

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-946

MEDICAL REVIEW(S)

Team Leader Memo for NDA 21-946
Xolegel (ketoconazole, USP) Gel, 2%

Submission date: 9/28/05

CDER Stamp date: 9/28/05

Applicant: Barrier Therapeutics..

Indication sought: topical treatment of seborrheic dermatitis

The applicant has requested approval for Xolegel Gel for the topical treatment of seborrheic dermatitis. In support of this indication, the applicant has submitted results from a single pivotal trial and two supportive trials. The applicant proposed the tradename Sebazole, however the accepted tradename is Xolegel.

Efficacy

The applicant submitted data from a single pivotal trial, BT1400N01-300-USA, and two supportive trials, to demonstrate the safety and efficacy of their product used once daily for fourteen days in the treatment of seborrheic dermatitis. The reader is referred to Dr. Brenda Carr's clinical review and Dr. James Gerbert's biostatistical review for a thorough discussion of the trials and results. Both reviewers found that the applicant convincingly demonstrated that their drug product, Xolegel Gel, is superior to vehicle in the treatment of seborrheic dermatitis.

In brief, the pivotal trial was a multi-center, prospective, randomized, double-blind, parallel group study of 459 subjects aged 12 and older who were randomized 1:1 to receive either ketoconazole 2% gel or vehicle gel treatment once daily for fourteen days. Efficacy was assessed at day 28, two weeks after the conclusion of treatment. Both of the supportive trials had four arms which compared ketoconazole 2% gel, desonide 0.5% gel, combination (ketoconazole 2% and desonide 0.5%) gel, and vehicle gel, each used once daily for fourteen days, with efficacy assessed at 28 days. In all three trials, ketoconazole gel 2% was superior to vehicle gel in the treatment of seborrheic dermatitis.

The robustness of the pivotal trial data as well as the consistency of the results from the supportive studies allows determination of efficacy.

Safety

The safety population included 1090 subjects with seborrheic dermatitis who were treated with Xolegel Gel. The integrated safety data base included 545 subjects with seborrheic dermatitis who were treated with Xolegel Gel in phase 3 vehicle-controlled trials. There were no deaths or serious adverse events attributed to study drug. Treatment related adverse events occurred in 7.3% of subjects treated with Xolegel and 6.4% of subjects treated with vehicle gel. The most common treatment-related adverse events occurred at the application site.

Collection of adverse events and assessment of local tolerance did not reveal unexpected safety signals.

Special Populations--Pediatrics

From Dr. Carr's review: "A partial pediatric waiver was granted for children less than 12 years of age in a communication forwarded to the applicant on August 3, 2004. There were 12 subjects between the ages of 12 and 18 in the clinical development program (eight received vehicle treatment and four received ketoconazole)." In addition to those subjects enrolled in the pivotal trial, sixteen subjects between the ages of 12 and 18 were enrolled in the long-term safety study.

Although there was low enrollment of adolescent subjects, because safety and effectiveness of Xolegel Gel can reasonably be extrapolated from adults to the adolescent age group, it is recommended that the INDICATIONS AND USAGE section specify the population that was enrolled in the phase 3 trial, i.e. "XOLEGEL Gel is indicated for the topical treatment of seborrheic dermatitis in immunocompetent adults and children 12 years and older." It is recommended that the Pediatric Use section read, "Safety and effectiveness in pediatric patients below the age of 12 age has not been established."

Post-marketing Commitments

From Dr. Jill Merrill's pharmacology/toxicology review: "The [Applicant] has agreed to perform a phase 4 dermal carcinogenicity study, to be initiated as soon as the sponsor receives drug approval."

Conclusion

In a single, robust pivotal trial, and in combination with supportive and non-clinical studies, the applicant has demonstrated the safety and efficacy of Xolegel Gel applied once daily for fourteen days for the treatment of seborrheic dermatitis in adults and children twelve years and older. I concur with the recommendations of the multi-disciplinary review team for approval for marketing.

Jill Lindstrom, MD

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

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Concur with the recommendation that Xolegel be approved for
marketing

CLINICAL REVIEW 21-946

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Reviewer Name Brenda Carr, M.D.
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(Proposed) Trade Name Sebazole Gel
Therapeutic Class topical antifungal
Applicant Barrier Therapeutics

Priority Designation S

Formulation gel for topical administration
Dosing Regimen once daily
Indication seborrheic dermatitis
Intended Population adults

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The applicant submitted a marketing application for a gel formulation of ketoconazole 2% proposed for the topical treatment of seborrheic dermatitis. Ketoconazole is currently marketed in tablet, cream and shampoo formulations. **Thus, the applicant's product represents a new dosage form. The applicant's product is not marketed in any country.**

The applicant conducted one adequate and well-controlled, pivotal Phase 3 study in which their product was compared to its vehicle in the once daily treatment of seborrheic dermatitis for a treatment duration of two weeks. Supportive efficacy data were provided from two additional Phase 3 studies. Safety data were provided from nine studies conducted under the clinical development program. From a clinical perspective, it is recommended that the application be approved.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

There are no risk management activities recommended at this time.

1.2.2 Required Phase 4 Commitments

There are no required Phase 4 commitments

1.2.3 Other Phase 4 Requests

There are no Phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The applicant conducted one adequate and well-controlled, pivotal Phase 3 study, BT1400N01-300-USA, in which their ketoconazole 2% gel was compared to its vehicle in the once daily treatment of seborrheic dermatitis. Supportive efficacy data were provided from two additional Phase 3 studies, BT200-USA-001 and BT200-INT-001. In all three studies, subjects were treated with study product once daily for 14 days, and efficacy was assessed at Day 28. The primary efficacy parameter was the proportion of subjects **"Effectively Treated" at Day 28**, defined as those subjects who at Day 28 had:

- erythema and scaling which did not exceed 0 (none) if the baseline score was 2 or ≤ 1 (mild); if the baseline score was 3 AND
- **an Investigator's Global Assessment of ≤ 1 (almost clear).**

The Phase 3 trials also provided for safety data. Additional safety data were provided by a percutaneous absorption study, four topical safety studies and a long-term safety study.

1.3.2 Efficacy

A total of 459 subjects were randomized in study BT1400N01-300-USA, and 459 subjects received at least one dose of study medication and comprised the intent-to-treat (ITT) population. In the ITT population, there were a total of 229 subjects (50%) in the ketoconazole group and 230 subjects (50%) in the vehicle group.

The results from the pivotal trial demonstrated that ketoconazole was superior to the vehicle gel in providing effective treatment of seborrheic dermatitis. Clinical success (i.e. subjects **"effectively treated"**) was observed at Day 28 for 25.3% of ketoconazole subjects and 13.9% vehicle gel subjects, and the difference was significant when the treatment groups were compared ($p = 0.0014$).

Superiority of ketoconazole gel to vehicle was also demonstrated in the supportive studies, in **both the applicant's analyses and alternative analyses performed by the statistical reviewer (because the "almost clear" state was not defined on the global scale in the supportive studies the alternative analyses considered only those subjects who were completely clear at efficacy assessment)**. In both analyses, the difference in success rates remains statistically significant. In study BT200-USA-001, 27.6% and 21.7% of ketoconazole-treated subjects were effectively treated, compared to 6.6% and 5.3% of vehicle-treated subjects in the applicant's and alternative analyses, respectively ($p < 0.001$ and $p = 0.0015$). Study BT200-INT-001, 36.8% and 30.5% of ketoconazole-treated subjects were effectively treated, compared to 22.0 and 15.8% of vehicle-treated subjects in the applicant's and alternative analyses, respectively ($p < 0.021$ and $p = 0.015$).

1.3.3 Safety

The applicant integrated the safety data from the Phase 3, vehicle-controlled studies (BT200-INT-01, BT200-USA-001, and BT400N01-300-USA) because of similar elements of study design, including study populations and treatment regimens. Thus, from these three studies, a total of 545 subjects received ketoconazole treatment, and 388 subjects received vehicle treatment. In the Phase 3 vehicle-controlled studies, a total of 40 subjects (7.3%) in the ketoconazole group experienced treatment-related adverse events compared to 25 subjects (6.4%) in the vehicle group. Most treatment-related adverse events in both treatment groups were listed under **"general disorders and administration site conditions"** system organ class and were related to the application site. Although the rates were similar, more treatment-related application site adverse events were reported for ketoconazole-treated subjects (5.5%) than for vehicle-treated subjects (4.4%). The most commonly reported treatment-related adverse event in **both treatment groups was "application site burning," and this event was reported at a higher incidence in subjects who received ketoconazole treatment (4.2%) than those who received**

vehicle (3.1%). Most treatment-related adverse events occurred during the treatment period. Most events were not of sufficient severity to make for interruption or discontinuation of treatment.

Reactions reported at the application site included: burning, dermatitis, discharge, dryness, erythema, irritation, pain, pruritus, pustules and “**reaction.**” **Sufficient numbers of subjects were** exposed to the product for the requisite time periods as recommended in the ICH E1A guideline. No new safety concerns were raised in the long-term safety study or in the overall development program.

1.3.4 Dosing Regimen and Administration

Dose-ranging studies were not done.

1.3.5 Drug-Drug Interactions

Drug-drug interaction studies were not done.

1.3.6 Special Populations

The applicant’s efforts to evaluate the effects of age, race and ethnicity and gender were adequate. There was no evidence of clinically significant effect for any of these parameters on safety or efficacy (to the extent that the parameters could be assessed, given the limited numbers of subjects in certain demographic groups). Pregnant and nursing women were excluded from study. Ketoconazole is in pregnancy category C. There were no particular concerns identified pertaining to the pediatric or geriatric age groups (although numbers were too limited for adequate assessment, particularly pediatric subjects). At this juncture, no data are thought needed for other populations.

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2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Ketoconazole is an azole antifungal of the imidazole class. Other imidazole antifungals include miconazole, clotrimazole, econazole, and oxiconazole. Azoles are thought to inhibit fungal growth through impairment of biosynthesis of ergosterol, the primary sterol for the cytoplasmic membrane.^{1,2,3} Azoles inhibit a cytochrome p-450-dependent enzyme, lanosterol 14 α -demethylase, resulting in the prevention conversion of lanosterol into ergosterol. Ultimately, growth of fungal cells and permeability of fungal cell membranes are compromised.^{2,3} Administration routes for imidazole antifungals include systemic (oral, intravenous), topical, and intravaginal. Topical azoles are reported as generally well-tolerated; however, irritation and burning are among the effects that have been reported.²

Ketoconazole is currently available in tablet, cream, and shampoo dosage forms. The applicant has developed a gel product, which represents a new dosage form, and proposes the product for “the topical treatment of seborrheic dermatitis.” The proposed dosing regimen is once daily for two weeks.

2.2 Currently Available Treatment for Indications

Seborrheic dermatitis is a common inflammatory skin disease that may affect the scalp, ears, face and/or trunk. The sites of involvement are so-called “seborrheic” areas, so named because of the number and level of activity of sebaceous glands at those locations.⁴ Particular sites of involvement on the face include the nasal creases, eyebrows and inter-brow region. On the trunk, sites of involvement may include the pre-sternal region, axillae and groin. The condition is characterized by somewhat oily scale overlying erythematous skin. Pruritus may be associated. Although the etiology of seborrheic dermatitis is not entirely understood, it is thought that *Malassezia furfur* (known also as *Pityrosporum ovale*) plays some role in its pathogenesis. Per the package inserts for approved ketoconazole 2% cream formulations, “It is postulated that the therapeutic effect of ketoconazole in seborrheic dermatitis is due to the reduction of *Malassezia furfur* (also known as *Pityrosporum ovale*), but this has not been proven.”

Ketoconazole 2% cream formulations are currently marketed for treatment of seborrheic dermatitis. Nizoral®, the original ketoconazole 2% cream formulation, was approved for this indication with a dosing regimen of “twice daily for 4 weeks or until clearing.” The applicant’s proposed dosing regimen of once daily for two weeks may thus reduce patient exposure and increase patient compliance.

Other available treatments include topical corticosteroids, sulfur-containing products and selenium sulfide products.

2.3 Availability of Proposed Active Ingredient in the United States

Ketoconazole is currently available by prescription in tablet, cream, and shampoo dosage forms (200 mg, 2% and 2%, respectively). A 1% shampoo formulation is approved for over-the-counter marketing for “control of flaking, scaling, and itching associated with dandruff” (per the approval letter).

2.4 Important Issues With Pharmacologically Related Products

There are two classes of azole antifungal agents: the imidazoles and the triazoles (ketoconazole is an imidazole). Most azoles under current development are reportedly of the triazole class primarily because:

- Systemic triazoles are metabolized more slowly.
- Systemic triazoles are said to have less effect on sterol synthesis in humans as compared to the imidazoles.¹

The most common adverse reaction reported for systemically-administered azoles is gastrointestinal upset. Nausea and vomiting have been reported. All systemically-administered azoles have reportedly been shown to cause liver enzyme abnormalities, and the potential for hepatotoxicity may be a significant concern.^{5,6}

2.5 Presubmission Regulatory Activity

A Pre-IND/End-of-Phase 2 meeting was held on February 23, 2004 (IND 67,820). The applicant had initially pursued development of a combination gel product containing ketoconazole USP 2% and desonide for treatment of seborrheic dermatitis. However, two four-arm, Phase 3 studies did not show the combination gel product to be superior to the monads, ketoconazole 2% gel and desonide gel. Because the studies did demonstrate that ketoconazole gel was superior to vehicle, the applicant proposed to conduct one additional Phase 3 pivotal trial to support a marketing application for the ketoconazole 2% gel for treatment of seborrheic dermatitis.

The applicant proposed to combine the results of the ketoconazole 2% gel only arms of the previously-conducted clinical trials and use as the second Phase 3 pivotal clinical trial. The Agency advised that the two previously-conducted studies might be supportive studies (rather than pivotal) for the ketoconazole 2% gel product. The applicant was further advised that pooled study analysis could be submitted, but might have little regulatory utility. The applicant was advised that for a 505(b)(1) submission, they would need to conduct at least one additional robust, sufficiently powered study to evaluate superiority of ketoconazole 2% gel over vehicle. The applicant was advised to discuss at what level of exposure hepatic and other systemic events occurred. The applicant was further advised to address long term safety, i.e. ICH E1A.

2.6 Other Relevant Background Information

The applicant's product is not marketed. However, per the applicant, the drug substance ketoconazole is licensed in more than 140 countries (Safety Update).

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The composition of the product is presented in the table below. Per the chemistry reviewer, the product absorption is between 200 to 360 nm, with a maximum 264 nm.

3.2.P.1 Table 1 Composition of Ketoconazole USP 2% Topical Gel (Formula BTX-1)

Ingredient	Quality Standard	Function	% w/w	
Ketoconazole	USP	Drug Substance	2.0	
Polyethylene Glycol 400	NF	/		
Propylene Glycol	USP			
Glycerin	USP			
PPG-15 Stearyl Ether				
Hydroxypropyl Cellulose	NF			
Ascorbic Acid	USP			
Butylated Hydroxytoluene	NF			
Citric Acid, Monohydrate	USP			
FD&C Yellow No. 6	FD&C			
D&C Yellow No. 10	D&C			
Dehydrated Alcohol	USP			34.0
Total				34.0

3.2 Animal Pharmacology/Toxicology

From the pharmacology/toxicology review:

“In a 90 day toxicity study in CD(SD)IGS BR CD-1 mice, ketoconazole gel was topically applied to the skin of 5 groups of mice (10/sex/group) at doses of 0 (placebo gel), 40, 80, 160, and 400 mg/kg (MSW00001; submitted/reviewed under IND 67,820 by Dr. Jill Merrill). An additional set of 54 animals/sex/group were treated (40 to 400 mg/kg) for toxicokinetic analyses. Toxicokinetic analysis revealed that animals were systemically exposed to ketoconazole. No accumulation occurred and a dose-response relationship in plasma drug concentrations was not observed on days 27 and 89. This phenomenon could be due to oral ingestion of compound due to animal grooming. Based on the results of this study, dermal application of ketoconazole to the mouse for up to 17 days (400 mg/kg) or a minimum of 90 consecutive days (40, 80, and 160 mg/kg) did not

produce mortality or clinical signs of toxicity. Irritation at the site of test article application was noted grossly at 160 and 400 mg/kg and microscopically at all dose levels examined (40, 80, and 160 mg/kg). In addition, pigmentation of the liver was observed at all dose levels and a higher incidence of renal hypertrophy was noted microscopically in the 80 and 160 mg/kg animals. Thyroid glands were also noted to be slightly heavier in all treated male groups (40, 80, and 160 mg/kg). However, microscopic examination of this organ did not reveal any notable structural changes so the biologic relevance of this change was unclear. Therefore, based on the above findings, a NOEL was not obtained for this study.”

