia, malignancies, serious infections requiring

hospitalization and hypersensitivity reactions. In addition, alefacept treatment involves a course of weekly intramuscular injections or an intravenous bolus weekly for 12 weeks, which are less convenient than a once-daily capsule (TAZORAL™).

Raptiva (efalizumab)is indicated "for the treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy." The most serious adverse reactions observed during treatment with efalizumab were serious infections, malignancies, thrombocytopenia, worsening of psoriasis and manifestation of other variants of psoriasis. Again the effects of long-term use are unknown, but increases in infection and malignancies are of potential concern.

Enbrel (etanercept), a TNF inhibitor, has recently received approval for the treatment of chronic, moderate to severe plaque psoriasis in adults, as well as for psoriatic arthritis. Although most adverse events are injection-site reactions, there have been infrequent observations of demyelinating disorders such as multiple sclerosis, allergic reactions, and aplastic anemia. There is a biologic basis for concern about the possible association of TNF inhibitors and lymphoma.

The above discussion illustrates that current treatments for psoriasis are far from ideal and new effective and potentially safer alternatives should be of great interest to patients and physicians. TAZORAL™ is effective in the treatment of moderate to very severe psoriasis and offers potentially important improvements in safety compared with some current systemic treatments. In addition, the availability of TAZORAL™ in a capsule that is taken once per day, with or without food, offers a simpler solution for the treatment of psoriasis than most current options.

3 NONCLINICAL PHARMACOLOGY AND TOXICOLOGY

The nonclinical pharmacologic, pharmacokinetic, and toxicological profile of oral and its active metabolite tazarotenic acid has been extensively evaluated in a variety of animal species. Tazarotenic acid binds selectively to RARβ and RARγ and decreases hyperproliferation and inflammation in psoriasis. The metabolic pathways of tazarotene were similar among man and animals with no gender differences and included ester

hydrolysis to form the active free acid (tazarotenic acid) and oxidation to form inactive sulfoxide and sulfone metabolites which were eliminated through urinary and fecal pathways.

3.1 Repeat-Dose Toxicology

Oral administration of tazarotene in multiple animal species produced effects that were characteristic of retinoid toxicity, with some toxicological selectivity that mirrors the selective RARβ and RARγ receptor activation of this drug. Target effects included skeletal, hepatic (including serum lipids), dermal, and testicular. Skeletal effects reflect activation of the bone and articular remodeling process, and include premature epiphyseal closure in younger animals, and vertebral hyperostosis in older animals. Hypercalcemia at very high doses was associated with systemic mineralization, renal failure, and mortality. Reversible increases in serum alkaline phosphatase were observed. Hepatic effects in animals included mild, reversible increases in serum enzymes and/or minimal hypertriglyceridemia and hepatocellular vacuolization and hypertrophy. Dermal effects were minimal erythema and were limited to dogs. Reversible testicular degenerative effects were observed in dogs at high doses. Similar testicular effects observed in dogs, but not humans given isotretinoin or acitretin, suggest a low risk of similar effects in humans given oral tazarotene.

3.2 Genotoxicity and Carcinogenicity

Tazarotene is not mutagenic or clastogenic. No carcinogenic effects were observed in rats following oral administration of tazarotene for 2 years or in mice following topical application of 0.1% tazarotene gel for 21 months.

3.3 Reproductive and Developmental Toxicity

No impairment of fertility or mating performance occurred in male rats treated for 70 days prior to mating with an oral dose of 1 mg/kg/day tazarotene. At a higher dose of 3 mg/kg/day, systemic toxicity characteristic of retinoids including effects on reproductive organs were observed, but with no effects on mating performance, fertility or the development of offspring. These male reproductive effects have been observed in animals, but not humans, given other retinoids. The lack of germ cell mutagenicity and lack of

developmental toxicity following paternal exposure demonstrates that tazarotene does not affect the reproductive outcome of naïve females mated with treated males.

No effect on parameters of mating performance or fertility was observed in female rats treated for 15 days prior to mating and continuing through day 7 of gestation (implantation) with oral doses of tazarotene up to 2 mg/kg/day. A decrease in the number of estrous stages and classical developmental effects of retinoids were observed at that dose.

As with other retinoids, when tazarotene was given orally to animals in embryofetal developmental toxicity studies, developmental delays, teratogenic effects, and post-implantation loss were observed with oral doses of tazarotene of 0.2 mg/kg/day.

In pre- and postnatal development studies in rats, F_1 stillbirths, decreased survival and body weights, retinoid malformations, developmental and behavioral delays and decreased reproductive capabilities of F_1 females were observed at an oral dose of 1 mg/kg/day.

Data suggest that tazarotene may be transferred to offspring via the milk of lactating animals; it is not known whether the drug is excreted in human milk.

4.0 CLINICAL PHARMACOKINETICS

4.1 Absorption, Distribution, Metabolism, and Excretion

Following oral administration of a 6 mg tazarotene solution in man, at least 83% of a tazarotene dose is rapidly absorbed and hydrolyzed quickly and extensively by serine-type esterases to tazarotenic acid, the only active entity in the systemic circulation. When 4.5 mg of tazarotene was administered once daily to healthy subjects for 2 weeks, tazarotenic acid concentration peaked at 95.2 ng/mL at 2 to 3 hours postdose. Tazarotenic acid is further metabolized to an inactive sulfoxide metabolite via CYP2C8 and/or flavin monooxygenase enzymes in the liver. Systemic drug exposure increased proportionally with doses up to 6.3 mg/day. Following administration of tazarotene once-daily orally, plasma tazarotenic acid has an effective half-life ranging from 7 to 12 hours at clinical doses.

Tazarotenic acid is highly bound to plasma proteins, with an unbound fraction of < 1%. It is not widely distributed to body tissues and there is no depot effect. Fecal elimination is the predominant elimination pathway, with almost 50% of the administered dose eliminated in the feces as tazarotenic acid. Approximately 20% of the dose was excreted in the urine as the inactive sulfoxide metabolite of tazarotenic acid

When 4.5 mg tazarotene was administered to healthy male subjects once daily for 2 weeks, only a very small proportion ($1/10,000^{th}$) of the oral dose was distributed to the semen as tazarotenic acid at 3 hours postdose. Semen generally was devoid of drug at 7 days after the last dose. The possibility of direct exposure of tazarotenic acid in semen to a human embryo through sexual intercourse is very small since human female cervix uteri is closed with a viscous plug for the duration of pregnancy after fertilization. Furthermore, the possibility of vaginal absorption of drug in semen and systemic exposure to the embryo/fetus and teratogenic risk is very small since the maximal vaginal dose is at least 11,600 times lower than the highest dose that did not affect embryofetal development in animals. Based on these data, there is no recommendation for the use of male condoms either during or after treatment with tazarotene

4.2 Examination of Subgroups and Potential Interactions

Peak tazarotenic acid concentrations observed in the phase 2 and 3 studies were consistently similar to those reported in the phase 1 pharmacokinetic studies in healthy subjects, indicating that systemic drug exposure is similar between psoriasis patients and healthy subjects. There was no evidence of drug accumulation over time with treatment for up to 52 weeks in the phase 3 studies. Subgroup analyses demonstrated that there is no need to adjust dose based on gender, body weight, or other demographic factors. In addition, coadministration of food had no influence on the bioavailability of tazarotenic acid. Tazarotenic acid excretion is not expected to be altered in the elderly and in patients with renal impairment since urinary excretion is minimal. The pharmacokinetics of oral tazarotene have not been evaluated in patients with hepatic impairment.

Tazarotenic acid neither induces nor inhibits cytochrome P450 enzyme activities at the dose of 4.5mg/day. In 3 interaction studies involving coadministration of TAZORAL™ and oral contraceptives (Ortho-Novum 1/35 and Ortho Tri-Cyclen) in healthy women of childbearing potential, tazarotenic acid did not affect the pharmacokinetics and pharmacodynamics of the components of these contraceptives.

5.0 OVERVIEW OF CLINICAL TRIALS AND STUDY DESIGN

5.1 Study Design

The efficacy of TAZORAL™ is based on the results of 1 phase 2 study and 4 phase 3 studies of patients with moderate to very severe plaque psoriasis. The phase 2 study (190168-026P) evaluated doses of 0.4 to 6.3 mg TAZORAL™ once daily. The phase 3 studies included 2 multicenter, double-blind, randomized, placebo-controlled studies comparing 4.5 mg versus placebo once daily for 12 weeks (studies 190168-048P and 190168-049P), and 2 open-label safety studies (190168-050P and 190168-052P) with no control group. Study 190168-050P evaluated the safety and efficacy of TAZORAL™ 4.5 mg once daily for up to 52 weeks. Study 190168-052P evaluated efficacy and safety over a further 12-week treatment period in patients who did not improve after 12 weeks of treatment with TAZORAL™ 4.5 mg or placebo in study 190168-048P or 190168-049P, thus providing experience with treatment for 24 weeks in patients who were treated with TAZORAL™ in the previous double-blind study. A follow-up posttreatment period of 4 weeks in study 190168-026P and 12 weeks in the other 4 studies allowed evaluation of the duration of the effects of on psoriatic lesions.

The principal design features are summarized in the following table (Table 5.1-1).

Table 5.1-1 Design Features of Clinical Studies of Psoriasis

Feature	190168-026P Stage 1	190168-026P Stage 2	190168-048P and 190168–049P	190168-050P	190168-052P
Dose per day	0.4, 0.6, 0.8, 1.1 mg	2.1, 2.8, 4.2, 6.3 mg	4.5 mg	4.5 mg	4.5 mg
Randomization	Randomized	Nonrandomized	Randomized	Nonrandomized	Randomized in prior study[a]
Blinding	Double-blind	Open-label	Double-blind	Open-label	Open-label
Control treatment	Placebo	None	Placebo	None	None
Patient population	Plaque psoriasis ≥ 20% body surface area, overall plaque elevation ≥ moderate	Plaque psoriasis ≥ 20% body surface area, overall plaque elevation ≥ moderate	Moderate to very severe plaque psoriasis ≥ 10% body surface area, overall lesional assessment score ≥ 3 (moderate)	Moderate to very severe plaque psoriasis ≥ 10% body surface area, overall lesional assessment score ≥ 3 (moderate)	Completed 12 weeks treatment in 190168-048P or -049P with no change or increase in overall lesional assessment (score ≥ 3)
Study duration and visit schedule	12-week treatment (visits day 0, weeks 1, 2, 4, 8, and 12) and 4-week posttreatment follow-up (visits weeks 14 and 16)	12-week treatment (visits day 0, weeks 1, 2, 4, 6, 8, 10, and 12) and 4-week posttreatment follow-up (visits weeks 14 and 16)	12-week treatment (visits weeks 0, 1, 2, 4, 8, and 12) and 12-week posttreatment follow-up (visits weeks 16, 20, and 24)	52-week treatment (visits weeks 0, 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52) and 12-week posttreatment follow-up (visits weeks 56, 60, and 64)	12-week treatment (visits day 0, weeks 1, 2, 4, 8, and 12) and 12-week posttreatment follow-up (visits weeks 16, 20, and 24)
Primary efficacy variables	Plaque elevation, overall lesional assessment	Plaque elevation, overall lesional assessment	Overall lesional assessment	Overall lesional assessment (no variable was defined as primary in protocol)	Overall lesional assessment (no variable was defined as primary in protocol)
Secondary and other efficacy variables	Global response to treatment, body surface area of involvement, scaling, erythema	Global response to treatment, body surface area of involvement, scaling, erythema	Plaque elevation, scaling, erythema, body surface area, overall global response to treatment, pruritus, scalp psoriasis, nail psoriasis	Plaque elevation, scaling, erythema, body surface area, overall global response to treatment, pruritus, scalp psoriasis, nail psoriasis	Plaque elevation, scaling, erythema, body surface area involvement, overall global response to treatment

[a] Randomized in study 190168-048P or 190168-049P.

5.2 Dose Selection

The TAZORAL™ dose of 4.5 mg once daily was chosen for the phase 3 studies based on the pharmacokinetic profile of tazarotene and on the efficacy and safety results of the phase 2 dose-escalation study. The phase 2 dose-escalation study of patients with moderate to severe plaque psoriasis (study 190168-026P) found that once-daily doses of 4.2 mg and 6.3 mg TAZORAL™ resulted in clinically significant improvements, whereas lower daily doses (0.4 mg to 2.8 mg) showed little antipsoriatic effect. The 4.2 mg dose appeared to be at least as effective as the 6.3 mg dose and was associated with fewer adverse events.

In the phase 2 study (190168-026P), clinical success was defined as an overall lesional assessment (OLA) score of mild, minimal, or none. There was no apparent dose response and only modest evidence of efficacy compared with placebo in the range of 0.4 to 2.8 mg/day (16.0% to 42.3% of patients had clinical success during the treatment period and 12.0% to 36.4% during the posttreatment period). However, there was a clinically significant increase in the incidence of clinical success both in patients treated with 4.2 mg/day (78.6% during the treatment period and 57.1% during the posttreatment period) and in patients treated with 6.3 mg/day (56.3% during the treatment period and 50.0% during the posttreatment period).

Similarly, TAZORAL™ in the dose range of 0.4 to 2.8 mg/day showed no apparent dose response and only modest evidence of efficacy for plaque elevation, erythema, and scaling scores as well as body surface involvement and global response to treatment during the treatment and posttreatment periods. In contrast, there were clinically significant improvements in these parameters in patients treated with 4.2 mg or 6.3 mg/day during treatment and posttreatment.

The commercial dose of 4.5 mg rather than 4.2 mg was chosen for formulation and manufacturing reasons. It would not be reasonable to expect differences in efficacy and safety between the 4.2 mg dose evaluated in phase 2 and the 4.5 mg dose taken into phase 3 trials.

Nonlinear mixed effects modeling was performed on blood sample data from psoriasis patients (studies 190168-048P, 190168-049P, and 190168-050P) to evaluate the effects of demographic variables (age, weight, height, sex, race, smoking, and alcohol drinking status), serum albumin concentration, creatinine clearance, and tazarotene dose on tazarotenic acid pharmacokinetic parameters. As none of these variables was found to have a consistent significant effect on tazarotenic acid pharmacokinetics, there is no need to adjust the dose of TAZORAL™ based on sex, body weight, or other demographic factors.

5.3 Efficacy Endpoints in Phase 3 Studies

The primary efficacy variable in the phase 3 studies was the OLA score, which was based on a 6-point scale, using photonumeric guidelines, that was developed by Allergan in consultation with the FDA to evaluate overall psoriasis severity. In the phase 3 studies, at least a 2-grade decrease in the OLA was defined by Allergan as a "clinical success" because this represents substantial clinical improvement. In addition, analyses also were performed on the numbers of patients whose OLA scores improved to minimal or none.

The OLA scale takes into account the most important features of psoriasis (primarily plaque elevation, but also takes into account scaling, and erythema). PASI (Psoriasis Area and Severity Index) was not used because of the known limitations (plaque elevation, scaling, and erythema are given equal weight and body surface area measurements are difficult to make accurately and reproducibly). Use of the OLA has allowed investigators to evaluate the severity of psoriasis in a consistent manner.

Secondary efficacy variables included plaque elevation, scaling, erythema, and body surface area involvement. These are standard efficacy assessments used in clinical trials of treatments for psoriasis. Other efficacy variables assessed included pruritus, scalp psoriasis, nail psoriasis, and overall physician's assessment of the global response to treatment (with the aid of baseline photographs). In addition, patients rated their satisfaction with the study treatment in 3 of the phase 3 studies (190168-048P, 190168-049P, and 190168-052P).

The same efficacy data were collected in all phase 3 studies except that scalp and nail psoriasis were not evaluated in study 190168-052P.

5.4 Statistical Methods and Analytical Issues

Efficacy analyses were performed using an intent-to-treat (ITT) population, defined as all randomized patients, regardless of whether or not treatment was received or administered. Safety analyses were based on a safety population which included all treated patients.

For the principal phase 3 studies (190168-048P and 190168-049P), the primary analysis of the OLA was based on the proportion of patients who had at least a 2-grade decrease from baseline (clinical success). The primary endpoint during the treatment period was the week 12 assessment. In the analyses of OLA scores and all other secondary efficacy variables (except scalp and nail psoriasis), missing data were imputed using a last observation carried forward (LOCF) approach.

In studies 190168-048P and 190168-049P, the following statistical methods for comparisons between TAZORAL™ and placebo were used:

- OLA (2-grade decrease, none/minimal), global response to treatment (moderate response or better; marked response or better): Cochran-Mantel-Haenszel test stratified by center. Treatment-by-center interactions were analyzed using the Breslow-Day test. Centers with small sample sizes were pooled using an algorithm based on geographic location. For pooling of the 2 placebo-controlled studies treatment-by-study interactions were also analyzed by the Breslow-Day test. There were no significant treatment-by-study interactions ($p > 0.10$), indicating that the 2 studies may be pooled.
- Plaque elevation, scaling, erythema, and body surface involvement: Wilcoxon rank sum test for baseline and changes from baseline at follow-up visits.
- Adverse event data were summarized by frequency tables and analyzed by Pearson's chi-square test or Fisher's exact test if at least 25% of the cell sizes were < 5.
- Laboratory data were analyzed by Wilcoxon rank sum test and shift tables. The median value was chosen as a measure of central tendency because nonparametric statistical methods were used.
- Radiographic x-ray, bone density, neuropsychiatric evaluations, and ophthalmological evaluation data were summarized by frequency tables.

6.0 CLINICAL EFFICACY

Substantial evidence of the efficacy of TAZORAL™ 4.5 mg capsules was demonstrated by results that were statistically and clinically superior to those observed with placebo treatment and that were consistent across all studies in which efficacy was evaluated.

6.1 Patient Population

The studies of patients with psoriasis included patients with at least moderate, stable plaque psoriasis that involved at least 10% of their body surface area (20% in the dose-ranging study 190168-026P) and who were on a stable dose of any concomitant medication for at least 3 months. The studies of TAZORAL™ excluded patients who had certain conditions and/or who used certain concomitant medications that might have prevented an adequate evaluation of the study medication, but who otherwise would be considered for treatment with an oral retinoid. Only study 190168-026P excluded females of childbearing potential.

The patient population included in the pivotal trials (studies 190168-048P, 190168-049P, and 190168-50P) was somewhat different in terms of age and gender from the adult US population with psoriasis, as reported in 2 population-based surveys conducted in the US. One was a survey of adults with psoriasis (Koo, 1996) and the other was the National Health Interview Survey (NHIS, 1996) to evaluate the prevalence of psoriasis and demographic characteristics of patients with psoriasis. The TAZORAL™ pivotal studies included a greater proportion of males (76%) than either of the 2 US surveys (47% and 54%). The proportion of clinical trial subjects aged > 65 relative to the NHIS was 9% vs 16%, respectively (similar data not available from the Koo study). (The clinical trials did not have an upper age limit for inclusion.) Approximately 77% of study patients reported their race/ethnicity as white compared with 92% and 96% in the Koo study and NHIS, respectively. Adult women of childbearing age (18 - 45 years of age) comprised 14% of the clinical trial population, and make up about 20% of the total U.S. psoriasis population. Also noteworthy is that, according to the NHIS, only 8% of all prevalent psoriasis is in children < 18 years of age.

6.1.1 Patient Disposition and Baseline Characteristics

The placebo-controlled, double-blind studies, including phase 2 study 190168-026P that included a placebo control in Stage 1, included 871 patients in the ITT population who were treated with either TAZORAL™ or placebo (Table 6.1.1-1). The open-label studies included 312 patients (306 ITT patients) in study 190168-052P who had been treated with TAZORAL™ or placebo in the double-blind, placebo-controlled studies plus 263 additional patients in study 190168-050P who were treated with TAZORAL™ for the first time. The only patients who were excluded from the ITT population were 16 patients in study 190168-048P (8 in the TAZORAL™ group and 8 in the placebo group) and 6 patients in study 190168-052P from a single site where there were compliance problems in recording efficacy data. (The data were analyzed with and without these excluded patients and no significant differences were found.) Discontinuation rates from each study are summarized in Table 6.1.1-1.

All studies included patients with moderate to severe or very severe plaque psoriasis. Table 6.1.1-2 summarizes the overall baseline characteristics of patients by study.

Table 6.1.1-1 Patient Disposition, All Studies in Patients with Psoriasis (ITT Population)

	Number (%) of Patients									
	Study Number									
	190168-048P [a]/ 190168-049P		190168-050P	190168-052P [a]		190168-026P				
	Taz 4.5 mg	Placebo	Taz 4.5 mg	Taz/Taz 4.5 mg	Placebo/ Taz 4.5 mg	Stage 1 Taz [b]	Stage 1 Placebo	Stage 2A Taz [c]	Stage 2B Taz 4.2 mg	Stage 2C Taz 6.3 mg
Dispensed study drug	340	350	263	89	217	105	25	21	14	16
Completed treatment period	307 (90.3)	314 (89.7)	156 (59.3)	78 (87.6)	195 (89.9)	77 (73.3)	16 (64.0)	16 (76.2)	12 (85.7)	12 (75.0)
Discontinued study during treatment period	33 (9.7)	36 (10.3)	107 (40.7)	11 (12.4)	22 (10.1)	28 (26.7)	9 (36.0)	5 (23.8)	2 (14.3)	4 (25.0)
Adverse events [d]	12 (3.5)	9 (2.6)	38 (14.4)	5 (5.6)	5 (2.3)	2 (1.9)	3 (12.0)	2 (9.5)	0 (0.0)	2 (12.5)
Lack of efficacy	4 (1.2)	12 (3.4)	20 (7.6)	2 (2.2)	7 (3.2)	15 (14.3)	4 (16.0)	1 (4.8)	0 (0.0)	1 (6.3)
Other reasons	17 (5.0)	15 (4.3)	49 (18.6)	4 (4.5)	10 (4.6)	11 (10.5)	2 (8.0)	2 (9.5)	2 (14.3)	1 (6.3)
Entered posttreatment period [e]	308	315	175	82	197	77	16	16	12	12
Completed posttreatment period	179 (58.1)	72 (22.9)	113 (64.6)	61 (74.4)	156 (79.2)	74 (96.1)	13 (81.3)	16 (100.0)	12 (100.0)	12 (100.0)
Discontinued during posttreatment period	129 (41.9)	243 (77.1)	62 (35.4)	21 (25.6)	41 (20.8)	3 (3.9)	3 (18.8)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse events	1 (0.3)	2 (0.6)	1 (0.6)	1 (1.2)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Need for treatment/lack of efficacy	117 (38.0)	233 (74.0)	47 (26.9)	14 (17.1)	27 (13.7)	2 (2.6)	2 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)
Other reasons	11 (3.6)	8 (2.5)	14 (8.0)	6 (7.3)	13 (6.6)	1 (1.3)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)

[a] 16 and 6 patients were excluded from the ITT population of 190168-048P and 190168-052P, respectively, due to compliance problems for efficacy data at 1 site.

