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*APPLICATION NUMBER:*

**22-404**

**MEDICAL REVIEW(S)**

Clinical Review  
Hala Shamsuddin MD  
NDA 22404  
Miconazole Lauriad buccal tablet 50 mg

## CLINICAL REVIEW

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Applicant	Bioalliance
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Dosing Regimen	50 mg once a day
Indication(s)	Oropharyngeal Candidiasis
Intended Population(s)	Adults with OPC

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## 1 Executive summary

Oropharyngeal candidiasis (OPC) is an opportunistic infection of the oral cavity. It usually occurs in patients with systemic T cell mediated immune deficiency, patients with local oral factors such as increased salivary glucose or salivary pH or decreased salivary flow, denture wearers, elderly patients and neonates. HIV infected patients and patients who have received radiation to the head and neck area are particularly at risk. Topical therapies available in the US include clotrimazole troches and nystatin administered several times a day. Systemic antifungal treatment is usually reserved for the treatment of patients with severe, recurrent or recalcitrant OPC.

Miconazole is an imidazole antifungal agent. It is available in the United States as a topical agent for the treatment of vaginal and skin yeast infection. Miconazole oral gel is available in Europe for the topical treatment of OPC, but is not available in the US. The sponsor, Bioalliance, has formulated miconazole into 50 mg tablets that adhere to the oral mucosa. The tablet results in salivary miconazole concentrations above the MIC<sub>90</sub> of most *Candida* species for a mean of 7 hours, with minimal systemic absorption. The sponsor is seeking approval of the miconazole buccal tablet for the local treatment of oropharyngeal candidiasis (OPC) in adults.

The sponsor submitted two non-inferiority design studies to evaluate the efficacy of miconazole buccal tablet (MBT) in the treatment of OPC. The first study was double blind, randomized, multicenter study that compared MBT to clotrimazole, both given for 14 days, for the treatment of OPC in HIV infected patients. The primary endpoint was resolution of oral lesions and oral symptoms on day 21. The sponsor and the reviewer defined the non-inferiority margin at 15%. MBT was non-inferior to clotrimazole for the treatment of OPC in HIV infected patients. In addition, MBT and clotrimazole resulted in similar mycologic cure rate, relapse rate and time to relapse. Failure of therapy was associated with severe OPC, CD4 count less than 50, and poor general performance status (higher ECOG grade).

The second study was open label with blinded evaluator, and compared MBT to miconazole oral gel, both given for 14 days, for the treatment of OPC in patients with head and neck cancer who had received radiation therapy. The primary endpoint was complete or partial resolution of oral lesions on day 14 (end of therapy). The sponsor defined the non-inferiority margin at 20%, but the reviewer considered a non-inferiority margin for complete resolution of symptoms of 12.5% to be more appropriate. MBT was non-inferior to miconazole gel for the treatment of OPC in patients with head and neck cancer who had received radiation therapy. However, MBT resulted in numerically lower mycologic cure rate, and numerically higher relapse rates and shorter time to relapse compared to miconazole oral gel. Failure of therapy was associated with absence of salivary secretion.

Resolution of lesions occurred less frequently in patients with head and neck cancer who had received radiation therapy compared to HIV infected patients regardless of the treatment administered. This is consistent with literature reports of lower efficacy of fluconazole in the treatment of OPC in patients with head and neck cancer compared to patients with HIV infection, and is attributed to xerostomia in patients with head and neck cancer that results in lower salivary concentrations of fluconazole. In the

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studies reviewed in this submission, patients with head and neck cancer had a higher degree of salivary gland dysfunction compared to HIV infected patients, and a smaller percentage of tablets adhering to the oral mucosa for at least 6 hours, thereby resulting in lower drug exposure and probably lower salivary concentrations.

Similarly, clinical cure (defined as resolution of lesions and symptoms) was lower in patients with head and neck cancer who had received radiation therapy compared to HIV infected patients. In addition, resolution of symptoms accompanied lesion resolution in HIV infected patients. In contrast, resolution of symptoms did not necessarily accompany lesion resolution in patients with head and neck cancer, probably because radiation therapy to the oral cavity and OPC result in similar symptoms.

Mycologic cure did not correlate with clinical cure in either population, consistent with literature reports. Mycologic cure was lower in HIV infected patients compared to patients with head and neck cancer, despite higher frequency of tablet adhesion and better salivary function (thus probably higher drug exposure). In addition, HIV infected patients were more likely to relapse and to have a shorter time-to-relapse regardless of treatment. The lower mycologic cure and rate of relapse probably reflects the higher degree of underlying systemic immunosuppression of HIV infected patients compared to patients with head and neck cancer.

Fourteen deaths and 13 other serious adverse events occurred in all the studies combined. None of the deaths or SAE were drug related. The most common all-causality adverse events noted in patients who received MBT were gastrointestinal disorders (nausea, diarrhea, vomiting, upper abdominal pain), and central nervous system disorders (dysgeusia, and headache). The frequency of all causality oral adverse events was similar in patients who received MBT compared to patients who received either clotrimazole or miconazole gel.

## **2 Recommendations on regulatory action**

The reviewer recommends approval of miconazole 50 mg buccal tablet given once a day for 14 days for the treatment of oro-pharyngeal candidiasis (OPC) in adults.

## **3 Introduction**

The sponsor (Bioalliance) is seeking approval of 50 mg miconazole buccal tablet (MBT) for the local treatment of oropharyngeal candidiasis (OPC) in adults.

The sponsor submitted data from four clinical trials. Trial 2000/01/01 evaluated serum and salivary pharmacokinetics of a single 50 mg and a single 100 mg miconazole buccal tablet (MBT) compared to three doses of miconazole oral gel in healthy subjects.

Trial 2002/01/02 was a randomized open label trial with blinded evaluator comparing the efficacy of 50 mg MBT once daily for 14 days to miconazole gel 125 mg four times daily for 14 days in the treatment of OPC in adults with head and neck cancer who had received radiation therapy. The primary endpoint was complete or partial resolution of oral lesions on day 14 (end of therapy).

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Trial 2002/01/03 was an open label non-comparative trial to evaluate the efficacy of 50 mg MBT once daily for 14 days in the treatment of OPC in HIV infected adults. The primary endpoint was complete or partial resolution of oral lesions on day 15.

Trial 2004/01/04 was a randomized double blind trial comparing the efficacy of 50 mg MBT once daily for 14 days to clotrimazole troches 10 mg four times daily for 14 days in the treatment of OPC in HIV infected adults. The primary endpoint was complete resolution of oral lesions and oral symptoms on day 21.

## 4 Background

Oropharyngeal candidiasis (OPC) is an opportunistic infection of the oral cavity. The main causative agent is *Candida albicans*, though non-albicans species have been implicated especially in patients with advanced HIV infection.

*Candida* colonizes the oral cavity of up to 60% of healthy adults. The frequency of colonization increases in individuals with abnormal T cell mediated immunity, individuals with oral mucosal injury resulting in xerostomia/decreased salivary flow, and individuals with increase in salivary pH or glucose, or decrease in salivary IgG and IgA concentrations. Thus, individuals at risk for OPC include immunocompromised individuals (especially recipients of chemotherapy and HIV-infected individuals), infants, the elderly, denture-wearers, individuals receiving broad-spectrum antibiotics, individuals using inhaled steroids, individuals who have received radiation to the salivary glands, and individuals with diabetes mellitus.

The main types of OPC are pseudomembranous (or thrush), and erythematous (or atrophic - includes denture stomatitis). Thrush is the most common manifestation. Oral lesions appear as white curd-like discrete plaques that leave an erythematous bleeding surface when removed. In erythematous or atrophic OPC, the oral lesions appear as diffuse red smooth patches. Many patients with oropharyngeal candidiasis are asymptomatic. The most common symptoms are a cottony feeling in the mouth, loss of taste, and pain on eating and swallowing.

The diagnosis of OPC is usually based on physical examination alone, and can be confirmed by KOH preparation of scrapings of the oral lesions showing budding yeasts with or without pseudohyphae. Cultures are rarely performed unless the disease is recalcitrant or recurrent, to rule out an azole-resistant organism. Recurrences are common if the underlying risk factors are still present. Clinical response is frequently achieved without mycologic response. However, relapse rates within one month of therapy tend to be higher in patients who do not achieve mycologic cure<sup>1,2</sup>.

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<sup>1</sup>Patton LL, Bonito AJ, Shugars DA. A systematic review of the effectiveness of antifungal drugs for the prevention and treatment of oropharyngeal candidiasis in HIV-positive patients. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001; 92:170.

<sup>2</sup> Vazquez JA. Therapeutic options for the management of oropharyngeal and esophageal candidiasis in HIV/AIDS patients. *HIV Clinical Trials* 2000;1:47-59

#### ***4.1 Oropharyngeal Candidiasis (OPC) in patients with HIV infection***

OPC is an immunologic marker of HIV infection. It is the most frequent opportunistic infection associated with HIV infection, occurring in about one third to one-half of HIV-infected individuals, and in up to 90% of patients with AIDS<sup>3</sup>. OPC is difficult to eradicate in HIV-infected patients not treated with highly active antiretroviral therapy (HAART). HAART has reduced the incidence of OPC in HIV infected individuals<sup>4</sup>, and resolution of OPC solely in response to initiation of HAART has been reported.

#### ***4.2 Oropharyngeal Candidiasis (OPC) in patients with head and neck cancer***

Acute oral effects of radiation therapy (RT) for head and neck cancer (HNC) include mucositis, odynophagia, dysphagia, hoarseness, and xerostomia. Administration of 10Gy to the salivary tissue results in temporary loss of salivary function, whereas 40-50Gy results in permanent loss of salivary function. Xerostomia increases the incidence and prevalence of oral colonization and infection with *Candida*<sup>5</sup>. In addition, xerostomia may decrease treatment response to systemic antifungal drugs by decreasing the penetration of the drug into saliva. Two studies of OPC treatment in patients with head and neck cancer reported cure rates to fluconazole lower than the reported cure rates in HIV infected individuals<sup>6,7</sup>.

Considerations for treatment choice include severity of the infection, host characteristics, drug effectiveness and ease of administration, gastric acidity (which may affect absorption of some systemic antifungal agents), drug-drug interactions, and cost. Topical and systemic antifungal agents are available. For topical drugs, successful therapy depends on adequate contact time between the drug and oral mucosa. For systemic drugs, successful therapy depends on the agent's ability to penetrate into saliva<sup>8</sup>. Local topical agents are recommended as the first line of therapy for most HIV-negative patients, and for HIV-infected patients with mild first OPC episode. Systemic agents are recommended for HIV-negative patients with recurrent OPC or OPC that has not responded to local therapy, and for HIV infected patients with moderate or severe OPC, recurrent OPC, or possibly patients with CD4 count less than 100 cells/mm<sup>3</sup>. The preferred systemic agent is oral fluconazole. For OPC refractory to

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<sup>3</sup> Repentigny L, Lewandowski D, Jolicoeur P. Immunopathogenesis of oropharyngeal candidiasis in HIV infection. Clin Micro Rev 2004; 17:729-759

<sup>4</sup> Pallela F et al. Declining morbidity and mortality among patients with advanced HIV infection. NEJM 1998; 338:853-860

<sup>5</sup> Velia RA et al. Candidal colonization and oral candidiasis in patients undergoing oral and pharyngeal radiation therapy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1997;84:149-53

<sup>6</sup> Finlay PM, Richardson MD, Robertson AG. A comparative study of the efficacy of fluconazole and amphotericin B in the treatment of oropharyngeal candidosis in patients undergoing radiotherapy for head and neck tumours. Br J Oral Maxillofac Surg 1996; 34:23-27

<sup>7</sup> Lefebvre JL, Domenge C. A comparative study of the efficacy and safety of fluconazole oral suspension and amphotericin B oral suspension in cancer patients with mucositis. Oral Oncol 2002; 38: 337-342

<sup>8</sup> Uptodate

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fluconazole, itraconazole, voriconazole, posaconazole, or Amphotericin B suspension are recommended. The usual treatment duration of uncomplicated disease is 7–14 days<sup>9</sup>.

### 4.3 Currently available treatments for OPC

**Table 1 Currently approved treatments for oropharyngeal candidiasis**

Drug	Form and route	Disadvantages
<b>Local</b>		
Clotrimazole	10 mg troches	five times a day, contains dextrose that may promote dental caries
Nystatin	Oral suspension or pastilles	four times a day, unpleasant taste, nausea, contains sucrose that may promote dental caries
<b>Systemic</b>		
Fluconazole	Oral tablet, oral suspension	Drug interactions, development of resistance with prolonged administration
Posaconazole	Oral suspension	Drug interactions, hepatic toxicity, bioavailability dependent on diet, cost

**Table 2 Other available antifungal agents used to treat OPC**

Drug	Form and route	Disadvantages
<b>Local</b>		
Amphotericin B	Oral suspension	three times a day
<b>Systemic</b>		
Itraconazole	Oral capsule, oral suspension	Drug interactions, hepatic toxicity, cost Capsules have poor bioavailability, suspension has unpleasant taste
Voriconazole	Oral tablet, oral suspension	Drug interactions, visual and hepatic toxicity, cost

## 5 Product information

Miconazole Lauriad 50 mg buccal tablets adhere to the upper gum and dissolve slowly, releasing miconazole in the oral cavity over several hours.

### 5.1 CMC

Miconazole USP (C<sub>18</sub>H<sub>14</sub>Cl<sub>4</sub>N<sub>2</sub>O) is the active ingredient in miconazole Lauriad buccal tablets (MBT). MBT contains Milk Protein Concentrate (MPC) produced in (b) (4) from bovine spongiform encephalopathy (BSE)-free material. MPC contains approximately 82% casein and 18% whey

<sup>9</sup> Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis 2009; 48:503-35.

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proteins ( $\beta$ -lactoglobulin). Upon ingestion, casein and  $\beta$ -lactoglobulin can induce hypersensitivity/allergic reaction in 0.1-0.5% of adults. All CMC facilities were found to be acceptable upon FDA inspection.

## 5.2 Toxicology:

The sponsor provided literature reviews describing miconazole toxicity, milk protein concentrate toxicity, and local tolerance of [REDACTED]<sup>(b) (4)</sup> formulations. In addition, the sponsor conducted studies to evaluate the local tolerance of miconazole [REDACTED]<sup>(b) (4)</sup> tablet. Toxicology findings are summarized.

### 5.2.1 Systemic effects:

In rats, the minimal lethal dose following oral administration was >2300 mg/kg, which is equivalent to a human dose of 384 mg/kg based on body-to-surface area comparisons. LD50 of IV miconazole is in the range of 60 to 100 mg/kg for mice, rats, guinea pigs, and dogs.

In dogs, oral doses of 40 mg/kg/d for 13 weeks resulted in hyaline degeneration of hepatocytes, oral doses of 20mg/kg/d for 12 months resulted in elevation of ALT and AST, and IV doses up to 40 mg/kg/d for 4 wks did not result in toxicity related to miconazole.

In rabbits, doses up to 20 mg/kg/d IV for 6 weeks to 6 months did not result in toxicity.

### 5.2.2 Local effects

The sponsor conducted studies to evaluate the local irritant effects of 50 mg MBT on the oral mucosa of hamsters. Twenty male and female hamsters received either normal saline or one 50 mg MBT tablet in each cheek once a day. The dose of miconazole was 5-6 times the LD50 dose. The animals tolerated the drug poorly due to systemic toxic effects. At necropsy, there were no macroscopic abnormalities of the oral mucosa and no esophageal or gastro-intestinal obstruction.

The sponsor also reviewed the literature for local tolerance of buccal adhesive preparations (testosterone buccal formulation, and miconazole buccal formulation 10 mg). The most common AEs reported with testosterone buccal tablet were gum or mouth irritation (9.2%), bitter taste (4.1%), gum pain (3.1%), gum tenderness (3.1%), gum edema (2.0%), and taste perversion (2.0%). No signs of local irritation were reported following use of the 10 mg miconazole nitrate [REDACTED]<sup>(b) (4)</sup> buccal tablet.

*Reviewer's comments: Hamsters died of systemic exposure, without local oral macroscopic findings. Local adverse events reported in clinical trials of the miconazole buccal tablet were similar to local adverse events reported for miconazole gel and for clotrimazole troche (Please refer to safety sections of individual clinical trials in this review).*

## 5.3 Microbiology

Miconazole is a synthetic imidazole antifungal agent with broad-spectrum *in vitro* activity against *Candida* species. MIC<sub>90</sub> of miconazole against *C. albicans* ranges from 0.03 to 1  $\mu$ g/mL, and against non-albicans *Candida* from 0.03 to 4  $\mu$ g/mL. Similar to other azoles, miconazole inhibits the biosynthesis of ergosterol, an essential component of the fungal cell wall, by inhibiting 14- $\alpha$ -demethylase. In addition, miconazole inhibits fungal oxidative enzymes, and fungal triglyceride and fatty acid synthesis resulting

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in the accumulation of reactive oxygen species and cell death. Similar to other azoles, AUC/MIC ratio, rather than the time above the MIC, is the relevant PD parameter. Also similar to other azoles, resistance is mediated by active drug efflux mechanisms, and to a lesser extent, by alteration of 14-  $\alpha$  - demethylase.

Because the National Committee for Clinical Laboratory Standards (NCCLS) has not established susceptibility breakpoints for miconazole, the extent of cross-resistance between miconazole and other azoles is unknown.

#### **5.4 PK/PD**

Miconazole is poorly absorbed following oral administration, with an oral bioavailability of approximately 25%. Oral ingestion of miconazole gel 85 mg three times a day for 3 days results in a mean  $C_{max}$  of 83.3 ng/mL. Systemic absorption following vaginal application occurs. A single 1200 mg vaginal insert results in a mean  $C_{max}$  10.7 ng/mL (miconazole vaginal gel package insert).

Miconazole is metabolized by the liver into pharmacologically inactive metabolites, and is eliminated unchanged in the feces with a terminal elimination half-life of 20 - 24 hours.

Miconazole is a substrate of CYP3A4 and a strong inhibitor of CYP2C9 and 3A4. Although systemic absorption of oral or vaginal miconazole preparations is low, clinically significant drug interactions have occurred. In a published report, oral ingestion of miconazole gel 85 mg three times a day for 3 days resulted in  $C_{max}$  of 83.3+/-54.6 ng/mL in 12 healthy subjects, and increased the AUC of a 60 mg single oral dose of etoricoxib by 1.69 fold, and the half-life by 10 hours<sup>10</sup>. Clinically significant drug interactions of miconazole oral gel and miconazole vaginal preparations with warfarin have been reported<sup>11,12</sup>.

The UK miconazole gel package label contraindicates the administration of the gel with drugs metabolized by CYP3A4 (astemizole, cisapride, dofetilide, mizolastine, pimozone, quinidine, terfenadine, ergot alkaloids, HMG-CoA reductase inhibitors, triazolam and midazolam). It also warns caution when used with drugs metabolized by CYP2C9 (warfarin, oral hypoglycemic agents, phenytoin), and when used with other drugs metabolized by CYP3A4 (HIV protease inhibitors, certain antineoplastic agents (vinca alkaloids, busulfan and docetaxel), certain Calcium channel blockers (verapamil), and certain immunosuppressive agents (cyclosporine, tacrolimus, sirolimus). Similarly, the French miconazole gel label contraindicates the administration of the gel with oral anticoagulants, cisapride, pimozone and oral hypoglycemics, does not recommend use in patients receiving halofantrine, and urges caution in patients receiving phenytoin.

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<sup>10</sup> Hynninen V, et al. Oral voriconazole and miconazole gel produce comparable effects on pharmacokinetics and pharmacodynamics of etoricoxib. Eur J Clin Pharmacol 2009; 65:89-95

<sup>11</sup> Pemberton MN, Oliver RJ, Theaker ED. Miconazole oral gel and drug interactions. Br Dental J 2004; 196:529- 531

<sup>12</sup>Thirion D J G, Zanetti L A F. Potentiation of warfarin's hypoprothrombinemic effect with miconazole vaginal suppositories. Pharmacotherapy 2000; 20: 98-99

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## 6 Availability of the proposed active ingredient in the US

Miconazole is available in the US in over the counter vaginal formulations for the treatment of vulvovaginal candidiasis, and over the counter dermal formulations of the treatment of fungal skin infections (such as tinea versicolor, serpigo, tinea cruris, and tinea pedis).