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Sources of the clinical data were trials conducted by the applicant.

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Study ID	No. of Study Centers	Study Start Date	Design Control Type	Study Drugs Control Drugs	Dose Route Regimen	Study Objective
		Study Completion Date				
<i>Phase III Vehicle-controlled Supportive Studies</i>						
Phase III BT200-USA-001	18 US Centers	Started: 10 Mar 2003 Completed: 24 Sep 2003	Double-blind, randomized, vehicle-controlled, multi-center, parallel, Phase III study	Ketoconazole USP 2% / desonide 0.05% topical gel	Thin layer Applied topically Once daily	To evaluate the efficacy and safety of a combination topical gel product containing ketoconazole USP 2% and desonide 0.05% as compared with the single agents Ketoconazole USP 2% topical gel and desonide 0.05% topical gel and topical gel vehicle in the treatment of moderate to severe seborrheic dermatitis.
		450 subjects planned 460 subjects enrolled				
Phase III BT200-INT-001	29 International Centers	Started: 26 Mar 2003 Completed: 15 Sep 2003	Double-blind, randomized, vehicle-controlled, multi-center, parallel, Phase III study	Ketoconazole USP 2% / Desonide 0.05% topical gel	Thin layer Applied topically Once daily	To evaluate the efficacy and safety of a combination topical gel product containing ketoconazole USP 2% and desonide 0.05% as compared with the single agents Ketoconazole USP 2% Topical Gel and desonide 0.05% topical gel and topical gel vehicle in the treatment of moderate to severe seborrheic dermatitis.
		450 subjects planned 489 subjects enrolled				
<i>Phase III Vehicle-controlled Pivotal Study</i>						
Phase III BT1400N01-300-USA	24 US Centers	Started: 13 May 2004 Completed: 02 Nov 2004	Double-blind, randomized, vehicle-controlled, multi-center, parallel, Phase III study	Ketoconazole USP 2% topical gel	Thin layer Applied topically Once daily	To evaluate the efficacy and safety of the to-be marketed formulation of a topical gel product containing Ketoconazole USP 2% Topical Gel as compared to gel vehicle in the treatment of seborrheic dermatitis.
		440 subjects planned 459 subjects enrolled				
<i>Long-term Safety Study</i>						
Long-term safety BT1400-N01-302-USA	27 US Centers	Start: 26 Aug 2004 Completed: 8 Jun 2005	Multi-center, open-label, non-controlled, long-term (up to 52 weeks) safety and efficacy study.	Ketoconazole USP 2% Topical Gel	Thin layer Applied topically Once daily	To evaluate the safety of Ketoconazole USP 2% Topical Gel therapy for up to 52 weeks in the treatment of seborrheic dermatitis.

4.3 Review Strategy

The review of efficacy was based primarily on the pivotal Phase 3 study, BT1400N01-300-USA, in which the applicant's ketoconazole gel 2% was compared to its gel vehicle. Supportive efficacy data were provided from two additional Phase 3 studies, BT200-USA-001 and BT200-INT-001. The review of safety is based on data from the aforementioned Phase 3 trials, a pharmacokinetic study (BT1400N01-303-USA), four Phase 1 dermal safety studies, and the long-term safety study, BT1400-N01-302-USA.

4.4 Data Quality and Integrity

Division of Scientific Investigations inspections were not requested. The applicant's analyses were reviewed, and independent analyses were performed by the biostatistics reviewer.

4.5 Compliance with Good Clinical Practices

The trials were conducted in accordance with the ethical principles of the Declaration of Helsinki and/or Title 21, US Code of Federal Regulations, Part 56 (21 CFR 56). The pivotal trial was conducted in accordance with the principles of the currently accepted version of the Declaration of Helsinki and in compliance with the International Conference on Harmonisation

E6 Good Clinical Practice Consolidated Guideline “and other applicable regulations.” Per the clinical study reports, subjects signed informed consent forms.

4.6 Financial Disclosures

The applicant certified that they had not entered into any financial arrangements with any of the clinical investigators.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The applicant conducted a percutaneous absorption study (BT1400N01-303-USA) of ketoconazole USP 2% gel in 18 subjects with severe seborrheic dermatitis with extensive affected body surface area (BSA) involvement. **Severe disease was defined on the Investigator’s Global Assessment scale as “intense (fiery red) erythema that does not blanch or coarse, thick scaling with flaking.”** Additionally, disease had to involve at least the scalp hairline, post-auricular areas, eyebrows and bridge of nose, and naso-labial folds. Male subjects were required to have seborrheic dermatitis present on the sternum. Study product was applied once daily for 14 consecutive days.

Subjects had an average of 3.8% BSA (range: 1.0% to 14.0%). Median trough and peak plasma concentrations of ketoconazole were 0.22 and 0.52 ng/mL, respectively, after one week and 0.21 and 0.52 ng/mL, respectively, after two weeks of treatment. The median AUC-based exposure at one week (10.08 ng.h/mL) was slightly higher than after two weeks of treatment (8.88 ng.h/mL). The median C_{max} was the same both weeks at 0.52 ng/mL. The median C_{max} was approximately 6700 times lower than the C_{max} after a single oral dose of 200 mg. The median AUC was approximately 1500 times lower as compared to oral dosing.

In 17 of the 18 subjects, the highest observed plasma concentration of ketoconazole was 2.2 ng/mL. In one subject, peak ketoconazole plasma levels were 13.9 ng/mL on Day 7 and 5.36 ng/mL on Day 14. At 14%, this subject had the highest affected BSA, and the amount of ketoconazole gel used was 2.3 times the highest amount used by the other subjects. Additionally, the applicant states that the amount this subject used was 38% more than the highest amount used in the pivotal Phase 3 trial. **Per the applicant, this subject’s C_{max} and AUC_{0-24} were still 250 and 77 times lower than what is reported after 200 mg ketoconazole orally.** This subject did not experience any adverse events.

One subject experienced an adverse event which was described as “facial swelling (both cheeks) Tx area.” However, the adverse event did not result in treatment being discontinued or interrupted. There were no serious adverse events reported in the study.

The clinical pharmacology/biopharmaceutics reviewer concluded that, **“The results of the Phase II study showed that the absorption of ketoconazole from Sebazole 2% topical gel was generally low, however, large intersubject variation was found.”**

5.2 Pharmacodynamics

The applicant did not conduct any pharmacodynamic studies. Per Goodman and Gilman, ketoconazole inhibits steroid biosynthesis and may therefore result in endocrinological effects, which may include menstrual irregularities, and in males, gynecomastia and decreased libido. Inhibition of cytochrome P450-dependent enzyme systems is the mechanism by which steroid biosynthesis is inhibited. Elevation of aminotransferases may occur with systemic administration, and drug-induced hepatitis has been reported (rarely).

5.3 Exposure-Response Relationships

The applicant did not conduct dose-ranging studies.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication is “for the topical treatment of seborrheic dermatitis.”

6.1.1 Methods

The primary data used to support the application were from the pivotal Phase 3 trial, BT1400-N01-300-USA. Supportive efficacy data were provided from two additional Phase 3 studies, BT200-USA-001 and BT200-INT-001. In all three studies, subjects were treated with study product once daily for 14 days. The treatment period was followed by a 14-day follow-up period, making for a study duration of 28 days.

6.1.2 General Discussion of Endpoints

The applicant was advised at the Pre-IND/End-of-Phase 2 meeting that the inclusion criteria for severity of disease in the pivotal study should be the same as those in the previous studies, i.e. a baseline score of 2 (moderate) or 3 (severe) for erythema and scaling and at least 1 (mild) for pruritus (the scales are presented below). Additionally, subjects in the new study should have **a baseline investigator’s global score of at least 3 (moderate)**. The applicant was further advised that the primary efficacy variable in the proposed new study should be the same as that in the previous studies, i.e. the proportion of subjects **who were “Effectively Treated” at day 28**, defined as scores of 0 for erythema and scaling, or of 1 if the baseline score was 3, and an Investigator Global Status score of 0, or of 1 if the baseline score was 3.

6.1.3 Study Design

Study BT1400-N01-300-USA was a multi-center, double-blind, randomized, vehicle-controlled, parallel group study. Subjects with seborrheic dermatitis were randomized to treatment with either ketoconazole USP 2% gel or vehicle (1:1 ratio). Study product was applied

once daily for 14 days and subjects were followed through Day 28. Per Section 3.1 of the protocol, affected areas could include the scalp hairline, the post-auricular area, the eyebrows and bridge of nose, the naso-labial folds, and the sternum (although sites of involvement were not specified in the Inclusion Criteria).

Inclusion Criteria:

1. Before screening, have read and signed the informed consent form after the nature of the study had been fully explained.
2. Be at least 12 years of age.
3. Demonstrate good health (or be stabilized on medication for a chronic disease) as determined by baseline medical history.
4. Have a baseline signs and symptoms score of at least 2 (moderate) for erythema and scaling and at least 1 (mild) for pruritus.
5. **Have a baseline Investigator's Global Assessment of at least 3 (moderate).**
6. Be able to consistently apply study medication, per instructions, to the affected areas once daily.
7. If woman of child bearing potential:
 - have had a negative urine pregnancy test, with a sensitivity of at least 25 mIU/mL, immediately prior to initiation of study therapy;
 - be using a reliable method of birth control. The following methods of birth control were considered to be reliable: intrauterine device (IUD); oral contraceptives (if in use for at least three months prior to Visit 1); contraceptive implant or depot injection; vaginal ring; contraceptive patch; diaphragm or cervical cap and spermicidal; condoms and spermicidal.

Comment: *Pertaining to baseline disease status, Inclusion Criteria in the pivotal study were the same as in the previously-conducted supportive studies. Subjects were required to be at least 18 years of age in the supportive studies (age of inclusion was down to 12 years in the pivotal study).*

Exclusion Criteria

1. Known hypersensitivity to any of the formulation components.
2. Subjects exhibiting any skin condition (e.g., psoriasis, atopic dermatitis, acne, etc.) or disease that might have required concurrent therapy or confounded the evaluation of drug safety and efficacy.
3. Pregnancy or nursing.
4. Treatment with any investigational drug or device within 30 days prior to Visit 1.
5. Subjects with known significant, co-existing, unstable gastrointestinal, renal, hepatic, pulmonary, cardiac, hematologic, endocrine, neurologic, or psychiatric disease.
6. Unstable subjects with a history of psychotic or affective disorders, including bipolar disorder, major depression, and schizophrenia.
7. Subjects that were known to be HIV positive or suffering from AIDS (Acquired Immune Deficiency Syndrome).
8. Use of systemic antifungals and corticosteroids within 30 days prior to baseline visit.
9. Use of topical treatments for seborrheic dermatitis on areas to be treated must have been discontinued within 14 days prior to study initiation. These included but were not limited to coal tar preparations, antiseborrheic and antidandruff shampoos, topical antifungals, and topical corticosteroids.

Comment: *There were no significant differences in the Exclusion Criteria as compared to those in the supportive studies.*

Subjects were evaluated on Days 0 (baseline), 7, 14, and 28 (14 days post-treatment). At each visit erythema, scaling and pruritus were to have been evaluated. The overall severity of the

erythema, scaling, and pruritus was determined after examining the scalp hairline; post-auricular area; eyebrows and bridge of nose; naso-labial folds; and sternum based on the following scales. [A single integer representing the score for the most severe sign (erythema or scaling) was reported for each subject]:

Erythema

- 0= None No evidence of erythema
- 1= Mild Barely perceptible erythema which is faint or patchy, blanches easily to the touch
- 2= Moderate Distinct erythema, more difficult to blanch
- 3= Severe Intense (fiery red) erythema, does not blanch

Scaling

- 0= None No scaling evident on lesions
- 1= Mild Barely detectable, scattered, small, flaking scales
- 2= Moderate Scales clearly visible and prominent
- 3= Severe Coarse, thick scales, with flaking onto clothes or skin

Pruritus

The Investigator asked the subject to rate the severity of itch using the following scale:

- 0= None No evidence of pruritus
- 1= Mild Present with minimal discomfort
- 2= Moderate Appreciable discomfort which interferes with daily activities
- 3= Severe Extreme discomfort which prevents the completion of daily activities and may disrupt sleep

Comment: *Sign and symptoms scales were the same in the pivotal and supportive studies.*

Additionally at each visit, the investigator made a global assessment of disease severity according to the following scale:

- 0 = Completely clear
- 1 = Almost clear - only slight pink color or trace amounts of scaling
- 2 = Mild - pink to red color, or slight scaling
- 3 = Moderate - distinct redness or clearly visible scaling
- 4 = Severe - severe score in erythema or scaling

Comment: *"Almost clear" was not defined on the investigator's global scale in the supportive studies. Thus, it is unclear what clinical criteria were applied when investigator's rated a subject as "almost clear" in the supportive studies.*

EFFICACY VARIABLES

The primary efficacy parameter was the **proportion of subjects "Effectively Treated" at Day 28**, defined as those subjects who at Day 28 had

- erythema and scaling which did not exceed 0 (none) if the baseline score was 2 or ≤ 1 (mild); if the baseline score was 3 AND

- an Investigator's Global Assessment of ≤ 1 (almost clear).

6.1.4 Efficacy Findings

A total of 459 subjects were randomized in study BT1400N01-300-USA, and 459 subjects received at least one dose of study medication and comprised the intent-to-treat (ITT) population (Table 14.1.2). In the ITT population, there were a total of 229 subjects (50%) in the ketoconazole group and 230 subjects (50%) in the vehicle group. There were a total of 382 per-protocol (PP) subjects, including 180 ketoconazole subjects (47%) and 202 vehicle subjects (53%).

Applicant Table 14.1.2 Summary of Subject Disposition; All Randomized Subjects

	Gel Vehicle	Ketoconazole	Total
	(N = 230)	USP 2% (N = 229)	(N = 459)
	n	n	n
Number of Randomized Subjects	230	229	459
Number of Randomized But Not Treated	0	0	0
Number of Treated Subjects	230	229	459
Number of Subjects Who Completed			
Treatment Period Only	2	0	2
Follow-up Period Only	0	0	0
Treatment & Follow-up Periods	220	222	442
Number of Discontinued Subjects From			
Treatment Period	8	7	15
Follow-up Period	2	0	2
Treatment & Follow-up Periods	10	7	17
Number of Intent-to-Treat Subjects	230	229	459
Number of Per Protocol Subjects	202	180	382

A summary table of all randomized subjects by study center is follows (applicant Table 14.1.1 from the clinical study report):

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Table 14.1.1
 Summary of Randomized Subjects by Center
 All Randomized Subjects

Center Number	Investigator	Grouped Center	Gel Vehicle	Ketoconazole	Total
			(N = 230)	USP 2% (N = 229)	(N = 459)
			n	n	n
001		1	8	8	16
002		2	12	12	24
004		4	12	11	23
005		28	12	12	24
006		6	10	10	20
007		7	8	8	16
008		8	8	8	16
009		9	8	8	16
010		10	12	12	24
011		27	11	13	24
012		12	12	12	24
013		29	12	12	24
014		14	8	8	16
015		15	8	8	16
016		29	6	8	14
017		30	8	7	15
018		30	12	12	24
020		20	13	11	24
021		28	6	8	14
022		22	8	8	16
023		23	12	12	24
024		27	5	5	10
025		25	8	8	16
026		26	11	8	19

Of the subjects randomized, 442 subjects (96.3%) completed the study: 222 subjects (96.9%) in the ketoconazole group and 220 subjects (95.7%) in the vehicle group. A total of 17 subjects (3.7%) discontinued, 15 of whom discontinued during the treatment period. Reasons for discontinuing the study were similar across treatment groups. Applicant Table 14.1.3 presents a summary of subjects who discontinued by treatment group:

From Applicant Table 14.1.3 Summary of Subject Discontinuation
 All Randomized Subjects

Variable	Gel Vehicle	Ketoconazole	Total
	(N = 230)	USP 2% (N = 229)	(N = 459)
	n	n	n
Number of Discontinued Subjects [n]	10	7	17
Reasons for Discontinuation			
Treatment Period [n]			
Adverse Event(s)	2	3	5
Treatment Failure	1	0	1
Subject Choice	4	1	5
Protocol Violation	0	1	1
Lost to Follow-Up	1	2	3
Other	0	0	0
Follow-up Period [n]			
Adverse Event(s)	0	0	0
Treatment Failure	0	0	0
Subject Choice	1	0	1
Protocol Violation	0	0	0
Lost to Follow-Up	0	0	0
Other	1	0	1

* Days on Study = ((Date of Last Visit Attended - Baseline Date) + 1).