[b] TAZORAL™ treatment groups: 0.4 mg (N=25), 0.6 mg (N=28), 0.8 mg (N=26), 1.1 mg (N=26).

[c] TAZORAL™ treatment groups: 2.1 mg (N=11), 2.8 mg (N=10).

[d] Includes patients in studies 190168-048P, 190168-049P, 190168-050P, and 190168-052P who discontinued treatment and were discontinued from the study, and patients who were discontinued from the treatment period but not from the study.

[e] Includes patients who completed treatment period but did not enter posttreatment period (100 TAZORAL™, 233 placebo in 190168-048P/190168-049P; 23 in 190168-050P; and 10 4.5 mg → 4.5 mg, 15 placebo → 4.5 mg in 190168-052P). Of these patients in the 190168-048P/049P studies, 89 in the TAZORAL™ and 217 in the placebo group went into the 190168-052P study.

Table 6.1.1-2 Baseline Patient Characteristics, All Studies of Patients with Psoriasis (ITT Population)

	Study Number								
	190168-048P/ 190168-049P		190168-050P	190168-052P	190168-026P				
					Stage 1		Stage 2A	Stage 2B	Stage 2C
Characteristic	**Taz 4.5 mg (N = 340)**	**Placebo (N = 350)**	**Taz 4.5 mg (N = 263)**	**Taz 4.5 mg (N = 306) [a]**	**Taz [b] (N = 105)**	**Placebo (N = 25)**	**Taz [c] (N = 21)**	**Taz 4.2 mg (N = 14)**	**Taz 6.3 mg (N = 16)**
Age (years)									
Mean ± SD	47.3 ± 12.9	47.1 ± 12.5	47.5 ± 13.0	46.3 ± 13.1	48.1	49.8 ± 11.8	48.8	49.3 ± 14.2	50.9 ± 12.6
Range	21 – 81	21 – 79	20 – 80	21 – 76	22 – 86	30 – 70	26 – 74	36 – 85	30 – 76
Sex, N (%)									
Male	245 (72.1)	257 (73.4)	180 (68.4)	240 (78.4)	90 (85.7)	20 (80.0)	15 (71.4)	12 (85.7)	10 (62.5)
Female	95 (27.9)	93 (26.6)	83 (31.6)	66 (21.6)	15 (14.3)	5 (20.0)	6 (28.6)	2 (14.3)	6 (37.5)
Race, N (%)									
Caucasian	260 (76.5)	265 (75.7)	219 (83.3)	226 (73.9)	74 (70.5)	19 (76.0)	16 (76.2)	8 (57.1)	14 (87.5)
Black	8 (2.4)	10 (2.9)	9 (3.4)	6 (2.0)	3 (2.9)	2 (8.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hispanic	64 (18.8)	66 (18.9)	23 (8.7)	67 (21.9)	23 (21.9)	3 (12.0)	4 (19.0)	6 (42.9)	2 (12.5)
Asian	4 (1.2)	3 (0.9)	5 (1.9)	2 (0.7)	5 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	4 (1.2)	6 (1.7)	7 (2.7)	5 (1.6)	0 (0.0)	1 (4.0)	1 (4.8)	0 (0.0)	0 (0.0)
Body Weight (kg)									
Mean ± SD	90.7 ± 20.8	91.2 ± 21.2	93.6 ± 20.0	91.6 ± 39.7	90.1	84.0 ± 16.5	89.1	95.9 ± 22.3	88.7 ± 27.2
Range	47.2 – 158.0	48.1 – 172.4	44.5 – 154.2	48.8 – 154.2	47 – 165	55 – 136	60 – 134	60.0 – 140.9	32.7 – 145.5
Mean OLA Score	3.4	3.4	3.4	3.4	3.6	3.7	3.3	3.3	3.3
Duration of Psoriasis (years)					Not reported				
Mean ± SD	17.9 ± 11.6	17.9 ± 11.9	21.3 ± 13.0	17.7 ± 12.2					
Range	0.3 – 61.0	0.3 – 61.0	1 – 58.5	0.3 – 61.0					

SD = standard deviation. Value provided only if available from individual study report.

[a] Study includes patients who completed 190168-048P and 190168-049P; 89 received TAZORAL™4.5 mg and 217 received placebo in prior study.

[b] TAZORAL™ treatment groups: 0.4 mg (N=25), 0.6 mg (N=28), 0.8 mg (N=26), 1.1 mg (N=26).

[c] TAZORAL™ treatment groups: 2.1 mg (N=11), 2.8 mg (N=10).

6.2 Efficacy Results

For each efficacy variable, the results from the 2 pivotal, phase 3 studies (190168-048P and 190168-049P) were very similar. For this reason, in the following sections the combined results of these studies are the focus of the discussion and the individual results from each study also are presented in the tables for completeness. The results of the phase 2 dose-ranging study (190168-026P) and the phase 3 open-label studies (190168-050P and 190168-052P) are briefly summarized for each variable and provide supportive data.

6.2.1 Overall Lesional Assessment (Primary Efficacy Variable)

Combined Phase 3 Studies

The **proportion of patients with clinical success**, defined as at least a 2-grade decrease from baseline in their OLA score, was significantly greater in the TAZORAL™ group compared with the placebo group from week 2 through week 24 ($p \leq 0.017$; Table 6.2.1-1 and Figure 6.2.1-1). The highest proportion of TAZORAL™ patients with at least a 2-grade decrease in their OLA score (31.5%) occurred at week 16, 4 weeks after treatment was completed.

Table 6.2.1-1 Number (%) of Patients with at Least a 2-Grade Decrease from Baseline in Overall Lesional Assessment (Based on LOCF) [a]

Visit	190168-048P		190168-049P		Combined	
	TAZORAL™ 4.5 mg (N = 158)	Placebo (N = 163)	TAZORAL™ 4.5 mg (N = 182)	Placebo (N = 187)	TAZORAL™ 4.5 mg (N = 340)	Placebo (N = 350)
Treatment Period [b]						
Week 1	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Week 2	3 (1.9%)	1 (0.6%)	7 (3.8%)*	0 (0.0%)	10 (2.9%)*	1 (0.3%)
Week 4	9 (5.7%)	4 (2.5%)	12 (6.6%)*	3 (1.6%)	21 (6.2%)*	7 (2.0%)
Week 8	27 (17.1%)*	6 (3.7%)	26 (14.3%)*	9 (4.8%)	53 (15.6%)*	15 (4.3%)
Week 12	43 (27.2%)*	7 (4.3%)	52 (28.6%)*	13 (7.0%)	95 (27.9%)*	20 (5.7%)
Posttreatment Period [b]						
Week 16	53 (33.5%)*	8 (4.9%)	54 (29.7%)*	11 (5.9%)	107 (31.5%)*	19 (5.4%)
Week 20	44 (27.8%)*	10 (6.1%)	46 (25.3%)*	14 (7.5%)	90 (26.5%)*	24 (6.9%)
Week 24	39 (24.7%)*	11 (6.7%)	38 (20.9%)*	13 (7.0%)	77 (22.6%)*	24 (6.9%)

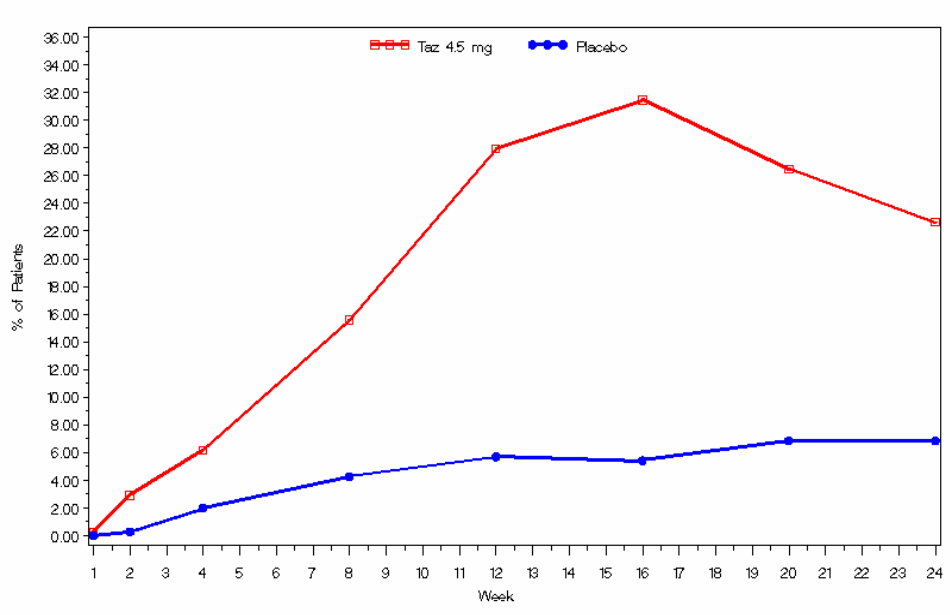
Abbreviations: LOCF = last observation carried forward

* TAZORAL™ significantly greater than placebo ($p \leq 0.017$, Cochran-Mantel-Haenszel test stratified by center).

[a] No treatment by-center effect at any time point (Breslow-Day test).

[b] Analyses performed using LOCF for the treatment and posttreatment periods.

Figure 6.2.1-1 Percentage of Patients with at Least a 2-Grade Decrease from Baseline in Overall Lesional Assessment (Based on LOCF); Studies 190168-048P and 190168-049P Combined



The proportion of patients with at least a 1-grade decrease from baseline in OLA score for studies 190168-048P and 190168-049P was statistically different between the treatment groups from week 2 through week 24 for the combined studies ($p = 0.002$). Almost 2/3 (65.6%) of patients had at least a 1-grade decrease from baseline with TAZORAL™ treatment.

For the combined studies, the proportion of patients with an **OLA score of minimal or none** was significantly greater in the TAZORAL™ group compared with the placebo group from week 8 through week 24 ($p \leq 0.035$; Table 6.2.1-3 and Figure 6.2.1-2). The highest proportion of patients with an OLA score of minimal or none (21.8%) occurred at week 16, 4 weeks after treatment was completed.

Table 6.2.1-3 Number (%) of Patients with an OLA Score of Minimal or None (Based on LOCF) [a]

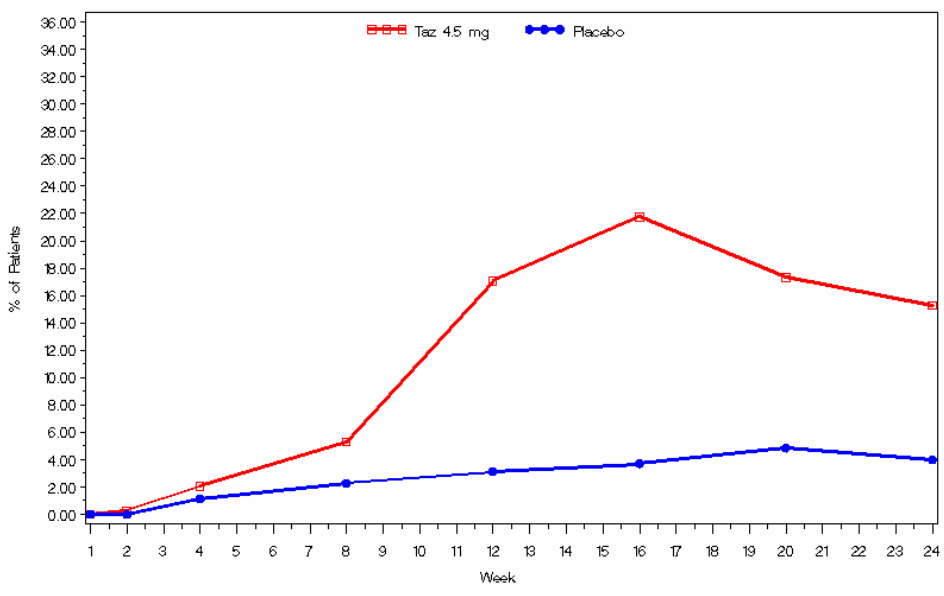
Visit	190168-048P		190168-049P		Combined	
	TAZORAL™ 4.5 mg (N = 158)	Placebo (N = 163)	TAZORAL™ 4.5 mg (N = 182)	Placebo (N = 187)	TAZORAL™ 4.5 mg (N = 340)	Placebo (N = 350)
Treatment Period [b]						
Week 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 2	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Week 4	3 (1.9%)	2 (1.2%)	4 (2.2%)	2 (1.1%)	7 (2.1%)	4 (1.1%)
Week 8	8 (5.1%)*	1 (0.6%)	10 (5.5%)	7 (3.7%)	18 (5.3%)*	8 (2.3%)
Week 12	24 (15.2%)*	2 (1.2%)	34 (18.7%)*	9 (4.8%)	58 (17.1%)*	11 (3.1%)
Posttreatment Period [b]						
Week 16	38 (24.1%)*	5 (3.1%)	36 (19.8%)*	8 (4.3%)	74 (21.8%)*	13 (3.7%)
Week 20	33 (20.9%)*	7 (4.3%)	26 (14.3%)*	10 (5.3%)	59 (17.4%)*	17 (4.9%)
Week 24	28 (17.7%)*	6 (3.7%)	24 (13.2%)*	8 (4.3%)	52 (15.3%)*	14 (4.0%)

* TAZORAL™ significantly greater than placebo ($p \leq 0.035$, Cochran-Mantel-Haenszel test stratified by center).

[a] No treatment-by-center effect at any time point (Breslow-Day test).

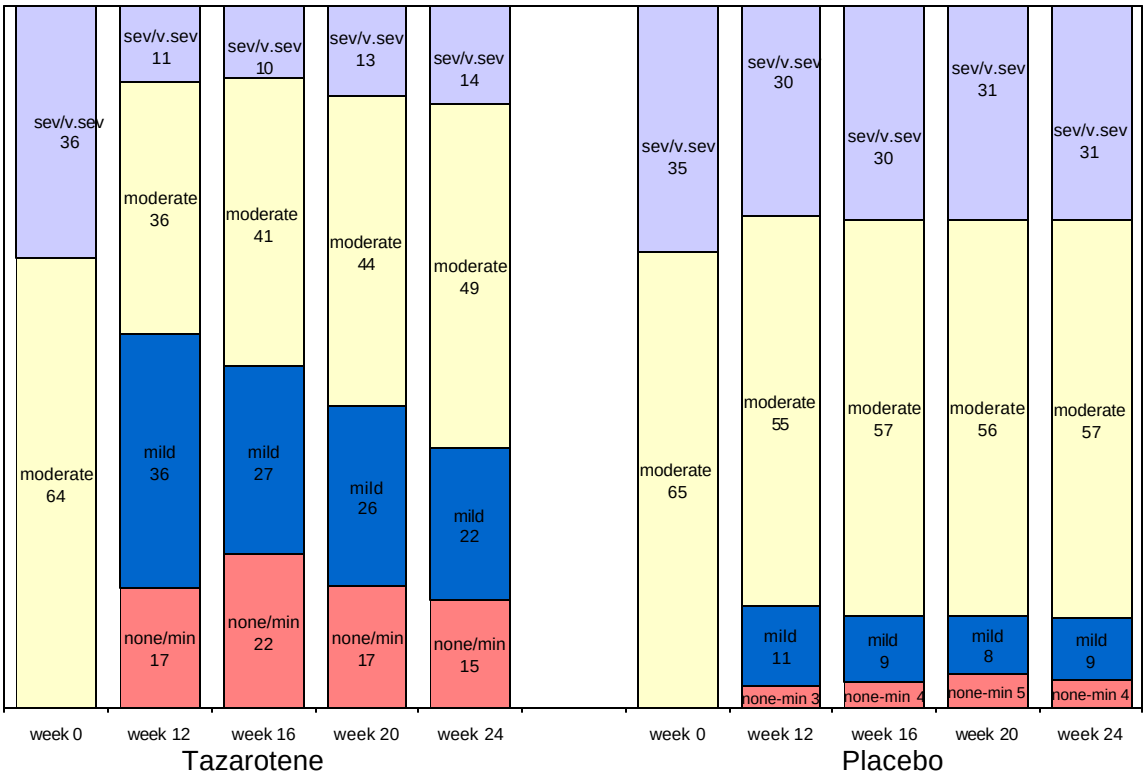
[b] Analyses performed using LOCF for the treatment and posttreatment periods.

Figure 6.2.1-2 Percentage of Patients with an OLA Score of Minimal or None (Based on LOCF); Studies 190168-048P and 190168-049P Combined:



The OLA data are presented in Figure 6.2.1-3 to demonstrate graphically how, compared with placebo, TAZORAL™ treatment shows greater decreases in the percentage of patients with OLA scores in the moderate and severe categories and greater increases in the percentage of patients whose OLA scores improved to mild or less. Over the 12-week treatment period, the percentage of patients with OLA scores indicating severe to very severe psoriasis decreased from 36% to 11% in the TAZORAL™ group and in the placebo group remained relatively unchanged, decreasing from 35% to 30%. At the end of treatment (week 12), the percentage of patients with improvement to scores of mild or less were also greater in the group than the placebo group; 53% with TAZORAL™ vs 14% with placebo.

Figure 6.2.1-3 **Percentage of Patients in Each Overall Lesional Severity Grade at Week 0, Week 12 (End of Treatment), and Weeks 16, 20, and 24 (Posttreatment)**



Other Studies

Clinical success in the open-label studies (190168-052P and 190168-050P) was defined in the same way as in the combined phase 3 studies. In study 190168-052P in patients who had no change or an increase in OLA after 12 weeks of prior treatment with TAZORAL™ or placebo, the proportion of patients with at least a 2-grade decrease from baseline (in study 190168-052P) in their OLA score progressively increased to 24.6% at week 20 in the 4.5 mg → 4.5 mg group, and to 31.1% at week 16 in the placebo → 4.5 mg group. The proportion of patients with an OLA score of minimal or none increased to 18.3% at week 16 in the 4.5 mg → 4.5 mg group, and to 19.4% at week 12 in the placebo → 4.5 mg group. These rates were similar to those for TAZORAL™-treated patients in the combined analysis of the phase 3 studies.

With treatment for 52 weeks in study 190168-050P, the proportion of patients achieving at least a 2-grade decrease in OLA score progressively increased to 35.0% at week 24, and remained at about that level (31.6% to 35.7%) for the remainder of the treatment period before starting to decline during posttreatment. Compared with the combined results for the phase 3 studies, the clinical success rate in the long-term study was slightly lower at week 12, but the maximum success rate was slightly higher. The proportion of patients achieving a score of minimal or none progressively increased to 20.2% at week 24 and remained at that level (19.0% to 21.7%) for the remainder of the treatment period before starting to decline during posttreatment. Compared with the combined results for the phase 3 studies, the proportion of patients with a score of minimal or none was lower at week 12 but the maximum proportion was similar.

6.2.2 Plaque Elevation, Scaling, and Erythema

Combined Phase 3 Studies

For the combined phase 3 studies, the mean decreases from baseline **plaque elevation score for all lesions** and for target lesions on the elbow or knee and on the trunk or limbs (other than elbow or knee) were significantly greater in the TAZORAL™ group than in the placebo group from week 1 through week 24. Similar decreases for **erythema** and **scaling** were apparent from weeks 8 and 2 respectively through week 24.

Other Studies

For patients in study 190168-052P (who had no change or an increase in their OLA score after 12 weeks of prior treatment with TAZORAL™ or placebo), the mean plaque elevation, erythema, and scaling scores progressively decreased through the 12 weeks of treatment.

With treatment for 52 weeks in study 190168-050P, the mean plaque elevation, erythema, and scaling scores progressively decreased until weeks 12 to 20 and remained at that level of improvement throughout the treatment period.

6.2.3 Body Surface Area Involved

Combined Phase 3 Studies

For studies 190168-048P and 190168-049P combined, the mean percentage of body surface involved at baseline (week 0) was similar for the TAZORAL™ (29.1%) and placebo (29.6%) groups. The mean decreases from baseline were significantly greater in the TAZORAL™ group than in the placebo group from week 8 through week 24 ($p < 0.001$). In the TAZORAL™ group, the mean change from baseline peaked at week 16 (–8.8%), 4 weeks after treatment was completed, and was still –8.2% at week 24. In the placebo group, mean changes from baseline ranged from 0.0% to –1.0%.

Other Studies

In patients in study 190168-052P who had no change or an increase in OLA after 12 weeks of prior treatment with TAZORAL™ or placebo, the mean percentage of body surface involved progressively decreased until week 16 in the 4.5 mg $\rightarrow$ 4.5 mg group (decrease of 8.6%) and until week 20 in the placebo $\rightarrow$ 4.5 mg group (decrease of 11.0%). This magnitude of reduction in body surface involved was similar to that seen in the TAZORAL™ groups in studies 190168-048P and 190168-049P combined.

With 52-week treatment in study 190168-050P, the mean body surface involved progressively decreased, reaching a maximum of 9.3% at week 32 and remaining at a similar level throughout the remainder of the treatment period (decreases of 8.8% to 9.3%). The magnitude of reduction was similar to that seen in the TAZORAL™ groups in studies 190168-048P and 190168-049P combined. These data indicate that tachyphylaxis does not seem to develop with TAZORAL™.

6.2.4 Global Response to Treatment

Combined Phase 3 Studies

For studies 190168-048P and 190168-049P combined, the percentage of patients with a **treatment response of moderate (approximately 50% improvement)** or better was greater in the TAZORAL™ group than the placebo group at each assessment time, and was significantly greater from week 4 to week 24 ($p < 0.001$, Table 6.2.4-1). In the TAZORAL™

group, the proportion of patients with a treatment response of moderate or better was greatest at weeks 12 and 16 (53.8% and 53.5%), and was 42.9% at week 24. In the placebo group, the percentage of patients with a treatment response of moderate or better ranged from 0.9% to 14.9%.

Table 6.2.4-1 Number (%) of Patients with a Treatment Response of Moderate or Better; ITT Population

Visit	190168-048P		190168-049P		Combined	
	TAZORAL™ 4.5 mg (N = 158)	Placebo (N = 163)	TAZORAL™ 4.5 mg (N = 182)	Placebo (N = 187)	TAZORAL™ 4.5 mg (N = 340)	Placebo (N = 350)
Treatment Period						
Week 1	6 (3.8)	2 (1.2)	2 (1.1)	1 (0.5)	8 (2.4)	3 (0.9)
Week 2	15 (9.5)*	5 (3.1)	8 (4.4)	9 (4.8)	23 (6.8)	14 (4.0)
Week 4	29 (18.4)*	13 (8.0)	33 (18.1)*	16 (8.6)	62 (18.2)*	29 (8.3)
Week 8	57 (36.1)*	15 (9.2)	69 (37.9)*	30 (16.0)	126 (37.1)*	45 (12.9)
Week 12	76 (48.1)*	17 (10.4)	107 (58.8)*	35 (18.7)	183 (53.8)*	52 (14.9)
Posttreatment Period						
Week 16	81 (51.3)*	16 (9.8)	101 (55.5)*	36 (19.3)	182 (53.5)*	52 (14.9)
Week 20	69 (43.7)*	17 (10.4)	90 (49.5)*	31 (16.6)	159 (46.8)*	48 (13.7)
Week 24	68 (43.0)*	17 (10.4)	78 (42.9)*	26 (13.9)	146 (42.9)*	43 (12.3)

* TAZORAL™ significantly different from placebo ($p \leq 0.050$, Pearson's chi square test).