## 7 Summary of presubmission regulatory activity related to submission

The sponsor had a type B pre-IND meeting (IND 69, 578) on July 30, 2004, and a type B pre-NDA meeting on August 12, 2008 to discuss completed and planned studies, primary endpoints and NI margin justification. The sponsor submitted 505 (b)(2) application for NDA 22-404 on February 5, 2009. On April 3, 2009, the sponsor received a Refuse to File letter. RTF issues pertained to the absence of code imprints on the tablets (21 CFR 206.10). The sponsor adequately addressed the issues, and resubmitted on June 15, 2009. NDA 22-404 was filed on June 17, 2009.

## 8 Clinical Trials conducted with miconazole Lauriad buccal tablet

**Table 3 Clinical trials conducted with miconazole Lauriad 50 mg buccal tablet (MBT)**

Trial number	Trial design	Treatment(s)	N	Trial population Geographic location(s)	Duration of therapy	Primary endpoint
BA2000/01/01	Open, single center, randomized, cross over, 3 periods  PK study	Miconazole Lauriad 50 mg buccal tablet once a day vs. 100 mg once a day vs. miconazole gel 125 mg 3x/day	18	Healthy subjects	One day	Plasma and salivary miconazole concentrations
BA2002/01/03	Open, multicenter, non-controlled sequential response adaptive design	Miconazole Lauriad 50 mg buccal tablet	Randomized 26 ITT 25 PP 19 Safety 25	HIV infected adults  France	14 days	Clinical success: complete or partial resolution of oral lesions at EOT
BA2004/01/04	Randomized, double blind, Non inferiority design	Miconazole Lauriad 50 mg buccal tablet once a day, vs. clotrimazole troches 10 mg 5x/day	MBT: Randomized 291 ITT 290 PP 240 Safety 290  Clotrimazole Randomized 287 ITT 287 PP 236 Safety 287	HIV infected adults  United States, Canada, and South Africa	14 days	Clinical cure: complete resolution of symptoms and oral lesions at day 21
BA2002/01/02	Open, evaluator blind, multicenter randomized Non inferiority design	Miconazole Lauriad 50 mg tablet once a day vs. miconazole oral gel 125 mg 4x/day	MBT Randomized 154 ITT 141 PP 107 Safety 147	Head and neck cancer patients who had received radiation therapy  France, Morocco,	14 days	Clinical success: complete or partial resolution of oral lesions at EOT

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			Gel Randomized 152 ITT 141 PP 106 Safety 147	Algeria, and Tunisia		
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## 8.1 Clinical Trial BA2000/01/01

### 8.1.1 Methods

This was a randomized, single center, cross-over trial to evaluate the pharmacokinetics of a single 50 mg miconazole Lauriad buccal tablet (MBT), a single 100 mg MBT, and three 125 mg doses of miconazole oral gel given over one day.

### 8.1.2 Trial Design

The primary objective was to determine PK parameters of miconazole in the saliva of 18 healthy subjects following the administration of a single miconazole buccal tablet containing 50 and 100 mg of miconazole compared to miconazole oral gel 125 mg three times a day.

The secondary objectives were to determine miconazole plasma concentration, tablet adhesion time, and tolerability/acceptability of the (b) (4) tablets.

### 8.1.3 Inclusion criteria

- Healthy 18-35 years old male or female
- Non smokers or light smokers (less than 5 cigarettes per day)
- Normal physical exam
- Normal hematology, liver, and serum glucose parameters
- Able to give consent
- If female, effective contraception for more than 3 months

### 8.1.4 Exclusion criteria

- Milk hypersensitivity
- Pregnant or lactating
- Smoker > 5 cigarettes/day
- Liver failure defined as ALT/AST > 5x normal, or PT < 80% normal
- Receiving medications likely to interact with miconazole: antiarrhythmics, anticoagulants (anti-vitamin K), sulfonylureas, astemizole, cisapride, phenytoin and anticholinergic medications

*Reviewer's comment: The inclusion and exclusion criteria are appropriate. Exclusion of patients receiving concomitant medications likely to interact with miconazole was based on the French prescribing information compendium for the oral gel.*

### 8.1.5 Study Events

Eighteen healthy subjects (nine men and nine women) were randomized in groups of six over 3 days. Each subject received the three treatments in a predefined order, with one-week wash out period between each treatment. The subjects applied the miconazole buccal tablet in the canine fossa on the upper gum. The tablet remained in the oral cavity until complete dissolution or loss of adhesion. In the event of detachment, the subject was to swallow the tablet. Subjects could eat and drink without restriction, but were to avoid chewing gum. The gel was administered at T 0 h, T 3.5 h, and T 8.5 h to allow a reasonable interval from meals. Subjects were to keep the gel in the mouth for 2-3 minutes before swallowing it.

Fifteen (15) salivary samples and eight (8) blood samples were obtained from each subject at predefined intervals on the day of medication administration. Tolerability of the drug was assessed by a questionnaire. Miconazole level was assayed using HPLC with a lower limit of detection of 0.4 µg/ml.

### 8.1.6 Data Quality:

The sponsor audited the study site and the clinical laboratory prior to study initiation.

### 8.1.7 Study Results

The peak concentration of the mean curve occurred 8 hours after administration of the 50 mg tablet, with a mean value of 8.19 µg/mL. The peak concentration of the mean curve occurred 6 hours after administration of the 100 mg tablet, with a mean value of 15.27 µg/mL. Three small peak concentrations occurred at 30 minutes after each application of the gel, with mean concentrations of 0.63, 0.72 and 0.99 µg/mL respectively.

**Table 4 Salivary miconazole concentrations following administration of gel,**

50 mg or 100 mg tablet - BA 2000/01/01

PK Parameters	MBT 50 mg N = 18	MBT 100 mg N = 18	Gel 125 mg N = 18
C max (µg/mL)			
Mean	15.1	39.1	1.6
SD	16.2	49.3	1.6
Range	0.4 - 65	1.7 - 179	0 - 6.6
T max, median, hours	7	6	0.5
AUC (0-12) µg.h/mL			
Mean	43.0	78.6	3.4
SD	32.0	78.4	4.1
Range	0 - 117	2 - 244	0-13.9
AUC (0-24) µg.h/mL			
Mean	55.1	136.2	3.1
SD	35.1	149.5	4.2
Range	0.4 - 128	2 - 607	0 - 24

*Reviewer's comment: PK of miconazole buccal tablet in saliva displayed linearity; the 100 mg tablet resulted in  $C_{max}$  and AUC almost twice as high as the 50 mg tablet. However, there was marked variability in PK parameters in the saliva. Both concentrations of the buccal tablet would result in high AUC/MIC ratio (the relevant PD parameter for efficacy).*

The sponsor explored the time salivary concentrations of miconazole were above 0.4 µg/mL (the lower limit of the assay detection), and above 1.0 µg/mL (the MIC<sub>90</sub> of miconazole against most *Candida* species). Salivary concentrations of miconazole were above 1.0 µg/mL for a mean time of around 7 hours in both the 50 mg and 100 mg tablet groups, compared to 0.6 hours in the gel group.

**Table 5 Duration of miconazole salivary concentration > 0.4 µg/mL and > 1.0 µg/mL,**

BA 2000/01/01

Duration	MBT 50 mg N = 18	MBT 100 mg N = 18	Gel 125 mg N = 18
Mean Time > 0.4 µg/mL, hours	10.2 +/- 6.1	13.6 +/- 8.0	1.5 +/- 2.2
Mean Time > 1.0 µg/mL, hours	7.2 +/- 3.4	7.11 +/- 5.3	0.6 +/- 1.7
Range	0 - 11	0 - 23	0 - 7

Adapted from study report page 40

*Reviewer's comment: Both tablet dose strengths resulted in more sustained miconazole concentrations in the saliva compared to the gel. This is expected since the tablets remain in place, while the gel is swallowed without significant systemic absorption. However, the variability was high.*

The 50 mg tablet adhered for 15.2 +/- 4.4 hours (range 9.6 – 24.2), while the 100 mg tablet adhered for 15.1 +/- 6.7 hours (range 4.8 – 24.2). Systemic absorption of miconazole occurred in 17 – 27 % of the subjects. When measurable, none of the serum concentrations was greater than 1.1 µg/mL.

**Table 6 Number of subjects with measurable plasma concentrations of miconazole - BA 2000/01/01**

	MBT 50 mg N = 18	MBT 100 mg N = 18	Gel 125 mg N = 18
Subjects	5/18 (27%)	3/18 (17%)	5 (27%)
Samples	5/162 (3%)	4/162 (2.4%)	10/162 (6.1%)

Adapted from study report page 42

*Reviewer's comment: When detected, blood levels of miconazole following a single oral mucosal application were below 110ng/mL, indicating low systemic absorption. 110ng/mL is at least seven fold lower than the level obtained after a single infusion of 522 mg of miconazole in healthy volunteers (7.5µg/mL), and is comparable to the serum level obtained after oral ingestion of 85 mg miconazole gel given 3 times a day for 3 days (mean  $C_{max}$  83.3ng/mL). The systemic level obtained after a single vaginal insertion of 1200 mg of miconazole is 10.7ng/mL, well below the detection level of the assay used in this*

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*study. Systemic absorption after swallowing the tablet or after repeated mucosal applications is not addressed in this study.*

*The low systemic absorption of miconazole buccal tablet indicates a low potential for drug interactions. The package insert for miconazole oral tablet as marketed in France (Loramyc) contraindicates the tablet in patients receiving oral anticoagulants, sulfonamide hypoglycemics, cisapride and pimozide, and does not recommend use in patients receiving halofantrine.*

### 8.1.7.1 Safety Evaluation:

Five subjects reported six adverse events, three events in the gel group, three events in the 100 mg group, and no events in the 50 mg group.

**Table 7 Summary of Adverse events – BA2000/01/01**

	MBT 50 mg N = 18	MBT 100 mg N = 18	Gel 125 mg N = 18
Patients with at least one AE	0	2 (11.1%)	3 (16.7%)
Patients with SAE	0	0	0
Patients with at least one drug related AE	0	2 (11.1%)	3 (16.7%)

**Table 8 All causality Adverse Events – study BA 2000/01/01**

System Organ Class/Preferred term MedDRA version 9.1	MBT 50 mg N = 18	MBT 100 mg N = 18	Gel 125 mg N = 18
Gastrointestinal disorder	0	2 (11.1%)	2 (11.1%)
Oral irritation	0	2 (11.1%)	1 (5.6%)
Abdominal pain	0	0	1 (5.6%)
Nervous system disorder	0	1 (5.6%)	1 (5.6%)
Headache	0	1	1

There were no serious adverse events, no changes in vital signs, and no changes in lab parameters.

Local tolerability and acceptability were assessed by a questionnaire regarding taste, tablet size, oral comfort, and any influence on daily activities. All 18 patients (100%) rated the local tolerability of the 50 or 100 mg tablets as highly acceptable or acceptable, compared to 4/18 patients (22.2%) in the gel group.

*Reviewer's comment: The 50 mg and 100 mg tablet adhesion time was similar and resulted in similar duration of salivary concentration above 1µg/mL. The sponsor appropriately chose the 50 mg dose for further clinical trials.*

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**8.2 Clinical Trial BA2002/01/03**

### **8.2.1 Methods**

This trial was an open-label, non-comparative, sequential response adaptive trial. The primary objective was to evaluate the efficacy (complete or partial resolution of lesions) of 14-days of 50 mg miconazole Lauriad buccal tablet for the treatment of oropharyngeal candidiasis in HIV-infected adults.

### **8.2.2 Trial Design**

The trial was a sequential response adaptive trial, and was to proceed in three stages. If the success rate (complete or partial resolution of OPC lesions at EOT) was less than 60% or greater than 80% for the initial 20 evaluable patients, enrollment would halt. Otherwise, 20 more patients would be enrolled, and the analyses repeated. If the success rate for these 40 patients was less than 60% or greater than 80%, the trial would halt. Otherwise, 20 more patients would be enrolled (maximum 60 patients).

An independent committee reviewed the data after 26 patients were enrolled. The first interim analysis showed the efficacy to be greater than 80%. Per study protocol, the study was halted.

### **8.2.3 Inclusion criteria**

- Age 18 or older
- Oropharyngeal candidiasis diagnosed by
  - clinical examination (thrush, erythema, mucositis, angular cheilitis) with or without associated symptoms (odynophagia, burning/soreness, xerostomia, modified taste, pharyngeal irritation) and
  - microbiologic confirmation (detection of *Candida* on direct examination, or if direct examination is negative, by positive fungal culture with a minimum of 100 colonies)
- HIV-positive patient with a documented viral load receiving stable antiretroviral treatment for at least two months, or not receiving antiretroviral treatment
- Able to give informed consent and to follow study protocol
- For women of child-bearing age, negative pregnancy test at inclusion, and use of effective contraception for study drug treatment duration (14 days)
- ECOG (Eastern Cooperative Oncology Group) performance grade less than 3

### **8.2.4 Exclusion criteria**

- Pregnant or breast-feeding
- Milk allergy or known history of hypersensitivity to one or more components of the study drug
- Liver failure defined as ALT/AST 5 times > UNL, or prothrombin time < 80%
- Esophageal or systemic candidiasis
- Concomitant administration of local or systemic antifungal agents
- Concomitant treatment likely to interact with miconazole: antiarrhythmics, anticoagulants/anti-vitamin K therapy, sulfonylurea oral hypoglycemics, astemizole, cisapride, phenytoin

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*Reviewer's comment: Inclusion and exclusion criteria are appropriate. Exclusion of patients receiving concomitant medications likely to interact with miconazole was based on the French prescribing information compendium for the oral gel.*

### 8.2.5 Study Events

The study duration was 45 days, with four scheduled visits.

**Table 9 Schedule of study events – BA2002/01/03**

	Inclusion Day -7 to -0	Treatment period			Post-treatment Day 45
		Day 1	Day 7	Day 15	
History and physical	X				
ECOG	X	X			
Informed consent	X				
Labs	X			X	
Oral exam	X	X	X	X	X
Mycology direct exam	X				
Fungal culture	X			X	X If relapse or progression
Patient questionnaire*	X		Collected	Collected	
Miconazole serum level**	X		X		

Adapted from study report page 27

\*Compliance, local tolerability, tablet adhesion

\*\*Serum levels of miconazole were measured by HPLC (limit of detection 100 ng/mL).

Patients applied the buccal tablet in the canine fossa on the upper gum in the morning. Patients could reposition the tablet if it dislocated, and could replace if it adhered for less than 6 hours. Patients could eat and drink without restriction, but were to avoid chewing gum.

The primary endpoint was Clinical Success on day 15. Clinical Success was defined as complete or partial response. Complete clinical response was defined as complete resolution of oral candidiasis lesions. Partial clinical response was defined as at least 50% improvement in the extent of the oral lesions compared to inclusion.

Secondary endpoints were

- Clinical Success at day 7
- Clinical Cure at day 15 defined as complete resolution of signs and symptoms.
- Relapse rate day 45 (30 days after end of therapy). Relapse was defined as reappearance of lesions that had been cured, or increase in the extent of lesions that had partially cleared
- Mycologic cure defined as complete eradication or less than 10 colonies per plate on day 15

In addition, duration of tablet adhesion, compliance, and local tolerability were assessed by a patient questionnaire.

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*Reviewer's comment: The primary endpoint was complete or partial resolution of lesions at end of therapy, regardless of symptoms. This is the same endpoint used for study BA2002/01/02 (MBT vs. miconazole gel for the treatment of OPC in patients with head and neck cancer), but not for study BA2004/01/04 (MBT vs. clotrimazole troches for the treatment of OPC in HIV infected patients), where the endpoint was clinical cure (complete resolution of lesions and symptoms) on day 21. In this trial, clinical cure at end of therapy was not a planned endpoint, but was added after discussions with the FDA in a pre-IND meeting after the data was locked (Pre-IND # 69,578).*

### 8.2.6 Data Quality

An independent committee reviewed the data. The sponsor audited one study center (center 3) at the conclusion of the trial. The audit certificate was included in the submission.

### 8.2.7 Patient Disposition

Eight centers in France enrolled twenty-six (26) patients between August 2002 and August 2003.

The ITT population included all subjects who received at least one dose of the study drug. One patient did not receive the drug; the ITT population included 25 patients.

The PP population included all subjects who

- had received at least 3 days of treatment
- had no protocol violation (three patients excluded – not on stable antiretroviral therapy)
- had an efficacy evaluation at day 15

Two patients withdrew consent, and one did not return for efficacy evaluation visit. The PP population included nineteen patients.

**Table 10 Patient disposition - BA2002/01/03**

Total enrolled	26
ITT population	25
Excluded from PP	6 (24%)
Not on stable antiretrovirals	3
Withdrew consent before taking 3 days of drug	1
Withdrew consent for AE	1
No efficacy evaluation on day 15	1
Per Protocol population	19

Derived from study report page 34

### 8.2.8 Efficacy Evaluation

#### 8.2.8.1 Patient Demographics

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**Table 11 Patient Demographics – BA2002/01/03**

	ITT N = 25	PP N = 19
Age (years), mean, SD	40.2 +/- 11.6	39.8 +/- 12.8
< 65	24 (96%)	18 (94.7%)
≥ 65	1 (4%)	1 (5.3%)
Gender		
Male	17 (68%)	15 (78.9%)
Female	8 (32%)	4 (21.1%)

Adapted from study report pages 40-44

**Table 12 Patient characteristics – BA2002/01/03**

	ITT N = 25	PP N = 19
ECOG grade		
0	9 (36%)	7 (36.8%)
1	9 (36%)	7 (36.8%)
2	7 (28%)	5 (26.3%)
Mean CD4	190 +/- 200	164 +/- 188
< 50	8 (32%)	6 (31.6%)
50-200	8 (32%)	8 (42.1%)
> 200 cells/mm <sup>3</sup>	9 (36%)	5 (26.3%)
Viral load, mean	92,564 +/- 173,210	108,578 +/- 181,822
< 10,000	12 (48%)	8 (42.1%)
10,000 to 100,000	6 (24%)	5 (26.3%)
> 100,000	7 (28%)	6 (31.6%)
Antiretroviral treatment		
Yes	17 (68%)	12 (63.1%)
No	8 (32%)	7 (36.9%)
Symptoms present	11 (44%)	9 (47%)
Symptoms absent	14 (56%)	10 (53%)

Adapted from study report pages 40-44, 49

*Candida albicans* was isolated from all patients, *Candida glabrata* from 2 patients, and *C. tropicalis* from one patient.

**Table 13 *Candida* species isolated at baseline – BA2002/01/03**

	ITT N = 25	PP N = 19
<i>C. albicans</i>	25 (100%)	19 (100%)
<i>C. glabrata</i>	2 (8.0%)	0
<i>C. tropicalis</i>	1 (4.0%)	1 (5.3%)

Some patients had more than one species isolated  
Derived from datasets

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*Reviewer's comment: Patients were enrolled across CD4 categories and ECOG grades. About one third had a CD4 count < 50, and about one third were not on anti-retroviral therapy. Slightly more than half were asymptomatic. Almost all the patients were younger than 65 years of age. Males outnumbered females, consistent with the epidemiology of HIV infection in Western Europe. Race was not reported.*

### 8.2.8.2 Primary Endpoint

The primary endpoint was Clinical Success (complete or partial resolution of oral candidiasis lesions). Partial resolution was defined as at least 50% improvement in the extent of the oral lesions compared to inclusion.