+ Days on Treatment Period = ((Date of Last Dose - Date of First Dose) + 1).

Days on Follow-up Period = ((Date of Last Visit Attended - Date of End of Treatment Visit) + 1).

Note: Subjects 006-1094 and 023-1363 discontinued treatment due to an adverse event but remained in the study.

The mean number of days in the treatment period was 15.0 for both treatment groups (standard deviation of 2.19 for the ketoconazole group and 2.18 for the vehicle group). Minimum and maximum number of days on treatment were 1 and 25, respectively for the ketoconazole group and 1 and 29, respectively for the vehicle group (information from Applicant Table 14.1.3).

Protocol Deviations

Protocol deviations and violations were defined in the Statistical Analysis Plan (Appendix 16.1.8, Section 8.4). All protocol deviations and violations are summarized by treatment group and magnitude in Table 14.3.2. No subjects or observations were excluded from the primary efficacy analysis. The most common minor deviations observed in the study were missed applications or application of medication for more than 14 days (231 subjects; 50.3%), followed by out-of-window visits (35 subjects; 7.6%). The most common major deviations were missed applications or application of medication for more than 14 days (36 subjects; 7.8%), followed by out-of-window visits (33 subjects; 7.2%). The most common protocol violations were "other" (5 subjects; 1.1%) and violation of inclusion/exclusion criteria (1 subject; 0.2%). The minor and major deviations as well as, the protocol violations were similar across treatment groups.

Table 14.3.2
 Protocol Deviations and Violations by Treatment Group and Magnitude of Effect
 All Randomized Subjects

Variable	Ketoconazole		Total (N = 459)
	Gel Vehicle (N = 230)	USP 2% (N = 229)	
	n(%)	n(%)	n(%)
Minor Deviations*			
Out of window visit	16 (7.0)	19 (8.3)	35 (7.6)
Missed visit	14 (6.1)	7 (3.1)	21 (4.6)
Missed application/Application of meds > 14 days	118 (51.3)	113 (49.3)	231 (50.3)
Dosing deviation	1 (0.4)	4 (1.7)	5 (1.1)
Disallowed medication	0 (0.0)	1 (0.4)	1 (0.2)
Viol. of Incl/Excl criteria	0 (0.0)	0 (0.0)	0 (0.0)
Other	8 (3.5)	7 (3.1)	15 (3.3)

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*Subjects with Minor Deviations are not excluded from the ITT, PP or SES analysis sets.
 Subjects with Major Deviations or Protocol Violations are excluded from the PP analysis set.
 Please see SAP section 8.4 for detailed description of categories.

Table 14.3.2
 Protocol Deviations and Violations by Treatment Group and Magnitude of Effect
 All Randomized Subjects

Variable	Ketoconazole		Total (N = 459)
	Gel Vehicle (N = 230)	USP 2% (N = 229)	
	n(%)	n(%)	n(%)
Major Deviations*			
Out of window visit	15 (6.5)	18 (7.9)	33 (7.2)
Missed visit	7 (3.0)	5 (2.2)	12 (2.6)
Missed application/Application of meds > 14 days	14 (6.1)	22 (9.6)	36 (7.8)
Dosing deviation	0 (0.0)	0 (0.0)	0 (0.0)
Disallowed medication	1 (0.4)	3 (1.3)	4 (0.9)
Viol. of Incl/Excl criteria	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)

Program/Output (Date): t_pvio.SAS/T_PVIO.LST (01MAR2005)

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Table 14.3.2
 Protocol Deviations and Violations by Treatment Group and Magnitude of Effect
 All Randomized Subjects

Variable	Gel Vehicle	Ketoconazole	Total
	(N = 230)	USP 2% (N = 229)	(N = 459)
	n(%)	n(%)	n(%)
Protocol Violations*			
Out of window visit	0 (0.0)	0 (0.0)	0 (0.0)
Missed visit	0 (0.0)	0 (0.0)	0 (0.0)
Missed application/Application of meds > 14 days	0 (0.0)	0 (0.0)	0 (0.0)
Dosing deviation	0 (0.0)	0 (0.0)	0 (0.0)
Disallowed medication	0 (0.0)	0 (0.0)	0 (0.0)
Viol. of Incl/Excl criteria	0 (0.0)	1 (0.4)	1 (0.2)
Other	0 (0.0)	5 (2.2)	5 (1.1)

Program/Output (Date): t_pvio.SAS/T_PVIO.LST (01MAR2005)

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Demographic and Other Baseline Characteristics

The demographic characteristics were similar across treatment groups ($p > 0.3$) and are summarized in the following table:

Applicant Table 14.1.4.1 Summary of Demographics by Treatment Group
 All Randomized Subjects

Variable	Gel Vehicle	Ketoconazole	Total	P-value
	(N = 230)	USP 2% (N = 229)	(N = 459)	
	n	n	n	
Age (years)				
n	230	229	459	0.3386*
Mean (Std Dev)	50.43 (17.162)	51.96 (17.828)	51.20 (17.495)	
Median	52.0	52.0	52.0	
(Min,Max)	(13.0,87.0)	(13.0,91.0)	(13.0,91.0)	
Gender [(n %)]				
Male	136 (59.1)	136 (59.4)	272 (59.3)	0.9914+
Female	94 (40.9)	93 (40.6)	187 (40.7)	
Race [n (%)]				
Caucasian	205 (89.1)	203 (88.6)	408 (88.9)	0.5688+
African-American	12 (5.2)	12 (5.2)	24 (5.2)	
Asian	1 (0.4)	0 (0.0)	1 (0.2)	
Hispanic	11 (4.8)	12 (5.2)	23 (5.0)	
Native American	1 (0.4)	0 (0.0)	1 (0.2)	
Other	0 (0.0)	2 (0.9)	2 (0.4)	

Baseline disease factors were similar across treatment groups with respect to

- duration of current episode,
- condition of current episode,
- prior treatment, and
- baseline disease characteristics pertaining to erythema score, pruritus score, and global evaluation score.

The scaling score for the ketoconazole group had a statistically greater percentage of subjects with severe scaling (25.8%) than did the vehicle group (17.8%) with $p=0.0267$. Baseline disease characteristics are summarized in applicant Table 14.1.4.2:

Table 14.1.4.2
 Summary of Baseline Disease Factors by Treatment Group
 All Randomized Subjects

Variable	Gel Vehicle (N = 230)	Ketoconazole USP 2% (N = 229)	Total (N = 459)	P-value
History of Seb. Derm. (years)				
n	230	229	459	0.3211*
Mean (Std Dev)	11.05 (12.152)	12.19 (13.526)	11.62 (12.854)	
Median	7.00	8.00	7.08	
(Min,Max)	(0.3,57.0)	(0.1,71.0)	(0.1,71.0)	
Yearly Freq. of Signs/Symptoms				
n	230	229	459	0.1129*
Mean (Std Dev)	1.98 (4.035)	2.68 (4.999)	2.33 (4.550)	
Median	1.00	1.00	1.00	
(Min,Max)	(1.0,50.0)	(0.0,52.0)	(0.0,52.0)	

Program/Output (Date): t_demoe.SAS/T_DEMOE.LST (01MAR2005) (PAGE 1 OF 4)

* P-values are based on two-way analysis of variance with factors for treatment and grouped study center.
 † P-values are based on a Cochran-Mantel-Haenszel general association test stratified by grouped study center.

Table 14.1.4.2
 Summary of Baseline Disease Factors by Treatment Group
 All Randomized Subjects

Variable	Gel Vehicle (N = 230)	Ketoconazole USP 2% (N = 229)	Total (N = 459)	P-value
Duration of Current Episode (mo.)				
n	230	229	459	0.6533*
Mean (Std Dev)	76.14 (124.30)	78.30 (131.33)	77.22 (127.72)	
Median	12.00	12.00	12.00	
(Min,Max)	(0.2, 648)	(0.0, 720)	(0.0, 720)	
Current Episode Status [n (%)]				
Stable	172 (74.8)	159 (69.4)	331 (72.1)	0.4601†
Remitting	18 (7.8)	19 (8.3)	37 (8.1)	
Exacerbating	40 (17.4)	51 (22.3)	91 (19.8)	
Prior Treatment [n (%)]				
No	72 (31.3)	81 (35.4)	153 (33.3)	0.3418†
Yes	158 (68.7)	148 (64.6)	306 (66.7)	

Program/Output (Date): t_demoe.SAS/T_DEMOE.LST (01MAR2005) (PAGE 2 OF 4)

Table 14.1.4.2

Summary of Baseline Disease Factors by Treatment Group
 All Randomized Subjects

Variable	Gel Vehicle (N = 230)	Ketoconazole USP 2% (N = 229)	Total (N = 459)	P-value
Erythema Score [n (%)]				
0 = None	0 (0.0)	0 (0.0)	0 (0.0)	0.7785+
1 = Mild	0 (0.0)	0 (0.0)	0 (0.0)	
2 = Moderate	196 (85.2)	193 (84.3)	389 (84.7)	
3 = Severe	34 (14.8)	36 (15.7)	70 (15.3)	
Scaling Score [n (%)]				
0 = None	0 (0.0)	0 (0.0)	0 (0.0)	0.0267+
1 = Mild	0 (0.0)	0 (0.0)	0 (0.0)	
2 = Moderate	190 (82.6)	170 (74.2)	360 (78.4)	
3 = Severe	40 (17.4)	59 (25.8)	99 (21.6)	

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Table 14.1.4.2

Summary of Baseline Disease Factors by Treatment Group
 All Randomized Subjects

Variable	Gel Vehicle (N = 230)	Ketoconazole USP 2% (N = 229)	Total (N = 459)	P-value
Pruritus Score [n (%)]				
0 = None	0 (0.0)	0 (0.0)	0 (0.0)	0.9443+
1 = Mild	119 (51.7)	117 (51.1)	236 (51.4)	
2 = Moderate	97 (42.2)	99 (43.2)	196 (42.7)	
3 = Severe	14 (6.1)	13 (5.7)	27 (5.9)	
Global Assessment Score [n (%)]				
0 = Completely Clear	0 (0.0)	0 (0.0)	0 (0.0)	0.0740+
1 = Almost Clear	0 (0.0)	0 (0.0)	0 (0.0)	
2 = Mild	0 (0.0)	0 (0.0)	0 (0.0)	
3 = Moderate	181 (78.7)	164 (71.6)	345 (75.2)	
4 = Severe	49 (21.3)	65 (28.4)	114 (24.8)	

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Extent of Exposure

The mean cumulative exposure was 7.16 grams product/per subject (Std=6.468). A table summarizing drug exposure in the pivotal trial follows:

Table 14.3.3
 Summary of Drug Exposure
 Safety Evaluable Subjects

Variable	Gel Vehicle (N = 220)	Ketoconazole USP 2% (N = 229)	Total (N = 459)
Product Used* (gm)			
n	221	220	441
Mean (Std Dev)	8.07 (6.855)	6.25 (5.932)	7.16 (6.468)
Median	6.0	4.0	5.1
(Min,Max)	(0.20,32.56)	(0.07,32.35)	(0.07,32.56)
Actual Number Doses Taken			
n	230	228	458
Mean (Std Dev)	14.4 (1.86)	14.3 (2.31)	14.3 (2.09)
Median	14.0	14.0	14.0
(Min,Max)	(3, 27)	(1, 23)	(1, 27)
% of Expected Doses†			
n	220	228	458
Mean (Std Dev)	102.67 (13.266)	101.88 (16.465)	102.28 (14.933)
Median	100.0	100.0	100.0
(Min,Max)	(21.4,192.9)	(7.1,164.3)	(7.1,192.9)

Program/Output (Date): v_expose.SAS/T_EXPOSE.LST (01MAR2005)

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* Product Used = (Tube A initial wt. - Tube A return wt.) + (Tube B initial wt. - Tube B return wt.) + (Tube C initial wt. - Tube C return wt.).

† % of Expected Doses = (Actual Number Taken/14).

Efficacy Results

Results from the analysis of effectively treated subjects are presented in Table 11.4.1. Clinical success was observed at Day 28 for 58 ketoconazole subjects (25.3%) and 32 vehicle gel subjects (13.9%), and the difference was significant when the treatment groups were compared (p = 0.0014). Thus, ketoconazole was superior to vehicle gel in providing effective treatment of seborrheic dermatitis.

Applicant TABLE 11.4.1 Summary of Clinical Success (ITT Subjects) (Study BT400N01-300-USA)

Clinical success*	Gel Vehicle (N = 230)	Ketoconazole (N = 229)	Total (N = 459)
Yes (n)	32	58	90
% success (n/N)	(13.9)	(25.3)	(19.6)
95% CI for % success	(9.7, 19.1)	(19.8, 31.5)	(16.1, 23.5)
p-value[#]	0.0014		
<p>* Clinical success is 'yes' if both erythema and scaling at day 28 are 'none' (=0) (or (≤1) if the baseline score was severe), and the Global Assessment score at day 28 is 'clear' (=0) or 'almost clear' (=1).</p> <p># p-value is based on a two-tailed CMH general association test stratified by grouped study site.</p> <p><i>Cross-reference: Table 14.2.1.1, Appendix 16.2.6.1</i></p>			

Comment: *The statistics reviewer's analyses yielded the same results.*

Sub-Group Analyses

The proportions of effectively treated subjects were summarized by age class, gender, and race class for the ITT population. There were no remarkable findings in the sub-group analyses.

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Clinical Review
 Brenda Carr, M.D.
 NDA 21-946
 Ketoconazole USP 2% Topical Gel

Applicant Table 14.2.1.3 Summary of Proportion Successfully Treated by Age Category Intent-To-Treat Subjects

	Gel Vehicle (N = 230)	Ketoconazole USP 2% (N = 229)	Total (N = 459)
Clinical Success by Age Category			
<= 35 years (N)	51	45	96
n (Yes)	10	8	18
% (Yes) (n/N)	(19.6)	(17.8)	(18.8)
35 - 49 years (N)	48	63	111
n (Yes)	3	14	17
% (Yes) (n/N)	(6.3)	(22.2)	(15.3)
49 - 65 years (N)	80	56	136
n (Yes)	11	19	30
% (Yes) (n/N)	(13.8)	(33.9)	(22.1)
> 65 years (N)	51	65	116
n (Yes)	8	17	25
% (Yes) (n/N)	(15.7)	(26.2)	(21.6)

Applicant Table 14.2.1.4 Summary of Proportion Successfully Treated by Gender Intent-To-Treat Subjects

	Gel Vehicle (N = 230)	Ketoconazole USP 2% (N = 229)	Total (N = 459)
Clinical Success by Gender			
Male (N)	136	136	272
n (Yes)	17	37	54
% (Yes) (n/N)	(12.5)	(27.2)	(19.9)
Female (N)	94	93	187
n (Yes)	15	21	36
% (Yes) (n/N)	(16.0)	(22.6)	(19.3)

Applicant Table 14.2.1.5 Summary of Proportion Successfully Treated by Race Intent-To-Treat Subjects

	Gel Vehicle (N = 230)	Ketoconazole USP 2% (N = 229)	Total (N = 459)
Clinical Success by Race			
Caucasian (N)	205	203	408
n (Yes)	30	54	84
% (Yes) (n/N)	(14.6)	(26.6)	(20.6)
African-American (N)	12	12	24
n (Yes)	1	2	3
% (Yes) (n/N)	(8.3)	(16.7)	(12.5)
Asian (N)	1	0	1
n (Yes)	0	0	0
% (Yes) (n/N)	(0.0)	()	(0.0)
Hispanic (N)	11	12	23
n (Yes)	1	2	3
% (Yes) (n/N)	(9.1)	(16.7)	(13.0)
Native American	1	0	1
n (Yes)	0	0	0
% (Yes) (n/N)	(0.0)	()	(0.0)
Other (N)	0	2	2
n (Yes)	0	0	0
% (Yes) (n/N)	(0.0)	(0.0)	(0.0)

Efficacy by Baseline Disease Severity

The proportion of successfully treated subjects at Day 28 is summarized by baseline Investigator's Global evaluation (ITT population) in Applicant's Table 14.2.1.7.