The percentage of patients with a **treatment response of marked (approximately 75% improvement)** or better was significantly greater in the TAZORAL™ group than in the placebo group from week 8 through week 24 ($p < 0.001$). In the TAZORAL™ group, the proportion of patients with a treatment response of marked or better was greatest at week 16 (33.5%), and was 29.4% at week 24. In the placebo group, the percentage of patients with a treatment response of marked improvement or better ranged from 0.0% to 8.9%.

The highest proportion of patients who had a treatment response of almost cleared was 18.5% at week 16 in the TAZORAL™ group compared with 4.6% at week 20 in the placebo group.

Other Studies

In study 190168-052P in patients who had no change or an increase in OLA after 12 weeks of prior treatment with TAZORAL™ or placebo, the proportion of patients who reported a global response of moderate or better progressively increased until week 16 (57.7% in the 4.5 mg → 4.5 mg group and 63.9% in the placebo → 4.5 mg group). This was somewhat higher than the 53.5% of patients in the TAZORAL™ groups in studies 190168-048P and 190168-049P combined who reported a global response of moderate or better.

With treatment for 52 weeks in study 190168-050P, the proportion of patients who reported a global response of moderate or better progressively increased until week 20 (68.4%) and remained at a similar level throughout the remainder of the treatment period (64.3% to 68.8%). The incidence of patients with a global response of moderate or better was higher than that seen in the TAZORAL™ groups in studies 190168-048P and 190168-049P combined.

6.2.5 Overall Pruritus Severity

Combined Phase 3 Studies

For studies 190168-048P and 190168-049P combined, the mean baseline overall pruritus score was 1.9 in the TAZORAL™ group and 1.8 in the placebo group, indicating moderate pruritus. The changes from baseline were significantly greater in the TAZORAL™ group than in the placebo group at weeks 8, 12, and 16 ($p \leq 0.004$). In the TAZORAL™ group, the mean change from baseline peaked at week 16 (–1.2). In the placebo group, the mean changes from baseline ranged from –0.2 to –0.8.

Other Studies

Patients in studies 190168-052P and 190168-050P had a similar magnitude of the reduction in pruritus severity as did patients in studies 190168-048P and 190168-049P combined.

6.2.6 Severity of Scalp Psoriasis

Combined Phase 3 Studies

The decreases from baseline in the overall severity of scalp psoriasis were significantly greater in the TAZORAL™ group than in the placebo group at weeks 8, 12, and 16 ($p \leq 0.004$). In the TAZORAL™ group, the mean change from baseline peaked at week 16 (–1.0), 4 weeks after the end of treatment, and was –0.8 at week 24. In the placebo group, the mean changes from baseline ranged from –0.1 to –0.8.

Other Studies

Scalp psoriasis was not evaluated in study 190168-052P. With treatment for 52 weeks in study 190168-050P, the maximum improvement in scalp psoriasis was seen at week 20 (decrease of 1.0) and continued at about the same level throughout the treatment period. The magnitude of the reduction in severity of scalp psoriasis was similar to that seen in the TAZORAL™ groups in studies 190168-048P and 190168-049P combined.

6.2.7 Severity of Nail Psoriasis

Combined Phase 3 Studies

In studies 190168-048P and 190168-049P combined, the decreases from baseline in the overall severity of fingernail and toenail psoriasis were small and were not significantly different between the TAZORAL™ and placebo groups at any assessment.

Other Studies

Nail psoriasis was not evaluated in study 190168-052P. With treatment for 52 weeks in study 190168-050P, improvements in nail psoriasis were small but appeared to increase with continued treatment.

6.2.8 Patient Satisfaction

At the end of the 12-week treatment period studies in 190168-048P, 190168-049P, and 190168-052P, patients rated their satisfaction with the study medication on a scale from extremely satisfied to extremely dissatisfied. In studies 190168-048P and 190168-049P

combined, patients treated with TAZORAL™ 4.5 mg reported significantly greater satisfaction with treatment compared with patients treated with placebo ($p < 0.001$). A greater proportion of patients treated with TAZORAL™ (79.5%) than with placebo (52.6%) were extremely, very, or somewhat satisfied with their study treatment.

In study 190168-052P, patient satisfaction with treatment at week 12 of the treatment period was greater than their satisfaction at week 12 of the previous double-blind studies. In the 4.5 mg → 4.5 mg and placebo → 4.5 mg groups, respectively, 72.6% and 80.1% were extremely, very, or somewhat satisfied with their study treatment at week 12 of this study compared with 56.3% and 43.2% at week 12 of the double-blind studies.

6.2.9 Comparison of Results in Subpopulations

The OLA clinical success rate and the proportions of patient with an OLA response of none or minimal at week 12 were further analyzed by patient age (< 45 years, 45 to 65 years, and > 65 years), sex, race (Caucasian, black, Asian, Hispanic, and others), geographic region (Canada, Latin America, and US), and baseline OLA severity (moderate, severe, very severe) in studies 190168-048P and 190168-049P combined. There was a consistent effect in favor of TAZORAL™ across the subgroups by age, sex, race, geographic region, and baseline OLA severity.

6.2.10 Persistence of Efficacy and/or Tolerance Effects

The primary and secondary efficacy variables in the combined results from the 2 phase 3 studies (as well as the individual studies) showed increasing efficacy throughout the treatment period from week 1 through week 12. Efficacy persisted after the end of the treatment period, as demonstrated by peak effects for many efficacy variables, including the primary OLA evaluations, 4 weeks after completion of treatment (week 16). At the end of the posttreatment period (week 24), efficacy had started to decline but results remained above pretreatment values.

Efficacy was maintained throughout 52 weeks of treatment in study 190168-050P. Improvement in all efficacy variables increased over time and reached a plateau that was maintained throughout the treatment period. The maximum improvement was observed at

week 12 for plaque elevation, week 16 for scaling, week 20 for erythema, week 32 for proportion of patients with OLA score of minimal or none and mean percentage body surface involvement, and week 36 for proportion of patients with at least a 2-grade decrease in OLA. For all efficacy variables, the values remained close to the peak levels throughout the remainder of the treatment period. In addition, efficacy results remained well above baseline values throughout the 12-week posttreatment period.

The data from the phase 3 studies demonstrate that the efficacy of oral TAZORAL™ administered as 4.5 mg capsules once daily generally persists after treatment over a period of 3 months and tachyphylaxis to the drug does not develop during a treatment period of up to 1 year.

In addition, it is of interest to note that some patients who did not respond to an initial 12-week treatment with TAZORAL™ in one of the double-blind studies (ie, had an OLA score of at least 3 at week 12 in one of the double-blind studies) demonstrated a good response with a second 12-week treatment in study 190168-052P. Among the patients previously treated with TAZORAL™ , the highest proportion with at least a 2-grade decrease in OLA score in study 190168-052P was 24.6% at week 20 of the study (8 weeks after stopping 24 weeks of treatment) and the highest proportion with an OLA score of minimal or none was 18.3% at week 16 (4 weeks after stopping 24 weeks of treatment).

7.0 CLINICAL SAFETY

7.1 Safety Database

The safety of TAZORAL™ is based on data from 5 studies (1 phase 2, 4 phase 3) of patients with moderate to very severe plaque psoriasis, 2 phase 2 studies of patients with nodular acne, 2 phase 1 studies of patients with cancer refractory to conventional therapy, and 12 bioavailability/pharmacokinetic studies in healthy volunteers. The numbers of patients included in these studies are summarized in Table 7.1-1.

Table 7.1-1 Number of Patients in Safety Database

Patient Population Study Number	Number of Patients TAZORAL™	 Placebo
Psoriasis		
190168-048P, 190168-049P	348	358
190168-050P	263	--
190168-052P [a]	312	--
190168-026P	156	25
All Psoriasis Studies [b]	987	383
Acne		
190168-027P	78	18
190168-040P	145	36
All Acne Studies	223	54
Refractory Cancer		
190168-511P/512P	34	--
Pharmacokinetic/Bioavailability		
Single dose	271	--
Multiple dose	178	--
All PK/Bioavailability Studies	449	--
All Studies	**1693**	**437**

[a] Study included 312 patients who completed 190168-048P or 190168-049P; 92 received TAZORAL™ 4.5 mg and 220 received placebo for 12 weeks in prior study.

[b] The total of 987 patients does not double count the 92 patients described in footnote a.

7.2 Extent of Exposure

In all studies TAZORAL™ was administered once daily. The studies of patients with psoriasis included 831 treated with TAZORAL™ 4.5 mg/day, 156 treated with other doses of TAZORAL™ (140 treated with 0.4 to 4.2 mg/day, and 16 treated with 6.3 mg/day), and 383 treated with placebo. Of the 831 patients treated with TAZORAL™ 4.5 mg, 640 (77%) were treated for ≥ 12 weeks, 261 (31%) were treated for ≥ 24 weeks, and 153 (18%) completed 48 weeks of treatment.

The studies of patients with acne or refractory cancer included 257 treated with TAZORAL™ and 54 treated with placebo. In the acne and refractory cancer studies that have been finalized (see Table 7.1-1), among patients treated with TAZORAL™, no patient

was treated with 4.5 mg/day, 54 were treated with 6.0 to 33.6 mg/day, and the other 203 patients were treated with 0.4 to 4.2 mg/day. Of the TAZORAL™-treated patients, 76% (196/256) were treated for ≥ 12 weeks and 35% (89/257) were treated for ≥ 24 weeks.

Six of the 12 bioavailability/pharmacokinetic studies were multiple-dose studies that included 178 patients who received TAZORAL™ for up to 28 days. Of these patients, 65 received 0.2 to 3.0 mg/day, 25 received 4.5 mg/day, and 88 received 6 to 12 mg/day.

7.3 Safety Assessments

The adverse effects of currently available oral retinoids are closely associated with hypervitaminosis A, which includes the characteristic mucocutaneous symptomatology (cheilitis, dry skin, dry eyes, desquamation, pruritus, alopecia, and nail abnormalities), lipid abnormalities (hypertriglyceridemia, hypercholesterolemia, and decreased high-density lipoprotein), ocular changes including decreased night vision, increased liver enzymes, hyperostosis, decreases in bone mineral density, extraskeletal calcification, and arthralgias and myalgias. The potential of TAZORAL™ to cause any of these adverse effects was investigated in the clinical studies. The safety assessments performed in each study are given in Table 7.3-1.

Except for the pooling of data from the 2 double-blind, placebo-controlled, pivotal studies, (190168-048P and 190168-049P) there was no pooling of safety data. The 2 double-blind studies were of identical design, assessed the same safety variables, and used the same methods and procedures for the collection of safety data. Moreover, there were no remarkable differences between the 2 studies in the results of any of the safety analyses.

Table 7.3-1 Safety Evaluations in Studies Included in Safety Summary, Other than Bioavailability/Pharmacokinetic Studies

Safety Evaluations	Psoriasis				Acne	
	Study Number					
	190168-048P, 190168-049P	190168-050P	190168-052P	190168-026P	190168-027P	190168-040P
Adverse events	X	X	X	X	X	X
Laboratory safety tests	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X
Physical examinations	X	X	X	X	X	X
Psychiatric assessments [a]	X	X	X			
Bone density (by dual x-ray absorptiometry) [b]	X	X	X			X
Ligament calcification and/or osteophyte formation [b]	X	X	X			X
Epiphyseal growth plate closure						X
Audiology [b, c]		X				
Ophthalmological evaluations [d]	X	X	X			
Treatment period (weeks)	12	52	12	12	12	24
Posttreatment period (weeks)	12	12	12	4	4	12

[a] Includes Brief Symptom Inventory survey, Mini International Neuropsychiatric Interview, and psychiatric questions.

[b] Evaluated at selected sites.

[c] Includes otoscopic inspection, tympanometry test, air and bone conduction tests.

[d] Includes visual acuity, biomicroscopy, ophthalmoscopy, and night vision findings, and electroretinography at selected sites in study 190168-050P only.

7.4 Common Adverse Events

7.4.1 Phase 3 Studies in Patients with Psoriasis

Studies 190168-048P and 190168-049P

In the 2 pivotal studies, during the treatment period (weeks 0 to 12) the overall incidence of all adverse events and the incidence of headache, back pain, foot pain, cheilitis, hyperglycemia, arthralgia, myalgia, joint disorder, nasal dryness, dry skin, rash, and dermatitis was significantly higher ($p \leq 0.05$) in the TAZORAL™ 4.5 mg group compared with the placebo group (Table 7.4.1-1). Most of these adverse events are typical of the adverse events associated with hypervitaminosis A.

Adverse events for which there was a substantial difference between the 2 treatment groups were cheilitis (65.5% TAZORAL™, 16.8% placebo), arthralgia (17.5% TAZORAL™, 7.3% placebo), and dry skin (23.6% TAZORAL™, 14.8% placebo). Noteworthy is the finding that the incidence of typical oral retinoid adverse events such as hypertriglyceridemia, hypercholesterolemia, abnormal liver function tests, increased SGOT, increased SGPT, desquamation, eye dryness, and alopecia was essentially the same for TAZORAL™ 4.5 mg and placebo.

The overall incidence of laboratory adverse events in the treatment period was similar for the 2 treatment groups (13.8% TAZORAL™ 4.5 mg, 15.6% placebo).

Most adverse events that occurred for TAZORAL™-treated and placebo-treated patients during the treatment period were of mild severity.

Table 7.4.1-1 Adverse Events that Occurred During the Treatment Period (Weeks 0 to 12) that Were Reported for ³ 5% of Patients in Either Treatment Group, Adverse Events for Which There Was a Significant Difference Between TAZORAL™ and Placebo, and Adverse Events Commonly Associated with the Use of Oral Retinoids; Studies 190168-048P and 190168-049P

Body System COSTART Code	Number (%) of Patients		p-value
	TAZORAL™ 4.5 mg (N = 348)	Placebo (N = 358)	
Overall	314 (90.2)	267 (74.6)	< 0.001*
Body as a Whole	155 (44.5)	143 (39.9)	0.216
Headache	65 (18.7)	43 (12.0)	0.014*
Infection	37 (10.6)	41 (11.5)	0.728
Back pain	23 (6.6)	10 (2.8)	0.016*
Asthenia	23 (6.6)	22 (6.1)	0.801
Foot pain	10 (2.9)	3 (0.8)	0.044*
Hormone level altered [a]	0 (0.0)	8 (2.2)	0.008*
Digestive	241 (69.3)	103 (28.8)	< 0.001*
Cheilitis	228 (65.5)	60 (16.8)	< 0.001*
Oral dryness	11 (3.2)	12 (3.4)	0.886
Liver function tests abnormal	4 (1.1)	4 (1.1)	> 0.999
Endocrine	3 (0.9)	1 (0.3)	0.367
Hypothyroidism	3 (0.9)	0 (0.0)	0.119
Thyroiditis	0 (0.0)	1 (0.3)	> 0.999
Metabolic and Nutritional Disorders	51 (14.7)	51 (14.2)	0.877
Hypertriglyceridemia	20 (5.7)	14 (3.9)	0.255
CPK increased	12 (3.4)	18 (5.0)	0.298
Hyperglycemia	7 (2.0)	0 (0.0)	0.007*
SGOT increased	3 (0.9)	3 (0.8)	> 0.999
SGPT increased	2 (0.6)	4 (1.1)	0.686
Hypercholesterolemia	1 (0.3)	1 (0.3)	> 0.999
Hypercalcemia	0 (0.0)	2 (0.6)	0.499
Hyperlipidemia	1 (0.3)	0 (0.0)	0.493
Musculoskeletal	122 (35.1)	65 (18.2)	< 0.001*
Arthralgia	61 (17.5)	26 (7.3)	< 0.001*
Myalgia	51 (14.7)	30 (8.4)	0.009*
Joint disorder	14 (4.0)	4 (1.1)	0.014*
Arthritis	7 (2.0)	5 (1.4)	0.527
Bone pain	2 (0.6)	0 (0.0)	0.243
Nervous	50 (14.4)	36 (10.1)	0.080
Emotional lability	11 (3.2)	11 (3.1)	0.946
Dizziness	9 (2.6)	4 (1.1)	0.147
Anxiety	5 (1.4)	2 (0.6)	0.280
Depression	5 (1.4)	7 (2.0)	0.594

Table 7.4.1-1 (continued)

Body System COSTART Code	Number (%) of Patients		p-value
	TAZORAL™ 4.5 mg (N = 348)	Placebo (N = 358)	
Respiratory	42 (12.1)	28 (7.8)	0.059
Nasal dryness	13 (3.7)	4 (1.1)	0.023*
Epistaxis	2 (0.6)	1 (0.3)	0.619
Rhinitis	8 (2.3)	6 (1.7)	0.553
Skin and Appendages	134 (38.5)	82 (22.9)	< 0.001*
Dry skin	82 (23.6)	53 (14.8)	0.003*
Pruritus	21 (6.0)	13 (3.6)	0.136
Rash	10 (2.9)	2 (0.6)	0.017*
Sun-induced erythema	5 (1.4)	1 (0.3)	0.119
Dermatitis	5 (1.4)	0 (0.0)	0.029*
Desquamation	3 (0.9)	1 (0.3)	0.367
Psoriasis worsened	3 (0.9)	3 (0.8)	> 0.999
Nail disorder	2 (0.6)	1 (0.3)	0.619
Alopecia	1 (0.3)	1 (0.3)	> 0.999
Hair disorder	1 (0.3)	1 (0.3)	> 0.999
Skin disorder	1 (0.3)	1 (0.3)	> 0.999
Special Senses	36 (10.3)	38 (10.6)	0.907
Eye dryness	8 (2.3)	6 (1.7)	0.553
Blepharitis	3 (0.9)	4 (1.1)	> 0.999
Conjunctivitis	3 (0.9)	3 (0.8)	> 0.999
Cataract	2 (0.6)	5 (1.4)	0.451
Visual acuity worsened	2 (0.6)	2 (0.6)	> 0.999
Urogenital	16 (4.6)	20 (5.6)	0.550

[a] Includes elevated TSH and T4, decreased T4, and abnormal thyroid function test.

* p =0.05.

During the posttreatment period (weeks 12 to 24), the overall incidence of adverse events was significantly different ($p \leq 0.05$) for TAZORAL™ 4.5 mg compared with placebo for overall adverse events, cheilitis, and emotional lability (Table 7.4.1-2). The incidence of cheilitis was significantly higher in the TAZORAL™4.5 mg group (48.4% versus 16.1%), and the incidence of emotional lability was significantly lower in the group (0.5% versus 4.6%). Most adverse events that occurred during the posttreatment period were of mild severity.

The overall incidence of laboratory adverse events in the posttreatment period was similar for the 2 treatment groups (12.2% TAZORAL™ 4.5 mg, 14.9% placebo).

Table 7.4.1-2 Adverse Events that Occurred During the Posttreatment Period (Weeks 12 to 24) that Were Reported for ³ 5% of Patients in Either Treatment Group, Adverse Events for Which There Was a Significant Difference Between TAZORAL™ and Placebo, and Adverse Events Commonly Associated with the Use of Oral Retinoids; Studies 190168-048P and 190168-049P

Body System COSTART Code	Number (%) of Patients		
	TAZORAL™ 4.5 mg (N = 213)	Placebo (N = 87)	p-value
Overall	168 (78.9)	59 (67.8)	0.043
Body as a Whole	65 (30.5)	25 (28.7)	0.760
Back pain	14 (6.6)	1 (1.1)	0.076
Infection	11 (5.2)	5 (5.7)	0.784
Headache	10 (4.7)	6 (6.9)	0.412
Hormone level altered [a]	1 (0.5)	3 (3.4)	0.075
Digestive	112 (52.6)	22 (25.3)	< 0.001*
Cheilitis	103 (48.4)	14 (16.1)	< 0.001*
Oral dryness	7 (3.3)	2 (2.3)	> 0.999
Liver function tests abnormal	1 (0.5)	2 (2.3)	0.203
Endocrine	0 (0.0)	1 (1.1)	0.290
Thyroiditis	0 (0.0)	1 (1.1)	0.290
Metabolic and Nutritional Disorders	24 (11.3)	8 (9.2)	0.598
Hypertriglyceridemia	10 (4.7)	2 (2.3)	0.519
CPK increased	6 (2.8)	4 (4.6)	0.483
Hyperglycemia	3 (1.4)	0 (0.0)	0.559
Hypercalcemia	1 (0.5)	1 (1.1)	0.497
Hypercholesterolemia	1 (0.5)	0 (0.0)	> 0.999
SGPT increased	0 (0.0)	2 (2.3)	0.083
SGOT increased	0 (0.0)	1 (1.1)	0.290
Musculoskeletal	62 (29.1)	18 (20.7)	0.135
Arthralgia	26 (12.2)	9 (10.3)	0.649
Myalgia	26 (12.2)	7 (8.0)	0.296
Joint disorder	5 (2.3)	0 (0.0)	0.326
Arthritis	4 (1.9)	2 (2.3)	> 0.999
Bone pain	1 (0.5)	0 (0.0)	> 0.999
Nervous	17 (8.0)	8 (9.2)	0.730
Dizziness	3 (1.4)	1 (1.1)	> 0.999
Depression	2 (0.9)	2 (2.3)	0.582
Emotional lability	1 (0.5)	4 (4.6)	0.026*
Anxiety	0 (0.0)	1 (1.1)	0.290
Respiratory	19 (18.9)	10 (11.5)	0.494
Nasal dryness	7 (3.3)	1 (1.1)	0.445
Rhinitis	6 (2.8)	2 (2.3)	> 0.999
Epistaxis	1 (0.5)	1 (1.1)	0.497

Table 7.4.1-2 (continued)

Body System COSTART Code	Number (%) of Patients		p-value
	TAZORAL™ 4.5 mg (N = 213)	Placebo (N = 87)	
Skin and Appendages	61 (28.6)	13 (14.9)	0.013*
Dry skin	35 (16.4)	7 (8.0)	0.058
Pruritus	8 (3.8)	0 (0.0)	0.110
Rash	8 (3.8)	0 (0.0)	0.110
Alopecia	4 (1.9)	1 (1.1)	> 0.999
Desquamation	3 (1.4)	0 (0.0)	0.559
Hair disorder	3 (1.4)	0 (0.0)	0.559
Sun-induced erythema	2 (0.9)	1 (1.1)	> 0.999
Nail disorder	2 (0.9)	0 (0.0)	> 0.999
Psoriasis worsened	1 (0.5)	0 (0.0)	> 0.999
Erythema	0 (0.0)	1 (1.1)	0.290
Skin disorder	0 (0.0)	1 (1.1)	0.290
Special Senses	25 (11.7)	9 (10.3)	0.730
Eye dryness	5 (2.3)	1 (1.1)	0.676
Cataract	3 (1.4)	2 (2.3)	0.630
Blepharitis	3 (1.4)	0 (0.0)	0.559
Visual acuity worsened	3 (1.4)	0 (0.0)	0.559
Conjunctivitis	3 (1.4)	1 (1.1)	> 0.999
Urogenital	10 (4.7)	5 (5.7)	0.772

[a] Includes changes in thyroid function tests.