**Table 14 Clinical Success day 15 – ITT and PP - BA2002/01/03**

	ITT N = 25	PP N = 19
Complete + Partial Response	21 (84.0%)	18 (94.7%)
Complete	13 (52.0%)	12 (63.1%)
Partial	8 (32.0%)	6 (31.6%)

Adapted from study report page 52, and derived from datasets

**Table 15 Clinical success by gender – ITT and PP - BA2002/01/03**

	ITT N 25	PP N 19
Males	17/17 (100%)	15/15 (100%)
Complete Response	10/17 (58.8%)	10/15 (66.7%)
Partial Response	7/17 (41.2%)	5/15 (33.3%)
Females	4/8 (50%)	3/4 (75.0%)
Complete Response	3/8 (37.5%)	2/4 (50%)
Partial Response	1/8 (12.5%)	1/4 (25.0%)

Derived from datasets

**Table 16 Clinical success by age – ITT and PP - BA2002/01/03**

	ITT N = 25	PP N = 19
< 65	20/24 (83.3%)	17/18 (94.4%)
Complete Response	12/24 (50%)	11/18 (61.1%)
Partial Response	8/24 (33.3%)	6/18 (33.3%)
≥ 65	1/1 (100%)	1/1 (100%)
Complete Response	1/1 (100%)	1/1 (100%)

Derived from datasets

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*Reviewer’s comment: Males had a numerically higher response than females in the ITT and PP populations. There were too few patients older than 65 years of age to allow any meaningful comparisons of response to patients younger than 65.*

### 8.2.8.3 Secondary Endpoints

In the ITT population, Clinical Success on day 7 was 80%, Clinical Cure on day 15 was 52%, and mycologic cure on day 15 was 28%. Of the symptomatic patients (11 in ITT, and 9 in PP), almost 82% resolved their symptoms on day 15. Of the patients who experienced complete or partial response (clinical success), 32% relapsed 4 weeks after EOT.

**Table 17 Summary of secondary endpoints – ITT and PP populations - BA2002/01/03**

	ITT N = 25	PP N = 19
Complete + Partial Response day 7	20 (80%)	17 (89.5%)
Complete	7 (28%)	5 (26.3%)
Partial	13 (52%)	12 (63.2%)
Resolution of symptoms day 15	9/11 (81.8%)	8/9 (88.9%)
Clinical cure day 15	13 (52%)	12 (63%)
Relapse day 45	8 (32%)	8 (42.1%)
Mycologic cure day 15	7 (28%)	6 (31.6 %)
*Mean time to relapse, days	15.2	15.2

Adapted from study report pages 48-56, and derived from datasets

\*not an endpoint, derived from datasets, calculated in patients who had complete or partial response

*Reviewer’s comment: 4/8 (50%) patients who relapsed had a CD4 count of < 50. Relapse rate of OPC after treatment with MBT in HIV infected patients is comparable to relapse rates after treatment with other topical or systemic agents (18-50%) (Darouiche 1998, Patton 2001).*

### 8.2.9 Safety Evaluation

The safety population included all patients who received at least one dose of miconazole tablet (25 patients).

#### 8.2.9.1 Drug exposure

The number of tablets taken was determined by the number of tablets remaining in the bottles returned and by patient diary. In case of discrepancy, the smaller number was used. Percent compliance was calculated as  $\{1 - \{(P-A)/A\}\} \times 100$ , where

P = the number of tablets scheduled = number of days on study x dosing regimen

A = the number of tablets actually taken = number of tablets dispensed – number of tablets returned

In the ITT population, 20/25 (80%) were more than 80% compliant.

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Six patients (24%) swallowed 11 tablets, four patients (16%) spat out nine tablets, and four patients (16%) replaced a tablet on 5 occasions. The tablet adhered for at least 6 hours in 22 patients (88%), for at least 12 hours in 18 patients (72%), and at least till bedtime in 14 (56%).

**Table 18 Duration of adhesion – ITT and PP populations - BA2002/01/03**

	ITT N = 25	PP N = 19
Number of tablets taken	311	246
Swallowed	11 (3.5%)	9 (3.6%)
Spat out	16 (5.1%)	12 (4.8%)
Duration of adhesion*		
Number of tablets adhering for 6 hours	233/242 (92.1%)	174/187 (93.0%)
Number of tablets adhering for 12 hours	145/258 (56.2%)	119/203 (58.6%)
Number of tablets adhering at bedtime	97/256 (37.9%)	85/202 (42.1%)
**Swallowed tablet on at least one occasion	6 (24%)	5 (26.3%)
**Spat out tablet on at least one occasion	4 (16%)	3 (15.8%)
**Took a second tablet on at least one occasion	4 (16%)	4 (21.1%)

Adapted from study report page 57 and derived from datasets

\*53 and 43 missing data for 6 and 12 hours respectively

\*\*Derived from datasets

*Reviewer's comment:* more than 90% of the tablets adhered for at least 6 hours, and slightly more than half adhered for at least 12 hours. This is less than the mean adhesion time of 15.2 hours (range 9-24 hours) in healthy subjects (Study BA2000/01/01).

Miconazole serum levels on day 7 were determined for 19 patients. All levels were < 0.1 µg/mL (the limit of quantification).

*Reviewer's comment:* No patient in this study had a detectable serum miconazole level, in contrast to study BA2000/01/01 in which 5/18 (27%) of healthy subjects had a detectable serum level on at least one occasion (5/162 samples). The lack of detection of serum miconazole in this study is likely due to the much lower frequency of blood sampling. Although 6/25 (24%) patients swallowed a tablet on at least one occasion, systemic absorption was still below the detection limit of the assay.

### 8.2.9.2 Adverse Events

Five patients reported six adverse events. Three events were considered drug related (nausea, gingival disorder, dysgeusia). One event (nausea) led to drug discontinuation. This event occurred on day 12, and resolved upon discontinuation of the drug. There were no clinically significant lab changes, no serious adverse events, and no deaths.

**Table 19 Summary of Adverse Events – BA 2002/01/03**

	Safety population N = 25
--	-----------------------------

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Patients with at least one AE	5 (20.0%)
Patients with at least one Drug related AE	3 (12.0%)
Patients with Serious AE	0 (0%)
AE leading to drug discontinuation	1 (4.0%)

Adapted from study report, and derived from datasets

**Table 20 All causality Adverse Events - BA 2002/01/03**

System Organ Class/Preferred term MedDRA version 9.1	Safety population N = 25
Gastrointestinal disorders	3 (12.0%)
Diarrhea	1 (4.0%)
Gingival disorder NOS	1 (4.0%)
Nausea	1 (4.0%)
General disorders and administration site condition	1 (4.0%)
Pyrexia	1 (4.0%)
Nervous system disorders	2 (8.0%)
Headache	1 (4.0%)
Dysgeusia	1 (4.0%)

Adapted from study report, and derived from datasets

*Reviewer's comments: the frequency of all oral adverse events (oral discomfort, oral burning, oral pain, gingival pain, gingival swelling, gingival pruritis, tongue ulceration, mouth ulceration, glossodynia, dry mouth, toothache, ageusia, dysgeusia and application site pain or discomfort) was 4.0% (1/25).*

### **8.3 Clinical Trial BA2004/01/04**

#### **8.3.1 Methods**

This was a randomized, double-blind, double-dummy, multicenter trial comparing miconazole Lauriad 50 mg buccal tablet (MBT) once daily for 14 days, to clotrimazole troches 10 mg 5 times a day for 14 days for the treatment of oropharyngeal candidiasis (OPC) in HIV-infected adults.

The primary objective was to compare the clinical cure of MBT with the clinical cure of clotrimazole troches in HIV infected adults at visit 5 (Test of Cure visit, day 17-22). Clinical cure was defined as complete resolution of signs and symptoms of OPC.

#### **8.3.2 Study Design**

The trial was non-inferiority design, with the hypothesis that MBT is non-inferior to clotrimazole with a one-side risk error level smaller than  $\alpha=0.025$ , and NI margin 15%. The co-primary populations for efficacy analyses were the intent-to-treat (ITT) and the Per Protocol (PP) populations.

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### 8.3.3 NI margin justification

Studies used to estimate the NI margin are listed in Appendix 2

#### 8.3.3.1 A) Estimation of placebo effect for trial BA 2004/01/04

The sponsor conducted a search using the electronic search engine Dialog. There were no placebo-controlled trials in the treatment of OPC in HIV infected patients. The sponsor identified three studies that compared placebo to an active comparator in other patients with OPC (Hughes 1983, Schechtman 1984, and Kirckpatrick 1978). Based on these studies, the sponsor estimated the placebo effect at around 20%.

*Reviewer's comment:* This reviewer conducted a Pubmed search using the term oropharyngeal candidiasis on August 6, 2009, and retrieved 775 references. There were no placebo-controlled trials in the treatment of OPC in HIV infected patients.

However, the reviewer identified three additional studies (Petersen 1980, Nyst 1992, Bastian 2004) to estimate placebo effect.

**Table 21 Studies used to estimate placebo response in patients with OPC**

<i>Citation</i>	<i>Study Design Patient Population</i>	<i>Rx arms Dose Duration</i>	<i>N Evaluable</i>	<i>Endpoint</i>	<i>Results</i>	<i>Comments</i>
<i>Kirckpatrick 1978</i>	<i>RDBPC  Chronic mucocutaneous candidiasis</i>	<i>Clotrimazole 10 mg 5x/d  Placebo  2 weeks</i>	<i>10  10</i>	<i>Resolution of lesions EOT</i>	<i>Clotrimazole 60%  Placebo 10%</i>	
<i>Petersen 1980</i>	<i>RDBPC  Chronic mucocutaneous candidiasis</i>	<i>Ketoconazole 200 mg/d  Placebo  6 months</i>	<i>6  6</i>	<i>Resolution of lesions EOT</i>	<i>Ketoconazole 100%  Placebo 0%</i>	<i>One patient in placebo had clinical response that lasted 3 weeks, and one has partial improvement that lasted 6 weeks.</i>
<i>Hughes 1983</i>	<i>RDBPC  Heme malignancy</i>	<i>Ketoconazole 200 mg/d  Placebo  2 weeks</i>	<i>36  20</i>	<i>Less than 5% coverage of 12 pre-specified sites of involvement in the oral cavity at EOT</i>	<i>Keto 72%  Placebo 20% (correlated with neutrophil recovery)</i>	<i>3/36 (8.3%) progressed in keto arm  6/20 (30%) progressed in placebo arm</i>
<i>Schechtman 1984</i>	<i>RDBPC  Heme malignancy</i>	<i>Clotrimazole 10 mg4/d  Placebo  Rx till cure or progression range 2-28 days</i>	<i>7  6</i>	<i>Resolution of lesions EOT (timing variable)</i>	<i>Clotrimazole 71.4%  Placebo 16.7%</i>	<i>2/7 (28.6%) progressed  5/6 (83.3%) progressed</i>
<i>Nyst 1992</i>	<i>Open</i>	<i>Nystatin</i>	<i>141</i>	<i>Resolution of</i>	<i>Nystatin (9%)</i>	<i>9% response to</i>

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	<i>HIV + adults Zaire</i>	<i>200000 u qid  Gentian violet 1.5 ml 0.5% bid  Keto 200 mg/d 2 weeks</i>	<i>enrolled  41.6% died at 2 weeks  72 evaluable</i>	<i>lesions at EOT</i>	<i>Gentian violet (42%)  Keto (43%)</i>	<i>nystatin can be considered pseudoplacebo rate</i>
<i>Bastian 2004</i>	<i>RDBPC Denture-related, steroid inhaler, post antibiotics, smokers</i>	<i>Miconazole gel 50 mg 4x/d  Miconazole chewing gum 4x/d  Placebo  4 weeks</i>	<i>28 gel  96 gum  16 placebo</i>	<i>Resolution of lesions EOT</i>	<i>Gel 48.2%  Gum 44.2%  Placebo 11.1%</i>	<i>Low compliance in the treatment arms</i>

*RDBPC: randomized double blind, placebo controlled  
EOT: End of therapy*

*There were no placebo-controlled trials in the treatment of OPC in HIV infected patients. One study (Nyst 1992) evaluated the efficacy of nystatin oral solution, gentian violet oral solution, and oral ketoconazole given for 14 days for the treatment of OPC in HIV infected adults in Zaire. 141 patients were enrolled. 59/141 died of their underlying disease by day 14, and were excluded from the analysis. The resolution rate at EOT was 2/23 (9%) for nystatin, 11/26 (42%) for gentian violet, and 10/23 (43%) for ketoconazole. The reviewer will consider the low response rate to nystatin equivalent to placebo (pseudo-placebo).*

*The two trials by Hughes 1983 and Schechtman 1984 were placebo-controlled in patients with underlying hematologic malignancy. In the study by Hughes et al 64 patients were randomized in 2:1 fashion to receive ketoconazole or placebo for 14 days. 36 ketoconazole patients and 20 placebo patients were evaluable. Response was defined as less than 5% coverage of 12 pre-specified sites of involvement in the oral cavity at the end of therapy. Response rates were 20% for placebo, and 72% for ketoconazole. Recovery of neutrophil count correlated with resolution of lesions, and 30% (6/20) of placebo patients progressed to develop esophageal candidiasis, compared to 8.3% (3/36) of ketoconazole patients.*

*In the study by Schechtman et al 16 patients with hematologic malignancy and OPC were randomized to receive clotrimazole troches or placebo for at least 48 hours after resolution of lesions. Seven patients in clotrimazole arm and six in placebo arm were evaluable. Treatment duration ranged between 2 and 28 days. 1/6 patients receiving placebo (16.7%) responded at end of therapy (duration of therapy not specified) vs. 5/7 in clotrimazole arm (71.4%). Of note, 5/6 (83.3%) placebo patients progressed, compared to 2/7 (28.6%) clotrimazole patients.*

*Two trials by Kirckpatrick and Petersen were placebo-controlled in patients with chronic oral candidiasis. In the study by Kirckpatrick (1978) 20 patients with chronic candidiasis (presumably chronic mucocutaneous candidiasis) who had failed nystatin or gentian violet therapy in the past were*

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*randomized to receive either clotrimazole troches or placebo for 2 weeks. 17/20 had oral lesions for more than five years. Response was defined as resolution of oral lesions 2-7 days after end of therapy. 1/10 (10%) responded in the placebo arm, compared to 6/10 (60%) in the clotrimazole arm. Petersen randomized 12 patients with mucocutaneous candidiasis to receive either placebo or ketoconazole for 6 months. Response was defined as resolution of oral lesions at EOT. No patients responded in placebo arm at EOT, although one patient showed transient resolution that lasted for 3 weeks, and one patient showed partial improvement that lasted 6 weeks.*

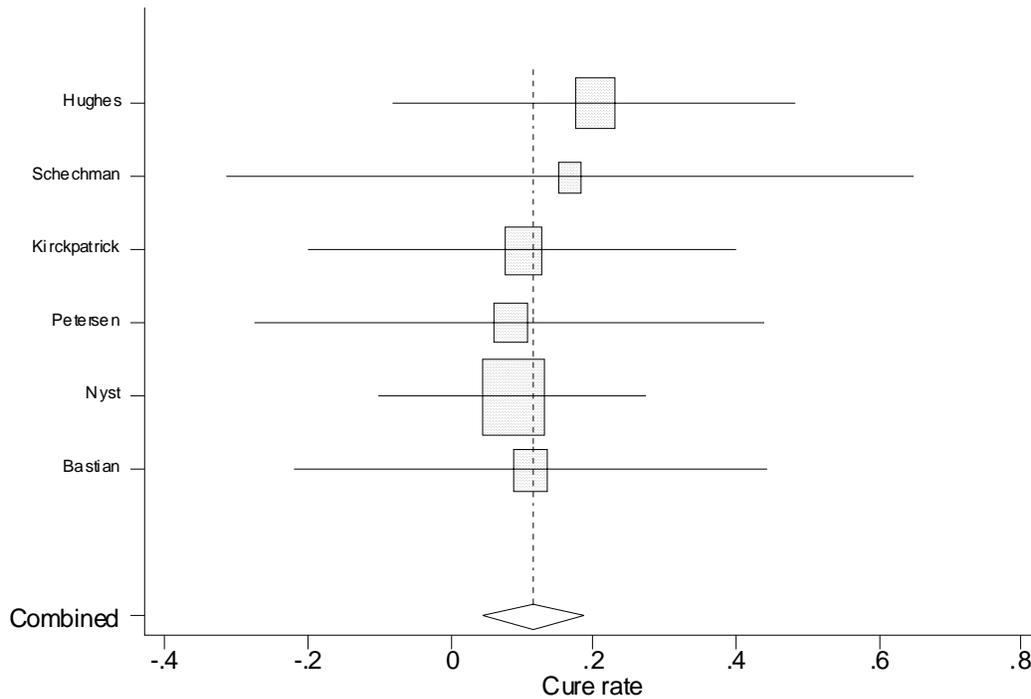
*The trial by Bastian was placebo controlled in patients with a variety of predisposing factors that included dentures, steroid inhalation, or smoking. None of the patients was systemically immunocompromised. Patients were randomized in an uneven fashion to receive miconazole gel, miconazole chewing gum, or placebo. 28 patients received the gel, 96 received the gum, and 16 received placebo for 4 weeks. Response was defined as resolution of oral lesions at the end of therapy. Placebo response rate was 11.1%.*

*Reviewer's comments: In the trial by Hughes, 30% of placebo recipients progressed to develop esophageal candidiasis, compared to 8% of ketoconazole recipients, highlighting the need to treat immunocompromised patients with OPC, and the perception that placebo controlled trials of OPC in these patients is unethical.*

*The trial populations studied show substantial heterogeneity and are not comparable to HIV infected adults in the underlying level, magnitude, and duration of local and systemic immunosuppression. Resolution of OPC in patients with hematologic malignancy in the studies cited correlated with resolution of neutropenia. In addition, these patients may have chemotherapy-induced mucositis that may alter salivary function compared to HIV infected adults. Patients with denture-associated oral candidiasis have purely local factors predisposing them to the disease, without systemic immunocompromise. In addition, patients with denture associated OPC are unlikely to progress to develop esophageal candidiasis if untreated, in contrast to patients with systemic immunocompromise. Generalizing the placebo response from these populations to the HIV infected population is difficult. Medical practitioners generally believe that patients with uncontrolled HIV infection or low CD4 counts are unlikely to clear OPC spontaneously.*

*None of these trials reported severity of OPC at baseline. The trials used different duration of therapy, and assessed response differently and at different intervals.*

*Meta-analysis of the six studies listed in the table yields a point estimate for placebo response of 11.5% (95% CI 4.3, 18.7%).*



Because the mortality in the Nyst study the mortality was high (not the case with the studies submitted in this NDA), meta-analysis excluding this study yields a placebo effect estimate 13.4% (95% CI 4.1%, 22.6%). Because the Peterson and Hughes studies used a different endpoint or different interval for clinical response, a meta-analysis that further excludes these studies yields a placebo effect estimate of 11.6% (CI -0.1%, 24.1%).

Using the largest upper bound of the 95% confidence interval from these analyses 25% can be used as a conservative estimate of the placebo effect in the NI margin justification.

### 8.3.3.2 B) Estimation of Clotrimazole effect trial BA 2004/01/04

The sponsor identified six clinical trials of clotrimazole for the treatment of OPC in HIV infected patients, and two trials in patients with hematologic malignancy. The sponsor estimates clotrimazole cure rate at 70%.

This reviewer performed a Pubmed search using the term oropharyngeal candidiasis on August 6, 2009, and retrieved 775 references. The reviewer did not identify any additional trials.