Table 14.2.1.7

Summary of Proportion Successfully Treated by Baseline Global Assessment Score Intent-To-Treat Subjects

Clinical Success* by Baseline Global Assessment Score	Gel Vehicle (N = 230)	Ketoconazole USP 2% (N = 229)	Total (N = 459)
3=Moderate (N)	181	164	345
n (Yes)	31	42	74
% (Yes) (n/N)	(17.1)	(26.2)	(21.4)
4=Severe (N)	49	65	114
n (Yes)	1	15	16
% (Yes) (n/N)	(2.0)	(22.1)	(14.0)

Program/Output (Date): t_succitb.SAS/T_SUCCGA.LST (01MAR2005)

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* Clinical success is 'Yes' if both erythema and scaling at Day 28 are 'none' (0) (or 'mild' (<=1) if the baseline score was 'severe'(3)), and the Global Assessment Score at Day 28 is 'almost clear' (<=1). Subjects with a missing value in any component of the success criteria at Day 28 will be classified as treatment failures. Note: At baseline, Global Assessment score ranges from 3 to 4 due to study inclusion criteria (See Protocol Section 4.2)

The percentage of subjects who were effectively treated was similar for ketoconazole-treated subjects regardless of the severity of baseline disease (moderate or severe). For vehicle-treated subjects, more subjects with moderate disease at baseline were effectively treated than those with severe disease.

Secondary efficacy was assessed by the change in signs and symptoms scores for erythema, scaling and pruritus at Day 14. The mean change in scaling at Day 14 was statistically greater for subjects treated with ketoconazole than for subjects treated with vehicle gel (-1.55 and -1.31; respectively; $p=0.0022$). The changes in erythema and pruritus at Day 14 were not statistically significant ($p = 0.1751$ and 0.3539 , respectively).

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Table 14.2.1.13

Summary of Clinical Assessment of Erythema
 Intent-to-Treat Subjects

	Gel Vehicle (N = 230)	Ketoconazole USP 2% (N = 229)	Total (N = 459)
	n	n	n
Baseline			
0=None	0 (0.0)	0 (0.0)	0 (0.0)
1=Mild	0 (0.0)	0 (0.0)	0 (0.0)
2=Moderate	196 (85.2)	193 (84.3)	389 (84.7)
3=Severe	34 (14.8)	36 (15.7)	70 (15.3)
Day 7 Score			
0=None	20 (8.7)	32 (14.0)	52 (11.3)
1=Mild	108 (47.0)	112 (48.9)	220 (47.9)
2=Moderate	81 (35.2)	74 (32.3)	155 (33.8)
3=Severe	12 (5.2)	6 (2.6)	18 (3.9)
Day 14 Score			
0=None	67 (29.1)	73 (31.9)	140 (30.5)
1=Mild	95 (41.3)	96 (41.9)	191 (41.6)
2=Moderate	49 (21.3)	46 (20.1)	95 (20.7)
3=Severe	11 (4.8)	6 (2.6)	17 (3.7)
Day 28 Score			
0=None	39 (17.0)	63 (27.5)	102 (22.2)
1=Mild	81 (35.2)	86 (37.6)	167 (36.4)
2=Moderate	85 (37.0)	63 (27.5)	148 (32.2)
3=Severe	17 (7.4)	10 (4.4)	27 (5.9)
Not Reported at Day 28 [n]	8	7	15

Note: Last observation carried forward method used to impute missing data at Day 7 and Day 14 only.

Comment: After 7 days of treatment, improvement in erythema was seen in both treatment groups (as evidenced by the percentage of subjects with no or mild erythema), and the percentages were similar between treatment groups for subjects with mild erythema at this time point. A higher percentage of ketoconazole-treated subjects had no erythema at Day 7. At the end of treatment (Day 14), the percentage of subjects with no or mild erythema was similar between treatment groups, but had increased as compared to the Day 7 results, suggesting continued improvement. At efficacy assessment, a higher percentage of ketoconazole subjects had no erythema, compared to vehicle subjects, while similar percentages in both treatment groups had mild erythema. At efficacy assessment, the percentage of subjects with severe erythema had increased from the end of treatment in both treatment groups, and the percentages were similar between treatment groups.

Table 14.2.1.15
 Summary of Clinical Assessment of Pruritus
 Intent-to-Treat Subjects

	Gel Vehicle (N = 230)	Ketoconazole USP 2% (N = 229)	Total (N = 459)
	n	n	n
Baseline			
0=None	0 (0.0)	0 (0.0)	0 (0.0)
1=Mild	119 (51.7)	117 (51.1)	236 (51.4)
2=Moderate	97 (42.2)	99 (43.2)	196 (42.7)
3=Severe	14 (6.1)	13 (5.7)	27 (5.9)
Day 7 Score			
0=None	100 (43.5)	110 (48.0)	210 (45.8)
1=Mild	89 (38.7)	90 (39.3)	179 (39.0)
2=Moderate	27 (11.7)	22 (9.6)	49 (10.7)
3=Severe	5 (2.2)	2 (0.9)	7 (1.5)
Day 14 Score			
0=None	134 (58.3)	139 (60.7)	273 (59.5)
1=Mild	65 (28.3)	66 (28.8)	131 (28.5)
2=Moderate	19 (8.3)	15 (6.6)	34 (7.4)
3=Severe	4 (1.7)	1 (0.4)	5 (1.1)
Day 28 Score			
0=None	83 (36.1)	110 (48.0)	193 (42.0)
1=Mild	86 (37.4)	76 (33.2)	162 (35.3)
2=Moderate	48 (20.9)	31 (13.5)	79 (17.2)
3=Severe	5 (2.2)	5 (2.2)	10 (2.2)
Not Reported at Day 28 [n]	8	7	15

Comment: In both treatment groups, improvement in pruritus was progressive through end of treatment as suggested by the increase in the percentage of subjects with no pruritus at Day 14. The percentages of subjects with no pruritus at the end of treatment was similar between treatment groups. A lower percentage of subjects treated with ketoconazole gel had severe pruritus at the end of treatment. The results suggest that vehicle may have some soothing effect. At efficacy assessment 14 days post-treatment (Day 28), a higher percentage of subjects treated with ketoconazole gel had no pruritus. The percentage of subjects with severe pruritus was similar between treatment groups at Day 28.

Table 14.2.1.14

Summary of Clinical Assessment of Scaling
 Intent-to-Treat Subjects

	Gel Vehicle (N = 230)	Ketoconazole USP 2% (N = 229)	Total (N = 459)
	n	n	n
Baseline			
0=None	0 (0.0)	0 (0.0)	0 (0.0)
1=Mild	0 (0.0)	0 (0.0)	0 (0.0)
2=Moderate	190 (82.6)	170 (74.2)	360 (78.4)
3=Severe	40 (17.4)	59 (25.8)	99 (21.6)
Day 7 Score			
0=None	43 (18.7)	59 (25.8)	102 (22.2)
1=Mild	117 (50.9)	97 (42.4)	214 (46.6)
2=Moderate	51 (22.2)	64 (27.9)	115 (25.1)
3=Severe	10 (4.3)	4 (1.7)	14 (3.1)
Day 14 Score			
0=None	92 (40.0)	108 (47.2)	200 (43.6)
1=Mild	77 (33.5)	75 (32.8)	152 (33.1)
2=Moderate	44 (19.1)	32 (14.0)	76 (16.6)
3=Severe	9 (3.9)	6 (2.6)	15 (3.3)
Day 28 Score			
0=None	48 (20.9)	82 (35.8)	130 (28.3)
1=Mild	76 (33.0)	75 (32.8)	151 (32.9)
2=Moderate	79 (34.3)	47 (20.5)	126 (27.5)
3=Severe	19 (8.3)	18 (7.9)	37 (8.1)
Not Reported at Day 28 [n]	8	7	15

Note: Last observation carried forward method used to impute missing data at Day 7 and Day 14 only.

Comment: Improvement in scaling was progressive through the end of treatment in both treatment groups. The percentage of subjects with no or mild scaling at the end of treatment and at efficacy assessment was higher in the ketoconazole group.

SUPPORTIVE STUDIES

The applicant conducted two Phase 3 studies to evaluate the efficacy and safety of a combination topical gel product containing ketoconazole USP 2% and desonide 0.05% compared to the monads ketoconazole USP 2% topical gel and desonide 0.05% topical gel and topical gel vehicle in the treatment of moderate to severe seborrheic dermatitis. The studies were double-blind, randomized, vehicle-controlled, parallel, and multi-centered. While the two studies were conducted under the same protocol, one study was conducted in the United States (BT200-USA-001), and the other was conducted in Europe (BT200-INT-001). The applicant is no longer pursuing development of a combination product; however, the data from the ketoconazole and vehicle arms were submitted in support of efficacy of the product under current development.

As with the pivotal study, subjects applied study treatment to the affected area(s) once daily for 14 days and were followed through Day 28. Study visits were at baseline and Days 3, 7, 14, and 28, and at each visit the overall severity of the erythema, scaling, and pruritus were evaluated based on four-point interval scales, and these scales were the same as were used in the pivotal trial. In addition, at baseline and Days 7, 14, and 28 the investigator provided a global evaluation of disease severity using a five-point interval scale. However, the “almost clear” state was not defined on the global scale in the protocol under which the supportive studies were conducted.

Study BT200-USA-001

In the U.S. study, 460 subjects were randomized, and 459 subjects were evaluable. Relevant to the application under current review are the 152 subjects who received ketoconazole treatment and the 76 subjects received vehicle treatment.

Applicant Table 2.7.3.2.1.1 Summary of Clinical Success (ITT Subjects)

<u>Clinical success*</u>	<u>Ketoconazole</u> (N=152)	<u>Gel Vehicle</u> (N=76)	<u>p-value</u>
Yes (n)	42	5	<0.001
% success (n/N)	27.6	6.6	
95% CI for % success	(20.7, 35.5)	(2.2, 14.7)	

Comment: Because the “almost clear” state was not defined on the global scale in the supportive studies, the statistical reviewer was requested to perform an analysis that considered only subjects who were completely clear at efficacy assessment. Ten subjects who were clinical successes under the applicant’s definition were not considered clinical successes under the new definition of completely clear (nine ketoconazole; one vehicle). The success rates under the new definition are presented in the following table (based on the new analysis performed by the statistical reviewer):

New Success Table (Study BT200-USA-001)

	Ketoconazole N=152	Vehicle N=76	P=0.0015
Success	33 (21.7%)	4 (5.3%)	

The difference in success rates remains statistically significant.

Study BT200-INT-001

A total of 489 subjects were enrolled in this study. Relevant to this application are the 164 subjects who received ketoconazole treatment and the 82 subjects who received vehicle treatment.

Applicant Table 2.7.3.2.2.1 Summary of Clinical Success (ITT Subjects)

Clinical success	<u>Ketoconazole</u> (N=164)	<u>Gel Vehicle</u> (N=82)	<u>p-value</u>
Yes (n)	60	18	0.021
% success (n/N)	36.8	22.0	
95% CI for % success	(29.2, 44.0)	(13.0, 30.9)	

Comment: *Again, the “almost clear” state was not defined on the global scale. A total of 15 subjects who were clinical successes under the applicant’s definition were not considered clinical successes under the new definition of success which considered only subjects who were completely clear on the global scale at efficacy assessment (ten ketoconazole; five vehicle). The success rates under the new definition are presented in the following table (based on the alternative analysis performed by the statistical reviewer):*

New Success Table (Study BT200-INT-001)

	Ketoconazole N=164	Vehicle N=82	P=0.015
Success	50 (30.5%)	13 (15.8%)	

The difference in success rates remains statistically significant.

6.1.5 Clinical Microbiology

Although the product is an antifungal, the proposed indication is not an infectious process.

6.1.6 Efficacy Conclusions

The applicant conducted one adequate and well-controlled, pivotal Phase 3 study, BT1400N01-300-USA, in which their ketoconazole 2% gel was compared to its vehicle in the once daily treatment of seborrheic dermatitis. Supportive efficacy data were provided from two

additional Phase 3 studies, BT200-USA-001 and BT200-INT-001. In all three studies, subjects were treated with study product once daily for 14 days, and efficacy was assessed at Day 28. Treatment duration was two weeks. The primary efficacy parameter was the proportion of subjects “Effectively Treated” at Day 28.

The results from the pivotal trial demonstrated that ketoconazole was superior to the vehicle gel in providing effective treatment of seborrheic dermatitis. Clinical success (i.e. subjects “effectively treated”) was observed at Day 28 for 25.3% of ketoconazole subjects and 13.9% vehicle gel subjects, and the difference was statistically significant when the treatment groups were compared ($p = 0.0014$). The percentage of subjects who were effectively treated was similar regardless of the severity of baseline disease 26.2% and 23.1% (moderate and severe disease, respectively).

In both treatment groups, improvement was seen in erythema, pruritus and scaling through the end of treatment (i.e. a general progressive increase in the percentages of subjects with “none” and/or “mild” severity), suggesting that vehicle may have some soothing effect. However, at the end of the 14-day treatment period, only the mean change in scaling was statistically greater for subjects treated with ketoconazole than for subjects treated with vehicle gel; the changes in erythema and pruritus were not statistically significant at this time point.

The results suggest that some treatment effect may persist into the post-treatment period, and it was in the post-treatment period that the results for erythema, pruritus and scaling diverge between treatment groups, i.e. the percentages of subjects in the “none” category were distinctly higher at Day 28 for subjects treated with ketoconazole gel. This may be attributable to some ketoconazole effect on *P. ovale* (which has been implicated as having some role in the pathogenesis of seborrheic dermatitis), and this effect would not have operative in the vehicle arm. However, it does appear that some treatment effect may be lost after discontinuation of therapy.

Superiority of ketoconazole gel to vehicle was also demonstrated in the supportive studies, in both the applicant’s analyses and the alternative analyses performed by the statistical reviewer (because the “almost clear” state was not defined on the global scale in the supportive studies the alternative analyses considered only those subjects who were completely clear at efficacy assessment). In both analyses, the differences in success rates were statistically significant, when ketoconazole gel was compared to vehicle. In study BT200-USA-001, 27.6% and 21.7% of ketoconazole-treated subjects were effectively treated, compared to 6.6% and 5.3% of vehicle-treated subjects in the applicant’s and alternative analyses, respectively ($p < 0.001$ and $p = 0.0015$). In study BT200-INT-001, 36.8% and 30.5% of ketoconazole-treated subjects were effectively treated, compared to 22.0% and 15.8% of vehicle-treated subjects in the applicant’s and alternative analyses, respectively ($p < 0.021$ and $p = 0.015$).

7 Integrated Review of Safety

7.1 Methods and Findings

Safety data from nine studies sponsored by the applicant were submitted in the marketing application. All studies were complete at the time of the submission of the marketing application

except for the long-term safety study (data through June 8, 2005 were submitted for the long-term study). The nine studies are:

Table 2.7.4.1.2.1: Subject Exposure to Ketoconazole USP 2% Topical Gel*

Study	Ketoconazole		Total
	USP 2%	Vehicle	
<i>Phase I Studies (Healthy Subjects)</i>			
21574.06	27	**	27
21547.07	72	**	72
BT0200N01-100USA	230	**	230
BT0200N01-101USA	30	**	30
<i>Phase II (Subjects with Disease)</i>			
BT1400N01-303-USA	18	0	18
<i>Phase III (Subjects with Disease)</i>			
BT200-INT-01	164	82	246
BT200-USA-001	152	76	228
BT1400N01-300-USA	229	230	459
BT1400N01-302-USA	527	0	527
Total	1,449	388	1,837

* This table includes all subjects who were exposed to the formulation proposed for marketing.

** These subjects were exposed to both active and vehicle formulations at the same time

The applicant reasonably integrated the safety data from the Phase 3, vehicle-controlled studies (BT200-INT-01, BT200-USA-001, and BT400N01-300-USA) because of similar elements of study design, including study populations and treatment regimens. Thus, from these three studies, a total of 545 subjects received ketoconazole treatment, and 388 subjects received vehicle treatment. The topical safety studies (conducted in healthy subjects) and the pharmacokinetic study (conducted in subjects with severe seborrheic dermatitis) were reported separately. The long-term safety study was also reported separately.

7.1.1 Deaths

One death was reported in the clinical development program, and it occurred in the long-term study: Subject 010-1005 experienced metastatic cancer with primary unknown (metastatic neoplasm). The event was unrelated to the study medication.

7.1.2 Other Serious Adverse Events

No serious adverse events were reported in any of the Phase 1 or 2 studies.