* p = 0.05.

Table includes any adverse event reported during the posttreatment period regardless of whether a patient also had the same adverse event during the treatment period.

There were no remarkable or consistent differences in overall adverse event rates for age (< 45, 45 to 65, > 65 years of age), gender (male, female), race (Caucasian, non-Caucasian), or region (Canada, Latin America, United States) subgroups.

Studies 190168-052P and 190168-050P

Study 190168-052P included patients who did not respond satisfactorily to treatment with either TAZORAL™ 4.5 mg or placebo in studies 190168-048P or 190168-049P. In study 190168-052P, all patients were treated with TAZORAL™ 4.5 mg and were categorized according to the treatment received in their prior study.

In study 190168-052, patients treated with TAZORAL™ 4.5 mg in the prior study (4.5 mg → 4.5 mg group), compared with those treated with placebo in the prior study (placebo → 4.5 mg group), had a significantly higher incidence of back pain (17.4% versus 7.7%), arthralgia (33.7% versus 14.1%), and alopecia (5.4% versus 0.9%) (Table 7.4.1-3). These data suggest that increasing the duration of treatment beyond 12 weeks, may increase the risk of these adverse events which are frequently associated with systemic retinoid therapy. The incidence of these adverse events in the placebo → 4.5 mg group were similar to their incidence in 190168-048P/190168-049P for patients treated with TAZORAL™ 4.5 mg for 12 weeks (back pain 6.6%, arthralgia 17.5%, and alopecia 0.3%).

Table 7.4.1-3 also summarizes adverse events that occurred in study 190168-050P. When comparing the incidence of adverse events in studies 190168-050P and 190168-052P, the longer duration of treatment in study 190168-050P (up to 52 weeks) needs to be considered. Of particular note is the observation that in these 2 studies rates of digestive, endocrine, metabolic and nutritional, and special senses adverse events were comparable, suggesting that these adverse events are not dependent on the duration of treatment.

In study 190168-050P in which patients received 4.5 mg for up to 52 weeks, adverse events also were analyzed by time of occurrence (weeks 0 to 24 and weeks 24 to 52). Summarized in Table 7.4.1-4 are those adverse events for which the rates during weeks 0 – 24 and weeks 24 – 52 differed by at least 5%.

Table 7.4.1-3 Adverse Events that Occurred During the Treatment Period that Were Reported for ³ 5% of Patients, and Adverse Events Commonly Associated with the Use of Oral Retinoids; Studies 190168-050P and 190168-052P

Body System COSTART Code	Number (%) of Patients		
	190168-050P	190168-052P	
	TAZORAL™ 4.5 mg (N = 263)	4.5 mg ® 4.5 mg (N = 92)	Placebo ® 4.5 mg (N = 220)
Overall	260 (98.9)	89 (96.7)	208 (94.5)
Body as a Whole	195 (74.1)	44 (47.8)	85 (38.6)
Infection	75 (28.5)	8 (8.7)	22 (10.0)
Back pain	58 (22.1)	16 (17.4)	17 (7.7)*
Headache	55 (20.9)	10 (10.9)	25 (11.4)
Asthenia	30 (11.4)	7 (7.6)	12 (5.5)
Foot pain	26 (9.9)	2 (2.2)	5 (2.3)
Leg pain	19 (7.2)	2 (2.2)	5 (2.3)
Flu syndrome	17 (6.5)	2 (2.2)	4 (1.8)
Hormone level altered [a]	7 (2.7)	0 (0.0)	4 (1.8)
Cardiovascular	30 (11.4)	2 (2.2)	9 (4.1)
Hypertension	17 (6.5)	1 (1.1)	4 (1.8)
Digestive	203 (77.2)	69 (75.0)	166 (75.5)
Cheilitis	169 (64.3)	66 (71.7)	151 (68.6)
Gastroenteritis	16 (6.1)	0 (0.0)	1 (0.5)
Nausea	16 (6.1)	4 (4.3)	10 (4.5)
Liver function tests abnormal	15 (5.7)	1 (1.1)	6 (2.7)
Diarrhea	13 (4.9)	6 (6.5)	9 (4.1)
Oral dryness	10 (3.8)	2 (2.2)	11 (5.0)
Endocrine	1 (0.4)	2 (2.2)	2 (0.9)
Hypothyroidism	1 (0.4)	2 (2.2)	0 (0.0)
Hyperthyroidism	0 (0.0)	0 (0.0)	1 (0.5)
Thyroid disorder	0 (0.0)	0 (0.0)	1 (0.5)
Thyroiditis	0 (0.0)	0 (0.0)	1 (0.5)
Hemic and Lymphatic	15 (5.7)	1 (1.1)	4 (1.8)
Metabolic and Nutritional Disorders	54 (20.5)	14 (15.2)	37 (16.8)
Hypertriglyceridemia	20 (7.6)	6 (6.5)	14 (6.4)
CPK increased	13 (4.9)	5 (5.4)	10 (4.5)
Hypercholesterolemia	4 (1.5)	0 (0.0)	3 (1.4)
Metabolic and Nutritional Disorders			
SGPT increased	3 (1.1)	1 (1.1)	1 (0.5)
SGOT increased	2 (0.8)	1 (1.1)	2 (0.9)
Hypercalcemia	1 (0.7)	0 (0.0)	1 (0.5)
Hyperlipidemia	0 (0.0)	0 (0.0)	1 (0.5)
Musculoskeletal	158 (60.1)	42 (45.7)	76 (34.5)
Arthralgia	95 (36.1)	31 (33.7)	31 (14.1)*
Myalgia	76 (28.9)	9 (9.8)	38 (17.3)

Table 7.4.1-3 (continued)

Body System COSTART Code	Number (%) of Patients		
	190168-050P	190168-052P	
	TAZORAL™ 4.5 mg (N = 263)	4.5 mg ® 4.5 mg (N = 92)	Placebo ® 4.5 mg (N = 220)
Musculoskeletal (continued)			
Arthritis	18 (6.8)	7 (7.6)	8 (3.6)
Joint disorder	16 (6.1)	2 (2.2)	4 (1.8)
Bone pain	4 (1.5)	0 (0.0)	0 (0.0)
Nervous	66 (25.1)	13 (14.1)	31 (14.1)
Paresthesia	17 (6.5)	1 (1.1)	5 (2.3)
Insomnia	16 (6.1)	2 (2.2)	2 (0.9)
Emotional lability	13 (4.9)	6 (6.5)	6 (2.7)
Anxiety	9 (3.4)	2 (2.2)	1 (0.5)
Depression	9 (3.4)	4 (4.3)	6 (2.7)
Dizziness	6 (2.3)	1 (1.1)	5 (2.3)
Respiratory	70 (26.6)	9 (9.8)	21 (9.5)
Rhinitis	15 (5.7)	2 (2.2)	4 (1.8)
Bronchitis	15 (5.7)	0 (0.0)	4 (1.8)
Nasal dryness	9 (3.4)	4 (4.3)	6 (2.7)
Epistaxis	6 (2.3)	0 (0.0)	1 (0.5)
Skin and Appendages	151 (57.4)	39 (42.4)	73 (33.2)
Dry skin	60 (22.8)	25 (27.2)	52 (23.6)
Pruritus	30 (11.4)	3 (3.3)	16 (7.3)
Alopecia	20 (7.6)	5 (5.4)	2 (0.9)*
Burning sensation on skin	10 (3.8)	1 (1.1)	3 (1.4)
Rash	8 (3.0)	1 (1.1)	1 (0.5)
Nail disorder	7 (2.7)	1 (1.1)	1 (0.5)
Sun-induced erythema	4 (1.5)	1 (1.1)	2 (0.9)
Desquamation	4 (1.5)	1 (1.1)	3 (1.4)
Skin irritation	4 (1.5)	0 (0.0)	0 (0.0)
Hair disorder	3 (1.1)	1 (1.1)	0 (0.0)
Erythema	2 (0.8)	0 (0.0)	0 (0.0)
Skin disorder	2 (0.8)	1 (1.1)	0 (0.0)
Special Senses	37 (14.1)	7 (7.6)	33 (15.0)
Eye dryness	6 (2.3)	1 (1.1)	3 (1.4)
Cataract	3 (1.1)	0 (0.0)	2 (0.9)
Deafness	2 (0.8)	0 (0.0)	0 (0.0)
Blepharitis	2 (0.8)	0 (0.0)	4 (1.8)
Conjunctivitis	2 (0.8)	0 (0.0)	1 (0.5)
Visual acuity worsened	2 (0.8)	1 (1.1)	2 (0.9)
Urogenital	32 (12.2)	2 (2.2)	8 (3.6)

[a] Includes changes in thyroid function tests.

* Study 190168-052P: adverse events rates significantly different ($p \leq 0.05$) for the 2 treatment groups.

Table 7.4.1-4 Adverse Events that Occurred During the Treatment Period for Which The Rates During Weeks 0 – 24 and 24 – 52 Differed by at Least 5%; Study 190168-050P

COSTART Code	Number (%) of Patients	
	Weeks 0 - 24 (N = 263)	Weeks 24 – 52 (N = 199)
Infection (Body as a Whole)	46 (17.5)	56 (28.1)
Headache	48 (18.3)	17 (8.5)
Back pain	31 (11.8)	48 (24.1)
Cheilitis	169 (64.3)	95 (47.7)

In study 190168-052P, the overall incidence of laboratory adverse events during the treatment period was similar for the 2 treatment groups (20.7%, 4.5 mg → 4.5 mg; 17.7%, placebo → 4.5 mg).

The incidence of adverse events in studies 190168-050P and 190168-052P during the posttreatment period is summarized in Table 7.4.1-5. In study 190168-052P, in the 4.5 mg → 4.5 mg group compared with the placebo → 4.5 mg group there was a significantly higher incidence of arthralgia.

The majority of adverse events that occurred during the treatment and posttreatment periods in studies 190168-050P and 190168-052P were of mild severity.

Table 7.4.1-5 Adverse Events that Occurred During the Posttreatment Period that Were Reported for ³ 5% of Patients, and Adverse Events Commonly Associated with the Use of Oral Retinoids; Studies 190168-050P and 190168-052P

Body System COSTART Code	Number (%) of Patients		
	190168-050P	190168-052P	
	TAZORAL™ 4.5 mg (N = 152)	4.5 mg ® 4.5 mg (N = 76)	Placebo ® 4.5 mg (N = 185)
Overall	132 (86.8)	64 (84.2)	163 (88.1)
Body as a Whole	75 (49.3)	28 (36.8)	62 (33.5)
Back pain	27 (17.8)	10 (13.2)	14 (7.6)
Infection	20 (13.2)	5 (6.6)	18 (9.7)
Headache	10 (6.6)	6 (7.9)	7 (3.8)
Asthenia	12 (7.9)	5 (6.6)	7 (3.8)
Foot pain	4 (2.6)	1 (1.3)	4 (2.2)
Hormone level altered [a]	1 (0.7)	0 (0.0)	2 (1.1)
Cardiovascular	19 (12.5)	2 (2.6)	4 (2.2)
Digestive	67 (44.1)	43 (56.6)	122 (65.9)
Cheilitis	58 (38.2)	43 (56.6)	111 (60.0)
Oral dryness	5 (3.3)	1 (1.3)	7 (3.8)
Liver function tests abnormal	3 (2.0)	0 (0.0)	2 (1.1)
Endocrine	1 (0.7)	2 (2.6)	2 (1.1)
Hypothyroidism	1 (0.7)	2 (2.6)	0 (0.0)
Hyperthyroidism	0 (0.0)	0 (0.0)	1 (0.5)
Thyroid disorder	0 (0.0)	0 (0.0)	1 (0.5)
Thyroiditis	0 (0.0)	0 (0.0)	1 (0.5)
Metabolic and Nutritional Disorders	13 (8.6)	8 (10.5)	29 (15.7)
Hypertriglyceridemia	7 (4.6)	5 (6.6)	11 (5.9)
CPK increased	2 (1.3)	2 (2.6)	5 (2.7)
Hypercholesterolemia	1 (0.7)	0 (0.0)	1 (0.5)
SGOT increased	0 (0.0)	0 (0.0)	1 (0.5)
SGPT increased	0 (0.0)	1 (1.3)	0 (0.0)
Hypercalcemia	1 (0.7)	0 (0.0)	1 (0.5)
Hyperlipidemia	0 (0.0)	0 (0.0)	1 (0.5)
Musculoskeletal	63 (41.1)	30 (39.5)	58 (31.4)
Arthralgia	30 (19.7)	19 (25.0)	25 (13.5)*
Myalgia	24 (15.8)	7 (9.2)	28 (15.1)
Arthritis	10 (6.6)	7 (9.2)	6 (3.2)
Joint disorder	6 (3.9)	1 (1.3)	2 (1.1)
Bone pain	1 (0.7)	0 (0.0)	0 (0.0)
Nervous	25 (16.4)	7 (9.2)	14 (7.6)
Depression	4 (2.6)	3 (3.9)	2 (1.1)
Emotional lability	4 (2.6)	3 (3.9)	2 (1.1)
Anxiety	2 (1.3)	1 (1.3)	1 (0.5)
Dizziness	1 (0.7)	0 (0.0)	3 (1.6)

Table 7.4.1-5 (continued)

Body System COSTART Code	Number (%) of Patients		
	190168-050P	190168-052P	
	TAZORAL™ 4.5 mg (N = 152)	4.5 mg ® 4.5 mg (N = 76)	Placebo ® 4.5 mg (N = 185)
Respiratory	20 (13.2)	4 (5.3)	12 (6.5)
Rhinitis	4 (2.6)	1 (1.3)	5 (2.7)
Nasal dryness	1 (0.7)	2 (2.6)	4 (2.2)
Skin and Appendages	59 (38.8)	21 (27.6)	64 (34.6)
Dry skin	26 (17.1)	11 (14.5)	42 (22.7)
Pruritus	10 (6.6)	1 (1.3)	10 (5.4)
Alopecia	7 (4.6)	4 (5.3)	6 (3.2)
Nail disorder	3 (2.0)	2 (2.6)	0 (0.0)
Hair disorder	2 (1.3)	0 (0.0)	1 (0.5)
Rash	1 (0.7)	0 (0.0)	1 (0.5)
Skin disorder	1 (0.7)	1 (1.3)	0 (0.0)
Sun-induced erythema	0 (0.0)	0 (0.0)	2 (1.1)
Desquamation	0 (0.0)	0 (0.0)	1 (0.5)
Skin carcinoma	1 (0.7)	4 (5.3)	2 (1.1)
Special Senses	10 (6.6)	3 (3.9)	16 (8.6)
Cataract	3 (2.0)	0 (0.0)	2 (1.1)
Eye dryness	2 (1.3)	1 (1.3)	0 (0.0)
Visual acuity worsened	2 (1.3)	1 (1.3)	1 (0.5)
Blepharitis	1 (0.7)	0 (0.0)	4 (2.2)
Conjunctivitis	0 (0.0)	0 (0.0)	0 (0.0)
Urogenital	8 (5.3)	4 (5.3)	6 (3.2)

[a] Includes changes in thyroid function tests.

* Study 190168-052P: adverse events rates significantly different ($p \leq 0.05$) for the 2 treatment groups. Table includes any adverse event reported during the posttreatment period regardless of whether a patient also had the same adverse event during the treatment period.

The incidence of laboratory adverse events during the posttreatment period was 11.2% in study 190168-050P, and was similar for the 2 treatment groups (14.5% 4.5 mg → 4.5 mg, 14.6% placebo → 4.5 mg) in study 190168-052P.

In all of the phase 3 studies, there was a relatively low incidence of metabolic and nutritional disorder adverse events, in particular, hypercalcemia, hypercholesterolemia, hypertriglyceridemia, and changes in liver function tests. In the 2 double-blind, placebo-controlled studies, the incidence of hypertriglyceridemia (reported as an adverse event) in the TAZORAL™ group was marginally higher than the incidence in the placebo group

(5.7% TAZORAL™, 3.9% placebo). In the TAZORAL™ group the incidence of other metabolic and nutritional disorder adverse events did not exceed 3%.

7.4.2 Phase 2 Study in Patients with Psoriasis

The only other study of patients with psoriasis was a 12-week dose-ranging study (190168-026P) that evaluated 0.4 mg to 6.3 mg. The study included too few patients (10 to 28 in each treatment group) to provide definitive information on dose-response relationships for specific adverse events. Except for cheilitis, no consistent dose-related increases in the incidence of any adverse event were apparent. The incidence of cheilitis was similar for placebo (4.0%) and TAZORAL™ 0.4 mg, 0.6 mg, 0.8 mg, 1.1 mg, and 2.1 mg (3.6% to 9.1%), and was lower for these doses compared with TAZORAL™ 2.8 mg, 4.2 mg, and 6.3 mg (30.0% to 35.7%). In both the treatment and posttreatment periods, most adverse events were of mild or moderate severity.

In study 190168-026P, for all doses of TAZORAL™ evaluated there were consistently low rates of metabolic and nutritional disorders (including increased liver function enzymes, hypertriglyceridemia, and hypercholesterolemia), nervous system adverse events (including depression), skin and appendage adverse events (including alopecia and desquamation, but not dry skin or pruritus), and endocrine-related adverse events.

7.5 Serious Adverse Events and Other Significant Adverse Events, All Studies of TAZORAL™

A serious adverse event was defined as any death, any life-threatening event, any event that requires or prolongs inpatient hospitalization, any event that results in significant or persistent disability or incapacity, any congenital abnormality/birth defect diagnosed in the child of a patient who participated in a study and received study drug, any other medically important event that, in the opinion of the investigator, may jeopardize the patient or require intervention to prevent one of the other outcomes listed above.

Tables 7.5-1 and 7.5-2 summarize the number of deaths, other serious adverse events, and discontinuations due to adverse events that occurred in completed studies of patients with psoriasis, studies of patients with acne, and bioavailability/pharmacokinetic studies in

healthy volunteers. These tables do not include serious adverse events or treatment discontinuations for patients in the oncology study.

In the 2 double-blind-placebo controlled studies, there were no remarkable differences between TAZORAL™ 4.5 mg and placebo in the incidence of serious adverse events or discontinuations due to adverse events. In the long-term study (190168-050P) rates of serious adverse events and discontinuations due to adverse events were higher compared with the shorter duration of treatment studies (190168-048P, 190268-049P, 190168-052P). It is unknown whether this is merely due to the longer duration of the study or an effect of greater exposure to TAZORAL™.

7.5.1 Deaths

Eleven patients died either during their participation or within 30 days of completing their participation in any of the studies. No death was a suicide. Ten of the 11 deaths were for patients in phase 1 oncology studies, who had cancer refractory to conventional therapy, and the other death was for a psoriasis patient in study 190168-050P. In the latter study, a 62 year-old male died in an airplane accident. The patient had been treated with TAZORAL™ 4.5 mg for 282 days at the time of his death. All deaths were considered by the investigators to be unrelated to treatment with study drug.

Table 7.5-1 Number of Deaths, Other Serious Adverse Events, and Discontinuations for Adverse Events in Either the Treatment or Posttreatment Periods; Studies of Patients with Psoriasis

	Number (%) of Patients							
	Study Number							
	190168-048P/ 190168-049P		190168-050P	190168-052P		190168-026P		
	Taz 4.5 mg	Placebo	Taz 4.5 mg	Taz 4.5 mg (Prior Study Placebo)	Taz 4.5 mg (Prior Study Taz 4.5 mg)	Stage 1 Taz [a]	Stage 1 Placebo	Stage 2 Taz [b]
Treated	348	358	263	92	220	105	25	51
Any serious adverse event	3 (0.9)	10 (2.8)	23 (8.7)	2 (2.2)	5 (2.3)	1 (1.0)	1 (4.0)	2 (3.9)
Deaths	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other serious adverse events	3 (0.9)	10 (2.8)	22 (8.4)	2 (2.2)	5 (2.3)	1 (1.0)	1 (4.0)	2 (3.9)
Treatment-related serious adverse events	1 (0.3)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued treatment and/ or study for adverse events [c]								
Any adverse event	18 (5.2)	16 (4.5)	48 (18.3)	6 (6.5)	7 (3.2)	2 (1.9)	3 (12.0)	4 (7.8)
Treatment-related adverse event	16 (4.6)	11 (3.1)	39 (14.8)	6 (6.5)	6 (2.7)	2 (1.9)	3 (12.0)	3 (5.9)
Serious adverse events	0 (0.0)	3 (0.8)	3 (1.1)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Laboratory adverse events	6 (1.7)	5 (1.4)	6 (2.3)	0 (0.0)	1 (0.5)	1 (1.0)	1 (4.0)	0 (0.0)

[a] TAZORAL™ treatment groups: 0.4 mg (N=25), 0.6 mg (N=28), 0.8 mg (N=26), 1.1 mg (N=26).

[b] TAZORAL™ treatment groups: 2.1 mg (N=11), 2.8 mg (N=10); 4.2 mg (N=14), 6.3 mg (N=16).

[c] Includes patients who discontinued treatment but remained in the study and entered the posttreatment period.