**Table 22 Studies to estimate efficacy of clotrimazole troches for the treatment of OPC**

Citation	Study Design Patient Population	Rx Arms Dose Duration	N Enrolled Evaluable	Endpoint	Results	Comments
Schechtman	RDBPC	Clotrimazole	7 clot	Resolution	Placebo 16.7%	5/6

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1984	Heme malignancy	10 mg 4/d Rx until cure or progression range 2-28 days	6 placebo	of lesions EOT (timing variable)	Clotrimazole 71.4%	progressed in placebo arm  2/7 progressed in clot arm
Thamlikitkul 1988	RDB Heme malignancy	Clotrimazole 10 mg 4/d Ketoconazole solution 200 mg/d 7 days	Clot 23 Keto 22	Resolution of lesions EOT (day 7)	100% both arms	5 died in each arm  Mycologic cure d 7 Clot 64% Keto 64%
Koletar 1990	R HIV +	Clotrimazole 10 mg 4x/d Fluconazole 100mg/d 14 days	17/20 16/19	Resolution of lesions EOT (d 14)	Clot 64.7% Fluc 100%	Mycologic cure d 14 Clot 20% Fluc 75%
Redding 1992	R investigator blind HIV +	Clot 10 mg 4x/d Fluc 100 mg/d 14 days	11/11 13/13	Resolution of lesions EOT (day 14)	Clot 73% Fluc 100%	Relapse day 42 Clot 83% Fluc 40%
Pons 1993	R HIV +	Clot 10 mg 4x/d Fluc 100 mg/d 14 days	136/158 152/176	Resolution of lesions EOT (d 14)	PP Clot 85.3% Fluc 90.8%	Relapse day 42 Clot 34% Fluc 23%  Mycologic cure d 14 Clot 48% Fluc 65%
Murray 1997	R Immunocompromised (83% HIV +) 13 years or older	Clot 10 mg 4x/d Itraconazole solution 200 mg/d 14 days	162 enrolled 74 clot 75 itra	Resolution of lesions and symptoms (cure) or resolution of lesions with improved sx) EOT (d 14)	Cure + improved Clot 70% Itra 77%	Clinical and mycologic cure Clot 30% Itra 53%  Relapse d 42 Clot 60% Itra 46 %  Median t to relapse Clot 28 d Itra 31 d

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Lippiyawan 2000	R, investigator blinded  HIV +	Clot 10 mg 4x/d	15/15	Resolution of lesions and symptoms EOT (d 7)	Clot 73.3%	Relapse d 42 Clot 62.5% Itra 33.4%
		Itra solution 100 bid  7 days	12/14		Itra 66.7%	
ANDA 76- 387	RDB  HIV +	Roxane lab clotrimazole	50/95	Resolution of lesions and symptoms d 21	Sponsor analyses Roxane 47.2%	Sponsor had excluded patients with positive fungal cx on day 15 from analysis regardless of clinical status
		Mycelex clotrimazole  14 days	47/94		Mycelex 45.1%	

R: randomized  
DB: double blind  
PC: placebo control  
EOT: end of therapy

*In the publication by Koletar et al 39 patients were randomized to receive either fluconazole or clotrimazole for 14 days, and evaluated response (resolution of oral lesions) at 7 and 14 days. Resolution of lesions at day 14 in the fluconazole arm was 16/16 (100%), and in the clotrimazole arm 11/17 (64.7%). Mycologic cure at day 14 was 75% and 20% respectively.*

*In the study by Redding et al 24 HIV + patients were randomized to receive fluconazole (13 patients) or clotrimazole (11 patients) for 14 days. Cure was defined as resolution of lesions at EOT. Fluconazole cure rate was 100%, compared to clotrimazole 73%. Relapse on day 42 was 40% vs. 83% respectively.*

*In the study by Pons et al 176 HIV + patients were randomized to receive fluconazole (152 evaluable) and 158 to receive clotrimazole (136 evaluable). 52 patients were excluded from the analysis “owing to a default on patient’s part, or reasons unrelated to study drug”. Cure was defined as resolution of lesions and symptoms at EOT. Improvement was defined as resolution of lesions with minimal symptoms. At 14 days, fluconazole resulted in cure in 90.8% (138/152), and improvement in 11/152. Clotrimazole resulted in cure in 85.3% (116/159) and improvement in 12/159. Mycologic cure was 65% vs. 48%, and relapse at day 42 was 34% vs. 23%.*

*In the study by Murray et al 162 patients (82.6% were HIV infected) were randomized to receive itraconazole or clotrimazole for 14 days. 75 and 74 patients were evaluable in the clotrimazole and itraconazole arms respectively. This study used the scoring system for signs and symptoms that the sponsor used in trial BA2004/01/04. Cure was defined as resolution of lesions and symptoms. Improvement was defined as resolution of lesions with decrease in symptom score. Response was defined as cure or improvement at end of therapy. Response to itraconazole was 77%, and to clotrimazole 70%. The rate of cure alone could not be derived from the data provided in the study. Relapse rate on day 42 was 46% in the itraconazole arm (median time to relapse 31 days) vs. 60% in the clotrimazole arm (median time to relapse 28 days).*

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*In a bioequivalency study conducted in ANDA 76-387 of two preparations of clotrimazole in the treatment of OPC in HIV infected patients, response was defined by the sponsor as resolution of lesions one week after 14 day treatment course. The sponsor excluded from the analyses patients who had a positive fungal culture at day 14. The FDA disagreed with the analysis, and considered these patients evaluable, since the endpoint is purely clinical and fungal cultures do not correlate with clinical symptoms. Per FDA analysis, response rate was 74% (37/50) for the generic product, and 76.6% (36/47) for the trade name product.*

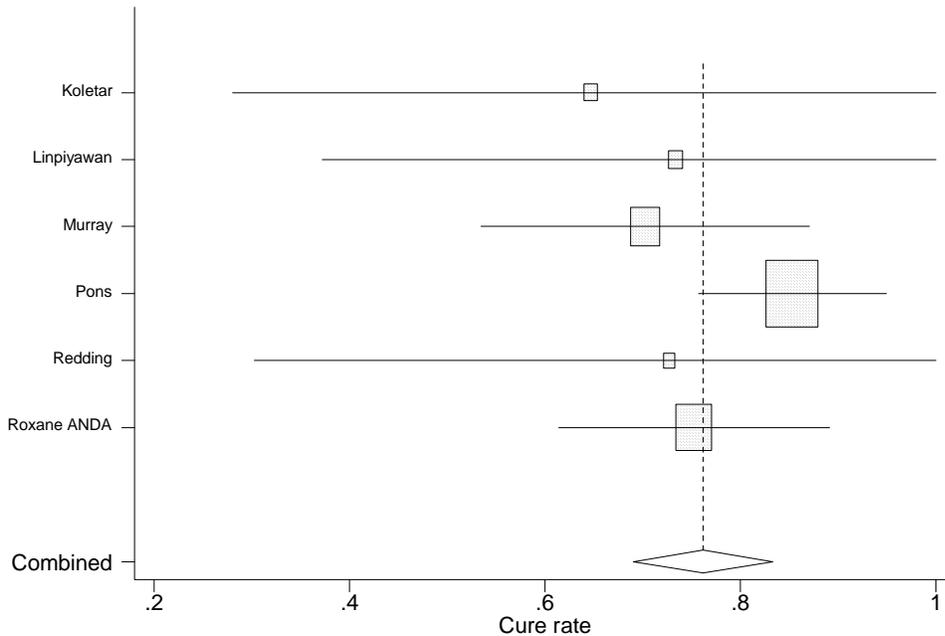
*In the study by Lippiyawan et al 29 patients were randomized to receive itraconazole or clotrimazole for 7 days. Cure was defined as resolution of lesions and resolution of symptoms at end of therapy. The response rate was 73.3% for clotrimazole vs. 66.7% for itraconazole. Relapse at 4 weeks post therapy was 62.5% vs. 33.3% respectively.*

*Two studies evaluated clotrimazole for the treatment of OPC in hematology patients. The duration of therapy in the study by Schechtman et al was not defined. The response rate in the study by Thamlikitkul et al was 100%.*

*Reviewer's comments: Many of the studies in HIV infected patients in were conducted in the era prior to the availability of highly active antiretroviral therapy. The studies used different clinical endpoints at different intervals.*

*Because the nature, magnitude and duration of immunodeficiency is different in hematology patients and HIV infected patients, and because there is enough data from the six studies conducted in HIV positive patients to estimate a clotrimazole response rate, the reviewer will exclude the results of two studies conducted in hematology patients from the meta-analysis.*

*Meta-analysis of the six studies of clotrimazole for the treatment of OPC in HIV infected adults yields a point estimate for clotrimazole treatment effect of 76.2% (95% CI 69.1%, 83.3%). Because the study by Murray used a different endpoint, excluding it from the meta-analysis yields a point estimate for clinical cure of 80.7% (95% CI 76.1%, 85.3%) using the fixed model, and a point estimate of 78.2% (CI 70.7%, 85.6%) using the random effects model.*



*The estimated cure rates and the low bounds of the confidence intervals were higher when the study by Murray was excluded rather than included in the analysis. Therefore, 70% will be used as a conservative estimate of clotrimazole cure rate.*

### 8.3.3.3 C) Calculation of the non-inferiority (NI) margin for study BA2004/01/04

The conservative estimate for clotrimazole treatment effect is 70%, and the conservative estimate for placebo effect is 25%. Treatment effect attributed to clotrimazole (M1) is therefore 45%. A non-inferiority margin of 15% preserves more than 50% of treatment effect. The reviewer agrees with the sponsor that a margin of 15% is justifiable for this study.

### 8.3.4 Study Proceedings

The trial was conducted at 30 sites across the United States, Canada, and South Africa between July 2006 and December 2007. Eligible patients were randomized in 1:1 fashion to receive active drug and placebo. Patients, investigators, and site personnel were blinded regarding which active drug was administered. The patient took the troches (containing active clotrimazole or placebo) first, and then applied the buccal tablet (containing miconazole or placebo) in the canine fossa on the upper gum in the morning. Patients could reposition the tablet if it dislocated, and could replace it if it adhered for less than 6 hours. Patients could eat and drink without restriction, but were to avoid chewing gum.

### 8.3.5 Inclusion criteria

- 18 yrs of age or older
- Clinical picture of OPC examination (thrush, erythema, mucositis) with or without associated symptoms (odynophagia, burning/soreness, xerostomia, modified taste, pharyngeal irritation)

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- Positive KOH examination of buccal swab
- Documented HIV seropositivity
- Patient on stable antiretroviral treatment for at least 2 months (or 1 month in case of treatment modification for reasons other than efficacy). Patients not on antiretroviral therapy were not to initiate therapy during antifungal treatment.
- Neutrophils  $> 750$  cells/mm<sup>3</sup>, platelet  $> 100,000$  cells/mm<sup>3</sup>
- ALT and AST  $\leq 5$  x normal
- ECOG grade less than 2
- For women of childbearing potential, use of an effective contraceptive method for at least 1 month prior to study initiation, and for the entire duration of the study
- Patient able to understand and sign consent

### 8.3.6 Exclusion criteria

- Pregnant or lactating
- Unable to understand consent or follow study protocol
- Full or partial upper dentures with an acrylic border in the canine fossa
- Systemic candidiasis or esophageal candidiasis documented by esophageal endoscopy
- Angular cheilitis only
- Received systemic antifungals within past 15 days, or local antifungals within past 7 days
- Milk allergy or known hypersensitivity to one of the components of the products
- Hereditary galactose intolerance, lactase enzyme deficiency, or glucose/galactose malabsorption
- Hepatocellular deficiency (INR  $> 1.7$ , AST and ALT  $> 5$ x normal)
- Concomitant therapy likely to interact with miconazole: antiarrhythmics (verapamil, diltiazem, propranolol, amiodarone, atenolol, metoprolol, sotalol, dofetilide, moricizine, mexiletine, disopyramide, procainamide, quinidine gluconate or sulfate, propafenone, flecainide, tocainide), anticoagulants (anti-vitamin K: acenocoumarol and warfarin), astemizole, cisapride, and phenytoin
- Receiving antibiotics at inclusion (prophylactic antibiotics used in the management of HIV infection, or treatment of tuberculosis were allowed)
- Life expectancy under 45 days

*Reviewer's comment: Inclusion and exclusion criteria are appropriate. Exclusion of patients receiving concomitant medications likely to interact with miconazole was based on the French prescribing information compendium for the oral gel.*

Patients could withdraw their consent to participate in the trial at any time. Investigators could terminate the participation of any patient in the trial early for any reason. The sponsor reserved the right to request the early withdrawal of patients who had serious protocol violations.

Reasons for early withdrawal were documented in the CRF.

### Protocol Amendments

The original protocol, dated 11 May 2006, was amended on 11 June 2007 to

- change duration of stable antiretroviral therapy to 1 month instead of 2 months for patients requiring change in antiretroviral treatment for reasons other than efficacy

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- change exclusion duration of prior systemic antifungal treatment from 1 month to 15 days
- allow inclusion of patients with stable TB being treated with anti-TB drugs
- classify partial response evaluation: partial clinical response, partial symptom response, and partial clinical/symptom response

### 8.3.7 Data Quality

The sponsor contracted an independent auditor, (b) (4), to audit six study sites: Two in the US (sites 101, 105) and four in South Africa (sites 401, 402, 405 and 413). Audit certificates were submitted with the study report.

*Reviewer’s comment: the sponsor did not provide reasons for choosing these particular sites for audit. However, sites 101 (in the US), 401, 402 and 405 (in South Africa) randomized almost 70% of the patients in the study. This reviewer selected sites 402 (randomized 21.8% patients) and 405 (randomized 19.6% of patients and reported numerically lower efficacy rates in both treatment arms compared to other sites) for DSI inspection. On October 16, 2009, the sponsor informed the FDA that on August 28, 2009 a fire at the storage facility for site 405 destroyed 35 boxes of documentation from study BA2004/01/04 including medical records and patient informed consent forms. The reviewer therefore requested inspection of site 401 (randomized 17% of patients) instead of site 405.*

*Inspection of sites 401 and 402 noted minor informed consent, protocol, recordkeeping, and drug dispensation violations. The inspector concluded that the “audited sites adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations, and that the violations identified should not have any significant impact on data integrity or subject safety. The data submitted by Bioalliance Pharma Inc. may be used in support of the indication”.*

### 8.3.8 Study Events

The study duration was up to 45 days, with five scheduled clinic visits.

**Table 23 Summary of scheduled visits – BA2004/01/04**

Visit 1	Screening
Visit 2	Randomization and treatment, day 1
Visit 3	On therapy, day 6-8
Visit 4	End of treatment, day 14-15
Visit 5	Test of cure TOC, day 17-22
Visit 6	Late post therapy, day 35-38

**Table 24 Schedule of study procedures and events - BA2004/01/04**

	Screening D -14 to 0 Visit 1	Randomization Day 1 Visit 2	Treatment (Rx) Day 6-8 Visit 3	End of Rx Day 14-15 Visit 4	Test of Cure TOC Day 17-22 Visit 5	Follow up Day 35-38 Visit 6
History	X					

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Informed consent						
Salivary gland function						
Labs	X			X		
Pregnancy test	X			X		
CD4 and viral load	X					
ECOG	X	X	X	X	X	X
Oral exam	X	X	X	X	X	X
KOH exam	X					
Fungal culture*	X		X if clinical cure or improvement		X	X if relapse
Plasma miconazole concentration			X			
Review of patient diary			X	X		
Drug accountability				X		

\*Susceptibility testing performed in cases of clinical failure.

Adapted from study report page 47

### 8.3.9 Efficacy Analysis

The primary endpoint was Clinical Cure at visit 5 (TOC visit, days 17-22). Clinical Cure was defined as complete resolution of oral lesions (oral lesions score 0) and symptoms (symptom score 0).

Oral lesions score (Murray scale):

0 = none

1 = single, localized

2 = multiple, localized

3 = extensive, confluent

Symptoms score (soreness/burning)

0 = absent

1 = mild

2 = moderate

3 = severe

Secondary endpoints were:

- Clinical Cure at day 7 (visit 3, days 6-8)
- Clinical Success (clinical cure or clinical improvement) at day 7 and TOC visit.
  - Clinical Cure: complete resolution of lesions and symptoms: lesions score 0 and symptom score 0.
  - Clinical Improvement: no visible lesions (lesions score 0), and minimal symptoms (symptoms score less than 2)
- Partial Response at TOC, defined as a decrease in the oral lesions score by  $\geq 1$  level and a decrease in the symptoms score by  $\geq 1$  level
- Mycologic cure (negative fungal cultures) at TOC visit
- Clinical and mycologic cure at TOC visit
- Time to relapse (the difference in days between TOC visit and date of relapse)

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- Rate of relapse on day 35 (Relapse was defined as an increase lesions or symptoms in patients who had clinical cure or clinical improvement)

Local tolerability was evaluated on day 1, day 7, and EOT using

- gingival inflammation index (score 0 = no inflammation, 3 = severe inflammation)
- questionnaire to evaluate oral comfort (gum pain when brushing, alteration in food taste, taste when not eating, and dry mouth on a scale of 0-3)
- patient diary to rate oral discomfort at application site

Compliance was assessed from the number of tablets returned by the patient at EOT visit (visit 4).

Percent compliance was calculated as  $\{1 - \{(P-A)/A\}\} \times 100$ , where

P = the number of tablets scheduled = number of days on study x dosing regimen

A = the number of tablets actually taken = number of tablets dispensed – number of tablets returned

Patients with compliance  $\geq 80\%$  were considered compliant.

### 8.3.9.1 Patient Disposition

Thirty sites across the United States, Canada, and South Africa enrolled 697 patients between July 2006 and December 2007. Of these, 119 were not eligible for randomization (reasons not specified).

578 patients were randomized, 291 to receive miconazole buccal tablet (MBT) 50 mg daily, and 287 to receive clotrimazole troches 10 mg 5 times daily.

The ITT population included all randomized patients who took at least one dose of study medication. One patient in the MBT group reported losing all his medications, and never started therapy. The ITT population included 290 in the MBT group and 287 in the clotrimazole group.

The PP population included all patients in the ITT population who

- did not have a major protocol violation
- had a positive fungal culture
- completed 10 days of therapy
- had an efficacy evaluation at the TOC visit
- were compliant within 71.4% and 120% range (please refer to Safety analysis/drug exposure for calculation of compliance)
- had not taken forbidden medications

The PP population included 240 patients in the MBT arm, and 236 in the clotrimazole arm.

**Table 25 Patients excluded from PP– BA2004/01/04**

	MBT N = 290	Clotrimazole N = 287
Negative fungal culture	0	4 (1.4%)
Compliance < 71.4% or >120%	26 (8.9%)	19 (6.6%)
Received less than 10 days of drug	9 (3.1%)	15 (5.2%)
Not on stable antiretrovirals	2 (0.7%)	5 (1.7%)

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TOC visit evaluation missing	13 (4.5%)	8 (2.8%)
Total	50 (17.2%)	51 (17.8%)

Derived from study report listing 16.2.2.

If a patient had more than one reason for exclusion, this reviewer used the following hierarchy for classification: less than 10 days on drug > compliance not between 71.4% and 120% > TOC evaluation missing > negative fungal culture > less than 2 months on stable antiretrovirals

Fifty patients were withdrawn from the study, 23 from the miconazole group, and 27 from the clotrimazole group. Reasons for study discontinuation are listed in the table below.