Three serious adverse events were reported in the vehicle-controlled Phase 3 studies, one in the supportive study BT200-USA-001 study (small intestinal obstruction) and two in the pivotal study BT1400N01-300-USA (pancreatic mass and femoral neck fracture). Two of the serious adverse events occurred in vehicle-treated subjects. None of the serious adverse events were considered to be related to study medication:

Subject 009-1514 (vehicle)

A 62-year-old Caucasian woman with multiple medical problems was hospitalized for small bowel problems on Study Day 0, and a small bowel obstruction was diagnosed. Study medication was temporarily discontinued. The obstruction resolved in 6 days. The investigator considered the event to be severe and unrelated to the study medication.

The subject also developed a cystitis of mild severity (on Study Day 1) and thrombophlebitis of moderate severity (on Study Day 5). The investigator considered the events to be unrelated to the study medication. Study medication was permanently discontinued on Day 10.

Subject 013-1194 (ketoconazole gel)

A 71-year-old Caucasian woman with a history of hypertension and hyperthyroidism began study treatment with ketoconazole gel on _____. On _____ she fell, fracturing a femoral neck and was hospitalized. She received one application of study medication. She was discontinued from the study (the event was considered resolved following treatment and with hospital discharge on _____). The investigator considered the event unrelated to study drug.

Subject 016-1256, (vehicle)

A 69-year-old Caucasian man with a history of seborrheic dermatitis, cardiac bypass surgery, arthritis, actinic keratosis and basal cell carcinoma began study treatment with vehicle gel on _____. On _____ the subject presented to his internist with intestinal complaints, and was found to have abnormal liver function tests. A CT scan revealed a 2.5 cm mass on the head of the pancreas and dilated bile ducts. The last application of study drug was on _____ and the subject withdrew from study the same day. The investigator considered the event to be unrelated to study treatment. **(The subject's sister conveyed to the investigator that the subject expired from a heart attack on _____)**

Serious Adverse Events in the Long-Term Safety Study BT1400N01-302-USA

Ten subjects experienced at least one serious adverse event in the long-term study. None of the events were considered by investigators to be related to study treatment, and the reviewer

agrees with this assessment. This was an open-label study, and all subjects received ketoconazole treatment. Narratives follow:

Subject 005-0508 is an 81-year-old Caucasian man with a history of bladder cancer who consented to the study on December 2, 2004. He was diagnosed with recurrent bladder cancer on _____ and underwent surgery for resection of bladder cancer on _____. The cancer and the surgery “resolved” on _____ and were reported as unrelated to the study medication. He continued in the study.

Subject 006-0625 is a 68-year-old Caucasian man with a history of arthritis who consented to the study on November 1, 2004. On _____ he experienced “severe infective arthritis” in the knee and required hospitalization. The incident was reported as unrelated to the study medication. The subject underwent surgical intervention and treatment with multiple antibiotics. The event did not resolve. The subject was withdrawn from the study.

Subject 007-0715 is a 43-year-old Caucasian man with a history of hypertension who consented to the study on November 15, 2004. He experienced severe chest pain beginning on _____ He under went cardiac catheterization and was treated with multiple medications (for hyperlipidemia, chest pain, back pain, anxiety, hypertension, and to prevent delirium). The event resolved on December 14, 2004. He initially continued in the study, but later elected to discontinue study participation and was withdrawn January 3, 2005.

Subject 013-1302 is a 70-year-old Caucasian man with a history that included hypertension and diverticulitis who consented to join the study on October 25, 2004. On _____ he experienced severe acute colonic obstruction with secondary intestinal ischemia which was reported as unrelated to the study medication. The subject had not revealed his history of diverticulitis at the screening visit. He was treated, and the event resolved on _____. He continued in the study.

Subject 017-1701 is a 53-year-old Hispanic man with a history type 1 diabetes and diabetic neuropathy who consented to the study on November 17, 2004. On _____ he experienced severe osteomyelitis of the left great toe which was reported as unrelated to the study medication. He was hospitalized and treated with intravenous antibiotics. The event resolved on April 10, 2005, and the subject continued in the study.

Subject 019-1915 is a 73-year-old Caucasian woman with a history of arthritis, and osteoporosis who consented to the study on September 29, 2004. On _____ she experienced a severe compression fracture to vertebrae T11 as a result of a fall, and both events were reported as unrelated to the study medication. Kyphoplasty was performed and the event resolved on _____. The subject continued in the study.

Subject 019-1921 is a 50-year-old Caucasian man who consented to the study on October 19, 2004. On _____, he was diagnosed with multiple myeloma which was reported as unrelated to the study medication. He discontinued the study medication and began treatment for the multiple myeloma. The event did not resolve.

Subject 020-2008 is a 59-year-old Caucasian man who consented to the study on November 4, 2004. On _____ he was diagnosed with prostate cancer which was reported as a serious adverse event unrelated to the study medication. The event did not resolve; he continued in the study.

Subject 022-2212 is a 64-year-old Caucasian man who consented to join the study on October 19, 2004. On _____ he underwent elective total knee replacement because of arthritis. The event was reported as resolved on _____. He continued in the study.

Subject 026-2606 is a 60-year-old Caucasian woman who consented to join the study on November 17, 2004. On _____ she experienced acute gastroenteritis with dehydration and fever which was reported as a serious adverse event unrelated to the study medication. She was hospitalized overnight. The event resolved on _____ and she continued in the study.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The following table presents the summary of subjects who discontinued from the Phase 3, vehicle-controlled studies.

Applicant Table 14.1.3.1 Summary of Subject Discontinuation
 All Randomized Subjects

Variable	Gel Vehicle (N = 388)	Ketoconazole USP 2% (N = 545)	Total (N = 933)
Number of Discontinued Subjects [n]	14	22	36
Reasons for Discontinuation			
Treatment Period [n]			
Adverse Event(s)	2	5	7
Treatment Failure	1	4	5
Subject Choice	5	4	9
Protocol Violation	1	2	3
Lost to Follow-up	2	6	8
Other	0	0	0
Follow-up Period [n]			
Adverse Event(s)	0	0	0
Treatment Failure	0	1	1
Subject Choice	1	0	1
Protocol Violation	0	0	0
Lost to Follow-up	0	0	0
Other	2	0	2

Comment: The percentage of dropouts was similar between treatment group (3.6% for vehicle and 4.0% for ketoconazole).

Adverse events associated with dropouts

A total of 22 subjects discontinued the Phase 3 studies due to adverse events, seven of whom were from the vehicle-controlled studies and 13 of whom were from the long-term safety study (i.e. within the first six months of the study). Of the seven subjects discontinued from the vehicle-controlled trials, five were treated with ketoconazole gel. Two additional subjects discontinued treatment due to an adverse event, but remained in the study (subjects 006-1094 and 023-1363 below). Two subjects discontinued from the Phase 1 photoallergenicity study due to adverse events (the events were pityriasis rosea and allergic contact dermatitis). The subjects who discontinued from the Phase 3 studies (including the long-term study) are presented in brief below:

BT1400N01-300-USA-001 (pivotal study)

Per Listing 16.2.7.4 in the study report for the pivotal trial and the Integrated Summary of Safety, subjects who discontinued due to an adverse event were (the severity and relatedness to treatment are as assessed by the investigator):

- **Subject 006-1094** (ketoconazole): A 36-year-old African-American female experienced severe facial burning and severe erythema both of which were considered by the investigator as possibly related to study treatment; the events resolved; experienced moderate swelling of the eyes which was considered possibly related to study drug; treatment dates: July 24, 2004 to August 2, 2004 (**Note:** discontinued treatment due to an adverse event, but remained in the study).
- **Subject 013-1194** (ketoconazole): A 71-year-old Caucasian female experienced a severe fracture of the left femoral neck that was unrelated to study treatment; treatment dates: August 11-August 16, 2004
- **Subject 015-1229** (ketoconazole): A 73-year-old Caucasian male experienced severe **worsening of Meniere's disease that was unrelated** to study treatment; treatment June 23-June 30, 2004
- **Subject 016-1253** (ketoconazole) A 61-year-old Caucasian female experienced moderate burning, redness and tenderness at the application site that were probably related to study drug; the events resolved; treatment July 1-July 7, 2004
- **Subject 023-1363** (ketoconazole) experienced a moderate kidney infection that was unlikely related to study drug; treatment was initiated on July 15, 2004 and stop date was not provided (**Note:** discontinued treatment due to an adverse event, but remained in the study).
- **Subject 015-1228** (vehicle) A 48-year-old Caucasian male experienced mild redness and stinging at the application site that were probably related to study drug; the events resolved; treatment dates: June 17-June 19, 2004
- **Subject 016-1256** (vehicle) experienced a severe pancreatic mass that was considered unrelated to study drug; treatment was initiated August 17, 2004 and the stop date was not provided.

BT200-USA-001 (supportive study)

One subject discontinued from this study due to an adverse event (the severity and relatedness to treatment are as assessed by the investigator):

Subject 002-1576 (ketoconazole): A 27-year-old Asian female experienced moderate burning on application of study medication on study Day 1; resolved in 3 days without treatment, and the investigator considered the event probably related to study medication. She experienced an exacerbation in pruritus at the treatment site of study day 3, and the investigator considered the event severe and probably related to the study medication. She was treated with oral Benadryl, and the event resolved in 4 days. On Study Day 4, she experienced severe irritant dermatitis on the face, which the investigator probably related to study medication. She was treated with Elidel and hydrocortisone; the event resolved in 4 days. The subject permanently discontinued study medication after study day 3 and was withdrawn from the study on study day 12 because of the adverse events.

BT200-INT-001 (supportive study)

One subject discontinued from this study due to an adverse event (the severity and relatedness to treatment are as assessed by the investigator):

Subject 038-5068 (ketoconazole): A 21-year-old male experienced a mild aggravation of pruritus at the application site that was possibly related to study drug; the adverse event was ongoing at the time of discontinuation; he received study drug for six days.

BT1400N01-302-USA (Long-term Safety Study)

A total of 13 subjects (2.5%) discontinued study treatment because of an adverse event in the period covered in the original submission: nine subjects (1.7%) discontinued in Months 0 to 3; four subjects (0.8%) discontinued in Months 4 to 6.

Subjects who discontinued due to an adverse event were (the severity and relatedness to treatment are as assessed by the investigator):

- **Subject 002-0202:** A 58-year-old Caucasian female consented to join the study on October 20, 2004; she experienced severe worsening depression beginning November 12, 2004; it was unrelated to the study medication; event resolved on Nov 17, 2004.
- **Subject 006-0625:** A 68-year-old Caucasian male who consented to join the study on November 1, 2004; on _____ he experienced severe infective arthritis in the knee, which required hospitalization; subject was withdrawn from the study in response to the event, which did not resolve.
- **Subject 006-0629:** A 29-year-old Caucasian male who consented to join the study on November 15, 2004; beginning on January 13, 2005 he experienced mild burning when applying the medication to affected areas; it was related to the study medication; event resolved on 15 January 15, 2005.
- **Subject 007-0701:** A 75-year-old Caucasian male who consented to join the study on October 25, 2004; beginning on February 1, 2005 he experienced mild insomnia which

was treated with lorazepam and did not resolve; event was unrelated to the study medication.

- **Subject 007-0709:** A 51-year-old Caucasian female who consented to join the study on November 4, 2004; beginning on November 16, 2004 she experienced moderate worsened dermatitis around the eyes which was treated with Aclovate (acclometasone) cream and resolved on December 3, 2004; event was probably related to the study medication.
- **Subject 007-0718:** A 56-year-old Caucasian male who consented to join the study on October 28, 2004; medical history included hypertension, hyperlipidemia, cerebrovascular accident, and acoustic neuroma; beginning on _____ he experienced moderate brain edema which was treated with dexamethasone and did not resolve; event was unrelated to the study medication.
- **Subject 009-0908:** A 55-year-old Caucasian male who consented to join the study on September 20, 2004; beginning on November 3, 2004; he experienced mild flaking in the scalp area which was treated with Clobex (clobetasol) shampoo and did not resolve; event was unrelated to the study medication.
- **Subject 009-0912:** A 33-year-old Caucasian female who consented to join the study on September 23, 2004; on _____ she experienced a mild petit mal seizure which was treated with Carbatrol (carbamazepine) and did not resolve; seizure was unrelated to the study medication.
- **Subject 018-1801:** A 72-year-old Caucasian male who consented to join the study on September 24, 2004; beginning on October 18, 2004, the subject experienced moderate contact dermatitis which was treated with Cetaphil cleanser and Vaseline (petroleum jelly); event was probably related to the study medication.
- **Subject 019-1912:** A 50-year-old Caucasian female who consented to join the study on September 29, 2004; beginning on October 2, 2004; she experienced moderate increased erythema to the face, moderate increased pruritus, and moderate increased scaling to the face; she was treated with hydroxyzine and prednisone; events did not resolve and were all probably related to the study medication.
- **Subject 019-1921:** A 50-year-old Caucasian male who consented to join the study on October 19, 2004. _____ he was diagnosed with severe multiple myeloma which was unrelated to the study medication.
- **Subject 020-2001:** A 52-year-old Caucasian male who consented to join the study on November 1, 2004; beginning on December 22, 2004, he experienced mild rosacea which did not resolve; the relatedness to the study medication was **“unassessable.”**
- **Subject 021-2106:** A 57-year-old Caucasian male who consented to join the study on September 9, 2004; beginning on September 15, 2004 he experienced moderate difficulty breathing; event was possibly related to the study medication: event resolved on September 17, 2004. (**Note:** The reviewer could find no additional information regarding this event in the case report form.)

Comment: Of the 22 subjects who discontinued due to adverse events, nine experienced skin-related adverse events, and for five of the subjects the events were specifically stated to be at the application sites (for three other subjects, the events involved the face).

7.1.3.3 Other significant adverse events

A total of 14 subjects experienced adverse events that resulted in interruption or discontinuation of treatment, but that did not result in discontinuation from the study. Twelve of these subjects were in the Phase 3 vehicle-controlled studies, and two were in the long-term safety study. All of the subjects in the vehicle-controlled studies received ketoconazole treatment. The events were: application site burning, application site erythema, eye swelling, kidney infection, sunburn, **“raised pimple-like lesions on forehead,”** bladder infection, contact dermatitis on chest, stinging on application of study medication, upper respiratory infection, facial skin rash, bilateral arthritis in knees, rosacea and **“increased redness to bilateral cheeks, hospitalized for repair of her left rotator cuff, as well, her left deltoid was pulled up.”**

7.1.4 Other Search Strategies

The dermal safety studies are discussed in Section 7.1.12. No other search strategies were employed.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

In the vehicle-controlled Phase 3 studies, adverse event data were collected at Days 7, 14 (end of treatment) and 28 (end of study). At each of these study visits, subjects were asked a series of open-ended questions pertaining to their general health (including concurrent medications), and they were asked whether their skin had worsened (with follow-up questions, if the answer was in the affirmative).

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

In the pharmacokinetic study (BT1400N01-303-USA) and all Phase 3 studies (BT200-INT-001, BT200-USA-001, BT1400N01-300-USA and the long-term safety study BT1400N01-302-USA), adverse events were coded using the Medical Dictionary of Regulatory Affairs (MedDRA). Adverse events were summarized by body system and preferred terminology. The same adverse event recorded by a subject at different visits counted as one event for that subject, and the strongest intensity and relationship to treatment was used to describe the event. At each level of summarization (system organ class or event) subjects were only counted once in the adverse event tables. In all of the studies, the severity, relationship to treatment and outcome were recorded for the adverse events.

In the Phase 1 dermal safety studies, adverse events were reported by terms used by the investigator.

7.1.5.3 Incidence of common adverse events

Overall, 156 subjects (16.7%) experienced at least one adverse event, 65 (7.0%) of whom experienced at least one treatment-related adverse event. Percentages of adverse events in each treatment group were similar. The largest number of adverse events occurred in the system organ class “general disorders and administration site conditions” (50 subjects, 5.4%), and application site reactions were the most commonly reported types of event in this category. Burning was the most commonly-reported application site reaction in both treatment groups. The second most commonly reported application site reaction in both treatment groups was erythema. The second largest number of adverse events was reported for the system organ class “infections and infestations” (27 subjects, 2.9%), and nasopharyngitis was the most frequently reported event in both treatment groups.

7.1.5.4 Common adverse event tables

Tables of adverse events follow. Applicant Table 2.7.4.2.1.1.5 contains an overall summary of adverse events for all safety evaluable subjects enrolled in the three vehicle-controlled Phase 3 studies. Applicant Table 2.7.4.2.1.1.6 summarizes the adverse events reported by 1% or more of the subjects.