Table 7.5-2 Number of Deaths, Other Serious Adverse Events, and Discontinuations for Adverse Events in Either the Treatment or Posttreatment Periods; Studies of Patients with Acne and Subjects in Bioavailability/ Pharmacokinetic Studies

	Number (%) of Patients					
	Study Number					Bioavailability/ Pharmacokinetic (12 Studies)
	190168-027P			190168-040P		
	Stage 1 TAZORAL™ [a]	Stage 1 Placebo	Stage 2 TAZORAL™ [b]	TAZORAL™ [c]	Placebo	TAZORAL™
Treated	53	18	25	145	36	449
Any serious adverse event	0 (0.0)	0 (0.0)	0 (0.0)	6 (4.1)	0 (0.0)	0 (0.0)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	7 (4.8)	0 (0.0)	0 (0.0)
Treatment-related serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.4)	0 (0.0)	0 (0.0)
Discontinued from study for adverse events						
Any adverse event	0 (0.0)	2 (11.1)	0 (0.0)	6 (4.1)	1 (2.8)	14 (3.1)
Treatment-related adverse event	0 (0.0)	1 (5.6)	0 (0.0)	4 (2.8)	1 (2.8)	3 (0.1)
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.4)	0 (0.0)	0 (0.0)
Laboratory adverse events	0 (0.0)	1 (5.6)	0 (0.0)	1 (0.7)	0 (0.0)	5 (0.9)

[a] TAZORAL™ treatment groups: 0.4 mg (N=18), 0.6 mg (N=18), 0.8 mg (N=17).

[b] TAZORAL™ treatment groups: 1.4 mg (N=14), 2.8 mg (N=11).

[c] TAZORAL™ reatment groups: 0.75 mg (N=35), 1.5 mg (N=37), 3.0 mg (N=37), 6.0 mg (N=36).

7.5.2 Other Serious Adverse Events

In the 2 pivotal phase 3 studies (190168-048P and 190168-049P), serious adverse events were reported for 8 patients (1 TAZORAL™, 7 placebo) during the treatment period and for 5 patients (2 TAZORAL™, 3 placebo) during the posttreatment period (Table 7.5-1). In these studies, the only serious adverse event that was judged by the investigator as related to treatment with TAZORAL™ was the following case of hospitalization for abdominal pain:

- Patient 3807-2380 (TAZORAL™ 4.5 mg) was hospitalized in the posttreatment period for abdominal pain, which was diagnosed on endoscopic retrograde cholangiopancreatography as severe ampullary stenosis and treated by dual sphincterotomy and stenting. The investigator thought the event was treatment-related because inflammation of the pancreatic duct could have been secondary to elevated triglycerides, which could have been exacerbated by the study drug. The patient had elevated fasting triglycerides (normal limits, 0.62 to 3.6 mmol/L [54.9 to 318.9 mg/dL]) throughout the study: screening, 6.38 (565.1 mg/dL) and 10.99 mmol/L (973.4 mg/dL); week 2, 6.86 mmol/L (607.6 mg/dL); week 4, 9.51 mmol/L (842.3 mg/dL); week 8, 15.81 mmol/L (1400.4 mg/dL) with re-tested values of 11.88 mmol/L (1052.3 mg/dL), 13.03 mmol/L (1154.1 mg/dL), and 62.38 mmol/L (5525.2 mg/dL); week 12 (end of treatment), 33.75 mmol/L (2989.4 mg/dL); week 16, 6.54 mmol/L (579.3 mg/dL); week 20, 8.95 mmol/L (792.7 mg/dL); and week 24, 4.47 mmol/L (395.9 mg/dL). The patient had no comorbid conditions at the onset of treatment.

In study 190168-052P there were no treatment-related serious adverse events. In study 190168-050P there was 1 serious adverse event that was possibly treatment related, a patient that was hospitalized for hypertension. In a phase-2 acne study, 2 patients had serious adverse events that were judged by the investigators to be at least possibly related to treatment: a hospitalization for depression and a miscarriage of pregnancy. In oncology studies, 3 patients had serious adverse events that were judged by the investigators to be at least possibly related to treatment: hospitalization for hypercalcemia and for malaise (TAZORAL™ dose of 33.6 mg/day), hospitalization for hypercalcemia (TAZORAL™ dose of 16.8 mg/day), and hospitalization for intestinal obstruction (TAZORAL™ dose of 25.2 mg/day).

In all studies there were no recognized cases of pseudotumor cerebri (benign intracranial hypertension), an infrequent complication associated with the use of some oral retinoids.

7.5.3 Other Significant Adverse Events

In studies that included a control (placebo) group, there were no remarkable differences in the discontinuation rates for all adverse events or treatment-related adverse events for patients treated with TAZORAL™ and patients treated with placebo (Tables 7.5-1, 7.5-2, and 7.5.3-1). Taking into account the duration of treatment, the discontinuation rates for all adverse events and treatment-related adverse events in the open-label studies were similar to those in the placebo-controlled studies. Nearly all of the adverse events that resulted in treatment/study discontinuation are among those adverse events commonly associated with the use of oral retinoids.

During the treatment period, the incidence of depression was 1.4% (5/348) in patients treated with TAZORAL™ in the placebo-controlled clinical trials and was not significantly different from the 2.0% (7/358) of patients treated with placebo. The following describes the instances of patients who discontinued from the phase 3 psoriasis studies due to depression or emotional lability. Of 348 patients treated with TAZORAL™ in the placebo-controlled studies, 1 patient discontinued from the study due to depression and 2 patients discontinued due to emotional lability (mood changes and irritability in 1 case and mood changes with accompanying anxiety, nervousness, paranoid reaction, visual disturbances, headache, and hypertonia in the other case). All 3 patients recovered without sequelae. Three patients treated with placebo were also discontinued from the studies due to emotional lability.

In the open-label study 190168-052P, of the 312 patients treated with TAZORAL™, there were 3 patients who discontinued the study due to emotional lability (mood disorder in 1 case in the TAZORAL™/ TAZORAL™ group; emotional instability in 1 patient with a history of emotional lability in the placebo/ TAZORAL™ group; 1 case in the TAZORAL™/ TAZORAL™ group in which the emotional lability was not otherwise specified) and 1 patient in the placebo/ TAZORAL™ group with a medical history of anxiety who discontinued due to a severe paranoid event ongoing at exit from the study.

In the open-label study 190168-050P, of the 263 patients treated with TAZORAL™, there were 2 patients who discontinued the study due to emotional lability (mood changes in 1 case and emotional instability with accompanying anxiety and asthenia in the second case

and 2 patients who discontinued due to depression (adjustment disorder with depressed mood in 1 case and depression with accompanying leg pain, hypertonia, and alopecia in the second case). Both cases of depression were ongoing at the end of their study participation. One case of emotional lability lasted 7 days, the other 26 days.

There were no discontinuations for suicidal ideation or attempted suicide.

Table 7.5.3-1 Treatment Discontinuation Rates for Adverse Events

	Discontinuation Rates [a]		
Studies	**TAZORAL™ 4.5**	**TAZORAL™ [b]**	**Placebo**
Psoriasis:			
Double-blind (190168-048P, 190168-049P)	5.2% (18/348)		4.5% (16/358)
Phase 3 studies (190168-048P, 190168-049P, 190168-050P, 190168-052P)	9.5% (79/831)		Not applicable
Open-label (190168-052P)	4.2% (13/312)		Not applicable
Open-label, long-term (190168-050P)	18.3% (48/263)		Not applicable
Phase 2 study (190168-026P)		2.7% (6/223)	12.0% (3/25)
All psoriasis studies	8.6% (85/987)		5.0% (19/383)
Acne (190168-027P, 190168-040P)		3.8% (6/156)	5.6% (3/54)
Bioavailability/pharmacokinetic (12 studies)	3.1% (14/449)		Not applicable

Table excludes study 190168-061P that has not been finalized and the 2 studies (190168-035P and 190168-511P/512P) of patients with refractory cancer.

[a] Percentage (number of discontinuations due to adverse events/number of patients in treatment group).

[b] All doses except for 4.5 mg.

One patient became pregnant during her participation in 1 of the 5 studies of TAZORAL™ for the treatment of psoriasis, and 3 patients became pregnant during their participation in 1 of the 2 studies of TAZORAL™ for the treatment of nodular acne. The outcomes of these pregnancies are summarized in Table 7.5.3-2.

Table 7.5.3-2 Pregnancy Outcomes for Patients who Became Pregnant During their Participation in the Studies of TAZORAL™

Study Number/ Patient Number	Treatment	Pregnancy Outcome	Fetal Exposure to TAZORAL™
190168-050P 3459-3213	TAZORAL™ 4.5 mg	Elective termination of pregnancy 10 days after diagnosis of pregnancy	None (negative pregnancy test 8 weeks after last dose of TAZORAL™). Pregnancy diagnosed 12 weeks after end of treatment
190168-040P 2427-1064	TAZORAL™ 0.75 mg	Elective termination of pregnancy 6 days after diagnosis of pregnancy	Information not available
190168-040P 2990-1010	TAZORAL™ 1.5 mg	Term delivery (38 weeks) of a healthy baby (a 26-month-old healthy infant with no known sequelae at last report)	15 days after presumed date of conception
190168-040P 3278-1027	TAZORAL™ 3 mg	Spontaneous abortion 18 days after discontinuing TAZORAL™	Approximately 17 days

7.6 Laboratory Tests

Treatment with the currently marketed oral retinoids is commonly associated with marked serum lipid alterations (increased plasma triglycerides, increased total cholesterol, and decreased HDL cholesterol), hepatotoxicity, elevations in fasting blood sugar and CPK, and decreases in thyroid hormones (TSH and T4). Presented in the following section are relevant laboratory data for oral TAZORAL™.

7.6.1 Double-blind, Placebo-controlled Studies

Table 7.6.1-1 gives the median changes from screening for selected laboratory tests for which there was a significant difference between the TAZORAL™ 4.5 mg and placebo groups at any timepoint after the start of treatment. Noteworthy are the following observations:

- Generally, in both treatment groups the median changes from baseline were small, and for many of the tests the changes in median values were in a direction that did not suggest an adverse effect of TAZORAL™, eg, decreased values of ALT (SGPT) and AST (SGOT).

- For both ALT and AST, the median changes from baseline were small (≤ 3 U/L), and were decreased from baseline in the TAZORAL™ group at all timepoints after week 4.

- For HDL cholesterol, changes from baseline in the TAZORAL™ group were decreased (maximum median decrease, 0.050 mmol/L), but were significantly different from placebo only at week 12.

- The median CPK in the placebo group was increased (median increases, 1.0 to 5.0 U/L) at all timepoints, but in the group it was decreased at weeks 4, 8, 12, and 20 (median decreases, 1.0 to 5.5 U/L).

- Compared with baseline, there were small increases in triglycerides (approximately 3% to 9%) with TAZORAL™ treatment at all visits except week 24 where there was no increase. Compared with placebo, changes in triglyceride values with TAZORAL™ were significantly greater only at weeks 4, 8, and 12.

- For thyroid stimulating hormone (TSH) there were small increases (approximately 5% to 14%) with TAZORAL™ treatment at all visits. Changes in TSH values were significantly different for the 2 treatment groups at weeks 1, 4, 8, and 12. At these times, the median changes in the TAZORAL™ 4.5 mg group were 0.070 to 0.210 µIU/mL and in the placebo group were -0.050 to 0.115 µIU/mL. Shift table data did not indicate any differences in percentages of patients with elevated TSH levels (above normal range) in the TAZORAL™ and placebo groups. In the treatment period, the percentage of patients whose TSH values increased from normal to high ranged from 1.5% to 3.3% in the TAZORAL™ group and 2.0% to 2.7% in the placebo group. Only 3 patients treated with TAZORAL ™4.5 mg had hypothyroidism recorded as an adverse event.

- For thyroxine (T4) there were small median decreases (approximately 2% to 4%) with treatment at all visits except week 1 (small increase) and week 2 (no change). The changes in T4 in the 2 treatment groups were significantly different at weeks 8 and 24. Shift table data did not indicate any differences in percentages of patients with decreased T4 levels (below normal range) in the TAZORAL™ and placebo groups. In the treatment period, the percentage of patients whose T4 values decreased from normal to low ranged from 0% to 0.3% in the TAZORAL™ group and 0% to 0.6% in the placebo group.

Table 7.6.1-1 Median Screening and Changes from Screening for Selected Laboratory Tests; Studies 190168-048P and 190168-049P

		Treatment Week					Post-treatment Week		
Laboratory Test	**Screening**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**
ALT (U/L)									
TAZORAL™ 4.5 mg	26.0	-1.0	-1.0	**-2.0***	**-3.0***	**-3.0***	-2.0	**-3.0***	-2.5
Placebo	26.0	0.0	-1.0	**-1.0**	**-1.0**	**-2.0**	-0.5	**0.0**	-1.0
AST (U/L)									
TAZORAL™ 4.5 mg	23.0	**1.0***	0.5	0.0	-1.0	-1.0	-2.0	**-2.0***	-2.0
Placebo	24.0	**0.0**	0.0	-1.0	0.0	-1.0	-1.0	**0.0**	-2.0
Alkaline Phosphatase (U/L)									
TAZORAL™ 4.5 mg	77.0	1.0	-1.0	-1.0	0.0	1.0	**4.0***	**6.0***	**7.0***
Placebo	77.5	0.0	-1.0	-1.0	-1.0	0.0	**1.0**	**1.0**	**2.0**
Creatine Phosphokinase (CPK) (U/L)									
TAZORAL™ 4.5 mg	91.0	2.0	1.0	**-3.0***	-1.0	**-5.5***	0.0	**-3.0***	7.0
Placebo	93.0	1.0	2.5	**2.0**	1.0	**5.0**	5.0	**2.0**	5.0
Gamma Glutamyl Transpeptidase (U/L)									
TAZORAL™ 4.5 mg	28.0	**1.0***	**2.0***	**2.0***	**2.0***	**2.0***	0.0	**0.0***	-1.0
Placebo	30.0	**-1.0**	**-1.0**	**-1.0**	**-1.0**	**0.0**	0.0	**1.0**	0.0
Glucose (mmol/L)									
TAZORAL™ 4.5 mg	5.30	0.10	0.00	**0.10***	0.10	0.00	0.10	0.10	0.00
Placebo	5.30	0.00	0.00	**0.00**	0.00	0.00	-0.10	-0.05	0.00
HDL Cholesterol (mmol/L)									
TAZORAL™ 4.5 mg	1.090	-0.050	-0.030	-0.030	-0.020	**-0.025***	-0.030	-0.020	0.000
Placebo	1.110	-0.030	-0.030	-0.020	0.000	**0.000**	0.000	0.030	0.010
Lactate Dehydrogenase (U/L)									
TAZORAL™4.5 mg	163.0	-1.0	-1.0	**-4.0***	**-6.0***	**-8.0***	**-9.0***	-9.0	-8.0
Placebo	162.0	-1.0	-2.0	**-1.0**	**-1.0**	**-2.0**	**-2.5**	-4.5	-8.0
Triglycerides (mmol/L)									
TAZORAL™4.5 mg	1.800	0.050	0.080	**0.120***	**0.090***	**0.170***	0.120	0.105	-0.010
Placebo	1.650	0.020	0.000	**-0.010**	**0.000**	**0.010**	0.020	0.090	0.035
TSH (µIU/mL)									
TAZORAL™4.5 mg	1.525	**0.130***	0.070	**0.210***	**0.130***	**0.125***	0.130	0.080	0.070
Placebo	1.510	**0.010**	0.030	**0.000**	**0.000**	**-0.050**	0.045	0.115	0.070
T4 (nmol/L)									
TAZORAL™4.5 mg	99.0	1.0	0.0	-2.0	**-2.0***	-2.0	-3.0	-3.0	**-4.0***
Placebo	100.0	-0.5	-1.0	-1.0	**0.0**	-2.0	-3.0	-2.0	**1.0**

* Significant difference ($p \leq 0.05$). Bolded values are those for which there was a significant difference between treatment groups.

The analyses of changes from baseline showed that the median changes generally were small and not of a magnitude to be of clinical concern. To evaluate the incidence of laboratory test values that may be of clinical concern, shifts from baseline (relative to the normal range) to each follow-up assessment were evaluated. Table 7.6.1-2 gives the percentages of patients with ALT, AST, GGT, CPK, glucose, triglycerides, total cholesterol, and TSH values that shifted from within the normal limits to above the upper limit of normal, and the percentages of patients with HDL cholesterol, TSH, and T4 values that shifted from within the normal limits to below the lower limit of normal. For each of these laboratory tests, at each timepoint a similar percentage of patients in the TAZORAL™ 4.5 mg and placebo groups had abnormal values. There was no evidence of a meaningful effect of TAZORAL™ on any of these laboratory parameters.

Table 7.6.1-2 Percentage (Number [a]) of Patients with Worsened (Relative to Baseline) Laboratory Test Values [b] Post-baseline for Laboratory Tests of Special Interest; Studies 190168-048P and 190168-049P

	Treatment Week			Post-treatment Week	
Laboratory Test	**4**	**8**	**12**	**16**	**24**
ALT (SGPT)					
TAZORAL™ 4.5 mg	3.0% (10/329)	4.7% (15/321)	3.6% (11/305)	4.9% (10/204)	7.1% (13/184)
Placebo	5.6% (19/340)	5.5% (18/327)	4.7% (15/317)	4.3% (4/92)	3.9% (3/77)
AST (SGOT)					
TAZORAL™ 4.5 mg	3.7% (12/324)	5.3% (17/320)	4.7% (14/301)	3.5% (7/201)	6.1% (11/181)
Placebo	5.7% (19/335)	4.0% (13/326)	5.1% (16/314)	4.3% (4/92)	2.7% (2/75)
GGT					
TAZORAL™ 4.5 mg	3.9% (13/332)	4.3% (14/323)	4.2% (13/308)	2.9% (6/206)	0.5% (1/184)
Placebo	1.2% (4/342)	2.1% (7/329)	2.8% (9/318)	5.4% (5/93)	5.2% (4/77)
CPK					
TAZORAL™ 4.5 mg	4.6% (15/327)	5.6% (18/320)	3.6% (11/304)	5.4% (11/205)	6.5% (12/184)
Placebo	6.5% (22/340)	7.3% (24/327)	5.7% (18/317)	5.6% (5/89)	7.8% (6/77)
Glucose					
TAZORAL™ 4.5 mg	4.0% (13/329)	2.5% (8/321)	3.9% (12/305)	4.9% (10/205)	4.9% (9/184)
Placebo	4.4% (15/340)	5.8% (19/327)	6.3% (20/316)	3.3% (3/92)	6.5% (5/77)
Triglycerides					
TAZORAL™ 4.5 mg	7.9% (26/330)	7.1% (23/323)	11.4% (35/308)	10.7% (22/206)	7.1% (13/184)
Placebo	6.7% (23/342)	7.6% (25/329)	6.6% (21/318)	5.6% (5/90)	14.1% (11/78)
Total Cholesterol					
TAZORAL™ 4.5 mg	2.1% (7/330)	1.9% (6/323)	1.6% (5/308)	1.5% (3/206)	0.0% (0/184)
Placebo	2.0% (7/342)	1.5% (5/329)	1.9% (6/318)	4.4% (4/90)	3.8% (3/78)
HDL Cholesterol					
TAZORAL™ 4.5 mg	3.3% (11/330)	4.0% (13/323)	3.6% (11/308)	4.4% (9/206)	1.6% (3/183)
Placebo	2.6% (9/342)	3.0% (10/329)	2.8% (9/318)	2.3% (2/88)	1.3% (1/78)
TSH (> upper limit)					
TAZORAL™ 4.5 mg	3.3% (11/331)	1.5% (5/323)	2.6% (8/308)	0.5% (1/205)	2.2% (4/183)
Placebo	2.0% (7/342)	2.7% (9/330)	2.2% (7/317)	5.6% (5/90)	2.6% (2/77)
TSH (< lower limit)					
TAZORAL™ 4.5 mg	0.6% (2/331)	0.3% (1/323)	0.0% (0/308)	0.5% (1/205)	1.6% (3/183)
Placebo	0.9% (3/342)	1.5% (5/330)	0.6% (2/317)	0.0% (0/90)	0.0% (0/77)
T4					
TAZORAL™ 4.5 mg	0.3% (1/328)	0.0% (0/321)	0.0% (0/305)	1.0% (2/204)	1.1% (2/183)
Placebo	0.0% (0/340)	0.6% (2/328)	0.6% (2/316)	0.0% (0/89)	0.0% (0/77)

[a] Number of patients with worsened laboratory values/number of patients evaluated at the follow-up visit and baseline.

[b] Values that changed from within the normal limits to above the upper limit of normal for ALT, AST, GGT, CPK, glucose, triglycerides, total cholesterol, and TSH, and values that changed to below the lower limit of normal for HDL cholesterol, TSH, and T4.

The analyses of the changes from the screening visit suggest that TAZORAL™ 4.5 mg, unlike other oral retinoids, does not significantly increase the risk of hepatotoxicity nor does it alter the lipid or thyroid function profiles, except possibly for a minimal elevation in triglycerides.

7.6.2 Open-label Studies in Patients with Psoriasis

Study 190168-052P

Treatment with TAZORAL™ 4.5 mg for 12 weeks for patients who previously had been treated with either TAZORAL™ 4.5 mg or placebo had no clinically significant effects on changes from baseline (screening value in the prior double-blind study) to weeks 12 or 24 for any laboratory test, except for modest increases in triglycerides and alkaline phosphatase. Over time, median changes from baseline were either small and/or represented an improvement. Changes in liver function and lipid profile test values (in terms of the proportions of patients whose values either improved or worsened relative to the normal range) showed no clinically relevant differences between the 2 treatment groups to suggest that a longer duration of treatment (24 versus 12 weeks) with TAZORAL™ 4.5 mg increased the risk of hepatotoxicity or hyperlipidemia.

Alkaline phosphatase was the only laboratory test for which there were consistent and significant differences between the 4.5 mg → 4.5 mg and placebo → 4.5 mg treatment groups. The median changes from baseline of the prior double-blind study were 15.0 U/L in the 4.5 mg → 4.5 mg group and 6.0 U/L in the placebo → 4.5 mg group at week 20. In both treatment groups, less than 10% of patients had alkaline phosphatase values that were above the upper limit of normal at any timepoint, and no patient had a value that was greater than twice the upper limit of normal.

In this 1-year study, the proportion of patients with alkaline phosphatase values that were above the upper-limit of normal increased from 0.8% at week 4 to 18.6% at week 56 and then declined to 8.8% at week 64. The clinical significance of these changes is unknown, but may represent a modest effect of TAZORAL™ on bone metabolism. There were no clinically meaningful changes in ALT, AST, GGT, or bilirubin to suggest the alkaline phosphatase changes represent a hepatotoxic effect.