**Table 26 Reasons for study discontinuation – study BA2004/01/04**

	MBT N = 290	Clot N = 287
Discontinued study	23 (7.9%)	27 (9.4%)
Inclusion criteria not satisfied	0	2 (0.7%)
Noncompliance or protocol deviation	7 (2.4%)	4 (1.4%)
Consent withdrawn	0	2 (0.7%)
Adverse event	2 (0.7%)	5 (1.7%)
Death	1 (0.3%)	4 (1.4%)
Lost to follow up	3 (1.0%)	6 (2.1%)
Other reason (not further specified)	10 (3.4%)	4 (1.4%)

Derived from study report listing 16.2.1

*Reviewer’s comment: the number of patients discontinued from the study and the number of patients excluded from PPpopulation were balanced between the two treatment arms. There were numerically more patients discontinued from the MBT treatment arm for “other” reasons that were not specified in the study report or the dataset.*

### 8.3.9.2 Patient Demographics

**Table 27 Patient Demographics – ITT - BA2004/01/04**

	MBT N = 290		Clotrimazole N = 287	
Age (mean), years	37.5		36.5	
< 65	286	98.6%	286	99.7%
≥ 65	4	1.4%	1	0.3%
Gender				
Male	117	40.3%	119	41.5%
Female	173	59.7%	168	58.5%
Race				
White/Caucasian	40	13.8%	37	12.9%
Black	232	80%	226	78.7%

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Hispanic	9	3.1%	10	3.5%
Other	9	3.1%	14	4.9%
Country				
United States	67	23.1%	62	21.6%
Canada	3	1%	3	1%
South Africa	220	75.9%	222	77.4%

Adapted from study report pages 61-62, and derived from datasets

**Table 28 Patient Demographics – PP - BA2004/01/04**

	MBT N = 240		Clotrimazole N = 236	
Age				
< 65	236	98.3%	235	99.6%
≥ 65	4	1.7%	1	0.4%
Gender				
Male	92	38.3%	92	39.0%
Female	148	61.7%	144	61.0%
Race				
White/Caucasian	34	14.2%	29	12.3%
Black	192	80%	186	78.8%
Hispanic	7	2.9%	9	3.8%
Other	7	2.9%	12	5.1%
Country				
United States	53	22.1%	50	21.2%
Canada	3	1.2%	2	0.8%
South Africa	184	76.6%	184	78.0%

Derived from datasets

*Reviewer’s comment: Because few patients were enrolled in Canada, and Canada and the US have similar HIV population epidemiologic characteristics, this reviewer will combine the demographic data obtained from US and Canada.*

*The two treatment groups were balanced as to age in the ITT and PP populations. 99.1% of patients (572/577) were younger than 65 years of age, consistent with the epidemiology of HIV infection.*

*The two treatment groups were balanced as to race and gender. However, within each treatment group, there was country variability. In the ITT population, all the white patients except one (76/77, 98.7%) and all the Hispanic patients were enrolled in North America, whereas 421/458 (91.9%) of black patients were enrolled in South Africa. This is consistent with the racial profile of the populations of North America and South Africa,*

**Table 29 Patient distribution by country and race – ITT – BA2004/01/04**

	White N = 77		Black N = 458	
	MBT	Clotrimazole	MBT	Clotrimazole

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	40	37	232	226
North America	40 (51.9%)	36 (46.8%)	19 (4.1%)	18 (3.9%)
South Africa	0	1 (0.3%)	213 (46.5%)	208 (45.6%)

Derived from datasets

**Table 30 Patient distribution by country and race – PP – BA2004/01/04**

	White N 63		Black N 378	
	MBT 34	Clotrimazole 29	MBT 192	Clotrimazole 186
North America	34 (100%)	29 (100%)	14 (7.3%)	14 (7.5%)
South Africa	0	0	178 (92.7%)	172 (92.5%)

Derived from datasets

94.4% (322/341) of females were enrolled in South Africa, where as males were enrolled equally between North America (46.5%) and South Africa (53.5%). 82.4% (112/136) of subjects enrolled in North America were males, consistent with the epidemiology of HIV infection in North America. 72.2% (322/446) of subjects enrolled in South Africa were females. This is consistent with the epidemiology of HIV infection in South Africa where HIV infected females outnumber HIV infected males by a ratio of 1.7, and a higher number of women seek HIV related care than men<sup>13, 14</sup>.

**Table 31 Patient distribution by country of origin and gender – ITT BA2004/01/04**

	Males N = 236		Females N = 341	
	MBT N = 117	Clot N = 119	MBT N = 173	Clot N = 168
North America	58 (49.6%)	54 (45.4%)	8 (4.6%)	11 (6.5%)
South Africa	59 (50.4%)	65 (54.6%)	165 (95.4%)	157 (93.5%)

Derived from datasets

**Table 32 Patient distribution by Country of origin and gender – PP BA2004/01/04**

	Males N 184		Females 292	
	MBT 92	Clot 92	MBT 148	Clot 144
North America	51 (55.4%)	41 (44.6%)	5 (3.4%)	11 (7.6%)
South Africa	41 (44.6%)	51 (55.4%)	143 (96.6%)	133 (92.4%)

Derived from datasets

69.2% (317/458) of black patients were females, whereas 71/77 (92%) of white patients were males.

<sup>13</sup>Kilmarx P. Global epidemiology of HIV. Current Opinion in HIV and AIDS 2009;4:240-246

<sup>14</sup> Garcia-Calleja JM et al. National population based HIV prevalence surveys in Sub-Saharan Africa: results and implications for HIV and AIDS estimates. Sex Transm Infect 2006;82(S III):64-70

**Table 33 Patient distribution by gender and race – ITT- BA2004/01/04**

	<i>White</i> N = 77		<i>Black</i> N = 458	
	<i>MBT</i> N = 40	<i>Clot</i> N = 37	<i>MBT</i> N = 232	<i>Clot</i> N = 226
<i>Males</i>	38 (95.0%)	33 (89.2%)	67 (28.9%)	74 (32.7%)
<i>Females</i>	2 (5.0%)	4 (10.8%)	165 (71.1%)	152 (67.3%)

*Derived from datasets*

**Table 34 Patient distribution by gender and race – PP - BA2004/01/04**

	<i>White</i> N 63		<i>Black</i> N 378	
	<i>MBT</i> 34	<i>Clot</i> 29	<i>MBT</i> 192	<i>Clot</i> 186
<i>Males</i>	33 (97.1%)	26 (89.6%)	50 (26.0%)	56 (30.1%)
<i>Females</i>	1 (2.9%)	3 (10.4%)	142 (74.0%)	130 (69.9%)

*Derived from datasets*

### 8.3.9.3 Patient Characteristics

**Table 35 Patient characteristics at randomization (visit 2) - ITT BA2004/01/04**

	<i>MBT</i> N = 290		<i>Clotrimazole</i> N = 287	
ECOG grade, visit 2				
0	229	79.0%	219	76.0%
1	60	20.7%	66	23.0%
2	1	0.3%	2	0.7%
Previous OPC history	48	16.6%	50	17.4%
Signs/oral lesions (at visit 2)				
0 = absent*	0		1	0.3%
1= single, localized	28	9.7%	30	10.5%
2= multiple, localized	164	56.6%	171	59.6%
3 = extensive, confluent	98	33.8%	85	29.6%
Symptoms (at visit 2)				
0 = absent	37	12.8%	35	12.2%
1 = mild	169	58.3%	168	58.5%
2 = moderate	80	27.6%	76	26.5%
3 = severe	4	1.4%	8	2.8%
Mean CD4 count	254 +/- 185 (n 143)		224 +/- 170 (n 157)	
Mean HIV viral load	119,424		116,130	

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Antiretroviral therapy	65	22.4%	83	28.9%
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Adapted from study report page 65, and derived from datasets

\*One patient's oral lesions resolved between visit 1 (screening) and visit 2 (randomization)

**Table 36 Patient Characteristics – PP population BA2004/01/04**

	MBT 240		Clotrimazole 236	
ECOG grade, visit 2				
0	188	78.3%	190	80.5%
1	51	21.3%	45	19.1%
2	1	0.4%	1	0.4%
Signs/oral lesions (at visit 2)				
0 = absent	0		0	
1= single, localized	25	10.4%	28	11.9%
2= multiple, localized	136	56.7%	142	60.1%
3 = extensive, confluent	79	32.9%	66	28.0%
Mean CD4 count	262 +/- 192		229 +/- 170	
Antiretroviral therapy	50	20.8%	69	29.2%

Derived from datasets

*Reviewer's comment:* The two treatment groups were balanced as to mean HIV viral load, ECOG functionality grade, severity of OPC at baseline, and previous history of OPC. Numerically more patients in the clotrimazole arm received antiretroviral therapy.

12-13% of patients were asymptomatic (compared to slightly more than half in study BA2002/01/03 (open trial of MBT in HIV infected adults). One patient in the Clotrimazole arm resolved OPC lesions spontaneously between screening and randomization visits.

This reviewer evaluated the distribution of patients at baseline according to receipt of concomitant medications and antibacterial agents, CD4 count, salivary gland function, Candida species isolated, and study site.

A similar percentage of patients in each treatment arm received concomitant medications and concomitant antibacterial agents. About 5% of patients in each treatment arm were receiving anti-TB therapy. The most commonly used antibacterial agent was trimethoprim/sulfamethoxazole (TMP/SMZ) for Pneumocystis prevention.

**Table 37 Patient distribution as to receipt of concomitant antibacterial agents - ITT BA2004/01/04**

	MBT N = 290		Clotrimazole N = 287	
At least one concomitant medication	236	81.4%	238	82.9%
At least one concomitant Antibacterial agent	128	44.1%	122	42.5%
TMP/SMZ	118	40.7%	114	39.7%
Anti-TB	16	5.5%	14	4.9%

Derived from datasets

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*Numerically more patients in the clotrimazole arm had a CD4 count less than 50. However, data was missing for almost 50% of patients in each treatment arm.*

**Table 38 CD4 count at randomization – ITT BA2004/01/04**

	<i>MBT</i> <i>N = 290</i>		<i>Clotrimazole</i> <i>N = 287</i>	
<i>No data</i>	<i>147</i>	<i>50.7%</i>	<i>130</i>	<i>45.3%</i>
<i>&lt; 50</i>	<i>5</i>	<i>1.7%</i>	<i>15</i>	<i>5.2%</i>
<i>50- ≤ 200</i>	<i>65</i>	<i>22.4%</i>	<i>70</i>	<i>24.4%</i>
<i>&gt; 200</i>	<i>73</i>	<i>25.2%</i>	<i>72</i>	<i>25.1%</i>

*Derived from datasets*

**Table 39 CD4 count at randomization – PP population BA2004/01/04**

	<i>MBT</i> <i>240</i>		<i>Clotrimazole</i> <i>236</i>	
<i>No data</i>	<i>97</i>	<i>40.4%</i>	<i>79</i>	<i>33.5%</i>
<i>&lt; 50</i>	<i>5</i>	<i>2.1%</i>	<i>15</i>	<i>6.4%</i>
<i>50- ≤ 200</i>	<i>65</i>	<i>27.4%</i>	<i>70</i>	<i>29.6%</i>
<i>&gt; 200</i>	<i>73</i>	<i>30.4%</i>	<i>72</i>	<i>30.5%</i>

*Derived from datasets*

*Patients were balanced as to salivary gland performance*

**Table 40 Salivary gland performance – ITT BA 2004/01/04**

	<i>MBT</i> <i>N = 290</i>	<i>Clotrimazole</i> <i>N = 287</i>
<i>Dry mouth</i>		
<i>Absent</i>	<i>77 (26.6%)</i>	<i>78 (27.2%)</i>
<i>Mild</i>	<i>133 (45.9%)</i>	<i>126 (43.9%)</i>
<i>Moderate</i>	<i>75 (25.9%)</i>	<i>78 (27.2%)</i>
<i>Severe</i>	<i>5 (1.7%)</i>	<i>5 (1.7%)</i>
<i>Have to sip liquids to swallow dry food</i>	<i>146 (50.3%)</i>	<i>134 (46.7%)</i>
<i>Mouth feels dry while eating</i>	<i>153 (52.8%)</i>	<i>149 (51.9%)</i>
<i>Difficulty swallowing any food</i>	<i>83 (28.6%)</i>	<i>79 (27.5%)</i>
<i>Amount of saliva too little</i>	<i>155 (53.4%)</i>	<i>151 (52.6%)</i>
<i>Amount of saliva too much</i>	<i>30 (10.3%)</i>	<i>35 (12.2%)</i>

*Adapted from study report page 65, and derived from datasets*

*One site in the US (site 101) and three sites in South Africa (sites 401, 402, and 405) randomized 68.3% of patients (394/577). In each study site, patients were distributed equally between treatment arms.*

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**Table 41 Patient distribution by study site - ITT BA2004/01/04**

	<i>MBT</i> N = 290		<i>Clotrimazole</i> N = 287	
101	33	11.4%	33	11.5%
401	45	15.5%	44	15.3%
402	63	21.7%	63	21.9%
405	56	19.3%	57	19.8%
Total	197	67.9%	197	68.5%
All other sites	93	32.1%	90	31.5%

Derived from datasets

**Table 42 Patient distribution by study site - PP BA2004/01/04**

	<i>MBT</i> N 240		<i>Clotrimazole</i> N 236	
101	30	12.5%	29	12.3%
401	39	16.3%	42	17.8%
402	57	23.8%	52	22.0%
405	43	17.9%	45	19.1%
Total	169	70.4%	168	71.2%
All other sites	71	29.6%	68	28.8%

Derived from datasets

Patients were balanced as to *Candida* species isolated at baseline. Around 87% of isolates in each treatment arm were *C. albicans*.

**Table 43 *Candida* species at baseline visit 1 – ITT population - BA2004/01/04**

	<i>MBT</i> 290	<i>Clot</i> 287
<i>C. albicans</i>	251 (86.6%)	250 (87.1%)
<i>C. tropicalis</i>	23 (7.9%)	15 (5.2%)
<i>C. parapsilosis</i>	6 (2.1%)	9 (3.1%)
<i>C. dublinensis</i>	3 (1.0%)	3 (1.0%)
<i>C. famata</i>	0 (0%)	1 (0.3%)
<i>C. guilliermondii</i>	3 (1.0%)	2 (0.7%)
<i>C. krusei</i>	2 (0.7%)	1 (0.3%)
<i>C. lusitaniae</i>	0 (0%)	1 (0.3%)
Negative culture	7 (2.4%)	3 (1.0%)

\*some patients had more than one species isolated

Derived from datasets

**Table 44 *Candida* species at baseline visit 1 – PP population - BA2004/01/04**

	<i>MBT</i> 240	<i>Clot</i> 236
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<i>C. albicans</i>	209 (87.1%)	211 (89.4%)
<i>C. tropicalis</i>	22 (9.2%)	12 (5.1%)
<i>C. dublinensis</i>	2 (0.8%)	3 (1.3%)
<i>C. guilliermondii</i>	3 (1.2%)	2 (0.8%)
<i>C. krusei</i>	2 (0.8%)	0 (0%)
<i>C. lusitaniae</i>	0 (0%)	1 (0.4%)
<i>C. parapsilosis</i>	6 (2.4%)	8 (3.2%)

Derived from datasets

In the miconazole group, the MIC<sub>90</sub> of miconazole ranged between 0.002 and 1. In the clotrimazole group, the MIC<sub>90</sub> of clotrimazole ranged between 0.001 and 0.5.

**Table 45 Distribution of miconazole MIC at baseline visit in patients who received miconazole tablet – ITT**

MIC 90 $\mu\text{g/mL}$	MBT N = 290
0.002	2 (0.7%)
0.004	1 (0.3%)
0.008	75 (25.8%)
0.015	100 (34.5%)
0.03	61 (21.3%)
0.06	15 (5.2%)
0.12	10 (3.5%)
0.25	10 (3.5%)
0.5	6 (2.1%)
1	5 (1.7%)
Missing data	5 (1.7%)

Derived from dataset

**Table 46 Distribution of Clotrimazole MIC at baseline in patients who received clotrimazole**

MIC 90 $\mu\text{g/mL}$	Clotrimazole N = 287
0.001	1 (0.3%)
0.002	8 (2.8%)
0.004	81 (28.2%)
0.008	137 (47.7%)
0.015	28 (9.8%)
0.03	15 (5.2%)
0.06	5 (1.7%)
0.12	2 (0.7%)
0.25	4 (1.4%)
0.5	1 (0.3%)
Missing data	5 (1.6%)

Derived from datasets

### 8.3.9.4 Primary endpoint:

The primary endpoint was Clinical Cure (complete resolution of oral lesions and symptoms) at day 17-22 (visit 5 – TOC).

In the ITT population, 60.7 % (176/290) of patients treated with MBT were cured compared to 65.2% (187/287) of patients treated with clotrimazole troches. The difference in clinical cure was -4.5% (95% confidence interval -12.4, 3.4%).

In the PP population, the cure rates were 68.3% in the MBT group, and 74.2% in the clotrimazole group (difference -5.9%, 95% CI -14, 2.2%).

**Table 47 Clinical cure at TOC visit– BA2004/01/04**

	MBT N = 290	Clotrimazole N = 287	Difference 95% CI
Clinical cure at TOC, ITT	176 (60.7%)	187 (65.2%)	-4.5% (-12.4%, 3.4%)
Clinical cure at TOC, PP	164 (68.3%)	175 (74.2%)	-5.9% (-14.0%, 2.2%)

Adapted from study report pages 68, and derived from datasets

*Reviewer’s comments: The lower bound of the 95% CI for the difference in cure rates between MBT and clotrimazole troches in the ITT and PP populations was within the protocol-defined NI margin of 15%. MBT is non-inferior to clotrimazole as defined.*

*The clinical cure rate in the clotrimazole arm is similar to the cure rate reported in the literature in HIV infected patients (please refer to NI margin justification).*

#### 8.3.9.4.1 Clinical Cure by age

**Table 48 Clinical Cure by age at TOC visit - BA2004/01/04**

		MBT		Clotrimazole	
ITT	≥65 years	1/4	25%	1/1	100%
	< 65 years	175/286	61.2%	186/286	65.0%
PP	≥65 years	1/4	25%	1/1	100%
	< 65 years	163/236	69.1%	174/235	74.0%

Derived from datasets

*Reviewer’s comments: In the ITT and PP populations, the cure rate among patients younger than 65 years of age was similar in the two treatment arms. There were too few patients older than 65 years of age to allow any conclusions regarding the comparative efficacy of the two treatments in older patients.*

**Table 49 Clinical Cure by gender TOC visit - BA2004/01/04**

		MBT		Clotrimazole	
ITT	Males	63/117	53.8%	72/119	60.5%
	Females	113/173	65.3%	115/168	68.5%
PP	Males	56/92	60.9%	64/92	69.6%
	Females	108/148	73%	111/144	77.1%

*Derived from datasets*

*Reviewer’s comments: Clinical cure was numerically lower in males who received the buccal tablet compared to males who received clotrimazole. In addition, within each treatment arm, males had a numerically lower cure rate compared to females.*

*Factors that theoretically may unfavorably influence cure rate include a lower CD4 count, receipt of concomitant antibacterial agents, increased severity of OPC at baseline, more debilitated state (higher ECOG grade) and non-receipt of antiretroviral therapy. None of these factors explained the lower response in males. These factors were similarly distributed in males who received MBT compared to males who received clotrimazole. Males and females had similar mean CD4 counts, males were more likely to receive antiretroviral therapy, more likely to have mild OPC (lesion score 1), more likely to have a lower ECOG score, and less likely to receive concomitant medications than females.*

**Table 50 Patient distribution by gender and receipt of antiretroviral therapy, severity of oral lesions at baseline, mean CD4 count, receipt of concomitant medications, and ECOG – ITT- BA2004/01/04**

	Males		Females	
	MBT N = 117	Clot N = 119	MBT N = 173	Clot N = 168
<i>On antiretrovirals</i>	45 (38.5%)	45 (37.8%)	20 (11.6%)	38 (22.6%)
<i>Oral lesions score</i>				
1	26 (22.2%)	21 (17.6%)	11 (6.4%)	15 (8.9%)
2	57 (48.7%)	66 (55.5%)	100 (57.8%)	104 (61.9%)
3	34 (29.1%)	32 (26.9%)	62 (35.8%)	49 (29.1%)
<i>Mean CD4 count</i>	246	192	260	246
<i>At least one concomitant med</i>	90 (76.9%)	87(73.1%)	146 (84.4%)	151 (89.9%)
<i>ECOG</i>				
0	99 (84.6%)	93 (78.1%)	130 (75.1%)	126 (75.0%)
1	18 (15.4%)	25 (21.0%)	42 (24.3%)	41 (24.4%)
2	0	1 (0.8%)	1 (0.6%)	1 (0.6%)