Applicant Table 2.7.4.2.1.1.5: Overall Summary of Adverse Events*

Number of Subjects	Gel Vehicle N=388 n (%)	Ketoconazole USP 2% N=545 n (%)	Total N=933 n (%)
Subjects with ≥ 1 AE	67 (17.3%)	89 (16.3%)	156 (16.7%)
Subjects with ≥ 1 treatment-related** AE	25 (6.4%)	40 (7.3%)	65 (7.0%)
Subjects with ≥ 1 serious AE	2 (0.5%)	1 (0.2%)	3 (0.3%)
Subjects who discontinued study due to an AE	2 (0.5%)	5 (0.9%)	7 (0.8%)
Subjects who interrupted/discontinued treatment due to AE	3 (0.8%)	9 (1.7%)	12 (1.3%)

** Includes events with relationship to study medication of possibly, probably, or certainly related.

* Integrated results of BT200-USA-001, BT200-INT-001 and BT1400N01-300-USA studies

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Applicant Table 2.7.4.2.1.1.6 Overall Summary of Adverse Events Reported by \geq 1% of Subjects*
 Safety Evaluable Subjects

System Organ Class Preferred Term	Gel Vehicle N=388 n (%)	Ketoconazole USP 2% N=545 n (%)	Total N=933 n(%)
Any Adverse Event	67 (17.3)	89 (16.3)	156 (16.7)
EYE DISORDERS	2 (0.5)	6 (1.1)	8 (0.9)
GASTROINTESTINAL DISORDERS	6 (1.5)	2 (0.4)	8 (0.9)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	17 (4.4)	33 (6.1)	50 (5.4)
Application site burning	12 (3.1)	23 (4.2)	35 (3.8)
Application site reaction	4 (1.0)	1 (0.2)	5 (0.5)
INFECTIONS AND INFESTATIONS	13 (3.4)	14 (2.6)	27 (2.9)
Nasopharyngitis	4 (1.0)	4 (0.7)	8 (0.9)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2 (0.5)	8 (1.5)	10 (1.1)
NERVOUS SYSTEM DISORDERS	8 (2.1)	8 (1.5)	16 (1.7)
Headache	3 (0.8)	6 (1.1)	9 (1.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	5 (1.3)	10 (1.8)	15 (1.6)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	8 (2.1)	10 (1.8)	18 (1.9)

NOTE: The same adverse event recorded by a subject at different visits count as one event for that subject, and the strongest intensity and relationship to treatment is used. At each level of summarization (System Organ Class and Preferred Term) subjects are only counted once.

Comment: *That burning and erythema were the most commonly-reported application site reaction in both treatment groups could be, at least in part, reflective of the underlying disease state or could suggest that the vehicle is somewhat irritating, although the efficacy results suggested that for some subjects, vehicle may have had some soothing effects .*

Long-Term Safety Study (BT1400N01-302-USA)

This was a multi-center, open-label, non-controlled, long-term study (up to 52 weeks). The **applicant's objective was to collect safety and efficacy** data on the long-term use of their product in the treatment of seborrheic dermatitis. However, the review will focus on the safety data.

Subjects were to apply study medication to the affected area(s) until the seborrheic dermatitis had cleared (as determined by the investigator), at which time daily use was stopped (in the vehicle-controlled studies usage was for a specified 14-day period). Following determination of a relapse by the investigator, daily use was resumed. Subjects who were applying medication **were evaluated every two weeks. The Investigator's Global Assessment is the overall average of severity of the more severe of two signs (erythema or scaling) associated with seborrheic dermatitis on the scalp hairline, post-auricular areas, eyebrows and bridge of nose, naso-labial**

folds, and sternum. The clinical rating was categorized into five levels: completely clear (0), almost clear (1), mild (2), moderate (3), and severe (4).

A total of 527 subjects were enrolled and treated in the study and comprised the ITT population. Of the 527, 429 subjects (81.4%) completed six months on the study, and 173 completed 12 months of treatment.

The median number of days on study in the first 6 months was 186 (range: 8–187). The median number of days on study overall (over 52 weeks) was 301 days (range: 8–381). The median number of actual doses taken among subjects who completed up to 6 months was 84 (range: 6–186). The median number of actual doses taken among subjects who completed up to 9 months was 117.5 (range: 14–278). The median number of actual doses taken among subjects who completed up to 12 months was 154 (range: 14–370).

Table 10-1. Summary of Subject Disposition (All Enrolled Subjects)

Variable	Ketoconazole USP 2% (N = 527)
	n
Number of Enrolled Subjects	527
Number Enrolled But Not Treated	0
Number of Enrolled Subjects	
6 Months	527
6 - 9 Months	429
6 - 12 Months	299
Number of Subjects Who Completed	
6 Months	429
6 - 9 Months	299
6 - 12 Months	173
Number of Discontinued Subjects	
6 Months	98
6 - 9 Months	130
6 - 12 Months	126
Number of Intent-to-Treat Subjects	527

A total of 336 subjects (63.8%) experienced at least one adverse event. 58 subjects (11.0%) experienced at least 1 treatment-related adverse event; 20 subjects (3.8%) experienced at least one serious adverse event; and 16 subjects (3.0%) discontinued study participation because of an adverse event. There were no treatment-related serious adverse events. One death occurred which was also unrelated to study treatment.

Table 12-1. Overall Summary of Adverse Events (Intent-to-Treat Subjects)

Variable	Ketoconazole USP 2%				Overall (N = 527)
	Months 0 - 3 (N = 527)	Months 4 - 6 (N = 527)	Months 7 - 9 (N = 429)	Months 10 - 12 (N = 299)	
	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with \geq 1 AE	215 (40.8)	167 (31.7)	96 (22.4)	54 (18.1)	336 (63.8)
Subjects with \geq 1 Treatment-Related* AE	40 (7.6)	14 (2.7)	6 (1.4)	2 (0.7)	58 (11.0)
Subjects with \geq 1 Serious AE	5 (0.9)	6 (1.1)	7 (1.6)	3 (1.0)	20 (3.8)
Subjects with \geq 1 Treatment-Related* Serious AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects who discontinued due to an AE	8 (1.5)	4 (0.8)	1 (0.2)	3 (1.0)	16 (3.0)
Subjects who Died	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)

* Includes events with a relationship to study medication of possibly, probably, or certainly related.
 Note: Subject 001-0123 and 017-1711 are the same subject enrolled at 2 sites. Data from 2 sites are included.

The percentage of subjects who experienced at least one adverse event was highest in Months 0–3 (40.8%) with progressive decrease over the course of the study to Months 10–12 (18.1%). A similar pattern was seen with regard to treatment-related adverse events: the highest percentage occurred in Months 0–3 (7.6%) and the lowest in Months 10–12 (0.7%). Discontinuations because of adverse events were also most frequent in Months 0–3 (1.5%).

The most common body systems for adverse events in the 12-month period were infections and infestations (204 subjects, 38.7%); skin and subcutaneous tissue disorders (73 subjects, 13.9%); injury, poisoning, and procedural complications (49 subjects, 9.3%); respiratory, thoracic, and mediastinal disorders (41 subjects, 7.8%); musculoskeletal and connective tissue disorders (40 subjects, 7.6%); gastrointestinal disorders (39 subjects, 7.4%); general disorders and administration site conditions (38 subjects, 7.2%); and nervous system disorders (29 subjects, 5.5%).

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Table 12-2. Overall Summary of Adverse Events Reported by $\geq 1\%$ of Subjects (Intent-to-Treat Subjects)

Preferred Term	Ketoconazole USP 2%
	Overall (N = 527)
	n (%)
Nasopharyngitis	59 (11.2)
Upper respiratory tract infection	43 (8.2)
Sinusitis	30 (5.7)
Influenza	23 (4.4)
Bronchitis	17 (3.2)
Headache	15 (2.8)
Actinic keratosis	13 (2.5)
Back pain	13 (2.5)
Dermatitis contact	12 (2.3)
Urinary tract infection	11 (2.1)
Application site burning	9 (1.7)
Application site reaction	9 (1.7)
Cough	9 (1.7)
Gastroenteritis viral	8 (1.5)
Post procedural pain	8 (1.5)
Hypertension	8 (1.5)
Gastroesophageal reflux disease	7 (1.3)
Back injury	7 (1.3)
Fall	7 (1.3)
Anxiety	7 (1.3)
Nasal congestion	7 (1.3)
Pharyngolaryngeal pain	7 (1.3)
Pruritus	7 (1.3)
Rosacea	7 (1.3)
Gastroenteritis	6 (1.1)
Pneumonia	6 (1.1)
Muscle strain	6 (1.1)
Acne	6 (1.1)

Note: Subject 001-0123 and 017-1711 are the same subject enrolled at 2 sites. Data from 2 sites are included.

A total of 39 subjects (7.4%) experienced adverse events that were graded severe. This included 14 subjects (2.7%) in Months 0–3, 15 subjects (2.8%) in Months 4–6, 9 subjects (2.1%) in Months 7–9, and 5 subjects (1.7%) in Months 10–12. (A subject could be counted more than once if he experienced a severe adverse event in more than one study period.) Severe events experienced by more than one subject were gastroesophageal reflux disease, chest pain, osteomyelitis, upper respiratory tract infection, skin laceration, back pain, prostate cancer, and cough (each experienced by 2 subjects); 3 subjects experienced severe headache. Four subjects experienced severe adverse events were possibly related to study medication: otitis externa of the right ear; cough/headache/runny nose; cough; and ear infection/sinus infection.

Most adverse events were graded mild or moderate: 133 subjects (25.2%) experienced mild adverse events and 164 subjects (31.1%) experienced moderate adverse events.

Table 12-4. Summary of Adverse Events Reported as Related to Study Medication for ≥ 2 Subjects (Intent-to-Treat Subjects)

System Organ Class Preferred Term	Ketoconazole USP 2%	
	Overall (N = 527)	
Any Adverse Event	n	(%)
Any Adverse Event	58	(11.0)
Eye disorders	4	(0.8) SOC total
Eyelid oedema	2	(0.4)
General disorders and administration site conditions	24	(4.6) SOC total
Application site burning	9	(1.7)
Application site erythema	3	(0.6)
Application site pruritus	2	(0.4)
Application site reaction	9	(1.7)
Infections and infestations	11	(2.1) SOC total
Nasopharyngitis	4	(0.8)
Upper respiratory tract infection	2	(0.4)
Nervous system disorders	2	(0.4) SOC total
Headache	2	(0.4)
Respiratory, thoracic and mediastinal disorders	9	(1.7) SOC total
Cough	5	(0.9)
Nasal congestion	4	(0.8)
Rhinorrhoea	2	(0.4)
Skin and subcutaneous tissue disorders	15	(2.8) SOC total
Dermatitis	2	(0.4)
Dermatitis contact	3	(0.6)
Erythema	3	(0.6)
Pruritus	3	(0.6)
Rosacea	2	(0.4)

A total of 127 subjects (24.1%) experienced skin-related adverse events. They occurred in 67 subjects (12.7%) in Months 0–3, 39 subjects (7.4%) in Months 4–6, 33 subjects (7.7%) in Months 7–9, and 16 subjects (5.4%) in Months 10–12. The most common skin-related events, affecting more than 5 subjects overall, were actinic keratosis (13 subjects, 2.5%), contact dermatitis (12 subjects, 2.3%), application site burning (9 subjects, 1.7%), application site reaction (9 subjects, 1.7%), pruritus (7 subjects, 1.3%), rosacea (7 subjects, 1.3%), and acne (6 subjects, 1.1%).

Ten subjects (1.9%) experienced events whose relationship to the study medication was certain, and all of these events occurred during Months 0–3. These included application site burning (two subjects), application site erythema (one subject), and application site reaction (seven subjects). Application site reaction was reported as probably related for three subjects (all during Months 0–3). Other events probably or possibly related to the study medication occurred in only 1 or 2 subjects each.

Adverse events that were reported as skin-related for more than 1% of subjects overall are summarized in Table 12-5. These events affected 18 subjects overall (3.4%), and most of these events occurred during Months 0-3 (14 subjects, 2.7%).

Table 12-5. Summary of Adverse Events Reported by ≥ 1% of Subjects that are Skin-Related and Application Site-Related (Intent-to-Treat Subjects)

System Organ Class Preferred Term	Ketoconazole USP 2%		
	Months 0 - 3 (N = 527)	Months 4 - 6 (N = 527)	Months 7 - 9 (N = 429)
	n (%)	n (%)	n (%)
Any Adverse Event	14 (2.7)	2 (0.4)	2 (0.5)
General disorders and administration site conditions	14 (2.7)	2 (0.4)	2 (0.5)
Application site burning	5 (0.9)	2 (0.4)	2 (0.5)
Application site reaction	9 (1.7)	0 (0.0)	0 (0.0)
	Months 10 - 12 (N = 299)	Overall (N = 527)	
	n (%)	n (%)	
Any Adverse Event	0 (0.0)	18 (3.4)	
General disorders and administration site conditions	0 (0.0)	18 (3.4)	
Application site burning	0 (0.0)	9 (1.7)	
Application site reaction	0 (0.0)	9 (1.7)	

There was one death in the 12-month study period: Subject 010-1005 experienced metastatic cancer of unknown primary source (metastatic neoplasm). It was unrelated to the study medication.

A total of 20 subjects (3.8%) experienced at least one serious adverse event, and none of these events were considered to be related to study medication. The most common system organ class for serious adverse events were neoplasms benign, malignant, and unspecified (5 subjects); and infections and infestations (4 subjects).

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Table 14.3.1.10

Overall Summary of Serious Adverse Events
 Intent-to-Treat Subjects

System Organ Class Preferred Term	Ketoconazole USP 2% (N = 527)
	n (%)
Any Adverse Event	20 (3.8)
Cardiac disorders	3 (0.6)
Atrial fibrillation	1 (0.2)
Cardiac failure congestive	1 (0.2)
Ischaemic cardiomyopathy	1 (0.2)
Myocardial infarction	1 (0.2)
Myocardial ischaemia	1 (0.2)
Gastrointestinal disorders	2 (0.4)
Colonic obstruction	1 (0.2)
Dysphagia	1 (0.2)
Gastroesophageal reflux disease	1 (0.2)
General disorders and administration site conditions	2 (0.4)
Chest pain	2 (0.4)
Infections and infestations	4 (0.8)
Gastroenteritis	1 (0.2)
Osteomyelitis	2 (0.4)
Wound infection	1 (0.2)
Injury, poisoning and procedural complications	2 (0.4)
Fall	2 (0.4)
Spinal compression fracture	1 (0.2)
Metabolism and nutrition disorders	1 (0.2)
Obesity	1 (0.2)
Musculoskeletal and connective tissue disorders	3 (0.6)
Back pain	2 (0.4)
Monoarthritis	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (0.9)
Bladder cancer recurrent	1 (0.2)
Metastatic neoplasm	1 (0.2)
Multiple myeloma	1 (0.2)
Prostate cancer	2 (0.4)
Pregnancy, puerperium and perinatal conditions	1 (0.2)
Abortion spontaneous	1 (0.2)
Respiratory, thoracic and mediastinal disorders	1 (0.2)
Acute respiratory failure	1 (0.2)
Vascular disorders	2 (0.4)
Aortic aneurysm	1 (0.2)
Aortic stenosis	1 (0.2)

A total of 16 subjects (3.0%) discontinued study treatments because of an adverse event: 8 subjects (1.5%) in Months 0–3; 4 subjects (0.8%) in Months 4–6, 1 subject (0.2%) in Months 7–9, and 3 subjects (1.0%) in Months 10–12. Subjects who discontinued in Months 0–6 have been

previously discussed. One subject discontinued in Months 7–9 because of contact dermatitis. **Three subjects discontinued in Months 10–12 for the following reasons: impetigo, congestive cardiac failure/ischemic cardiomyopathy/myocardial ischemia, and metastatic neoplasm.**

Review of Safety of Topical Ketoconazole

In a search of unpublished literature on the safety of topical and shampoo formulations of ketoconazole (using the _____ database), the applicant identified 179 reports. Of those documents, seven were clinical studies, and three were expert reports specifically addressing the safety of ketoconazole in topical and shampoo formulations. Eleven reports were Periodic Safety Update Reports (PSURs). A search of the National Library of Medicine's PubMed database yielded no publications specifically addressing the issue of safety in the use of topical or shampoo formulations of ketoconazole. **A search using the terms "safety" and "topical ketoconazole 2%" identified 14 publications, four of which provided safety data from clinical studies using topical or shampoo formulations of ketoconazole. A search in the PubMed database using the terms "topical ketoconazole" and "absorption" found two clinical studies where systemic absorption of ketoconazole was studied in infants. The search also identified a case report that provided data on blood levels of ketoconazole obtained when topical ketoconazole was used to treat a 50-year-old female kidney transplantation patient. Searching the terms "hepatic" and "topical ketoconazole" found one pertinent review article.**

According to the applicant, the adverse events reported in the expert reports and clinical studies were mainly local, e.g. burning, pruritus, irritation). The PSURs contained reports of a few instances of irritation or burning sensation during treatment with either ketoconazole cream or shampoo. Rarely, allergic skin reactions such as contact dermatitis have been associated with either ketoconazole or a component of the formulation. **According to the applicant, "There are no known systemic adverse reactions definitively attributable to ketoconazole absorption from topical application and limited published data confirm that ketoconazole is minimally to not absorbed systemically when applied topically."**

7.1.5.5 Identifying common and drug-related adverse events

In the Phase 3 vehicle-controlled studies, a total of 40 subjects (7.3%) in the ketoconazole group experienced treatment-related adverse events compared to 25 subjects (6.4%) in the vehicle group. Most treatment-related adverse events in both treatment groups were listed under **"general disorders and administration site conditions" system organ class and were related to the application site.** Although the percentages were similar, more treatment-related application site adverse events were reported for ketoconazole-treated subjects (5.5%) than for vehicle-treated subjects (4.4%). The most commonly reported treatment-related adverse event in both treatment groups was **"application site burning," and this event was reported at a higher incidence in subjects who received ketoconazole treatment (4.2%) than those who received vehicle (3.1%).** This suggests that while vehicle may be somewhat irritating, the addition of ketoconazole may increase the potential for irritancy.