Study 190168-050P

In this study of patients treated with TAZORAL™ 4.5 mg for up to 52 weeks, the changes in laboratory test values generally agreed with the results of the other phase 3 studies. Shown in Table 7.6.2-1 are the median changes from screening for ALT, AST, GGT, total

cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides, TSH, T4, alkaline phosphatase, and LDH. For many of these tests, the changes from screening were in the direction of what is normally considered a beneficial effect, such as decreases in ALT, AST, LDH, total cholesterol, LDL cholesterol, and increases in HDL cholesterol. GGT was consistently increased from screening over the entire treatment period, but median increases were small. After week 8, the median changes in alkaline phosphatase progressively increased though week 56 (4 weeks after the end of treatment) and then declined. During the treatment period, the median triglycerides values were increased from baseline at all assessment times, except at week 36 when the median value was unchanged from baseline. The increases in median triglyceride value at most assessments were small but represented a statistically significant change from screening. The greatest increase in median values was 0.155 mmol/L (13.7 mg/dL) at week 4, and represented an increase of approximately 10% over the median screening value. With longer treatment, median triglyceride values showed a trend towards smaller increases. Throughout the treatment and posttreatment periods, median TSH values were only modestly increased (less than 20%) and median T4 values were decreased somewhat (less than 10%) from screening. There was no indication that increases in TSH and decreases in T4 were dependent on the duration of treatment.

Further analyses evaluated the proportions of patients whose laboratory test values worsened relative to their values at screening. The proportions of patients with ALT, AST, GGT, LDH, total cholesterol, HDL cholesterol, LDL cholesterol, TSH, and T4 values that worsened from screening generally were less than 7% at all assessments times (Table 7.6.2-2). For each of these tests, there was no indication that the proportions of patients with values that worsened increased over the 52-week treatment period and 12-week posttreatment period.

The percentages of patients with alkaline phosphatase values that worsened from screening increased from 0.8% at week 4 to 18.6% at week 56 (4 weeks after the end of treatment), and then declined to 8.8% at week 64. These changes paralleled the changes in median values which progressively increased from 1.0 U/L at week 12 to 22.0 U/L at week 56 (Table 7.6.2-1). The percentage of patients with triglyceride values that worsened remained relatively stable over the treatment period, and ranged from 11.9% at week 28 to 7.8% at week 52.

Table 7.6.2-1 Median Screening and Median Changes from Screening for Selected Laboratory Tests; Study 190168-050P

Test	Screening	Treatment Period							Posttreatment Period	
		Week 4	Week 12	Week 20	Week 28	Week 36	Week 44	Week 52	Week 56	Week 64
ALT (U/L)	24.0	-1.0 *	-3.0 *	-3.0 *	-4.0 *	-3.0 *	-3.0 *	-3.0 *	-2.0 *	-3.0 *
AST (U/L)	23.0	1.0 *	-1.0	-1.0	-1.0 *	-1.0 *	-2.0 *	-1.0	-1.0 *	0.0
GGT (U/L)	26.0	2.0 *	2.0 *	2.0 *	1.0 *	2.0 *	2.5 *	3.0 *	0.0	-1.0
Alkaline phosphatase (U/L)	74.0	-1.0	1.0	6.0 *	8.0 *	14.0 *	15.0 *	16.0 *	22.0 *	16.0 *
LDH (U/L)	166.0	-1.0	-8.0 *	-13.0 *	-13.0 *	-14.0 *	-16.5 *	-15.0 *	-14.0 *	-8.5 *
Total Cholesterol (mmol/L)	5.17	-0.055	-0.080 *	-0.200 *	-0.130 *	-0.210 *	-0.180 *	-0.280 *	-0.260 *	-0.300 *
HDL-C (mmol/L)	1.090	-0.030 *	0.020	0.000	0.030 *	0.030 *	0.020	0.030 *	0.020	0.030 *
LDL-C (mmol/L)	3.210	-0.100 *	-0.130 *	-0.250 *	-0.200 *	-0.290 *	-0.290 *	-0.240 *	-0.310 *	-0.360 *
Triglycerides (mmol/L)	1.610	0.155 *	0.110 *	0.070 *	0.150 *	0.000	0.120 *	0.010	0.025	-0.080
TSH (µIU/L)	1.480	0.210 *	0.210 *	0.070 *	0.190 *	0.250 *	0.240 *	0.140 *	0.270 *	0.050
T4 (nmol/L)	100.0	-3.0 *	-4.0 *	-6.5 *	-6.0 *	-9.0 *	-5.0 *	-3.0 *	-4.0 *	-5.5 *

* Significant (p = 0.05) within group change from baseline.

Table 7.6.2-2 Percentage (Number [a]) of Patients with Values of Selected Laboratory Tests that Worsened [b] from Screening; Study 190168-050P

Test	Treatment Period							Posttreatment Period	
	Week 4	Week 12	Week 20	Week 28	Week 36	Week 44	Week 52	Week 56	Week 64
ALT (U/L)	2.8% (7/250)	2.6% (6/228)	1.9% (4/208)	1.6% (3/183)	3.6% (6/168)	3.8% (6/157)	3.9% (6/152)	1.4% (2/144)	3.6% (4/112)
AST (U/L)	3.6% (9/249)	3.6% (8/225)	3.4% (7/207)	2.2% (4/181)	3.0% (5/168)	1.3% (2/154)	3.3% (5/152)	2.1% (3/143)	1.8% (2/110)
GGT (U/L)	6.0% (15/252)	3.9% (9/229)	3.8% (8/211)	4.3% (8/185)	2.4% (4/170)	3.8% (6/160)	3.3% (5/153)	6.2% (9/145)	3.5% (4/113)
AP (U/L)	0.8% (2/252)	1.7% (4/229)	3.8% (8/211)	7.0% (13/185)	10.0% (17/170)	12.5% (20/160)	12.4% (19/153)	18.6% (27/145)	8.8% (10/113)
LDH (U/L)	2.1% (5/243)	0.9% (2/223)	0.5% (1/206)	0.6% (1/177)	0.6% (1/167)	0.6% (1/156)	0.7% (1/151)	0.7% (1/139)	0.9% (1/108)
TC (mmol/L)	3.6% (9/252)	2.6% (6/229)	1.9% (4/211)	2.7% (5/185)	2.4% (4/170)	1.9% (3/160)	2.6% (4/154)	0.7% (1/144)	0.9% (1/112)
HDL-C (mmol/L)	2.0% (5/252)	1.3% (3/229)	1.4% (3/211)	1.6% (3/185)	1.8% (3/170)	2.5% (4/160)	1.3% (2/154)	3.5% (5/144)	4.5% (5/112)
LDL-C (mmol/L)	0.0% (0/237)	0.0% (0/211)	0.0% (0/199)	0.0% (0/171)	0.0% (0/160)	0.7% (1/150)	0.0% (0/143)	0.0% (0/135)	0.0% (0/107)
Triglycerides (mmol/L)	8.7% (22/252)	8.3% (19/229)	8.5% (18/211)	11.9% (22/185)	10.6% (18/170)	9.4% (15/160)	7.8% (12/154)	8.3% (12/144)	5.4% (6/112)
TSH (µIU/L)	2.0% (5/252)	2.6% (6/229)	3.8% (8/209)	3.8% (7/185)	4.1% (7/170)	4.5% (7/157)	3.9% (6/155)	3.5% (5/144)	0.9% (1/111)
T4 (nmol/L)	0.8% (2/250)	1.3% (3/228)	0.5% (1/208)	0.5% (1/184)	1.8% (3/168)	1.3% (2/156)	0.6% (1/154)	2.1% (3/143)	0.9% (1/110)

[a] Number of patients with worsened value/number evaluated.

[b] A value that worsened was one that changed from within or below the normal range to above the normal range for alkaline phosphatase, ALT, AST, GGT, LDH, total cholesterol, LDL cholesterol, and triglycerides and from within the normal range to below the normal range for HDL cholesterol. For TSH and T4, a value that worsened was one that changed from within the normal range to above or below the normal range.

7.7 Calcification and/or Osteophyte Formation

In the phase 3 studies of patients with psoriasis and 1 study of patients with acne (190168-040P), ligament calcification and/or osteophyte formation was evaluated using lateral x-rays of the cervical spine and both ankles (calcanei). In these studies, x-rays were obtained for all patients at the screening visit, weeks 12 and 24 (studies 190168-048P, 190168-049P, 190168-052P, and 190168-040P), and the screening visit, weeks 24, 52, and 64 (study 190168-050P) or at the time of early termination from the study. For evaluation of axial hyperostosis, each calcification/ossification of the cervical spine at each of the 7 vertebral levels and at each of the 12 thoracic levels (study 190168-040P only) was graded using a 4-point scale with 0 = none, 1 = extent < 1/3 vertebral body height, 2 = extent 1/3 to 2/3 vertebral body height, and 3 = extent > 2/3 vertebral body height.

For evaluation of appendicular hyperostosis, dorsal and plantar proliferative entheseal changes of the calcaneus were graded by the central reading center using a 4-point scale with 0 = none, 1 = mild cortical proliferative changes, 2 = small local spur, and 3 = large spur. When scoring images, any difference between images of less than 1 grade was designated with a 0.5 score, resulting in possible scores of 0.5, 1.5, or 2.5. For both radiological assessments, x-rays were digitized at the central imaging center and evaluated by a radiologist. The assessments were made using the digital images and a computer-based reading system. The digital images were presented to the radiologist on high-resolution monitors, with images for all visits for a patient in a randomized display to mask the chronological sequence and treatment in the double-blind studies. It should be noted that in the placebo-controlled trials, even in the absence of exposure to TAZORAL™, up to 22% of cervical vertebrae and up to 46% of ankles showed some calcification and/or osteophyte formation.

7.7.1 Cervical Spine

In studies 190168-048P and 190168-049P, at the screening visit the majority of vertebrae were graded 0 (TAZORAL™ 79.2%, placebo 79.9%). At weeks 12 and 24, no vertebra in the group and only 1 in the placebo group had a score that differed from the screening score by at least 1 grade.

In study 190168-052P, at week 12 of the prior double-blind study, all patients had ligament and/or osteophyte formation scores that were unchanged from screening. By week 24, 11.9% of patients in the 4.5 mg → 4.5 mg group and 1.8% in the placebo → 4.5 mg group had vertebra with a change score of 0.5 to 1.0 grade. As noted by Pennes et al (1988), changes in the ligament calcification and/or osteophyte formation scores of 0.5 or 1 grade are of questionable radiological significance. At weeks 12 and 24 no patient had a vertebra with a change score of greater than 1 grade, and 8 patients (11.9%) had an increase of 0.5 to 1.0 grade.

In study 190168-050P, no patient had an improved calcification/osteophyte formation score at any assessment. Table 7.7.1-1 gives the number of patients at weeks 24, 52, and 64 whose screening calcification/osteophyte formation scores had worsened (increased). No patient at week 24 and 9 patients at weeks 52 and 64 had calcification/osteophyte formation scores for at least 1 vertebra that were increased from screening by 1.5 or 2.0 grades. One patient at week 52 also had a calcification/osteophyte formation score for 1 vertebra that was increased from screening by 3.0 grades.

Table 7.7.1-1 Number (%) of Patients with a Change From Screening in Ligament Calcification and/or Osteophyte Formation Score of the Cervical Spine; Study 190168-050P

Change in Calcification/ Osteophyte Score [a]	Week 24 N = 197	Week 52 N =193	Week 64 N = 123
Worsened			
0.5 to 1.0 grade	11 (5.6)	33 (17.1)	24 (19.5)
1.5 to 2.0 grades	0 (0.0)	9 (4.7)	9 (7.3)
2.5 to 3.0 grades	0 (0.0)	1 (0.5)[b]	0 (0.0)

[a] Worst grade change for any vertebra evaluated.

[b] patient dropped out during the posttreatment period due to a need for treatment

Week 52 = end of treatment period, week 64 = end of posttreatment period

In study 190168-040P of patients with acne, there were no changes in the scores for any of the cervical or thoracic vertebrae from screening to the last follow-up evaluation and there was no radiological evidence of bone calcification.

7.7.2 Dorsal and Plantar Ankle

In studies 190168-048P and 190168-049P, the majority of pretreatment dorsal and plantar ankle radiographs in both treatment groups were graded 0. At weeks 12 and 24, no patient in either the TAZORAL™ or placebo groups had a dorsal ankle score that was increased (worsened) from screening. At weeks 12 and 24, 1 patient in the TAZORAL™ group and none in the placebo group had a plantar ankle score that was increased from screening by at most 1.0 grade.

In study 190168-050P, at weeks 24, 52, and 64 most patients had no change in their dorsal or plantar ankle scores. No patient at any assessment had a dorsal or plantar ankle score that improved (decreased) from screening. The only changes in dorsal or plantar ankle scores were seen at weeks 52 and 64, at which times approximately 5% of dorsal ankle scores and approximately 4% of plantar ankle scores were increased by 0.5 to 1.0 grade (Table 7.7.2-1). As previously stated, changes in the ligament calcification and/or osteophyte formation scores of 0.5 or 1 grade are of questionable radiological significance. Only 2 patients had an ankle ligament calcification or osteophyte formation score of greater than 1 grade.

In study 190168-052P, no patient at weeks 12 or 24 had a dorsal or plantar ankle score that was increased from screening in the prior double-blind study.

Table 7.7.2-1 Number (%) of Patients with Grade Changes (Worsening) from the Screening Visit in Dorsal or Plantar Ankle Ligament Calcification/Osteophyte Score; Study 190168-050P

Grade Changes (Worsening) in Calcification/Osteophyte Score [a]		Treatment		Posttreatment [b]
		Week 24 N = 197	Week 52 N = 193	N = 123
Dorsal Ankle	0.5 – 1.0 grade	0 (0.0)	10 (5.2)	7 (5.7)
	1.5 – 2.0 grades	0 (0.0)	0 (0.0)	0 (0.0)
	2.5 – 3.0 grades	0 (0.0)	0 (0.0)	0 (0.0)
Plantar Ankle	0.5 – 1.0 grade	0 (0.0)	6 (3.1)	5 (4.1)
	1.5 – 2.0 grades	0 (0.0)	2 (1.0)	0 (0.0)
	2.5 – 3.0 grades	0 (0.0)	0 (0.0)	0 (0.0)

[a] Worst grade change in either ankle.

[b] 12 weeks after the end of treatment.

Studies 190168-050P and 190168-052P were open-label studies and did not include a placebo group; there were some minimal hyperostotic and ligamentous calcification changes.

In study 190168-040P of patients with acne, increases in dorsal ankle scores from pretreatment to last follow-up were seen in 4 patients: a 2-grade increase in 2 of 29 patients in the TAZORAL™ 6.0 mg group, and a 0.5-grade increase in 1 of 28 patients in the TAZORAL™ 3.0 mg group, and a 2-grade increase in 1 of 28 patients in the TAZORAL™ 1.5 mg group. There were no increases in dorsal ankle scores for the 28 patients in the TAZORAL™ 0.75 mg group or for the 33 patients in the placebo group. No patient had a change in plantar ankle score.

Long-term treatment, but not short-term treatment with TAZORAL™, appears to increase the potential for worsening ligament calcification and/or osteophyte formation, particularly in the cervical spine. However, the clinical relevance of these radiographic changes, the majority of which are subtle, is uncertain. As studies in the literature do not use the same scoring system—and generally record simply the presence of calcification without evaluating changes in its severity—the oral TAZORAL™ data are not easily compared with published data. However, these effects on ligamentous calcification and osteophyte formation are consistent with the similar, well-known effects of other systemic retinoids when administered chronically.

7.8 Bone Density

Bone mineral density (BMD) changes were evaluated at selected centers in the 4 phase 3 studies of patients with psoriasis and in 1 study of patients with nodular acne. Bone density was evaluated using DXA to obtain scans of the spine and proximal femur at the screening visit, end of treatment, and end of the posttreatment period (studies of psoriasis only), or at the time of early termination from the study. In the placebo-controlled trials, for lumbar spine and femoral neck, there were no differences between the TAZORAL™ and placebo groups in terms of median percentage changes in BMD from screening values. For total hip, there was a small but significantly greater change in BMD (+0.16%) in the TAZORAL™-treated group relative to the placebo group (-0.41%). In study 190168-052P there were no

significant differences in BMD values from screening at 12 or 24 weeks of therapy. In the 1-year study 190168-050P, there were no significant changes in BMD from screening in the lumbar spine at 24 or 52 weeks of therapy. For the total hip and femoral neck, there were significant decreases in BMD from screening at weeks 24 and 52 (range -0.29% to -0.92%). The maximum median percentage loss in spinal BMD in phase 3 studies with oral TAZORAL™ was 1.56% at any timepoint. Considering the precision error for DXA measurement of spinal BMD is reported to be 1%, this would not represent a significant reduction in BMD (Mazess and Barden, 1989).

In each of the phase 3 studies there was considerable variability in BMD scores of the lumbar spine, total hip, and femoral neck, with intrapatient BMD decreases as well as increases. Such variability is consistent with findings in BMD evaluations reported in the literature (Haddaway et al, 1992; Patel; et al, 2000; Phillipov et al, 2001). These data suggest that the incidence of patients with at least a 5% loss in BMD in the lumbar spine, total hip, and femoral neck increases as the duration of treatment increases, but this would be expected with greater frequency over time. However, at least for the lumbar spine and femoral neck, the incidence of patients with at least a 5% gain in BMD also increases as the duration of treatment increases (although not to quite the same extent as it does with losses in BMD). Thus, some of these apparent losses and gains in BMD may reflect variations in the dual x-ray absorptiometry technique used to assess BMD (as has previously been reported in bone density evaluations by others [Phillipov et al, 2001]). In addition there is variance in bone mineral density at any given age and significant increase after 50 years of age (Haddaway et al, 1992). Nevertheless, despite this, the data do suggest some increased propensity for a 5% or greater reduction in BMD with oral TAZORAL™ therapy of 24 weeks or more.

In studies 190168-048P and 190168-049P, the distributions of percentage change from screening in BMD of the lumbar spine, total hip, and femoral neck from the screening visit to weeks 12 and 24 were not significantly different ($p > 0.05$) for the TAZORAL™ 4.5 mg and placebo groups. The distributions of the percentage changes are summarized in Table 7.8-1.

Table 7.8-1 Changes in Bone Mineral Density from Screening to Weeks 12 and 24; Studies 190168-048P and 190168-049P

	Number [a] (%) of Patients					
	Lumbar Spine		Total Hip		Femoral Neck	
Percentage Change	Taz 4.5 mg	Placebo	Taz 4.5 mg	Placebo	Taz 4.5 mg	Placebo
Week 12 (end of treatment period)						
≤ -5	4/95 (4.2%)	0/95 (0.0%)	0/95 (0.0%)	1/95 (1.1%)	1/95 (1.1%)	2/95 (2.1%)
> -5 to < 5	82/95 (86.3%)	88/95 (92.6%)	94/95 (98.9%)	94/95 (98.9%)	91/95 (95.8%)	92/95 (96.8%)
≥ 5	9/95 (9.5%)	7/95 (7.4%)	1/95 (1.1%)	0/95 (0.0%)	3/95 (3.2%)	1/95 (1.1%)
Week 24 (end of posttreatment period)						
≤ -5	3/69 (4.3%)	1/40 (2.5%)	1/71 (1.4%)	2/40 (5.0%)	4/71 (5.6%)	2/40 (5.0%)
> -5 to < 5	59/69 (85.5%)	37/40 (92.5%)	67/71 (94.4%)	38/40 (95.0%)	62/71 (87.3%)	38/40 (95.0%)
≥ 5	7/69 (10.1%)	2/40 (5.0%)	3/71 (4.2%)	0/40 (0.0%)	5/71 (7.0%)	0/40 (0.0%)

[a] Number of patients with change/number of patients evaluated.

In study 190168-052P, as in studies 190168-048P and 190168-049P, there was considerable variability in the changes in bone density over time (Table 7.8-2). The distributions of percentage change in bone density were significantly different ($p = 0.05$) for the 4.5 mg → 4.5 mg and placebo → 4.5 mg groups only for total hip at week 12.

Table 7.8-2 Percentage Change in Bone Mineral Density from Screening of Prior Study; Study 190168-052P

	Number [a] (%) of Patients					
	4.5 mg ® 4.5 mg			Placebo ® 4.5 mg		
Percentage Change	Week 12 of Prior Double-blind Study	Week 12	Week 24	Week 12 of Prior Double-blind Study	Week 12	Week 24
Lumbar Spine						
= -5	2/31 (6.5%)	2/30 (6.7%)	3/24 (12.5%)	0/71 (0.0%)	3/61 (4.9%)	5/53 (9.4%)
> -5 to < 5	28/31 (90.3%)	27/30 (90.0%)	21/24 (87.5%)	65/71 (91.5%)	55/61 (90.2%)	43/53 (81.1%)
≥ 5	1/31 (3.2%)	1/30 (3.3%)	0/24 (0.0%)	6/71 (8.5%)	3/61 (4.9%)	5/53 (9.4%)
Total Hip						
= -5	0/30 (0.0%)	3/29 (10.3%)	3/23 (13.0%)	0/71 (0.0%)	3/60 (5.0%)	3/53 (5.7%)
> -5 to < 5	30/30 (100%)	24/29 (82.8%)	20/23 (87.0%)	71/71 (100%)	57/60 (95.0%)	50/53 (94.3%)
≥ 5	0/30 (0.0%)	2/29 (6.9%)	0/23 (0.0%)	0/71 (0.0%)	0/60 (0.0%)	0/53 (0.0%)
Femoral Neck						
= -5	1/30 (3.3%)	4/29 (13.8%)	4/23 (17.4%)	1/71 (1.4%)	4/60 (6.7%)	4/53 (7.5%)
> -5 to < 5	27/30 (90.0%)	22/29 (75.9%)	19/23 (82.6%)	69/71 (97.2%)	54/60 (90.0%)	49/53 (92.5%)
≥ 5	2/30 (6.7%)	3/29 (10.3%)	0/23 (0.0%)	1/71 (1.4%)	2/60 (3.3%)	0/53 (0.0%)

Placebo → 4.5 mg = received placebo in study 190168-048P or 190168-049P and TAZORAL™ 4.5 mg in study 190168-052P; 4.5 mg → 4.5 mg = received TAZORAL™ 4.5 mg in study 190168-048P or 190168-049P and study 190168-052P.

Week 12 = end of treatment period, week 24 = end of posttreatment period.

[a] Number of patients with change/number of patients evaluated.

In study 190168-050P, BMD decreases of ≥ 5% were seen in all 3 areas studied (lumbar spine, total hip, and femoral neck) (Table 7.8-3). Increases in BMD of ≥ 5% also were seen in all 3 areas studied, but the percentages of patients with ≥ 5% increases were less than the percentages of patients with ≥ 5% decreases in the total hip and femoral neck areas. For the lumbar spine, a similar or greater percentage of patients had ≥ 5% increases as had ≥ 5% decreases.