*Derived from datasets*

**8.3.9.4.3 Cure rate by race**

**Table 51 Clinical Cure by race at TOC visit - BA2004/01/04**

		MBT		Clotrimazole	
ITT	White	24/40	60.0%	28/37	75.7%
	Black	140/232	60.3%	143/226	63.3%
	Hispanic and other	12/18	66.7%	16/24	66.7%
PP	White	24/34	70.6%	23/29	79.3%
	Black	130/192	67.7%	136/186	73.1%
	Hispanic and other	10/14	71.4%	16/21	76.2%

Derived from datasets

*Reviewer's comments: In both the ITT and PP populations, white patients who received clotrimazole had a numerically higher cure rate compared to white patients who received MBT, or to black patients who received either treatment.*

*Similarly, patients from the US who received clotrimazole had a numerically higher cure rate compared to patients from the US who received MBT, or patients from South Africa who received either treatment. As already noted, male patients who received clotrimazole had numerically higher cure rate compared to males who received MBT.*

**Table 52 Clinical Cure by country at TOC visit - BA2004/01/04**

	Country	MBT		Clotrimazole	
ITT	US	41/67	61.2%	47/62	75.8%
	SA	133/220	60.5%	138/222	62.2%
	Canada	2/3	66.6%	2/3	66.6%
PP	US	37/53	69.8%	41/50	82.0%
	SA	125/184	67.9%	133/184	72.3%
	Canada	2/2	100%	1/3	33.3%

Derived from datasets

*The country, gender, and race effects are related. The numerically higher cure rate among US patients who received clotrimazole mirrors the higher cure rate among white patients who received clotrimazole and reflects the fact that almost all the white patients were enrolled in the US. In addition, males were more likely to have been enrolled in the US. (Please refer to demography)*

*Patients from the US were five times more likely to be receiving antiretroviral therapy, more likely to have less severe OPC and to be more functional (lower ECOG grade) compared to patients from South Africa. In addition, US patients who received clotrimazole were more likely to be on antiretroviral therapy, to have less severe OPC and lower ECOG score compared to US patients who received MBT or South African patients who received either treatment.*

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**Table 53 Patient distribution as to country and receipt of antiretrovirals – ITT BA2004/01/04**

	US		South Africa	
	MBT N = 67	Clot N = 62	MBT N = 220	Clot N = 222
<i>On antiretrovirals</i>	42 (62.7%)	47 (75.8%)	22 (10%)	34 (15.3%)

*Derived from datasets*

**Table 54 Distribution Race and antiretrovirals – ITT BA2004/01/04**

	White		Black	
	MBT N = 40	Clot N = 37	MBT N = 232	Clot N = 226
<i>On antiretrovirals</i>	27 (67.5%)	28 (75.7%)	33 (14.2%)	46 (20.4%)

*Derived from datasets*

**Table 55 OPC Severity and ECOG by country at baseline - ITT BA2004/01/04**

	US		South Africa	
	MBT N = 67	Clot N = 62	MBT N = 220	Clot N = 222
<i>OPC severity</i>				
Score 0	0	1 (1.6%)	0	0
Score 1	21 (31.3%)	19 (30.6%)	6 (2.7%)	10 (4.5%)
Score 2	40 (59.7%)	40 (64.5%)	123 (55.9%)	129 (58.1%)
Score 3	6 (9.0%)	2 (3.2%)	91 (41.4%)	83 (37.4%)
<i>ECOG</i>				
Grade 0	63 (94.0%)	54 (87.1%)	163 (74.1%)	163 (73.4%)
Grade 1	4 (6.0%)	7 (11.3%)	56 (25.5%)	58 (26.1%)
Grade 2	0	1 (1.6%)	1 (0.4%)	1 (0.4%)

*Derived from datasets*

### 8.3.9.5 Exploratory efficacy evaluation

The reviewer evaluated the effect of ECOG grade, CD4 count, severity of OPC at baseline, salivary gland function, receipt of antiretroviral therapy, study site, *Candida* species isolated at baseline, *Candida* MIC, and duration of adhesion on the cure rate.

#### 8.3.9.5.1 Cure by ECOG grade

*Cure was similar in both treatment arms in patients with the same ECOG grade. However, patients with a higher ECOG grade (lower patient functional state), had a numerically lower cure rate compared to patients with lower ECOG grade, indicating lower response to local therapy in more debilitated patients.,*

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**Table 56 Clinical Cure by ECOG - BA2004/01/04**

		MBT		Clot	
ITT	ECOG 0	150/229	65.5%	157/219	71.7%
	1	25/60	41.7%	30/66	45.5%
	2	1/1	100%	0/2	0
PP	ECOG 0	139/188	73.9%	147/190	77.4%
	ECOG 1	25/51	49.0%	28/45	62.2%
	2	0/1	0	0/1	0

*Derived from datasets*

### 8.3.9.5.2 Cure by CD4 count at baseline

*CD4 count at baseline was missing for almost half the patient in either treatment arm (please refer to demographics). Cure was similar in both treatment arms in patients in the same CD4 category. However, patients with CD4 counts < 50 had a numerically lower cure rate compared to patients with higher CD4 counts.*

**Table 57 Clinical cure by CD4 - BA2004/01/04**

	CD4 count	MBT		Clot	
ITT	< 50	2/5	40.0%	8/15	53.3%
	50 – 200	41/65	63.1%	49/70	70.0%
	> 200	45/73	61.6%	49/72	68.0%
PP	< 50	2/5	40.0%	7/15	46.7%
	50 – 200	37/65	56.9%	44/70	62.9%
	> 200	42/73	57.5%	48/72	66.7%

*Derived from datasets*

### 8.3.9.5.3 Cure by severity of OPC at baseline

*The cure rate was similar in patients with moderate disease (score 2), numerically higher in patients with mild disease who received clotrimazole, and numerically higher in patients with severe disease who received MBT. The higher rate of cure in patients with mild disease who received clotrimazole mirrors the numerically higher cure rate observed in male, white and US patients who received clotrimazole.*

*Patients with severe baseline OPC lesions (score 3) had numerically lower cure rate compared to patients with mild or moderate OPC (scores 1 and 2).*

**Table 58 Clinical cure by severity at randomization – population BA2004/01/04**

		MBT		Clotrimazole	
	Score 0	0/0		1/1	

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ITT	Score 1	19/28	67.9 %	29/30	96.6%
	Score 2	102/164	62.2%	116/171	67.8%
	Score 3	55/98	56.1%	41/85	48.2%
	Total	176/290	60.7%	187/287	65.2%
PP	Score 0	0/0		0/0	
	Score 1	18/25	72.0 %	27/28	96.4%
	Score 2	97/136	71.3%	110/142	77.5%
	Score 3	49/79	62.0%	38/66	57.6%
	Total	164/240	68.3%	175/236	74.2%

Derived from datasets

#### 8.3.9.5.4 Clinical cure by receipt of antiretroviral therapy (ART)

*In patients receiving anti-retroviral therapy, clotrimazole had a numerically higher cure rate. The cure rate was similar in patients not receiving anti-retroviral therapy.*

*In the MBT treatment group, cure rate was similar in patients who were receiving antiretroviral therapy, and patients who were not. In the clotrimazole treatment group, cure rate was numerically higher among patients who were receiving antiretroviral therapy.*

*The higher response in patients who were receiving clotrimazole and anti-retroviral therapy is reflective of country, gender and race differences already noted.*

**Table 59 Clinical cure by ART - BA2004/01/04**

	Receiving Antiretrovirals	MBT		Clotrimazole	
ITT	Yes	40/65	61.5%	63/83	75.9 %
	No	136/225	60.4%	124/204	60.8%
PP	Yes	33/50	66%	57/69	82.6%
	No	131/190	68.9%	118/167	70.6%

Derived from datasets

#### 8.3.9.5.5 Cure by salivary gland function at baseline

*Cure rate was numerically higher in patients who received clotrimazole and were without dry mouth at baseline. In both treatment arms, patients with dry mouth at baseline had a lower cure compared to patients without dry mouth.*

**Table 60 Cure by salivary gland function at baseline – ITT- BA2004/01/04**

	MBT N = 290	Clotrimazole N = 287
Dry mouth at baseline		

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<i>Absent</i>	51/77 (66.2%)	56/78 (71.8%)
<i>Mild</i>	82/133(61.7%)	83/126 (65.9%)
<i>Moderate</i>	38/75 (50.7%)	45/78 (57.7%)
<i>Severe</i>	5/5 (100%)	3/5 (60%)

Derived from datasets

### 8.3.9.5.6 Cure by study site

Patients at Site 405 (in South Africa) had a numerically lower response to either treatment compared to patients at other sites. Patients at site 405 were more likely to have severe OPC at baseline (severity score 3), and less likely to be receiving antiretroviral therapy compared to patients at other sites. ECOG grade and salivary gland function did not explain the lower response in patients at site 405.

**Table 61 Cure at TOC by site - BA2004/01/04**

		<i>MBT</i>		<i>Clotrimazole</i>	
ITT	<i>Site 101 (US)</i>	23/33	69.7%	25/33	75.8%
	<i>Site 401 (SA)</i>	30/45	66.7%	32/44	72.7%
	<i>Site 402 (SA)</i>	40/63	63.5%	41/63	65.1%
	<i>Site 405 (SA)</i>	31/56	55.4%	29/57	50.9%
	<i>All other sites</i>	52/93	55.9%	60/90	66.7%
	<i>Overall</i>	176/290	60.7%	187/287	65.2%
PP	<i>Site 101</i>	23/30	76.7%	23/29	79.3%
	<i>Site 401</i>	29/39	74.4%	32/42	76.2%
	<i>Site 402</i>	39/57	68.4%	40/52	76.9%
	<i>Site 405</i>	28/43	65.1%	27/45	60.0%
	<i>All other sites</i>	45/71	63.4%	53/68	77.9%
	<i>Overall</i>	164/240	68.3%	175/236	74.2%

Derived from datasets

**Table 62 Patients with OPC severity score 3 at largest study sites - ITT BA2004/01/04**

	<i>MBT</i>	<i>Clot</i>
<i>Site 101</i>	0	0
<i>Site 401</i>	29/45 (64.4%)	26/44 (59.1%)
<i>Site 402</i>	13/63 (20.6%)	16/63 (25.4%)
<i>Site 405</i>	32/56 (57.1%)	27/57 (47.4%)

Derived from datasets

**Table 63 Patients receiving antiretrovirals by site (largest study sites) - ITT BA2004/01/04**

	<i>MBT</i>	<i>Clot</i>
<i>Site 101</i>	23/33 (69.7%)	28/33 (84.4%)

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Site 401	0/45 (0%)	6/44 (13.6%)
Site 402	12/63 (19.0%)	11/63 (17.5%)
Site 405	9/56 (16.1%)	9/57 (15.8%)

Derived from datasets

**Table 64 ECOG by site (- ITT BA2004/01/04)**

	<i>MBT</i>	<i>Clot</i>
<i>Site 101</i>		
<i>ECOG 0</i>	31/33 (93.9%)	28/33 (94.8%)
<i>1</i>	3/33 (6.1%)	5/33 (5.2%)
<i>2</i>	0	0
<i>Site 401</i>		
<i>ECOG 0</i>	44/45 (97.8%)	43/44 (97.7%)
<i>1</i>	1/45 (2.2%)	1/44 (2.3%)
<i>2</i>	0	0
<i>Site 402</i>		
<i>ECOG 0</i>	31/63 (49.2%)	31/63 (49.2%)
<i>1</i>	32/63 (50.8%)	32/63 (50.7%)
<i>2</i>	0	0
<i>Site 405</i>		
<i>ECOG 0</i>	52/56 (92.8%)	53/57 (93.0%)
<i>1</i>	4/56 (7.2%)	3/57 (5.3%)
<i>2</i>	0	1/57 (1.7%)

Derived from datasets

**Table 65 Salivary gland function by site — ITT BA2004/01/04**

	<i>MBT</i>	<i>Clot</i>
<i>Site 101</i>		
<i>Dry mouth Absent</i>	1/33 (3.0%)	2/33 (6.1%)
<i>Mild</i>	26/33 (78.8%)	20/33 (60.6%)
<i>Moderate</i>	6/33 (18.2%)	11/33 (33.3%)
<i>Severe</i>	0	0
<i>Site 401</i>		
<i>Dry mouth Absent</i>	7/45 (15.5%)	5/44 (11.4%)
<i>Mild</i>	15/45 (33.3%)	24/44 (53.3%)
<i>Moderate</i>	20/45 (44.4%)	14/44 (31.8%)
<i>Severe</i>	3/45 (6.7%)	1/44 (2.3%)
<i>Site 402</i>		
<i>Dry mouth Absent</i>	20/63 (31.7%)	27/63 (42.9%)
<i>Mild</i>	24/63 (38.1%)	17/63 (27.0%)
<i>Moderate</i>	19/63 (30.2%)	19/63 (30.1%)
<i>Severe</i>	0	0
<i>Site 405</i>		
<i>Dry mouth Absent</i>	13/56 (23.2%)	11/57 (19.3%)
<i>Mild</i>	35/56 (62.5%)	33/57 (57.9%)

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Moderate	8/56 (14.3%)	1/573 (22.8%)
Severe	0	0

Derived from datasets

### 8.3.9.5.7 Cure by MIC

Miconazole MIC did not correlate with clinical cure in patients who received MBT (Rsquare 0.0119). Similarly, Clotrimazole MIC did not correlate with clinical cure in patients who received clotrimazole (Rsquare 0.0096).

### 8.3.9.5.8 Cure by Candida species isolated at baseline

Clinical Cure rate in patients who had *Candida albicans* isolated at baseline was lower than cure rate in patients who had *C. tropicalis* isolated at baseline. The number of isolates of other *Candida* species was too small to allow any meaningful conclusions. None of 10 patients with negative cultures at baseline achieved clinical cure. Clinical cure rate for each *Candida* species was similar between the two treatment arms.

**Table 66 Clinical cure by *Candida* species isolated at baseline – ITT – BA 2004/01/04**

	MBT 290	Clotrimazole 287
<i>C. albicans</i>	162/251 (64.5%)	173/250 (69.2%)
<i>C. tropicalis</i>	19/23 (82.6%)	11/15 (73.3%)
<i>C. dublinensis</i>	1/3 (33.3%)	3/3 (100%)
<i>C. famata</i>	0 (0%)	0/1 (0%)
<i>C. guilliermondii</i>	3/3 (100%)	1/2 (50%)
<i>C. krusei</i>	1/2 (100%)	1/1 (100%)
<i>C. lusitaniae</i>	0	1/1 (100%)
<i>C. parapsilosis</i>	6/6 (100%)	8/9 (88.9%)
No yeast isolated at baseline	0/7 (0%)	0/3 (0%)

Derived from datasets

Some patients had more than one species isolated

**Table 67 Clinical cure by *Candida* species - PP - BA 2004/01/04**

	MBT 240	Clotrimazole N 236
<i>C. albicans</i>	147/209 (70.3%)	163/211 (77.3%)
<i>C. tropicalis</i>	19/22 (86.4%)	9/12 (75.0%)
<i>C. parapsilosis</i>	6/6 (100%)	6/8 (75%)
<i>C. dublinensis</i>	1/2 (50%)	3/3 (100%)
<i>C. guilliermondii</i>	3/3 (50%)	1/3 (33.3%)
<i>C. krusei</i>	1/2 (50%)	0/0

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<i>C. lusitaniae</i>	0/0	0/1 (50%)
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Derived from datasets

Some patients had more than one species isolated

### 8.3.9.5.9 Clinical Cure by duration of adhesion

*Duration of adhesion did not correlate with clinical cure (Rsquare 0.0056). However, around 91% of the tablets adhered for at least 6 hours (please refer to safety/drug exposure section). The poor correlation between adhesion time and response indicates that adherence for longer than 6 hours may not provide additional clinical benefit.*

### 8.3.9.6 Secondary efficacy endpoints

The secondary endpoints were Clinical Cure at day 7, Clinical Success (cure or improvement of lesions and symptoms) at day 7 and TOC visit, partial response (decrease of lesions by  $\geq 1$  point, or decrease of symptoms by  $\geq 1$  point) at TOC visit, relapse at day 35, and mycologic cure at TOC visit.

**Table 68 Secondary endpoints - ITT BA2004/01/04**

	MBT N = 290		Clotrimazole N = 287	
Clinical cure at day 7	67	(23.1%)	71	(24.1%)
Clinical success at day 7	92	(31.7%)	89	(31%)
Clinical success at TOC visit	188	(64.8%)	199	(69.3%)
Partial response at day 7	139	(48.0%)	140	(48.8%)
Partial response at TOC visit	67	(23.1%)	51	(17.8%)
Mycologic cure at TOC visit	79	(27.2%)	71	(24.7%)
Relapse on day 35	51	(27.9%)	53	(26.9%)
Mean Time to relapse (days)	16.0		15.2	

Adapted from study report page 68-75, and derived from datasets

**Table 69 Secondary endpoints - PP BA2004/01/04**

	MBT N 240		Clot N 236	
Clinical cure at day 7	60	25.0%	63	26.7%
Clinical success at day 7	82	34.2%	78	33.1%
Clinical success at TOC visit	173	72.1%	185	78.4%
Partial response day 7	120	(50%)	123	(42.9%)
Partial response TOC visit	55	(22.9%)	44	(18.6%)
Mycologic Cure at TOC visit	73	30.4%	64	27.1%
Relapse on day 35	45	26.8%	49	26.6%
Mean time to relapse (days)	15.7		16.0	

Derived from datasets

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*Reviewer's comments: Clinical cure at day 7 was similar in the two treatment arms, indicating that the rapidity of response between the two treatments was similar. Clinical success (cure or improvement) on day 7 or TOC visit was also similar between the two treatment arms.*

*Similar to clinical cure at TOC visit, males, patients from the US, and white patients who received clotrimazole had a numerically higher clinical success rate.*

**Table 70 Clinical success at TOC by age, gender, country, and race –BA2004/01/04**

		MBT		Clotrimazole	
ITT	Males	67	57.3%	74	62.2%
	Females	121	69.9%	125	74.4%
	> = 65	1/4	25%	1/1	100%
	< 65	187/286	65.4%	198/286	69.2%
	US	44/67	65.7%	49/62	79.0%
	SA	143/220	65.0%	149/222	67.2%
	Canada	2/3	66.6%	2/3	66.6%
	White	25/40	62.5%	28/37	75.7%
	Black	150/232	64.7%	155/226	68.6%
	Hispanic	9/9	100%	8/10	80.0%
Other	4/9	44.4%	8/14	57.1%	
PP	Males	60/92	65.2%	66/92	71.7%
	Females	113/148	76.4%	119/144	82.6%
	> = 65	1/4	25.0%	1/1	100%
	< 65	172/236	72.9%	184/235	78.3%
	US	40/53	75.5%	43/50	86.0%
	SA	131/184	71.2%	141/184	76.6%
	Canada	2/2	100%	1/3	33.3%
	White	25/34	73.5%	23/29	79.3%
	Black	137/192	71.4%	146/186	78.5%
	Hispanic	7/7	100%	8/9	88.9%
Other	4/7	57.1%	8/12	66.6%	

Derived from datasets

*Rate of relapse at day 35 (3 weeks post-therapy) was similar between the two treatment arms (around 27%). Time to relapse was also similar between the two treatment arms (around 16 days). The relapse rate reported in the literature for HIV infected patients treated with clotrimazole is 40 – 50%. The relapse rate in either treatment arm in this study is higher than the rate reported for fluconazole (around 20%)<sup>15</sup>.*

*Mycologic cure occurred in 25-27% of patients in the ITT population and was similar between the treatment arms. The mycologic cure reported in the literature for clotrimazole is 20 to 48%<sup>15</sup>. Around 20% of patients in each arm achieved clinical and mycologic cure. Around 6% of patients in each*

<sup>15</sup> Darouiche RO. Oropharyngeal and esophageal candidiasis in immunocompromised patients: Treatment issues. Clin Infect Dis 1998; 26:259.