Most of the treatment-related adverse events were reported during the treatment period, with 7.3% ketoconazole subjects and 6.2% gel vehicle subjects experiencing adverse events. In the

14-day, post-treatment follow-up period, adverse events were reported in approximately 0.3% in both groups.

Applicant Table 2.7.4.2.1.1.7 Summary of Adverse Events Reported as Related to Study Medication***
 Safety Evaluable Subjects

System Organ Class Preferred Term	Gel Vehicle N=388 n (%)	Ketoconazole USP 2% N=545 n (%)	Total N=933 n(%)
Any Adverse Event	25 (6.4)	40 (7.3)	65 (7.0)
EYE DISORDERS	2 (0.5)	4 (0.7)	6 (0.6)
Eye irritation	1 (0.3)	3 (0.6)	4 (0.4)
Eye swelling	1 (0.3)	1 (0.2)	2 (0.2)
Keratoconjunctivitis Sicca	1 (0.3)	0 (0.0)	1 (0.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	17 (4.4)	30 (5.5)	47 (5.0)
Application site burning	12 (3.1)	23 (4.2)	35 (3.8)
Application site dermatitis	1 (0.3)	0 (0.0)	1 (0.1)
Application site discharge	0 (0.0)	1 (0.2)	1 (0.1)
Application site dryness	1 (0.3)	0 (0.0)	1 (0.1)
Application site erythema	3 (0.8)	5 (0.9)	8 (0.9)
Application site irritation	0 (0.0)	2 (0.4)	2 (0.2)
Application site pain	0 (0.0)	1 (0.2)	1 (0.1)
Application site pruritus	1 (0.3)	2 (0.4)	3 (0.3)
Application site reaction	4 (1.0)	1 (0.2)	5 (0.5)
INFECTIONS AND INFESTATIONS	2 (0.5)	1 (0.2)	3 (0.3)
Application site pustules	1 (0.3)	1 (0.2)	2 (0.2)
Impetigo nos	1 (0.3)	0 (0.0)	1 (0.1)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0 (0.0)	1 (0.2)	1 (0.1)
Pyogenic granuloma	0 (0.0)	1 (0.2)	1 (0.1)
NERVOUS SYSTEM DISORDERS	1 (0.3)	2 (0.4)	3 (0.3)
Dizziness	0 (0.0)	1 (0.2)	1 (0.1)
Headache	1 (0.3)	0 (0.0)	1 (0.1)
Paraesthesia	0 (0.0)	1 (0.2)	1 (0.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	4 (1.0)	5 (0.9)	9 (1.0)
Acne	2 (0.5)	1 (0.2)	3 (0.3)
Dermatitis nos	0 (0.0)	1 (0.2)	1 (0.1)
Dry skin	0 (0.0)	1 (0.2)	1 (0.1)
Erythema	0 (0.0)	1 (0.2)	1 (0.1)
Nail discolouration	1 (0.3)	0 (0.0)	1 (0.1)
Pain of skin	0 (0.0)	1 (0.2)	1 (0.1)
Pruritus	1 (0.3)	2 (0.4)	3 (0.3)
Pruritus aggravated	0 (0.0)	1 (0.2)	1 (0.1)
Swelling face	0 (0.0)	1 (0.2)	1 (0.1)

**Includes events with relationship to study medication of possibly, probably, or certainly related.

NOTE: The same adverse event recorded by a subject at different visits count as one event for that subject, and the strongest intensity and relationship to treatment is used. At each level of summarization (System Organ Class and Preferred Term) subjects are only counted once.

* Integrated results of BT200-USA-001, BT200-INT-001 and BT1400N01-300-USA studies

7.1.5.6 Additional analyses and explorations

Most treatment-related adverse events related to the application site and occurred during the treatment period. Most events were not of sufficient severity to make for interruption or discontinuation of treatment.

7.1.6 Less Common Adverse Events

Events that occurred at an incidence of < 1% in ketoconazole-treated subjects were: ear pain (0.4%), Meniere's disease (0.2%), conjunctivitis (0.2%), dry eye (0.2%), eye irritation (0.6%), eye swelling (0.2%), abdominal pain upper (0.2%), dyspepsia (0.2%), gastroesophageal reflux disease (0.2%), loose stools (0.2%), nausea (0.2%), application site discharge (0.2%), application site erythema (0.9%; 0.8% in vehicle group), application site irritation (0.4%; none in vehicle), application site pain (0.2%), application site pruritus (0.4%; 0.3% in vehicle), application site reaction (0.2%), fatigue (0.2%), influenza-like illness (0.2%), peripheral edema (0.2%), hypersensitivity (0.4%; none in vehicle), application site pustules (0.2%), bladder infection (0.2%), ear infection (0.2%), herpes simplex (0.2%), influenza (0.2%), kidney infection (0.2%), nasopharyngitis (0.7%; 1% in vehicle group), sinusitis (0.2%), sinusitis NOS (0.4%), upper respiratory tract infection (0.2%), burns second degree (0.2%), exposure to toxic agent (0.2%), femoral neck fracture (0.2%), foot fracture (0.2%), joint sprain (0.2%), muscle strain (0.2%), post procedural pain (0.2%), sunburn (0.2%), blood cholesterol increased (0.2%), gout (0.2%), arthralgia (0.4%), back pain (0.2%), osteochondrosis (0.2%), pain in extremity (0.2%), tendonitis (0.2%), malignant melanoma in situ (0.2%), pyogenic granuloma (0.2%), dizziness (0.2%), paresthesia (0.2%), nephrolithiasis (0.2%), dysmenorrhea (0.2%), cough (0.6%), laryngitis (0.2%), nasal congestion (0.2%), pharyngolaryngeal pain (0.2%), rhinitis allergic (0.2%), rhinitis nos (0.2%), acne (0.2%), dermatitis contact (0.2%), dermatitis nos (0.4%), dry skin (0.2%), eczema nummular (0.2%), erythema (0.4%), pain of skin (0.2%), pruritus (0.4%), pruritus aggravated (0.2%), swelling face (0.2%), urticaria nos (0.2%), operation nos (0.2%), arterial stenosis nos (0.2%), and hypertension (0.2%).

Comment: Most events that occurred at an incidence of < 1% occurred at the 0.2% level meaning only a single report of the event. Of events that occurred at an incidence of < 1%, "application site erythema" was the most frequently reported event in both treatment groups and occurred at similar frequencies in ketoconazole and vehicle-treated subjects (0.9% and 0.8%, respectively).

7.1.7 Laboratory Findings

Routine laboratory data (chemistry, hematology, and urinalysis) were collected only in the percutaneous absorption study (18 subjects). Laboratory tests were done on Days 1, 7 and 15. There were no clinically relevant laboratory findings other than an elevated baseline serum glucose level in one subject.

7.1.8 Vital Signs

These data were not routinely collected in the development program.

7.1.9 Electrocardiograms

These data were not routinely collected in the development program.

7.1.10 Immunogenicity

This section is not applicable.

7.1.11 Human Carcinogenicity

Controlled trials were not of sufficient duration to permit assessment of carcinogenicity.

7.1.12 Special Safety Studies

Phototoxicity (21574.06)

This was a Phase 1, non-randomized, investigator-blind, placebo-controlled study to determine the phototoxic response potential for male and female subjects 18 to 65 years of age, in good general health, with a Fitzpatrick Skin type of I-III. Five study medications (Ketoconazole USP 2% Topical Gel, topical gel vehicle, combination Ketoconazole USP 2% / Desonide 0.05% topical gel, Desonide 0.05% topical gel and untreated control) were applied simultaneously, with one patch of the same medication on either side of the spine for 24 hours. Patches on the left side were then removed and irradiated within 10 minutes with 16 Joules/cm² of UVA irradiation (ranging from 320 to 400 nm), followed by 0.75 MED UVB (ranging from 290 to 320 nm). A total of 12 subjects enrolled and 11 completed the repeated study. Safety was assessed by the appraisal of skin responses and adverse events.

Results

Reactions were scored according to the scale below:

Table 1. Scoring System

Inflammatory Response

Inflammatory response graded on a scale of 0 to 3

- 0 = No visible reaction**
 - + = Slight, confluent or patchy erythema.**
 - 1 = Mild erythema (pink)**
 - 2 = Moderate erythema (definite redness)**
 - 3 = Strong erythema (very intense redness)**
-

Untreated irradiated sites showed more grades > 0 compared to untreated non-irradiated sites; however, no grades > 0 were observed at 24, 48 or 144 hours (for irradiated or non-irradiated

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sites). The applicant's product and vehicle showed more grades > 0 at irradiated sites than at non-irradiated sites. For the applicant's product, no grades > 0 were observed at 24, 48 or 144 hours on the non-irradiated; one subject had a + reading at 24 and 48 hours at an irradiated site. In the vehicle group, most reactions > 0 occurred at the one-hour reading.

Conclusion: Under conditions of the study, the applicant's product gave no indication of phototoxicity.

Photoallergy (21574.07)

This was a Phase 1, single-center, non-randomized, investigator-blind, placebo-controlled study to determine contact photoallergy potential, where male and female subjects, 18 to 65 years of age, in good general health with a Fitzpatrick Skin type of I-III were enrolled.

The four study medications (Ketoconazole USP 2% Topical Gel, topical gel vehicle, combination Ketoconazole USP 2% / Desonide 0.05% topical gel and desonide 0.05% topical gel) were applied simultaneously to the paraspinal area once daily, twice a week for three weeks. There was a two-week rest phase, followed by a 24-hour challenge application where duplicate test materials were applied to each side of the spine. Half the patches were removed approximately 24 hours after application and were irradiated within 10 minutes with 16 Joules/cm² of UVA irradiation (ranging from 320 to 400 nm), followed by 0.75 MED UVB (ranging from 290 to 320 nm). Patches on the remaining sites served as controls.

A total of 35 subjects were enrolled and 31 of those were evaluable. Safety was assessed by the appraisal of skin responses and adverse events.

Results

Most subjects showed mild to moderate erythema to the UV exposures received during the induction phase (same scale as in phototoxicity study), and the vehicle showed more moderate responses and fewer mild ones than the active products. During challenge, only grade + or grade 1 (slight or mild erythema, respectively) were observed at any sites for all treatment groups.

Conclusion: Under conditions of the study, the applicant's product gave no indication of photosensitization potential.

Repeated Insult Patch Test (BT0200N01-100-USA)

This was a Phase 1, double-blind study to determine contact sensitization potential (primary) and assess skin irritation potential (secondary). Males and females, 18 years of age or older were enrolled. The five study medications (Ketoconazole USP 2% Topical Gel, Topical gel vehicle, combination Ketoconazole USP 2% / Desonide 0.05% Topical Gel, Desonide 0.05% gel and Nizoral® (ketoconazole) 2% Cream) were applied simultaneously to each subject's back, with one patch per medication. This was done three times a week for three weeks (induction phase).

There was a two-week rest period, followed by a single challenge patch application. A total of 230 subjects were enrolled and included in the safety data. Tolerability was assessed by

skin reaction determinations to evaluate the contact sensitization potential of the study medications. Treatment-emergent adverse events were documented.

Results

Reactions were scored according to the scale below. Sustained reactions of grades 3 and 4 on re-challenge were considered to be evidence of sensitization.

- Grade 0 = No sign of irritation**
 - Grade 1 = Slight erythema**
 - Grade 2 = Noticeable erythema with slight infiltration**
 - Grade 3 = Erythema with marked edema**
 - Grade 4 = Erythema with edema and blistering**
-

During the challenge phase, there was one **Grade 4 reaction at 48 hours for the applicant's product** and none at 72 and 96 hours. During the induction phase, most scores for the applicant's product were zero; however, scores of 2, 3 and 4 were reported. Of the five Grade 4 reactions, three were reported following the 72-hour patch applications.

Conclusions: Under conditions of the study, the applicant's caused no contact sensitization. Per the study report, ketoconazole gel was judged by the investigator as "slightly irritating."

Cumulative Irritation Test (BT0200N01-101-USA)

This was a Phase 1, double-blind, within-subject, positive-control study to determine cumulative irritation potential. Males and females 18 years of age or older were enrolled. The six medications (Ketoconazole USP 2% Topical Gel, topical gel vehicle, combination Ketoconazole USP 2% / Desonide 0.05% Topical Gel, Desonide 0.05% gel, Nizoral® (ketoconazole) 2% Cream and the positive control, sodium lauryl sulfate) were **applied simultaneously to each subject's back, with one patch per medication. The same medication patches were applied to the same sites every 24 hours (or 48 hours if the patch was applied Saturday) for 21 consecutive days. A total of 30 subjects were enrolled and included in the safety database. Tolerability was assessed by the evaluation of irritation potential. Additionally, adverse events were documented, along with their severity, relationship to study medications and outcome.**

Results

The same scale was used as was used in the Repeated Insult Patch Test (see above). While **most reports for the applicant's product were Grade 0 (422)**, there were 12 Grade 2 reports and 5 Grade 3 reports.

Conclusion: Under conditions of the study, ketoconazole gel was judged by the investigator as “somewhat irritating.”

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Ketoconazole is not in a class with a history of abuse or withdrawal phenomena. There would appear to be limited potential for abuse of this product and no apparent withdrawal symptoms.

7.1.14 Human Reproduction and Pregnancy Data

There are no adequate and well controlled studies in pregnant women. A pregnancy occurred during the long-term safety study:

#005-0507: a 36-year-old African-American woman who consented to join the study on December 2, 2004. At a study visit on _____ the subject had a positive pregnancy test and was discontinued from the study. On _____ the fetus died because of a premature rupture of membranes (spontaneous abortion), and the subject underwent dilatation and curettage. The event was reported as a severe and serious adverse event unrelated to the study medication. It resolved on 25 Oct 2005.

7.1.15 Assessment of Effect on Growth

The protocol for the pivotal Phase 3 study allowed for enrollment of subjects 12 years and older. Assessment of the effect of the product on growth was not done.

7.1.16 Overdose Experience

There has been no experience of overdose with ketoconazole topical gel. No incidents of accidental ingestion have been reported.

7.1.17 Postmarketing Experience

Ketoconazole topical gel is not marketed.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The primary safety data sources are characterized in the following table:

Applicant Table 2.7.4.1.2.1: Subject Exposure to Ketoconazole USP 2% Topical Gel*

Study	Ketoconazole USP 2%	Vehicle	Total
<i>Phase 1 Studies (Healthy Subjects)</i>			
21574.06	27	**	27
21547.07	72	**	72
BT0200N01-100USA	230	**	230
BT0200N01-101USA	30	**	30
<i>Phase 2 (Subjects with Disease)</i>			
BT1400N01-303-USA	18	0	18
<i>Phase 3 (Subjects with Disease)</i>			
BT200-INT-01	164	82	246
BT200-USA-001	152	76	228
BT1400N01-300-USA	229	230	459
BT1400N01-302-USA	527	0	527
<i>Total</i>	1,449	388	,837

* This table includes all subjects who were exposed to the formulation proposed for marketing.