Table 7.8-3 Percentage Changes in Bone Mineral Density; Study 190168-050P

	Number [a] (%) of Patients		
Percentage Change	**Week 24**	**Week 52**	**Week 64**
Lumbar Spine			
= -5	6/85 (7.1%)	11/91 (12.1%)	7/56 (12.5%)
> -5 to < 5	69/85 (81.2%)	69/91 (75.8%)	39/56 (69.6%)
≥ 5	10/85 (11.8%)	11/91 (12.1%)	10/56 (17.9%)
Total Hip			
= -5	2/86 (2.3%)	5/91 (5.5%)	7/59 (11.9%)
> -5 to < 5	83/86 (96.5%)	86/91 (94.5%)	50/59 (84.7%)
≥ 5	1/86 (1.2%)	0/91 (0.0%)	2/59 (3.4%)
Femoral Neck			
= -5	8/86 (9.3%)	11/91 (12.1%)	10/59 (16.9%)
>- 5 to < 5	72/86 (83.7%)	75/91 (82.4%)	46/59 (78.0%)
≥ 5	6/86 (7.0%)	5/91 (5.5%)	3/59 (5.1%)

[a] Number patients with change/number patients evaluated.

Week 52 = end of treatment period, week 64 = end of posttreatment period.

Because the 2 open-label studies (190168-050P and 190168-052P) did not include a placebo group, it is difficult to make definitive conclusions regarding the risk of BMD changes due to TAZORAL™.

The radiographic and DXA data are consistent with effects of TAZORAL™ on ligamentous calcification, osteophyte formation, and bone mineral density, which are similar to the well-known effects of other systemic retinoids.

7.9 Neuropsychiatric Evaluations

In the phase-3 studies, neuropsychiatric evaluations were performed pretreatment, during treatment, and posttreatment and included a self-administered neuropsychiatric symptom survey (Brief Symptom Inventory), structured modules taken from the Mini International Neuropsychiatric Interview, and directed questions relating to thoughts of suicide and mood changes that may impair daily activities. No increased risk to patients treated with TAZORAL™ 4.5 mg was suggested by the analyses of these psychiatric measures. There were no reported cases of suicide or attempted suicide in any of the studies of TAZORAL™. No

increased risk of depression in TAZORAL™-treated patients was noted in the phase 3 studies (Table 7.9-1).

Table 7.9-1 Rates of Depression in Phase 3 Studies of TAZORAL™

Study/ Treatment	Treatment Period	Posttreatment Period
190168-048P, 190168-049P		
TAZORAL™ 4.5 mg	1.4% (5/348)	0.9% (2/213)
Placebo	2.0% (7/358)	2.3% (2/87)
190168-052P		
TAZORAL™ 4.5 mg in prior study	4.3% (4/92)	3.9% (3/76)
Placebo in prior study	2.7% (6/220)	1.1% (2/185)
190168-050P		
TAZORAL™ 4.5 mg	3.4% (9/263)	2.6% (4/152)

7.10 Ophthalmological Evaluations

The results of the ophthalmological evaluations (visual acuity, biomicroscopy, vitreous pathology, optic disk, ERG, night vision) in the phase 3 studies of psoriasis did not indicate that patients treated with TAZORAL™ 4.5 mg are at greater risk of vision impairment than patients treated with placebo, or that the risk of vision impairment increases with treatment for up to 1 year (see Table 7.10-1).

Best-corrected visual acuity was measured for each eye using an Early Treatment Diabetic Retinopathy Study chart. A 2-line or greater change from baseline, using Snellen equivalent scores, was considered clinically significant. The biomicroscopy examinations included evaluation of the condition of the lids/lashes, lid margins, conjunctiva, anterior chamber, cornea, iris, and lens. Observations were recorded using a 5-point scale with 0 = none, 0.5 = trace, 1 = mild, 2 = moderate, and 3 = severe.

Table 7.10-1 Changes from Screening in Ophthalmological Evaluations in Studies of Patients with Psoriasis

	Number [a] (%) of Patients					
	190168-048P/ 190168-049P		190168-052P		190168-050P	
Ophthalmological Evaluation	**Taz 4.5 mg**	**Placebo**	**4.5 mg ® 4.5 mg**	**Placebo ® 4.5 mg**	**Taz 4.5 mg**	
(Changes from Screening)	**Week 12**	**Week 12**	**Week 12**	**Week 12**	**Week 24**	**Week 52**
≥ 2 line decrease (worsening) in visual acuity	26/320 (8.1%)	22/329 (6.7%)	9/85 (10.6%)	12/203 (5.9%)	10/198 (5.1%)	19/197 (9.6%)
Visual acuity worsened (reported as an adverse event)	2/348 (0.6%)	2/358 (0.6%)	1/92 (1.1%)	2/220 (0.9%)	1/263 (0.4%)	2/199 (1.0%)
≥ 1 point increase in biomicroscopy score	58/320 (18.1%)	66/330 (20.0%)	14/85 (16.5%)	47/203 (23.2%)	47/198 (23.7%)	41/197 (20.8%)
Optic disc change (from normal to abnormal)	0/319 (0.0%)	4/330 (1.2%)	6/85 (7.1%)	4/203 (2.0%)	4/198 (2.0%)	3/196 (1.5%)
Seeing or reading in low or dim light (from no difficulty to difficulty)	2/319 (0.6%)	3/330 (0.9%)	2/85 (2.4%)	1/202 (0.5%)	3/197 (1.5%)	2/197 (1.0%)

Placebo → 4.5 mg = received placebo in study 190168-048P or 190168-049P and TAZORAL™ 4.5 mg in study 190168-052P; 4.5 mg → 4.5 mg = received TAZORAL™ 4.5 mg in study 190168-048P or 190168-049P and study 190168-052P.

[a] Number of patients with condition/number of patients evaluated.

Electroretinographic studies performed in 28 patients in study 190168-050P showed no significant deleterious effect of treatment with TAZORAL™ 4.5 mg.

7.11 Auditory Evaluations

In study 190168-050P, auditory evaluations were conducted for 59 patients at 6 selected sites. A change in hearing, which may represent a potential ototoxic event, was defined as significant equivalent air and bone conduction threshold changes at frequencies = 4000 Hz and/or significant air conduction threshold changes at frequencies > 4000 Hz.

Two patients had equivalent air and bone conduction threshold changes at frequencies = 4000 Hz. One of these patients had equivalent air and bone conduction threshold changes at frequencies = 4000 Hz and air conduction threshold changes > 4000 Hz. It is possible that these patients experienced an ototoxic event during the study. However, neither patient

complained of hearing loss during the study. One patient reported a 20-year history of occupational noise exposure and during the screening audiological examination, the examiner noted limited reliability in the patient's responses.

Hearing loss was recorded as an adverse event for 3 patients treated with TAZORAL™; 1 in study 190168-048P and 2 in study 190168-050P. One patient 190168-048P study had a worsening of her hearing loss which was not thought to be related to therapy and was recorded as a left-sided, asymmetric, sensorineural hearing loss. The patient was on concomitant medications that have been associated with ototoxicity including furosemide and celecoxib. In study 190168-050P, 1 patient had increased scale in her ears and was referred to an ENT physician who irrigated both ears. The patient's hearing loss resolved the same day. The patient had also used medication that have been associated with ototoxicity (ibuprofen and zolmitriptan). The second patient in study 190168-050P had a history of hearing loss and also used concomitant medications that have been associated with ototoxicity (citalopram, celecoxib, rofecoxib, furosemide, and tramadol). Due to the fact that the patient's hearing was not tested during screening and because she reported a preexisting hearing loss, it was not possible to determine if the sensorineural component of her hearing loss reflects an ototoxic event.

8.0 POSTMARKETING RISK MANAGEMENT PLAN

8.1 Background

The TAZORAL™ risk management program or PACT™ (Partnership to Promote Awareness and Compliance to Avoid Teratogenicity) is a new risk minimization action plan designed specifically for TAZORAL™ and patients with moderate-to-very severe plaque psoriasis. In addition, it goes beyond many other risk management programs in that it incorporates insights gained from recent FDA advisory committee meetings on other programs, as well as the FDA's recent draft guidances on risk management.

PACT™ considers the unique characteristics of moderate to very severe psoriasis and its treatment. Specifically, while psoriasis can appear at any age, it is mainly a disease of adults, with only 8% of prevalent U.S. cases in patients under the age of 18 years. In fact, the mean

age of psoriasis patients is in the mid- to-late 40s and the average age of onset is approximately 30 years. Almost 20% are over age 65 years. Approximately half of all prevalent cases are male (National Psoriasis Foundation, 2003; National Health Interview Survey 1996). Females of childbearing age make up 20% to 30% of the population. Psoriasis is also a chronic, lifelong disease for which there is currently no cure.

The PACT™ program incorporates a number of improvements over other risk management programs, summarized previously in Section 1.5.

8.2 Risk Minimization Action Plan (RiskMAP)

Consistent with FDA's draft risk management guidances for industry, Allergan, Inc. is proposing a postapproval risk management plan (PACT™) for TAZORAL™ that includes a risk minimization action plan, or RiskMAP, to protect patients against the risk of teratogenicity and enable the continuing and iterative process of assessing the product's benefit-risk profile balance.

As recommended by the FDA, in the case of a known and serious risk related to the use of a specific product, measures to minimize risk beyond routine pharmacovigilance practices (eg, a RiskMAP) may be necessary to adequately protect patients. The goal of a RiskMAP is to minimize a product's known risk(s) while preserving its benefits. FDA recommends that "RiskMAPs be used judiciously to minimize risks without encumbering drug availability or otherwise interfering with the delivery of product benefits to patients." (Guidance for Industry Development and Use of Risk Minimization Action Plans, 2004)

Because of the potential teratogenic effects of TAZORAL™, a RiskMAP focused on preventing fetal exposure to TAZORAL™ is appropriate and necessary. The proposed RiskMAP has several key components, including: targeted education for all patients; a mandatory registry of prescribers, pharmacies, and females of childbearing potential; and a pregnancy exposure follow-up study of women who have become pregnant while taking TAZORAL™.

8.2.1 Goals

The goals of PACT™ are:

- No pregnant woman shall be prescribed TAZORAL™
- No woman taking TAZORAL™ shall become pregnant.

8.2.2 Objectives and Risk Minimization Tools

Table 8.2.2-1 Physician Objectives and Tools

Physician Objectives	Tools
Understand potential birth defect risks Understand procedures to minimize risks Follow PACT™ guidelines and procedures Understand that females of childbearing potential are limited to a 30-day supply of drug (no refills) and must have a laboratory-based pregnancy test every month, and that all other patients are limited to a 30-day supply of drug with no more than 2 refills	*What Prescribers Need to Know* Brochure Prescriber Introduction Letter Prescriber registration and certification test
Enroll all females of childbearing potential in the mandatory pregnancy prevention registry	Web- or phone-based enrollment system
Ensure all females of childbearing potential have an office visit each month Ensure that all females of childbearing potential have 2 laboratory-based pregnancy tests prior to initiating therapy with TAZORAL™ Assure laboratory-confirmed pregnancy testing is completed monthly for all females of childbearing potential and documented into the PPR system	Reminder checklist on the TPA Entry of pregnancy test results into mandatory registry
Be sure that a woman is not pregnant before treatment, during treatment, and for 1 month after treatment is stopped	*What Prescribers Need to Know* Brochure Negative pregnancy test result required in order to activate a TPA

Table 8.2.2-1 Physician Objectives and Tools (continued)

Counsel all patients about the potential risks of birth defects Assure that females of childbearing potential have the knowledge and commitment to use an effective combination of 2 forms of birth control simultaneously Counsel patients not to share the drug and not to donate blood during therapy or for 1 month after discontinuation of therapy	*What Prescribers Need to Know* Brochure Use of patient tools including both the general informed consent for all patients and the female informed consent form, *What Women Need to Know* brochure, Patient Video /CD-ROM, and Medication Guide Counseling checklist on TPA

Table 8.2.2 -2 Pharmacy Objectives and Tools

Pharmacy Objectives	Tools
Pharmacies must not dispense a prescription for TAZORAL™ to anyone without an appropriate TPA For females of childbearing potential, pharmacies must validate patient eligibility via the PPR system and only dispense TAZORAL™ to qualified patients within the time limits and quantities specified on the TPA Pharmacies must understand that females of childbearing potential are limited to a 30-day supply of drug and must requalify every month for a new prescription, and that all other patients are limited to a 30-day supply of drug with no more than 2 refills	Pharmacist Introduction Letter and Dispensing Guide Prescription Authorization form Package Insert Medication Guide Pharmacist Reminder Cards Pharmacy registration in risk management system Process for pharmacies to validate that patient is qualified (by accessing system) prior to dispensing drug Pharmacy certification that all pharmacists are trained in PACT™ procedures Test to document understanding of PACT™ procedures Toll-free telephone counseling services staffed by health professionals

Table 8.2.2-3 Patient Objectives and Tools

Patient Objectives	Tools
All patients must understand that they must not share TAZORAL™ All patients must understand that they must not donate blood while taking TAZORAL™ and for 1 month after discontinuation of therapy	*What Women Need to Know* and *What Men Need to Know* Brochures Medication Guide Informed Consent Form for all patients Patient Video/CD Rom Counseling from the prescriber at least every 3 months Information on drug blister packaging Toll-free telephone counseling services staffed by health professionals
Females of childbearing potential must demonstrate that they are not pregnant with a laboratory-confirmed pregnancy test before taking TAZORAL™ (both initially and for each new prescription)	To promote awareness and understanding of testing: *What Women Need to Know* Brochure Medication Guide Informed Consent Forms Patient Qualification Form Information on drug blister packaging To promote Systems Compliance: TPA Pregnancy testing (lab-confirmed) Pregnancy prevention registry (pregnancy testing recorded by physician in the system and validated by pharmacist)
Females of childbearing potential must go through the reeducation process each month to assure understanding of: the potential consequences of becoming pregnant) and how to avoid pregnancy	*What Women Need to Know* Brochure Medication Guide Informed Consent Forms Patient Qualification Form Contraception Counseling Referral Form Patient Video/CD Rom Counseling from the prescriber Patient Qualification Checklist Information on drug blister packaging Correct completion of knowledge and compliance assessments each month in order to qualify and activate new prescription Toll-free telephone counseling services staffed by health professionals

Table 8.2.2-3 Patient Objectives and Tools (Continued)

Patient Objectives	Tools
Females of childbearing potential must use an effective combination of 2 forms of birth control	*What Women Need to Know* Brochure Medication Guide Informed Consent Forms Patient Qualification Form Information on drug blister packaging Contraceptive Counseling Referral Form Counseling from the prescriber Patient Video/CD Rom Patient Qualification Checklist Knowledge and compliance testing conducted each month through PPR Negative pregnancy test needed to activate TPA Toll-free telephone counseling services staffed by health professionals
Females of childbearing potential must participate in PPR, the mandatory pregnancy prevention registry In the event that a female of childbearing potential does have a pregnancy while taking TAZORAL™, she should enroll in the Pregnancy Exposure Follow-up Study	Web- or phone-based enrollment system Brochure on Pregnancy Exposure Follow-up Study

8.2.3 Summary of PACT™ Process

8.2.3.1 Physician and Pharmacy Registration and Certification

Physicians will receive educational materials on the TAZORAL™ RiskMAP and the product's risk of teratogenicity. After studying the prescriber educational materials, the physician must access the PPR system to register. In order to be certified, he or she will have to agree to abide by the program's requirements and then pass a knowledge test demonstrating understanding of the risks associated with TAZORAL™ and their knowledge of the program's requirements. Prescribers will be assigned a prescriber ID number. Once the physician is certified, he/she will be a registered prescriber and will receive a set of risk management materials, including patient education materials, consent forms, and TPA forms.

Each qualified prescribing physician is given specialized TPA forms that must be completed to initiate the prescribing of TAZORAL™ for any patient. This authorization specifies the gender and childbearing potential of the patient. A Prescription Authorization for females of childbearing potential must confirm that: the patient is of childbearing potential (determined by physician) and that the risks including pregnancy were discussed with the patient.

Pharmacies must be registered in the mandatory registry and will be assigned a pharmacy ID number. Pharmacies must also certify that all pharmacists who may dispense TAZORAL™ have been adequately trained on the PACT™ requirements. Each pharmacy's representative must access the system and pass a brief test to document his/her understanding of the program.

8.2.3.2 Patient Flow

When a physician and a moderate-to-very severe psoriasis patient determine that TAZORAL™ may be an appropriate treatment for the patient's psoriasis, the physician must then educate the patient about the drug, its risks including teratogenicity, and the requirements of PACT™. Several tools are used to provide patients with a thorough review of the risks of using TAZORAL™. All patients receive a gender-specific brochure (*What Women Need to Know* or *What Men Need to Know*) from their physician that provides complete background information about the uses and risks of using the product. All patients sign an informed consent form that describes the major risks and side effects of TAZORAL™ and contains statements regarding elements of PACT™.

The brochure for females describes the need for effective birth control and provides background information that permits women to make an informed choice of birth control methods. The physician must determine whether the patient is of childbearing potential. Females who have had a hysterectomy or who are postmenopausal with no menses for 12 consecutive months are not considered to be of childbearing potential. An additional signed consent form, as well as a signed patient qualification form, are required to qualify females of childbearing potential and include: a description of the risk of TAZORAL™ related to birth defects; the need for pregnancy prevention; a commitment that the patient will undergo the necessary pregnancy testing and will use 2 forms of birth control

(simultaneously and continuously for 1 month before, during, and for 1 month after discontinuing therapy with TAZORAL™). An instructional video/CD-ROM and additional resource materials are provided for females of childbearing potential. Women must then be enrolled in the PPR, in which pregnancy tests will be documented and education messages will be reinforced and tested for understanding. They will also be given a brochure describing the formal pregnancy exposure follow-up study. In the event that an exposed pregnancy occurs, the woman will be strongly encouraged to contact the appropriate study personnel to enroll in the pregnancy exposure study. If the physician learns of the pregnancy, he/she will notify the pregnancy registry as well. Registry staff will provide registry brochures for discussion with the patient. Registry staff will also monitor the PPR to identify any positive pregnancy test results and communicate this information with the physician.

During the initial consultation visit, when the decision is made to pursue qualification of the patient for treatment, the first laboratory-based pregnancy test is ordered and conducted. Assuming negative results are confirmed, the patient should return for a second office visit and have a second laboratory-based test conducted during the first 5 days of the menstrual period immediately preceding the start of treatment with TAZORAL™. Pregnancy test results are documented in the system by the physician.

These patients should be on 2 effective forms of contraception for 1 month prior to initiation of therapy, at least 1 of which is a primary form. Effective forms of contraception include both primary and secondary forms of contraception. Primary forms of contraception include: tubal ligation, partner's vasectomy, intrauterine devices, birth-control pills, and injectable/implantable/insertable/transdermal hormonal birth-control products. Secondary or barrier methods of contraception include: diaphragms, latex condoms, and cervical caps; each must be used with a spermicide. During the second office visit, a woman will also be given an inactive TPA for a 30-day supply of drug (no refills).

In order for a female of childbearing potential to become qualified to receive a 30-day supply of TAZORAL™, her physician must register her and enter her pregnancy test results into the PPR. She will be assigned a patient ID number and then must successfully complete the knowledge and understanding assessments, including questions about birth control

compliance, and assuming her pregnancy test results were negative, will then qualify and activate her TPA. She may then take her prescription to a registered pharmacy to be filled. The prescription must be filled and dispensed within 7 days from the patient's qualification date (ie, date of negative pregnancy test) and must be for a 30-day supply only (no refills). If the patient has a positive pregnancy test, no pregnancy test, or does not register in the system, she will not qualify to have her prescription activated. The pharmacist will refer a patient who is disqualified to the toll-free help-line for assistance. Through interactions with the system every month she is on TAZORAL™ until 1 month after discontinuation, she will be reminded of the risks of pregnancy, the importance of compliance with 2 acceptable forms of birth control, and tested on her understanding of these issues. She will also have her pregnancy testing results documented on a regular basis in order to obtain a new prescription each month. Should a patient discontinue therapy for more than a month and then start another course of drug at a later time, she will be reentered into the system using the same patient ID (and, therefore, not be counted as a new prescription). Discontinuations will be monitored and patients will be instructed by their physician (with follow-up reminders from registry staff, if needed) to complete a laboratory-based pregnancy test 30 days posttreatment. These results will be entered into the PPR system by the physician.

Physicians will counsel males and females of non-childbearing potential using the supporting educational materials, including the gender-specific brochure (*What Women Need to Know* or *What Men Need to Know*) that provides complete background information about the uses and risks of using the product. A TPA for these patients must confirm that: the patient is a male or a female not of childbearing potential, and that the product's risks were discussed with the patient. The completed TPA will then be sufficient for males and females of non-childbearing potential to purchase TAZORAL™. The prescription must be filled within 7 days from the qualification date (to ensure adequate recall of the educational messages) and must be for no more than a 30-day supply with no more than 2 refills. The qualification date for these patients is the date of the office visit. In this manner, patients will be ensured of being counseled by the physicians and reminded of the risks of sharing drug or donating blood at least every 3 months.

Pharmacists must not dispense a prescription for TAZORAL™ to a pregnant woman. The only authorized method for male and female patients of non-childbearing potential to receive an initial prescription for TAZORAL™ is by presenting the pharmacy with a completed TPA form from the physician. The only authorized method for female patients of childbearing potential to be dispensed TAZORAL™ is for the patient to qualify through the registry system (including a negative pregnancy test within the time limits). The pharmacist then validates qualification of a female patient of childbearing potential by accessing the system using the pharmacy ID number prior to dispensing drug. The pharmacist also enters the lot number, NDC code, and the quantity of drug dispensed. Resource materials for pharmacists include the package insert, an introduction letter and dispensing guide, the Prescription Authorization process, reminder materials, and telephone numbers to contact if they have any questions regarding program implementation. A *Medication Guide*, which summarizes important medication information, is dispensed to all patients as part of the product packaging. Toll-free telephone counseling services staffed by health professionals are available for all patients who desire additional counseling or have questions about TAZORAL™ or effective birth control.

In the event that a woman does become pregnant while taking TAZORAL™, or begins treatment while pregnant, she will be strongly encouraged to enroll in the Pregnancy Exposure Follow-Up Study. Study staff will provide brochures for discussion with the patient, will monitor the PPR to identify any positive pregnancy test results, and will communicate with the physician. Objectives of the pregnancy exposure study include: tracking of the rates of pregnancy outcomes (eg, live births, spontaneous abortion, stillbirth, congenital abnormalities) and root cause analysis of each pregnancy. A woman may be enrolled by a healthcare provider or pharmacist, or she may initiate enrollment herself by contacting the study's toll free number. The pregnancy exposure study will include a formal study protocol, in keeping with the FDA's Guidance for Industry on pregnancy exposure registries. Consent will be requested to follow up with relevant healthcare practitioners (eg, dermatologist, obstetrician, pediatrician), and every effort will be made to follow up on any exposed pregnancy. The design of this study will be finalized in consultation with the FDA and other appropriate clinical experts. Regular study monitoring reports will be submitted to the FDA.