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*treatment arm experienced mycologic eradication without clinical cure, and around 40% experienced clinical cure without mycologic eradication.*

**Table 71 Mycologic cure TOC – BA2004/01/04**

		MBT	Clotrimazole
ITT	<i>Mycologic Cure</i>	79 (27.2%)	70 (24.4%)
	<i>Clinical Cure</i>	176 (60.7%)	187 (65.2%)
	<i>Clinical and Mycologic cure</i>	61 (21%)	54 (18.8%)
	<i>Clinical cure but mycologic failure</i>	115 (39.7%)	133 (46.3%)
	<i>Mycologic cure but clinical failure</i>	18 (6.2%)	17 (5.9%)
PP	<i>Mycologic Cure</i>	73 (30.4%)	64 (27.1%)
	<i>Clinical Cure</i>	164 (68.5%)	175 (74.2%)
	<i>Clinical and Mycological cure</i>	56 (23.3%)	50 (21.2%)
	<i>Clinical cure but mycologic failure</i>	108 (45%)	125 (52.9%)
	<i>Mycologic cure but clinical failure</i>	17 (7.1%)	14 (5.9%)

*Adapted from study report page 72-74, derived from datasets*

*In both treatment arms, Mycologic cure was lower for C. albicans compared to C. tropicalis. The number of isolates of other Candida species was too low to allow any meaningful conclusions. Mycologic cure rates for each Candida species was similar between the two treatment arms.*

**Table 72 Mycologic Cure by Candida species - ITT BA2004/01/04**

	MBT N = 290	Clotrimazole N = 287
<i>C. albicans</i>	66/251 (26.3%)	56/250 (22.4%)
<i>C. tropicalis</i>	9/23 (39.1%)	6/15 (40.0%)
<i>C. parapsilosis</i>	3/6 (50.0%)	4/9 (44.4%)
<i>C. dublinensis</i>	0/3 (0%)	0/3 (0%)
<i>C. famata</i>	0 (0%)	0/1 (0%)
<i>C. guilliermondii</i>	1/3 (33.3%)	2/2 (100%)
<i>C. krusei</i>	0/2 (50.0%)	0/1 (0%)
<i>C. lusitaniae</i>	0/2 (0%)	1/1 (100%)

Derived from datasets

**Table 73 Mycologic cure by Candida species – PP - BA2004/01/04**

	MBT 240	Clotrimazole 236
<i>C. albicans</i>	60/209 (28.7%)	51/211 (24.1%)
<i>C. tropicalis</i>	9/22 (40.1%)	6/12 (50.0%)
<i>C. parapsilosis</i>	6/6 (100%)	6/8 (75%)
<i>C. dublinensis</i>	0/2	0/3
<i>C. famata</i>	0	0/1

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<i>C. guilliermondii</i>	1/3 (33.3%)	2/2 (100%)
<i>C. krusei</i>	0/2 (0%)	0 (0%)
<i>C. lusitaniae</i>	0	1/1

Derived from datasets

Resistance to miconazole or to clotrimazole did not develop during therapy.

**Table 74 Distribution of miconazole MIC at baseline and TOC in patients who received miconazole tablet - ITT**

MIC90 µg/mL	At baseline 285 isolates	At TOC visit 180 isolates
0.002	2 (0.7%)	1 (0.6%)
0.004	1 (0.3%)	3 (1.7%)
0.008	75 (26.3%)	27 (15.0%)
0.015	100 (35.1%)	67 (29.4%)
0.03	61 (21.4%)	53 (29.4%)
0.06	15 (5.3%)	4 (2.2%)
0.12	10 (3.5%)	6 (3.3%)
0.25	10 (3.5%)	8 (4.4%)
0.5	6 (2.1%)	8 (4.4%)
1	5 (1.7%)	3 (1.7%)

Derived from datasets

**Table 75 Distribution of clotrimazole MIC at TOC in patients who received clotrimazole - ITT**

MIC90 µg/mL	At baseline 282 isolates	At TOC 182 isolates
0.001	1 (0.3%)	2 (1.1%)
0.002	8 (2.8%)	5 (2.7%)
0.004	81 (28.2%)	50 (27.4%)
0.008	137 (47.7%)	75 (41.2%)
0.015	28 (9.8%)	31 (17.0%)
0.03	15 (5.2%)	7 (3.8%)
0.06	5 (1.7%)	6 (3.3%)
0.12	2 (0.7%)	3 (1.6%)
0.25	4 (1.4%)	2 (1.1%)
0.5	1 (0.3%)	0
2	0	1 (0.5%)

Derived from datasets

Progression was not an endpoint. Less than 1% of patients in either treatment arm progressed to more severe oral disease or to esophageal disease.

**Table 76 Progression at TOC –BA2004/01/01**

		MBT	Clotrimazole
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ITT	Progression day 7	1/290	(0.3%)	2/287	(0.7%)
	Progression at TOC visit	2/290	(0.7%)	3/287	(1.0%)
PP	Progression day 7	0/240	(0%)	1/236	(0.4%)
	Progression TOC	2/240	(0.8%)	2/236	(0.8%)

Derived from datasets

### 8.3.10 Efficacy conclusions:

*The primary endpoint was clinical cure (resolution of signs and symptoms) on day 17-22, i.e. 3-8 days after EOT. The NI margin for this study was 15%. MBT 50 mg daily for 14 days was non-inferior to clotrimazole troches 10 mg 4 times a day for 14 days for the treatment of OPC in HIV infected individuals.*

*The study was conducted in the US, Canada, and South Africa. Around 95% of women were enrolled in South Africa, whereas men were enrolled equally in South Africa and North America. This is consistent with the epidemiology of HIV infection, which is more common in males in North America, but more common in females in Africa. In addition, women in Africa seek HIV related care more frequently compared to men. Consistent with the racial makeup of the population in the US and South Africa, the majority of black patients were enrolled in South Africa, while almost all the white patients were enrolled in the US. Patients from the United States were more functional, more likely to have less severe OPC and five times more likely to be receiving antiretroviral therapy compared to patients from South Africa, probably reflecting earlier and better access to HIV related care in the US.*

*The two treatment arms were balanced as to age, gender, race, ECOG grade, previous history of OPC, receipt of concomitant antibacterial agents, salivary gland function, severity of OPC at baseline, and Candida species isolated. Numerically more patients in the clotrimazole arm were receiving antiretroviral therapy, whereas numerically more patients in the clotrimazole arm had a CD4 count less than 50 (however, CD4 data was missing for almost half the patients).*

*Variables that correlated with numerically higher response to either treatment were higher CD4 count, lower ECOG grade, lower OPC severity score, and absence of dry mouth at baseline. The cure rate for men was numerically lower than the cure rate for women in both treatment arms. None of the above variables explained the difference, especially since men were more likely to have a lower ECOG grade, and more likely to have mild OPC compared to women.*

*Male patients, white patients, patients from the US, or patients receiving antiretroviral therapy who received Clotrimazole had a numerically higher clinical cure rate compared to their respective counterparts who received MBT. US patients were more likely to be white (almost all the white patients were enrolled in the US), male, and receiving antiretroviral therapy. In addition, white patients or US patients who received clotrimazole were more likely to have a lower ECOG grade and less severe OPC compared to black patients or South African patients.*

*The cure rate obtained for clotrimazole in this study was 65% in the ITT population and 74.2% in the PP population. This is similar to the cure rates reported in the literature, and to the lower bound of the 95% CI for clotrimazole efficacy obtained in the meta-analyses (please refer to NI margin justification section). Relapse rate at day 35 was around 27% in each treatment arm, with mean time to relapse of*

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15-16 days. The relapse rate in patients treated with clotrimazole in this trial is lower than the relapse rates reported in the literature (40-50%), possibly because most of the studies that reported relapse of OPC after clotrimazole therapy were prior to the availability of highly active anti-retroviral therapy. The relapse rates after either topical treatment in this trial is higher than the rate reported for systemic fluconazole (around 20%).

Mycologic cure occurred in 27% of patients in either treatment group, similar to the rate reported in the literature for clotrimazole. Mycologic cure did not correlate with clinical cure, consistent with literature reports for other antifungal agents in the treatment of OPC. Clinical progression of OPC was infrequent, occurring in less than 1% of patients in either treatment arm.

The correlation between tablet adhesion and clinical response was poor. Around 91% of the tablets adhered for at least 6 hours (please refer to safety/drug exposure section). The poor correlation between adhesion time and response indicates that adherence for longer than 6 hours may not provide additional clinical benefit.

In conclusion, miconazole buccal tablet once daily for 14 days is non-inferior to clotrimazole five times daily for 14 days in the treatment of OPC in HIV infected individuals as measured by resolution of oral lesions and symptoms on day 21. In addition, miconazole buccal tablet and clotrimazole result in similar mycologic cure rate, relapse rate on day 35, and time to relapse.

### 8.3.11 Safety Evaluation

The safety population included all patients who received at least one dose of the study drug. The safety population included 290 patients who received miconazole tablet and 287 who received clotrimazole troches.

#### 8.3.11.1 Drug Exposure

Compliance was calculated from the number of tablets returned by the patient at EOT visit (visit 4).

Percent compliance was calculated as  $\{1 - \{(P-A)/A\}\} \times 100$ , where

P = the number of tablets scheduled = number of days on study x dosing regimen

A = the number of tablets actually taken = number of tablets dispensed – number of tablets returned

Patients with compliance  $\geq 80\%$  were considered compliant.

**Table 77 Patient compliance – Safety population - BA2004/01/04**

	MBT N = 290	Clot N = 287
Compliance within 71.4% and 120%	253 (87.2%)	250 (87.1%)
Compliance range (mean)	28.6% - 164.3% (97.6%)	17.1% - 174.3% (95.5%)

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Tablet adhesion

In the MBT group, 76 patients replaced 216 tablets. In the clotrimazole group, 72 patients replaced 216 tablets. In each treatment arm, around 91% of tablets adhered at least 6 hours, and around two-thirds adhered at least 12 hours, and almost half adhered until bedtime.

**Table 78 Number of tablets adhering – safety population - BA2004/01/04**

	MBT N = 290	Placebo buccal tablet N = 287
Total number of buccal tablets applied	3983	3863
Adhering at least 6 hours	3617 (90.8%)	3535 (91.6%)
Adhering at least 12 hours	2641 (66.3%)	2752 (71.2%)
Adhering until bedtime	1797 (45.1%)	1917 (49.6%)
Number of tablets replaced	216 (5.4%)	216 (5.6%)
*Patients with tablets adhering at least 6 hours	282 (97.3%)	276 (96.2%)
*Patients with tablets adhering at least 12 hours	254 (87.6%)	252 (87.8%)
*Patients with tablets adhering until bedtime	229 (78.9%)	225 (78.4%)

Adapted from study report page 92 and \*derived from datasets

At visit 3, the systemic levels of miconazole were below the limit of quantification (100 ng/mL) in all 40 subjects tested.

*Reviewer’s comments: Compliance, tablet adhesion and tablet replacement were similar between the two treatment arms. The number of tablets swallowed was not provided. None of the patients who received active miconazole buccal tablet (MBT) had a serum level above 100ng/mL, the limit of detection of the assay. The low systemic level implies a low potential for drug interactions. However, drug interactions have been reported in the literature with miconazole gel (please refer to PK/PD section).*

**8.3.11.2 Adverse Events**

In the MBT group, 161 patients reported at least one AE, 158 in the treatment phase, and three in the follow up phase. Sixty-nine (69) patients reported at least one drug related AE, and 10 patients reported at least one serious AE (including five deaths). No patient developed a drug related SAE. One patient developed an AE that led to discontinuation of the study drug.

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In the clotrimazole group, 152 patients reported at least one AE, 146 in the treatment phase and six in the follow up phase. Sixty-five (65) patients reported at least one drug related AE, and nine patients reported at least one serious AE (including six deaths). No patient developed a drug related SAE, and no patient developed an AE that led to discontinuation of the study drug. One patient became pregnant during treatment.

**Table 79 Summary of Adverse Events - BA2004/01/04**

	MBT N = 290		Clot N = 287	
Patients with at least one treatment emergent AE	158	(54.5%)	146	(50.9%)
Patients with at least one Serious Adverse event (including deaths)	10	(3.4%)	9	(3.1%)
Patients with at least one Drug related AE	69	(23.8%)	65	(22.6%)
Patients with at least one Drug related SAE	0	0%	0	0%
Deaths	5	(1.7%)	6	(2.1%)
AE leading to discontinuation of drug	1	(0.3%)	0	0%
AE leading to discontinuation from study	2	(0.7%)	3	(1.0%)

Adapted from study report pages 92-93, and derived from datasets

*Reviewer's comments: Overall AE incidence was similar between the two treatment arms. However, within each treatment arm, a higher percentage of women than men experienced all causality adverse events and drug related adverse events.*

**Table 80 Distribution of AE by gender BA2004/01/04**

	Male		Female	
	MBT N = 117	Clot N = 119	MBT N = 173	Clot N = 168
Patient with at least one AE	53 (45.3%)	50 (42.0%)	105 (60.7%)	96 (57.1%)
Patients with at least one Drug related AE	21 (17.9%)	14 (11.7%)	48 (27.7%)	51 (30.3%)
Patients with Serious AE	4 (3.4%)	4 (3.4%)	6 (3.5%)	5 (3.0%)
Death	2 (1.7%)	1 (0.8%)	3 (1.7%)	5 (3.0%)

Derived from datasets

*Potential causes for the observed gender-related difference in adverse events frequency include differences in drug absorption or metabolism and differences in the severity of underlying illness or concomitant medications administered. Clotrimazole is not systemically absorbed, and none of the patients had a detectable serum miconazole level. Thus, gender related differences in systemic drug exposure are unlikely to account for the difference in AE rates between males and females. Gender related differences in severity of underlying illness and receipt of concomitant medications may explain the higher incidence of AE among women. Women were numerically more likely to have a higher ECOG grade and to be on concomitant medications compared to men. Because the majority of the women were enrolled in SA, and the majority of men were enrolled in the US, country related differences in reporting of adverse events may also explain the gender differences in AE rates.*

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**Table 81 ECOG by gender BA2004/01/04**

	<i>Male</i>		<i>Female</i>	
	<i>MBT</i> N = 117	<i>Clot</i> N = 119	<i>MBT</i> N = 173	<i>Clot</i> N = 168
<i>ECOG 0</i>	99 (84.6%)	93 (78.1%)	130 (75.1%)	126 (75.0%)
<i>1</i>	18 (15.4%)	25 (21.0%)	42 (24.3%)	41 (24.4%)
<i>2</i>	0	1 (0.8%)	1 (0.6%)	1 (0.6%)

*Derived from datasets*

**Table 82 Concomitant meds by gender BA2004/01/04**

	<i>Male</i>		<i>Female</i>	
	<i>MBT</i> N = 117	<i>Clot</i> N = 119	<i>MBT</i> N = 173	<i>Clot</i> N = 168
<i>At least one concomitant med</i>	90 (76.9%)	87(73.1%)	146 (84.4%)	151 (89.9%)

*Derived from datasets*

### 8.3.11.2.1 All causality Adverse Events

**Table 83 Treatment Emergent AEs in ≥ 2% of patients BA2004/01/04**

System Organ Class/Preferred term MedDRA version 9.1	MBT N = 290	Clot N = 287
<b>Patients with AE during treatment phase</b>	<b>158 (54.5%)</b>	<b>146 (50.9%)</b>
<b>Gastrointestinal disorders</b>	<b>75 (25.9%)</b>	<b>68 (23.7%)</b>
Diarrhea	26 (9.0%)	23 (8.0%)
Nausea	19 (6.6%)	22 (7.7%)
Vomiting	11 (3.8%)	9 (3.1%)
Abdominal pain, upper	5 (1.7%)	8 (2.8%)
Dry mouth	8 (2.8%)	5 (1.7%)
<b>Infections and infestations</b>	<b>46 (15.9%)</b>	<b>49 (17.1%)</b>
URI	6 (2.1%)	7 (2.4%)
Gastroenteritis	4 (1.4%)	8 (2.8%)
<b>Nervous system disorders</b>	<b>38 (13.1%)</b>	<b>24 (8.4%)</b>
Headache	22 (7.6%)	19 (6.6%)
ageusia	7 (2.4%)	1 (0.3%)
<b>Blood and lymphatic disorders</b>	<b>20 (6.9%)</b>	<b>24 (8.4%)</b>
Anemia	8 (2.8%)	5 (1.7%)
Lymphopenia	5 (1.7%)	6 (2.1%)
neutropenia	2 (0.7%)	6 (2.1%)
<b>General administration site</b>	<b>20 (6.9%)</b>	<b>24 (8.4%)</b>
Fatigue	8 (2.8%)	5 (1.7%)
Pain	3 (1.0%)	8 (2.8%)
<b>Respiratory/thoracic/mediastinal</b>	<b>15 (5.2%)</b>	<b>22 (7.7%)</b>
Cough	8 (2.8%)	5 (1.7%)

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Pharyngeal pain	2 (0.7%)	7 (2.4%)
<b>Investigations</b>	<b>16 (5.5%)</b>	<b>18 (6.3%)</b>
Increased GGT	3 (1%)	8 (2.8%)
<b>Skin and SC tissue</b>	<b>17 (5.9%)</b>	<b>12 (4.2%)</b>
<b>Musculoskeletal and connective tissue</b>	<b>15 (5.2%)</b>	<b>18 (6.3%)</b>

Adapted from study report page 95 and derived from datasets

*Reviewer's comments: GI disorders, infections and infestations, and nervous system disorders were the most common adverse events in each treatment arm. Ageusia was more frequent in patients who received miconazole tablet, whereas elevated GGT, pharyngeal pain, and neutropenia were more frequent in patients who received clotrimazole.*

*The frequency of each oral adverse event Preferred Term as coded in the datasets (oral discomfort, oral burning, oral pain, gingival pain, gingival swelling, gingival pruritis, tongue ulceration, mouth ulceration, glossodynia, dry mouth, toothache, ageusia, and dysgeusia) and the frequency of application site pain or discomfort were similar between the treatment arms. The frequency of all oral and application site AE was also similar between the treatment arms (35 patients in the MBT arm (12.1%) compared to 27 patients (9.4%) in the clotrimazole arm).*

#### **8.3.11.2.2 Deaths**

There were eleven deaths during the study, five in the MBT group and six in the clotrimazole group. Of the five deaths in the MBT group, two died in the treatment phase and three in the follow up phase. All six deaths in the Clotrimazole group occurred in the treatment phase.

*Reviewer's comments: Case report forms and narratives for all the deaths were reviewed. The reviewer concurs with the sponsor that none of the deaths was related to the study drug. Deaths were due to complications of opportunistic infections (Pneumocystis jiroveci pneumonia (2), Cryptococcal meningitis (2), Tuberculosis (2), sepsis (2), diarrhea with severe volume depletion (1), pneumonia (2)).*

#### **8.3.11.2.3 Serious Adverse Events**

Ten patients (including 5 deaths) in MBT group and nine patients (including 6 deaths) in the clotrimazole group had a serious AE.

*Reviewer's comments: The CRF and narratives for the patients who experienced a serious AE were reviewed. The reviewer concurs with the sponsor that none of the serious adverse events were drug related. All SAEs were due to complications of HIV infection or opportunistic infection (anemia (3), Shigella infection (1), volume depletion (1), multiple falls due to AIDS dementia (1), and pneumonia (2)).*

#### **8.3.11.2.4 Study or Drug discontinuation due to AE**

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Two patients in the miconazole group discontinued the study due to an AE. One AE developed in the follow up phase (progressive retroviral infection), and one developed in the treatment phase (dysphagia) and led to discontinuation of the study drug.

Three patients in the clotrimazole group discontinued the study due to AE (pneumonia, multiple falls due to AIDS dementia, volume depletion, *Shigella* infection). All three developed the AE in the follow up phase. One patient in the clotrimazole group became pregnant on treatment (day 13). She had missed her scheduled IM norethisterone enantate injection for contraception. The patient gave birth to a healthy male baby.