** These subjects were exposed to both active and vehicle formulations at the same time.

Routine laboratory tests were done only in the percutaneous absorption study (Days 1, 7 and 15) which enrolled only 18 subjects. There were no clinically relevant laboratory findings other than an elevated baseline serum glucose level in one subject. Generally, all tests reasonably applicable were conducted to assess the safety of the new drug. However, additional laboratory testing (e.g. in Phase 3) might have been helpful in characterizing the potential for systemic effect from use of the product (which, admittedly, is probably low). There was adequate experience with the drugs in regard to overall numbers of subjects exposed and durations of exposures.

7.2.1.1 Study type and design/patient enumeration

See tables of clinical studies in Section 4.2 and Section 7.2.1.

7.2.1.2 Demographics

The following table provides overall demographic information for the development program.

Applicant Table 2.7.4.1.3.1: Demographics for Clinical Pharmacology Studies Ketoconazole USP 2% Topical Gel

Study	21574.06	21574.07	BT0200N01 100-USA	BT0200N01 101-USA	Total
Number of Enrolled Subjects	27	72	230	30	359
Age (years)					
Mean	43.7	40.2	44.5	53.4	44.3
Range	19 - 64	18 - 64	18 - 82	21 - 78	18 - 82
Gender					
Male	3 (11.1%)	11 (15.3%)	60 (26.1%)	10 (33.3%)	84 (23.4%)
Female	24 (88.9%)	61 (84.7%)	170 (73.9%)	20 (66.7%)	275 (76.6%)
Race					
Black	0 (0.0%)	0 (0.0%)	142 (61.7%)	6 (20.0%)	148 (41.2%)
Caucasian	27 (100.0%)	68 (94.4 %)	84 (36.5%)	24 (80.0%)	203 (56.6%)
Indian	0 (0.0%)	0 (0.0%)	3 (1.3%)	0 (0.0%)	3 (0.8%)
Other	0 (0.0%)	4 (5.6%)	1 (0.4%)	0 (0.0%)	5 (1.4%)

Modified Table 2.7.4.1.3.2: Demographics for BT1400N01-303-USA (Pharmacokinetic study)

Number of Enrolled Subjects	18
Age (years)	
Mean	45.4
Range	19.0-70.0
Gender	
Male	10 (56.0%)
Female	8 (44.0%)
Race	
Caucasian	9 (50.0%)
Black	6 (33.0%)
Hispanic/Latino	3 (17.0%)

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Table 2.7.4.1.3.3 Summary of Phase III Study Demographics by Treatment Group
(Safety Subjects)
Ketoconazole USP 2% Topical Gel

	BT200-INT-001		BT200-USA-001		BT400N01-300-USA		Pooled		
	Ketoconazole USP 2%	Vehicle	Ketoconazole USP 2%	Vehicle	Ketoconazole USP 2%	Vehicle	Ketoconazole USP 2%	Vehicle	Total
Age (years)*									
N	164	82	152	76	229	230	545	388	933
Mean	38.9	39.3	50.64	49.96	51.96	50.43	47.7	48.0	47.8
(Std Dev)	(15.37)	(10.87)	(16.49)	(16.47)	(17.83)	(17.16)	(17.57)	(17.45)	(17.51)
Gender N (n %)									
Male	102 (62.2)	50 (61.0)	97 (63.8)	49 (64.5)	136 (59.4)	136 (59.1)	335 (61.0)	235 (61.0)	570 (61.0)
Female	62 (37.8)	32 (39.0)	55 (36.2)	27 (35.5)	93 (40.6)	94 (40.9)	210 (39.0)	153 (39.0)	363 (39.0)
Race N (n %)									
Caucasian	162 (98.8)	82 (100.0)	116 (76.3)	66 (86.8)	203 (88.6)	205 (89.1)	481 (88)	353 (91)	834 (89)
African/American	1 (0.6)	0 (0.0)	19 (12.5)	4 (5.3)	12 (5.2)	12 (5.2)	32 (6)	16 (4)	48 (5)
Asian	1 (0.6)	0 (0.0)	2 (1.3)	0 (0.0)	0 (0.0)	1 (0.4)	3 (1)	1 (<1)	4 (<1)
Latino/Hispanic	0 (0.0)	0 (0.0)	13 (8.6)	6 (7.9)	12 (5.2)	11 (4.8)	25 (5)	17 (4)	42 (5)
Native American	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0)	1 (<1)	1 (<1)
Other	0 (0.0)	0 (0.0)	2 (1.3)	0 (0.0)	2 (0.9)	0 (0.0)	4 (1)	0 (0)	4 (<1)

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There were 933 subjects with a mean age of 47.8 and a standard deviation of 17.51. Sixty one percent of the subjects were males and 39% were females. Eighty-nine percent of the subjects were Caucasian, while 5% were African-American and 5% were Hispanic/Latino. Less than 1% of the subjects were Asian, Native American or Other.

7.2.1.3 Extent of exposure (dose/duration)

In the integrated data for the three vehicle-controlled Phase 3 studies (BT200-USA-001, BT200-INT-001, BT1400N01-300-USA), 933 subjects received an average of 14.07 applications of study drug during the studies. Duration of treatment durations was 14 days in all studies. The total amount of study medication used was found by summing up the differences between the dispensing weight and the return weight of the individual tubes. The median total usage was 7.4 g, ranging from 0.0 to 42.9 g. For the percentage of expected doses, the actual number of doses that were applied was divided by 14. Overall, 100.51% of the expected doses were applied.

A total of 527 subjects received topical treatment in the long-term safety study (BT1400N01-302-USA). The median number of doses taken during months 0 to 6 was 89, ranging from 14 to 186.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

All studies that provided data were submitted in the marketing application.

7.2.2.2 Postmarketing experience

The applicant's product is not marketed.

7.2.2.3 Literature

Secondary source data were provided in the Safety Update and included a review of safety of the active ingredient ketoconazole in currently marketed topical and shampoo formulations. (contain between 1% and 2% ketoconazole). The applicant retrieved data from Periodic Safety Update Reports (PSURs) dating back to 1993 and from unpublished literature and expert reports since 1988 residing in the _____

_____ database. The applicant also searched the National Library of Medicine's PubMed database for publications providing data on the safety or systemic absorption of topical or shampoo formulations of ketoconazole.

7.2.3 Adequacy of Overall Clinical Experience

An adequate number of subjects were exposed to the drug to characterize its safety in the short-term (14 days) and long-term (up to one year). Doses and durations of exposure were adequate to assess the safety of the product for its intended use. Other than not including laboratory testing, the designs of the vehicle-controlled and open-label (long-term safety) studies were generally adequate to answer safety questions. However, the risk for systemic effect from use of the product is probably low under conditions of intended use. The percutaneous absorption revealed low systemic exposure generally. Topical safety was adequately assessed in the development program in the Phase 3 efficacy and/or safety studies and the Phase 1 dermal safety studies. There was adequate experience with the drugs in regard to overall numbers of subjects exposed and durations of exposures.

There was adequate experience with the drugs in regard to overall numbers of subjects exposed and durations of exposures.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Per the pharmacology/toxicology review, the applicant completed a repeat dose dermal toxicity study in mice. Additionally, the applicant has submitted a protocol for two-year dermal carcinogenicity study. The pharmacology/toxicology reviewer found no non-clinical safety issues that were relevant to clinical use.

7.2.5 Adequacy of Routine Clinical Testing

Routine laboratory monitoring was conducted only in the percutaneous absorption study. Additional laboratory testing in the development program would have been helpful in characterizing the potential for systemic effect(s) **from use of the applicant's topical product**. However, the level of risk for systemic effect from use of the applicant's **product is generally** likely low given the extent of systemic exposure that would result from the intended use (see percutaneous absorption study). Factors that would limit potential exposure include the proposed indication (which generally has limited extent of body surface area involvement) and the frequency (once daily) and duration of treatment (two weeks). Other marketed 2% ketoconazole formulations have been well tolerated when for the same indication with more frequent dosing (twice daily) and for longer durations (four weeks or longer). However, it is understood that extent of exposure can be impacted by formulations

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The applicant did not conduct drug-drug interaction assessment.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The assessment of local tolerance and relatively inadequate assessment of systemic tolerance have been previously discussed. There are no recommendations for further study.

7.2.8 Assessment of Quality and Completeness of Data

See Sections 7.2.3, 7.2.5. and 7.2.7

7.2.9 Additional Submissions, Including Safety Update

The applicant submitted a four-month Safety Update on January 27, 2006. The submission provided new safety information from the long-term safety study, BT1400N01-302-USA (specifically, data through month 12 of that study). Additionally, the submission provided a review of safety of topical ketoconazole. Also, see Section 7.2.2.3.

The safety update did not reveal any new safety concerns.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

In the Phase 3 vehicle-controlled studies, a total of 40 subjects (7.3%) in the ketoconazole group experienced treatment-related adverse events compared to 25 subjects (6.4%) in the vehicle group. Most treatment-related adverse events in both treatment groups were listed under **“general disorders and administration site conditions” system organ class and were related to the application site.** Although the rates were similar, more treatment-related application site adverse events were reported for ketoconazole-treated subjects (5.5%) than for vehicle-treated subjects (4.4%). The most commonly reported treatment-related adverse event in both treatment groups was **“application site burning,”** and this event was reported at a higher incidence in subjects who received ketoconazole treatment (4.2%) than those who received vehicle (3.1%). One interpretation of these results is that while vehicle may be somewhat irritating, the addition of ketoconazole may increase the potential for irritancy.

Most treatment-related adverse events related to the application site and occurred during the treatment period. Most events were not of sufficient severity to make for interruption or discontinuation of treatment.

Reactions reported at the application site included: burning, dermatitis, discharge, dryness, erythema, irritation, pain, pruritus, pustules and **“reaction.”**

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The applicant reasonably integrated the safety data from the Phase 3, vehicle-controlled studies because of similar elements of study design, including study populations and treatment regimens. **The applicant's approach to pooling was acceptable.**

7.4.1.2 Combining data

The pooling was accomplished by combining of the numerator events and denominators for the selected studies. The combined safety data were reviewed above. See Section 7.1 (and sub sections) of this review.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

For subjects who discontinued treatment due to a treatment-related adverse event (some type of application site reaction), the adverse event(s) generally occurred within the first seven daily doses of study drug.

7.4.2.2 Explorations for time dependency for adverse findings

More subjects experienced adverse events during the active treatment phase than in the follow-up phase. For subjects who discontinued treatment due to a treatment-related adverse event (some type of application site reaction), the adverse event(s) generally occurred within the first week of treatment.

7.4.2.3 Explorations for drug-demographic interactions

The percentage of subjects experiencing adverse events was generally similar between treatment groups for all demographic groups, i.e. **age, race (reported as "Caucasian" and "non-Caucasian") and sex. Adverse events were most commonly reported in the "general disorders and administration site conditions" system organ class for all demographic groups. The most commonly reported adverse event was application site burning for all demographic groups, and the event was more often reported for ketoconazole-treated subjects. The numbers of pediatric subjects and non-Caucasian subjects were too low to adequately explore adverse event rates in these subgroups.**

7.4.2.4 Explorations for drug-disease interactions

These explorations were not done.

7.4.2.5 Explorations for drug-drug interactions

These explorations were not done.

7.4.3 Causality Determination

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Dose-ranging studies were not conducted.

8.2 Drug-Drug Interactions

The applicant did not conduct drug interaction studies.

8.3 Special Populations

There are no special dosing recommendations for demographics based on the clinical trial data. Tolerance of the product has not been adequately evaluated with coexisting states such as hepatic or renal insufficiency. The product has not been adequately in the pediatric population or in pregnant or lactating women.

8.4 Pediatrics

A partial pediatric waiver was granted for children less than 12 years of age in a communication forwarded to the applicant on August 3, 2004. There were 12 subjects between the ages of 12 and 18 in the clinical development program (eight received vehicle treatment and four received ketoconazole). Two subjects experienced adverse events, and the events were application site burning, application site reaction (both of which occurred with vehicle treatment) and headache (ketoconazole treatment).

8.5 Advisory Committee Meeting

This section is not applicable.

8.6 Literature Review

See Section 7.2.2.3.

8.7 Postmarketing Risk Management Plan

There are no recommendations for a specific postmarketing risk management plan.

8.8 Other Relevant Materials

None

9 OVERALL ASSESSMENT

9.1 Conclusions

The applicant conducted one adequate and well-controlled, pivotal Phase 3 study, BT1400N01-300-USA, in which their ketoconazole 2% gel was compared to its vehicle in the once daily treatment of seborrheic dermatitis. Supportive efficacy data were provided from two additional Phase 3 studies, BT200-USA-001 and BT200-INT-001. In all three studies, subjects were treated with study product once daily for 14 days, and efficacy was assessed at Day 28.

The results from the pivotal trial demonstrated that ketoconazole was superior to the vehicle gel in providing effective treatment of seborrheic dermatitis. Clinical success (i.e. subjects “effectively treated”) was observed at Day 28 for 25.3% of ketoconazole subjects and 13.9% vehicle gel subjects, and the difference was significant when the treatment groups were compared ($p = 0.0014$).

Superiority of ketoconazole gel to vehicle was also demonstrated in the supportive studies, in both the applicant’s analyses and the alternative analyses performed by the statistical reviewer (because the “almost clear” state was not defined on the global scale in the supportive studies the alternative analyses considered only those subjects who were completely clear at efficacy assessment). In both analyses, the differences in success rates were statistically significant, when ketoconazole gel was compared to vehicle. In study BT200-USA-001, 27.6% and 21.7% of ketoconazole-treated subjects were effectively treated, compared to 6.6% and 5.3% of vehicle-treated subjects in the applicant’s and alternative analyses, respectively ($p < 0.001$ and $p = 0.0015$). In study BT200-INT-001, 36.8% and 30.5% of ketoconazole-treated subjects were effectively treated, compared to 22.0% and 15.8% of vehicle-treated subjects in the applicant’s and alternative analyses, respectively ($p < 0.021$ and $p = 0.015$).

In the Phase 3 vehicle-controlled studies, a total of 40 subjects (7.3%) in the ketoconazole group experienced treatment-related adverse events compared to 25 subjects (6.4%) in the vehicle group. Most treatment-related adverse events in both treatment groups were listed under “general disorders and administration site conditions” system organ class and were related to the application site. Although the rates were similar, more treatment-related application site adverse

events were reported for ketoconazole-treated subjects (5.5%) than for vehicle-treated subjects (4.4%). The most commonly reported treatment-related adverse event in both treatment groups was **“application site burning,”** and this event was reported at a higher incidence in subjects who received ketoconazole treatment (4.2%) than those who received vehicle (3.1%). This may suggest that while the vehicle may be somewhat irritating, the addition of ketoconazole may increase the potential for irritancy.

Most treatment-related adverse events were related to the application site and occurred during the treatment period. Most events were not of sufficient severity to make for interruption or discontinuation of treatment.

Reactions reported at the application site included: burning, dermatitis, discharge, dryness, erythema, irritation, pain, pruritus, pustules and **“reaction.”**

No new safety concerns were raised in the development program.

9.2 Recommendation on Regulatory Action

From a clinical perspective, it is recommended that the application be approved.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

There are no recommendations for any specific risk management activities.

9.3.2 Required Phase 4 Commitments

There are no required Phase 4 commitments.

9.3.3 Other Phase 4 Requests

There are no Phase 4 requests.

9.4 Labeling Review

Although it was not requested, the applicant did develop a Patient Package insert. The Division of Medication Errors and Technical Support **did not recommend use of the applicant’s** proposed proprietary names Sebazole and _____ because, “the proprietary name Sebazole, the primary concerns related to look-alike and/or sound-alike confusion between Sebazole and Sebizole, Sebazole (veterinary product), Spectazole, or Ketozole. In reviewing the proprietary name _____the primary concerns related to sound-alike confusion between _____and Sebizole or **Sebazole.**”

9.5 Comments to Applicant

None

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10 APPENDICES

10.1 Review of Individual Study Reports

10.2 Line-by-Line Labeling Review

11 DRAFT PACKAGE INSERT

10 Page(s) Withheld

 Trade Secret / Confidential

X Draft Labeling

 Deliberative Process

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REFERENCES

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