8.2.4 PACT™ Program Evaluation

The primary metric for evaluating program success will be the pregnancy rate. Other evidence-based metrics will be used to evaluate the effectiveness of PACT™ including health outcomes; process measures; comprehension and knowledge assessments; and prescribing patterns:

Health Outcomes

- Pregnancy rates
- Pregnancy counts
- Pregnancy outcomes

Process Measures

- Pregnancy testing compliance
- Compliance with TPA
- Comparison of registered healthcare providers to those actually prescribing and dispensing the drug to identify unregistered physicians/pharmacies
- Contraception compliance (self-reported)
- Root cause/failure analysis – pregnancies and positive pregnancy tests

Understanding and Knowledge Assessments (Females of Childbearing Potential)

- Patient's knowledge of pregnancy risks
- Patient's access to educational materials
- Patient's knowledge of effective contraception methods

Data sources for evaluating these outcomes are presented in Tables 8.2.4-1, 8.2.4-2. and 8.2.4-3.

Table 8.2.4-1 Data Sources for Outcome Measures

Outcome Measure	Data Source
Pregnancy rate in exposed females of childbearing potential	PPR
Pregnancy rate in 30-days post exposure period in exposed females of childbearing potential	PPR
Number of pregnancies • Total number of exposed pregnancies • Existing pregnancies at the time of initiation of TAZORAL™	PPR Pregnancy Exposure Follow-Up Study Spontaneous Adverse Event Reports
Number of exposed births and number with and without malformations	Pregnancy Exposure Follow-Up Study Spontaneous Adverse Event Reports

Table 8.2.4-2 Data Sources for Process Measures

Process Measure	Data Source
Comparison of the list of registered physicians and pharmacies to those who are actually prescribing or dispensing the product	Market Research Data (this method will cover over 90% of scripts) Discrepancies (eg, unregistered prescribers or pharmacies) will receive intervention (eg, phone calls, mailing of enrollment brochures, or visit by a clinical or sales representative)
Proportion of females of childbearing potential who had 2 documented negative pregnancy tests prior to initial prescription	PPR
Proportion of females of childbearing potential who had a documented negative pregnancy test prior to renewal prescription	PPR
Proportion of females of childbearing potential who had positive pregnancy test results: • Renewals refused • False positives resolved	PPR
Proportion of females of childbearing potential who recall TPA use	PPR

Table 8.2.4-2 Data Sources for Process Measures (continued)

Process Measure	Data Source
Proportion of sampled prescriptions in females of childbearing potential dispensed with • a TPA • TPA appropriately filled out	Market Research Data or possible audit
Proportion dispensed with correct quantity (30 days with or without refills) based on patient type	Market Research Data
Proportion of females of childbearing potential who self-report compliance with contraception guidelines – abstinence or simultaneous use of 2 effective measures	PPR
Analysis of failures (root cause analysis of exposed pregnancies and positive pregnancy tests) • pregnancy testing • TPA • contraceptive use • understanding	PPR Pregnancy Exposure Follow-Up Study

Table 8.2.4-3 Data Sources for Understanding and Knowledge Assessment

Assessments	Data Source
Proportion of females of childbearing potential who know of • risk of birth defects • risk of miscarriage	PPR
Proportion of females of childbearing potential who recall reviewing certain educational materials such as: • brochure • video • consent form and check list	PPR
Proportion of females of childbearing potential with correct understanding of "use of 2 effective methods"	PPR

PACT™ progress and evaluation updates will be submitted to FDA on a regular basis, and if appropriate, changes to the program will be made in consultation with the agency.

9.0 BENEFITS AND RISKS

9.1 Benefits Conclusions

TAZORAL™ is a highly effective treatment for moderate to very severe plaque psoriasis as demonstrated in 2 pivotal, double-blind, randomized, placebo-controlled phase 3 studies that evaluated TAZORAL™ 4.5 mg capsules administered once daily for 12 weeks. The primary efficacy variable in these studies was the OLA, which was based on a 6-point scale, using photonumeric guidelines, to evaluate overall psoriasis severity. In these studies, an OLA score of none or minimal was achieved by 17% of patients at the end of treatment (week 12), improving to 22% of patients 4 weeks after treatment had ended (week 16). A 2-grade improvement in OLA score was achieved by 28% of patients at the end of treatment and 32% of patients 4 weeks later.

Additionally, 13% of patients with an unsatisfactory response to TAZORAL™ 4.5 mg treatment (after an initial treatment period of 12 weeks) who received a second 12-week course of treatment, achieved an OLA score of none or minimal; 22% had at least a 2-grade OLA score improvement. This indicates the importance of continuing therapy in patients who might be slow responders.

In both placebo-controlled studies, improvements in all measures of psoriasis severity peaked at 4 weeks after the end of therapy (week 16) and only gradually declined thereafter, through the remainder of the 12-week posttreatment period. Thus, TAZORAL™ is associated with good maintenance of effect.

Results from a long-term (52-week), open-label safety study strongly support the findings of the two, 12-week, pivotal studies. Improvement in all efficacy variables increased over a period of approximately 6 months, reaching a plateau that was maintained throughout the 52-week treatment period and only slowly decreased during the 12-week posttreatment period. This study illustrates that tachyphylaxis does not occur with chronic TAZORAL™ therapy and confirms both the good maintenance of effect after discontinuing therapy.

While the exact mechanism of action of oral retinoids in psoriasis is unknown, it is presumed that the effects are mediated primarily through the retinoic acid receptor RAR?, since this is

the major type of retinoic acid receptor found in skin. This concept fits with the retinoic acid receptor binding profile of tazarotenic acid (the primary active metabolite of tazarotene), which binds to and transactivates RARß and RAR? primarily. Acitretin also is able to bind to RARß and RAR? (as well as RARa), so presumably its mechanism of action in psoriasis is similar to that of tazarotene. However, most probably the real differences between tazarotene and acitretin is the more specific RAR transactivation profile of tazarotene compared with acitretin, manifested in the improved side effect profile of TAZORAL™ compared with acitretin and summarized in the next section.

9.2 Risk Conclusions

TAZORAL™ 4.5 mg capsules were shown to be safe and the side effect profile well-characterized in the treatment of moderate to very severe plaque psoriasis in 2 phase 3 double-blind randomized placebo-controlled trials involving administration of a single 4.5 mg capsule once daily over a period of 12 weeks, as well as in open-label, noncontrolled trials with treatment for up to 1 year.

TAZORAL™ had no clinically significant adverse effects on physical examination findings. Most of the adverse events that did occur were typical of those adverse events that are associated with other oral retinoids (also typically associated with hypervitaminosis A), but with an important diminution in the incidence and severity of many of the classic signs and symptoms. The systemic effects of oral retinoids (acitretin, etretinate, isotretinoin, bexarotene and tretinoin), as well as excessive vitamin A, are well-recognized and include mucocutaneous and cutaneous effects, effects on lipid metabolism, hepatic effects, ocular effects, effects on thyroid functioning, and musculoskeletal effects (with chronic dosing). In the phase 3 studies, there was no evidence to suggest that TAZORAL™ is associated with an increased risk of depression, suicidal ideation, suicide, or other neuropsychiatric events.

TAZORAL™ was associated with some, but not all, of the cutaneous and mucocutaneous adverse effects typical of other orally administered retinoids. Cheilitis, generally mild in severity, occurred in approximately two-thirds of TAZORAL™-treated patients in each of the phase 3 clinical trials; perhaps a little less than reported for acitretin or isotretinoin, but

common enough to be considered a typical retinoid-induced phenomenon. Dry skin was also apparent in about 25% of TAZORAL™-treated patients, but the incidence of pruritus, rash, nail disorders, desquamation and some other cutaneous effects were significantly reduced compared with other systemic retinoids. Alopecia was reported in only 7.6% of patients in the 1-year TAZORAL™ study. This may be compared with the incidence rate for alopecia of about 60% reported for acitretin.

Other adverse events associated with the use of TAZORAL™ that are typical of other oral retinoids included arthralgia, myalgia, and pain in various areas, including joints. The incidence of such symptoms for TAZORAL™ seems to be similar to the rates for acitretin and isotretinoin. This would lead to the conclusion, perhaps, that such adverse events are mediated through RAR for which these 3 retinoids share a common activation profile, namely RARß and ?. TAZORAL™ may have effects on bone in some patients when given chronically over a period of 1 year, with manifestations of hyperostosis, extraskeletal ligament calcification and small decreases in bone density. Again, this seems typical of the other retinoids, acitretin and isotretinoin, specifically when administered chronically.

TAZORAL™ was associated with a very low incidence of ophthalmic adverse events. Typically no more than a few patients complained of even minor ocular symptoms or of any type of vision problem. This may be contrasted with the 20% or more incidence of such problems with acitretin and the almost 40% incidence of conjunctivitis reported for isotretinoin. One could speculate, again, that the greater specificity in terms of RAR binding and activation is responsible for TAZORAL™'s significantly better safety profile in this regard.

Consistently across the phase 3 trials, TAZORAL™ was not associated with symptoms reflecting dryness of nasal passages and epistaxis was uncommon. These events are quite common with acitretin (more than 10% incidence of epistaxis reported) and isotretinoin (more than 20% incidence of epistaxis reported).

TAZORAL™ was not commonly associated with laboratory abnormalities. Modest elevations in mean triglyceride values were reported with TAZORAL™, however, only rarely were clinically significant elevation of triglycerides noted in individual patients.

Abnormal lipid and liver function tests were infrequent with TAZORAL™ treatment. The data for TAZORAL™ contrasts sharply with equivalent data for acitretin, isotretinoin, and bexarotene. These agents are frequently associated with clinically significant changes in liver enzymes and sometimes marked elevations in triglycerides. The contrast in TAZORAL™'s effects on liver function tests and blood lipids versus other retinoids may be due to acitretin, tretinoin, isotretinoin, and bexarotene directly or indirectly activating RARa as well as RXR, whereas tazarotene only binds weakly to RARa and not at all to RXR.

Bexarotene is associated with changes in thyroid functioning in a majority of patients, whereas no consistent, clinically significant changes were seen with TAZORAL™. Alkaline phosphatase also showed consistent, but small and clinically insignificant increases during long-term therapy with TAZORAL™. The clinical significance of these changes in alkaline phosphatase is unknown at this time, but the changes may represent a modest effect of TAZORAL™ on bone metabolism. There were no clinically meaningful changes in ALT, AST, GGT, or bilirubin to suggest the alkaline phosphatase changes represent a hepatotoxic effect of TAZORAL™.

No effects of TAZORAL™ were identified that would limit a patient's ability to drive or operate heavy machinery. There were no effects of TAZORAL™ on vital signs.

In the studies of TAZORAL™, no drug-drug or drug-food interactions were identified or expected. TAZORAL™ may be taken with or without food, once each day at a time that is convenient to the patient. However, because the adverse event profile of TAZORAL™ resembles, in part, hypervitaminosis A, patients should not concomitantly use daily vitamin A supplements of over 5000 IU.

TAZORAL™ has not been evaluated in the treatment of young adults (< 21 years of age) or children with psoriasis, although it has been evaluated in a pilot study in patients with severe, nodular acne, as young as 16 years. Among adults with psoriasis, 21 years of age or older, TAZORAL™ was equally effective across age, race, and gender subgroups. There was no evidence that the adverse event profile of TAZORAL™ differed across age, race, and gender subgroups.

Because of TAZORAL™'s safety profile, periodic routine laboratory tests are generally not required but may be prudent in patients with a known history of hypertriglyceridemia or in patients judged to be at risk of hypertriglyceridemia.

Like other systemic retinoids, tazarotene is teratogenic in animals. Women must not take TAZORAL™ if pregnant, or become pregnant while taking TAZORAL™. Under the mandatory Risk Management Program (see Section 8.0, Summary of the Risk Management Program), women of childbearing potential are required to receive a variety of educational materials and must have 2 negative pregnancy tests before receiving a prescription for TAZORAL™. TAZORAL™ will be prescribed to women of childbearing potential only as a 30-day supply with no refills; all other patients will be eligible for up to 2 refills.

Tazarotenic acid (the active metabolite of TAZORAL™) is rapidly eliminated from the body, with an effective half-life of 7 to 12 hours, and is not stored in body tissues (fat). Thus, after discontinuation of treatment, levels of tazarotenic acid or its metabolites decrease to undetectable levels within approximately 1 week. Since the minimum teratogenic dose of TAZORAL™ is unknown, following discontinuation of TAZORAL™ therapy, women will be advised to continue to use effective contraception for 1 month. At this time, tazarotenic acid should be completely eliminated from the body. This contrasts sharply with the metabolism and elimination of acitretin, which can be metabolized to etretinate in the presence of alcohol. Of great significance, is the fact that etretinate has a long half-life, is stored readily in body fat, and can be detected in plasma years after treatment has ended. Women are warned not to become pregnant for 3 years after discontinuing therapy with acitretin. TAZORAL™ should, therefore, have a major advantage over acitretin in women of childbearing potential who wish to become pregnant following treatment or who become pregnant inadvertently following discontinuation of treatment.

In a pharmacokinetic study of TAZORAL™ in 24 healthy males treated with TAZORAL™ 4.5 mg for 14 days, the mean tazarotenic acid concentrations in semen were slightly lower than those in plasma. Based on the total amount of tazarotenic acid in these semen samples and on the results of fertility and embryofetal development studies in animals, the presence of tazarotenic acid in semen is not likely to pose any risk to the developing embryo/fetus. In

addition, retinoids are not known to affect spermatogenesis or sperm morphology in humans (Torok et al, 1987; Kadar et al, 1989). For these reasons, there is no recommendation for the use of male condoms either during or after treatment with TAZORAL™. This is consistent with the labeling for acitretin and isotretinoin.

9.3 Overall Conclusions

TAZORAL™ 4.5 mg is safe and effective in the treatment of moderate to very severe plaque psoriasis.

A single, convenient daily oral dose of 4.5 mg, taken with or without food, is appropriate for all patients. TAZORAL™ has a rapid onset of action, showing efficacy as early as 2 weeks. It has sustained effects for up to 3 months after the end of treatment. Tachyphylaxis was not noted during 52 weeks of therapy.

TAZORAL™ was well-tolerated and associated with a low incidence of treatment-limiting adverse events. Adverse events were mostly mild in severity. TAZORAL™ was associated with minimal changes in laboratory parameters. It has little propensity to affect liver functioning and lipids, except for a minimal effect on triglycerides. Long-term treatment with TAZORAL™ may be associated with effects on bone, similar to those of other systemic retinoids. TAZORAL™ is not expected to interact with other drugs making it a good choice for patients on concomitant medications.

Allergan is committed to implementing a comprehensive risk management program to prevent exposure of pregnant women to the teratogenic risk associated with TAZORAL™. Tazarotenic acid has a short half-life of 7 to 12 hours and is not stored in body tissues, allowing females of childbearing potential to safely become pregnant within a relatively short time after ending treatment.

Since there are no cures for psoriasis or treatment options that are effective in all patients, TAZORAL™ will provide another safe, effective treatment option for patients with moderate to very severe plaque psoriasis.

10.0 REFERENCES

Camisa C. Psoriasis, 1st edition. Cambridge, MA: Blackwell Scientific Publications; 1994.

Esgleyes-Ribot T, Chandraratna RA, Lew-Kaya DA, et al. Response of psoriasis to a new topical retinoid, AGN 190168. J Am Acad Dermatol 1994;30:581-590.

Haddaway MJ, Davie MW, McCall IW. Bone mineral density in healthy normal women and reproducibility of measurements in spine and hip using dual-energy X-ray absorptiometry. Br J Radiol 1992;65:213-217.

Kadar L, Torok L, Geiger JM. Spermatological investigations in psoriatic patients treated with acitretin. In: Reichert U, Shroot B, eds. Pharmacology of Retinoids in the Skin. Pharmacol Skin. Basel: Karger, 1989;3:253-254.

Koo J. Population-based epidemiologic study of psoriasis with emphasis on quality of life assessment. Dermatol Clin 1996;14:485-496.

Mayo Clinic. Mayo Clinic website, diseases and conditions page. Available at: http://www.mayoclinic.com/index.cfm. Accessed December 20, 2002.

Mazess RB, Barden HS. Bone densitometry for diagnosis and monitoring osteoporosis. Proceed Soc Exper Biol 1989; 261-271

McClure SL, Valentine J, Gordon KB. Comparative tolerability of systemic treatments for plaque-type psoriasis. Drug Saf 2002;25:913-927.

National Psoriasis Foundation web site (www.psoriasis.org), 2003.

Patel R, Blake GM, Rymer J, Fogelman I. Long-term precision of DXA scanning assessed over seven years in forty postmenopausal women. Osteoporos Int 2000;11:68-75.

Pennes DR, Martel W, Ellis CN, Vorhees JJ. Evolution of skeletal hyperostoses caused by 13-cis-retinoic acid therapy. Am J Roentgenol 1988;151:967-973.

Phillipov G, Seaborn CJ, Philips PJ. Reproducibility of DXA: potential impact on serial measurements and misclassification of osteoporosis. Osteoporos Int 2001;12:49-54.

Sherman SI, Gopal J, Haugen BR, et al. Central hypothyroidism associated with retinoid X receptor-selective ligands. New Engl J Med 1999;340:1706-1709.

Torok L, Kadar L, Kasa M. Spermatological investigations in patients treated with etretinate and isotretinoin. Androgia 1987;19:629-633.

National Health Interview Survey (NHIS), 1996. US Department of Health and Human Services, National Center for Health Statistics web site (www.cdc.gov/NCHS/nhis.htm), 2004.

Guidance for Industry Development and Use of Risk Minimization Action Plans, Draft Guidance. FDA website (www.fda.gov/cder/guidance/5766dft.doc), 2004.

van de Kerkhof PCM. On the limitations of the psoriasis area and severity index (PSAI). Br J Dermatol 1992;126:205.

11.0 APPENDICES

11.1 Measurement Scales Used in the Clinical Studies

The following scales were used to evaluate patient response in the clinical studies described in this briefing package.

Overall Lesional Assessment (OLA) was measured using the following 6-point scale and photographic guidelines:

0 = None: no plaque elevation above normal skin level; may have residual nonerythematous discoloration; no psoriatic scale

1 = Minimal: essentially flat with possible trace elevation; may have up to moderate erythema (red coloration); no psoriatic scale

2 = Mild: slight but definite elevation of plaque above normal skin level; may have up to moderate erythema (red coloration); fine scales, with some lesions partially covered

3 = Moderate: moderate elevation with rounded or sloped edges to plaque; moderate erythema (red coloration); somewhat coarser scales, with most lesions partially covered

4 = Severe: marked elevation with hard sharp edges to plaque; severe erythema (very red coloration); coarse thick scales, with virtually all lesions covered and a rough surface

5 = Very Severe: very marked elevation with very hard sharp edges to plaque; very severe erythema (extreme red coloration); very coarse thick scales, with all lesions covered and a very rough surface

Plaque Elevation was measured over the entire body and on 2 specific target lesions (1 target lesion on the knee or elbow; the other target lesion on the trunk or limb, excluding the knee or elbow) using the following 5-point severity scale:

0 = none: no evidence of plaque above normal skin level

1 = mild: slight but definite elevation above normal skin level

2 = moderate: moderate elevation with rounded or sloped edges to plaque

3 = severe: marked elevation with hard, sharp edges to plaque

4 = very severe: very marked elevation with very hard sharp edges to plaque

Scaling was measured over the entire body and on 2 specific target lesions (1 target lesion on the knee or elbow; the other target lesion on the trunk or limb, excluding the knee or elbow) using the following 5-point severity scale:

0 = none: no evidence of scaling on the lesions

1 = mild: mainly fine scales, with some lesions at least partially covered

2 = moderate: somewhat coarser scales, with most lesions at least partially covered

3 = severe: coarse, thick scales, with virtually all lesions covered; rough surface

4 = very severe: very coarse thick scales, with all lesions covered; very rough surface

Erythema was measured over the entire body and on 2 specific target lesions (1 target lesion on the knee or elbow; the other target lesion on the trunk or limb, excluding the knee or elbow) using the following 5-point severity scale:

0 = none: no evidence of erythema

1 = mild: light red coloration

2 = moderate: red coloration

3 = severe: very red coloration

4 = very severe: extreme red coloration

Percent Body Surface Area Involvement was measured as accurately as possible using the patient's hand as a guide (open hand with the fingers together and the thumb tucked to the side is approximately equal to 1% of the patient's total body surface area) and using the Rule of Nines, as follows:

Head = 9% of total body surface area

Anterior trunk = 18% (9% each, upper and lower)

Posterior trunk = 18% (9% each, upper and lower)

Right leg = 18%

Left leg = 18%

Both arms = 18% (9% each)

Genitalia = 1%

Overall Global Response To Treatment, compared with the condition at the baseline visit, was measured following 7-point scale:

0 = completely cleared: except for possible residual non-erythematous discoloration

1 = almost cleared: very significant clearance in disease, with only traces of disease remaining (approximately 90% improvement)

2 = marked response: significant improvement with some disease remaining (approximately 75% improvement)

3 = moderate response: intermediate improvement, between slight and marked improvement (approximately 50% improvement)

4 = slight response: some improvement but significant disease remains (approximately 25% improvement)

5 = condition unchanged

6 = condition worsened

11.2 TAZORAL™ Prescription Authorization

For All Of Your Patients Did You:

- ❑ Ask if patient understands the risk of using TAZORAL™ and if she or he has any questions

For Your Female Patients Of Childbearing Potential Did You:

Reinforce potential risks including pregnancy

- ❑ Reinforce patient responsibility not to become pregnant
- ❑ Reinforce different and effective forms of birth control
- ❑ Review patient's choices of birth control
- ❑ Remind patient of Emergency Contraception
- ❑ Conduct pregnancy testing
- ❑ Enroll patient in the Pregnancy Prevention Registry

TAZORAL™ PRESCRIPTION AUTHORIZATION

TAZORAL™ Prescription Authorization

Dr. John Doe (Registry #)
1 ABC Way
Anytown, USA 10009
Phone Number

PATIENT INFORMATION
Name: _____
Address: _____
Birthdate: _____

PATIENT TYPE

Female of childbearing potential ☐

Risks (including pregnancy) discussed ☐

Date pregnancy test ordered ☐

Pregnancy Prevention Registry #: _____

NO REFILLS

OR

Female not of childbearing potential ☐ **or** **Male** ☐

Risks (including pregnancy) discussed ☐

Qualification date _____
(date of prescription)

Number of refills ☐ **0** ☐ **1** ☐ **2**

NOTE: Must be dispensed within 7 days of qualification date above.

TAZORAL™ _____ **Quantity** _____
(dosing instructions) *(limit 30)*

Signature: _____ License #: _____

Date: _____ DEA #: _____

xxx-xx-xx