*Reviewer's comments: The case report form for the patient who discontinued the drug due to an AE was reviewed. OPC had shown a partial response to treatment on day 7 but the patient developed dysphagia on study day 8. There was no assessment whether the dysphagia was due to the development of esophageal candidiasis. There were no symptoms of a local allergic reaction to the drug. The reviewer considers this AE not related to the study drug.*

*Clotrimazole is not systemically absorbed. Ineffective contraception due to missed norethisterone, rather than drug interactions, most likely accounted for the pregnancy of the patient who received clotrimazole.*

### 8.3.11.2.5 Laboratory changes

Elevation of GGT was reported as an adverse event in three patients in the MBT group and eight patients in the clotrimazole group.

*Reviewer's comments: Renal function, electrolytes and bilirubin were not included in the lab data submitted. Elevations of AST, ALT or Alkphos more than 5x baseline did not occur in any patient in the MBT group. Increased GGT was reported as an adverse event in three patients in the MBT group and eight patients in the clotrimazole group. As calculated from the datasets, increase of GGT 3x above baseline occurred in six patients in each group.*

**Table 84 Elevation of liver enzymes - BA2004/01/04**

Change from baseline	MBT N = 290	Clot N = 287
ALT ≥ 3x increase above baseline	2 (0.7%)	7 (2.4%)
ALT ≥ 5x increase above baseline	0	1 (0.3%)
AST ≥ 3x increase above baseline	0	3 (1.0%)
AST ≥ 5x increase above baseline	0	1 (0.3%)
Alkphos ≥ 3x increase above baseline	0	0
Alkphos ≥ 5x increase above baseline	0	0
GGT ≥ 3x increase above baseline	6 (2.1%)	6 (2.1%)
GGT ≥ 5x increase above baseline	2 (0.7%)	1 (0.3%)

*Derived from datasets*

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**8.3.11.2.6 Local Tolerability**

The sponsor assessed local tolerability (gum pain, altered taste, dry mouth) by a patient questionnaire. Gingival inflammation at application site was assessed by the investigator.

**Table 85 Local tolerability BA2004/01/04**

	MBT N = 290			Clotrimazole N = 287		
	Visit 2 Randomization	Visit 3 Day 7	End of study	Visit 2 Randomization	Visit 3 Day 7	End of study
Mild/Moderate/severe gingival inflammation at application site	76 (26.2%)	53 (18.3%)	1 (0.3%)	65 (22.6%)	34 (11.8%)	1 (0.3%)
Mild/Moderate/severe gum pain	174 (60.0%)	66 (22.7%)	1 (0.3%)	155 (54.0%)	55 (19.2%)	2 (0.7%)
Mild/Moderate/severe altered taste when eating	201 (69.3%)	104 (35.9%)	0	205 (71.4%)	93 (32.4%)	0
Mild/Moderate/severe altered taste when not eating	189 (65.2%)	96 (33.1%)	0	201 (70.0%)	82 (28.6%)	0
Mild/Moderate/severe Dry mouth	213 (73.4%)	110 (37.9%)	1 (0.3%)	208 (72.5%)	108 (37.6%)	1 (0.3%)

Derived from listings 14.3.11, 14.3.12.1, 14.3.12.2, 14.3.12.3, 14.3.12.4 and from datasets

*Reviewer's comments: As reported by the patients' questionnaire, the oral symptoms present at baseline resolved by the end of study in almost all patients regardless whether they experienced OPC cure.*

*A higher percentage of patients who received miconazole tablet had gingival inflammation at the tablet application site on day 7 (18.3% vs. 11.8%).*

### 8.3.11.3 Safety conclusions

*Around 91% of the tablets adhered at least 6 hours, and almost half adhered until bedtime. None of the patients had a detectable serum miconazole level, indicating minimal systemic absorption and low potential for significant drug interactions.*

*There were no serious AEs or deaths that appeared to be related to either study drug. The incidence of all causality treatment emergent was similar in the two treatment arms. AE occurring in more than 2% of patients who received miconazole included nausea, vomiting, diarrhea, dry mouth, URI, headache, ageusia, anemia, fatigue and cough. Ageusia was more frequent in patients who received miconazole tablet, while increased GGT, neutropenia, and pharyngeal pain were more frequent in patients who received clotrimazole. Drug related AE occurring in more than 2% of patients who received miconazole tablet included nausea, vomiting, diarrhea, dry mouth, headache, and ageusia.*

*In both treatment groups, women had a higher frequency of common adverse events compared to men, probably due to the higher degree of general debility (higher ECOG) and more frequent receipt of concomitant medications in women. Because the majority of women were enrolled in SA, and the*

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*majority of men were enrolled in the US, country related differences in AE reporting cannot be ruled out.*

*The frequency of all causality oral adverse events (oral discomfort, oral burning, oral pain, gingival pain, gingival swelling, gingival pruritis, tongue ulceration, mouth ulceration, glossodynia, dry mouth, loss of taste, altered taste and application site adverse events) was 12.1% in patients who received MBT compared to 9.4% of patients who received clotrimazole. Application site gingival inflammation on day 7 of therapy was more frequent in miconazole recipients compared to clotrimazole recipients (18.3 vs. 11.8%).*

## **8.4 Clinical Trial BA 2002/01/02**

### **8.4.1 Methods**

This was an open randomized trial to compare the safety and efficacy of miconazole buccal tablet (MBT) 50 mg once a day for 14 days to miconazole gel 125 mg four times a day for 14 days in the treatment of OPC in patients with head and neck cancer who had received radiation therapy.

### **8.4.2 Study Design**

The sponsor considered a double blind, double-dummy design unfeasible due to inability to reproduce the taste and appearance of the gel in placebo form. Initially, an evaluator aware of patient allocated therapy assessed response. The sponsor met with the French regulatory agency (AFSSaPS) after the trial had enrolled 71 patients, and 59 patients were assessed for clinical response by an unblinded evaluator. The French agency recommended blind evaluator assessment and changing the study design to non-inferiority. Subsequently, the sponsor amended the protocol to increase patient enrollment to compensate for the patients who did not have blind assessment, to require that an evaluator who was unaware of patient's allocated treatment determine clinical efficacy, and to define a non-inferiority margin of 20%.

The efficacy rate of miconazole gel in the treatment of oropharyngeal candidiasis in head and neck cancer patients who had received radiation therapy is unknown. The sponsor assumed the success rate of miconazole gel to be 52%, equivalent to the response to amphotericin B as reported in the study by Lefebvre et al (2002). Considering an alpha of 5%, beta of 10%, and drop out rate of 10%, the sponsor calculated the number of patients needed at 227.

### **8.4.3 NI margin justification**

Studies used to estimate NI margin are listed in appendix 2

#### **8.4.3.1 Estimation of placebo response for trial BA2002/01/02**

There are no placebo-controlled trials in the treatment of OPC in patients with head and neck cancer.

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Please refer to the estimation of placebo effect performed for study BA2004/01/04 (placebo effect 95% CI -0.1%, 24.1%).

### 8.4.3.2 Estimation of miconazole gel response for trial BA2002/01/02

There are no trials evaluating miconazole gel for the treatment of OPC in patients with head and neck cancer. The sponsor identified seven trials that evaluated miconazole gel for the treatment of OPC in a variety of patients (Freitag 1983, Schaad 1983, Tsubura 1991, Hoppe 1996, 1997, Blignaut 1999, Bastian 2004). The reviewer performed a Pubmed search using the term oropharyngeal candidiasis on August 6, 2009, and retrieved 775 references. The reviewer identified four additional trials that evaluated topical miconazole (tablet to suck then swallow, or a (b) (4) tablet) for the treatment of OPC (Roed-Peterson 1978, Ravera 1999, Brickner 1996, VanRoey 2004).

**Table 86 Studies used to estimate efficacy of topical miconazole for the treatment of OPC**

<i>Citation</i>	<i>Study design Population</i>	<i>Drug Dose Duration</i>	<i>N</i>	<i>Endpoint</i>	<i>Result</i>	<i>Comments</i>
<i>Freitag 1983</i>	<i>R unblinded  Infants and toddlers</i>	<i>Miconazole gel 25 mg 4x/d  Nystatin 100000 U 4x/d 6 days</i>	<i>Miconazole 14  Nystatin 12</i>	<i>Resolution at EOT (6 days)</i>	<i>Miconazole gel 92.8%  Nystatin 85.7%</i>	<i>Results Not applicable to other populations</i>
<i>Schaad 1983</i>	<i>R unblinded  Hospitalized pediatric patients</i>	<i>Miconazole gel 25 mg 4x/d  Nystatin 100,000 U 4x/ 7 days, if no resolution, 7 more days</i>	<i>Miconazole 23  Nystatin 24</i>	<i>Resolution at EOT (7 or 14 days)</i>	<i>Day 7 Miconazole gel 65% Nystatin 54%  Day 14 Gel 100% Nystatin 75%</i>	
<i>Tsubura 1991</i>	<i>Open  HIV+, solid tumors, heme malignancy</i>	<i>Miconazole gel 100 mg 4x/d  2 weeks</i>	<i>41 ITT 32 per protocol</i>	<i>Not clear</i>	<i>PP "highly effective" 50%  "effective" 37.5%  Overall: 87.5%</i>	<i>ITT Highly effective + effective: 68.3%</i>
<i>Hoppe 1996</i>	<i>R  Infants</i>	<i>Nystatin gel #1 250,000 U 1x/d for 10 days  Nystatin gel #2</i>	<i>Nystatin #1: 35  Nystatin #2:</i>	<i>Resolution on day 14</i>	<i>Nystatin #1: 42.8%  Nystatin #2:</i>	<i>Results Not applicable to other populations</i>

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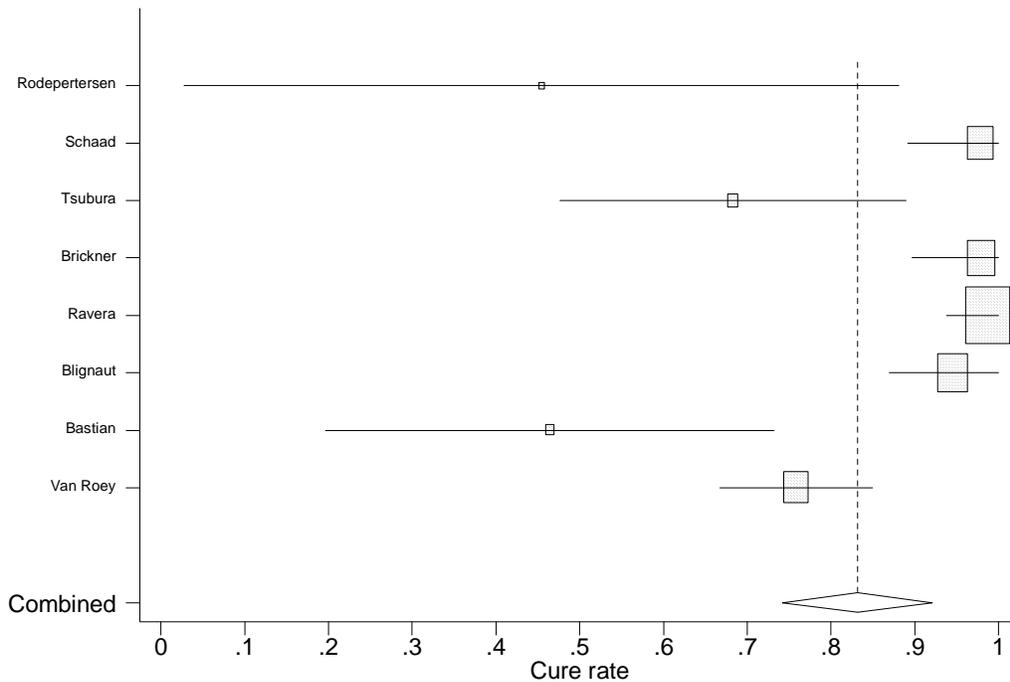
		50,000 4x/d for 14 days  Miconazole gel 25 mg 4x/d for 8 days	33  Miconazole 27		48.5%  Miconazole: 85.1%	
Hoppe 1997	R Infants	Nystatin gel 100,000 U 4x/d  Miconazole gel 25 mg 4x/d  2 weeks	PP population Nystatin 85 Miconazole 98  (ITT 107, 105)	Resolution Variable timing	On day 5 Nystatin 21.2% Miconazole 84.7%  On day 8 Nystatin 37.6% Miconazole 96.9%  On day 12 Nystatin 54.1% Miconazole 99%	ITT: Miconazole day 8: 90.8%  On day 12 92.4%  Results Not applicable to other populations
Blignaut 1999	Open HIV + South Africa	Miconazole 2% gel (? Exact dose) 3x/d  Fluconazole 200 mg/d  Duration not specified	73 miconazole  27 fluconazole	Not clear	Miconazole 94.5%  Fluconazole Not specified	Patients with "severe" OPC received fluconazole
Bastian 2004	DBPC Denture-related, steroid inhaler, post antibiotics, smokers	Miconazole gel 50 mg 4x/d  Miconazole chewing gum 4x/d  Placebo  4 weeks	28 gel  96 gum  16 placebo	Resolution of lesions EOT (d 28)	Placebo 11.1%  Gum 44.2%  Gel 48.2%	
Roed-Petersen 1978	Open uncontrolled  No apparent underlying disease  Failed nystatin,	Miconazole tablet to suck then swallow 250 mg 4x/d  14 days after resolution of lesions	11	Resolution of lesions (d 14 or 21)	Day 14: 45.5%  Day 21: 63.6%	

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	<i>gentian violet, or ampho B</i>					
<i>Brinckerer 1976, 1977</i>	<i>Open Heme malignancy</i>	<i>Miconazole tablet to suck then swallow 250 mg 4x/d Till 2 days after resolution of lesions</i>	<i>24 patients 35 episodes</i>	<i>Resolution of lesions at EOT (d variable and not specified)</i>	<i>100%</i>	<i>Mean duration of treatment 5 days – range not stated</i>
<i>Ravera 1999</i>	<i>Randomized HIV + adults with OPC and EC Uganda</i>	<i>Miconazole tablet to suck then swallow 250 mg 4x/d Nystatin 100,000 3.d 7 days</i>	<i>85 with OPC, 77/85 had EC (40 miconazole, 37 nystatin)</i>	<i>Resolution of lesions at EOT (d 7)</i>	<i>For OPC, 100% cure in both arms</i>	<i>For EC miconazole 92.5% Nystatin 21.6%</i>
<i>Van Roey 2004</i>	<i>Randomized HIV + adults Uganda</i>	<i>Miconazole (b) (4) buccal tablet 10 mg/d Ketoconazole 400 mg po/d 7 days, if no resolution, 7 more</i>	<i>ITT MBT 178 Keto 179 PP MBT 167 Keto 165</i>	<i>Resolution of lesions EOT (7 or 14 days)</i>	<i>on day 7 PP MBT 80.8% Keto 83% on day 14 PP MBT 92.8% Keto 96.4%</i>	<i>ITT 7 days MBT 75.8% Keto 76.5% 14 days MBT 87% Keto 88.8% Relapse 14 day post rx MBT 30.8% Keto 23%</i>

*Reviewer’s comments: The patient population used in these studies is highly heterogeneous, and include otherwise healthy infants, HIV infected adults, patients with hematologic malignancy, and patients with a variety of local predisposing factors. Treatment response in one group cannot be extrapolated to another group due to differences in local and systemic factors predisposing to OPC. None of the studies cited include a population comparable to patients with head and neck cancer who had received radiation therapy, where xerostomia plays a major role in pathogenesis of the disease and may affect salivary drug concentrations. In addition, treatment duration, definition of response, and timing of response evaluation were all heterogeneous.*

*The studies by Hoppe (1996 and 1997) and Freitag (1983) were excluded from the meta-analysis – all performed in infants). Meta-analysis of the remaining eight studies yields a point estimate for miconazole success rate of 83.2% (95% CI 74.25, 92.1%).*



*Review of the literature identified two studies that evaluated treatment of OPC in patients with head and neck cancer (Finlay et al, 1996 and Leve 2002). Finlay treated 73 patients with head and neck cancer who had received radiation therapy with either amphotericin B lozenges 4x/d for 14 days or fluconazole 50 mg orally once daily for 7 days. Clinical cure plus improvement at EOT was noted in 72% of patients who received amphotericin and 92% of patients who received fluconazole (Clinical cure was 44% vs. 73%). Lefebvre et al compared 123 patients who received fluconazole suspension 50 mg once daily to 120 patients who received amphotericin 0.5 gm suspension 3x daily for 7 to 14 days. Clinical cure was noted in 21% in the fluconazole arm vs. 14% in the amphotericin arm (cure plus improvement was 53% vs. 52%).*

*Because of the considerable heterogeneity of populations studied and because the literature suggests that clinical response to OPC treatment in patients with head and neck cancer who had received radiation therapy is lower compared to other populations due to salivary gland dysfunction, we agreed with the sponsor’s estimate of 50% for miconazole cure .*

### 8.4.3.3 Calculation of the NI margin for study BA2002/01/02

*The upper bound of the 95% CI for the placebo effect (complete resolution of lesions) was 25%, and the estimate for miconazole effect (complete resolution of lesions) is 50%. The treatment effect attributed to miconazole (MI) is therefore 25%.*

*The reviewer will therefore use NI margin of 12.5%, rather than 20% as suggested by the sponsor.*

### 8.4.4 Study Proceedings

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Thirty-six (36) sites across France, Morocco, Tunisia, and Algeria enrolled patients between April 2002 and June 2004. Eligible patients were randomized in 1:1 fashion to receive miconazole tablet or miconazole gel. Patients, investigators, and site personnel were not blinded regarding which active drug was administered, but an evaluator who was unaware of the patient's allocated therapy determined clinical efficacy after the study had already enrolled 71 patients (Please refer to Study Design). Patients applied the buccal tablet in the canine fossa on the upper gum in the morning. Patients could reposition the tablet in the event of dislocation, and could replace it only once if it adhered for less than 6 hours. Patients could eat and drink without restriction, and could brush their teeth, but were to avoid chewing gum.

#### 8.4.5 Inclusion criteria

- Age 18 or older
- Oropharyngeal candidiasis diagnosed by
  - clinical examination (thrush, erythema, mucositis, angular cheilitis) with or without associated symptoms (odynophagia, burning/soreness, xerostomia, modified taste, pharyngeal irritation) and
  - microbiologic confirmation (detection of Candida on direct examination, if direct examination is negative, by positive fungal culture with a minimum of 100 colonies)
- Head and neck cancer treated with radiation therapy 6-10 weeks prior to study inclusion
- ECOG 2 or less
- Able to give informed consent and to follow study protocol
- For women of child-bearing age, use of effective contraception for more than 3 months prior to study inclusion and maintained for study duration (2 months)

#### 8.4.6 Exclusion criteria

- Pregnant or breast-feeding
- Milk allergy or known history of hypersensitivity to one or more components of study drugs
- Liver failure defined as ALT/AST > 5 times UNL, or prothrombin time < 80% normal
- Esophageal or systemic candidiasis
- Administration of systemic antifungal treatments within 14 days prior to study enrollment
- Concomitant treatment with the potential to interact with miconazole: antiarrhythmics (verapamil, diltiazem, propranolol, amiodarone, atenolol, metoprolol, sotalol, dofetilide, moricizine, mexiletine, disopyramide, procainamide, quinidine gluconate or sulfate, propafenone, flecainide, tocainide), anticoagulants (anti-vitamin K: acenocoumarol and warfarin), sulfonyleurea oral hypoglycemics, astemizole, cisapride, and phenytoin

*Reviewer's comments: Patients with negative KOH were not included in study BA2004/01/04 (MBT compared to clotrimazole in HIV infected patients). In this study evaluating the efficacy of MBT in patients who had received radiation therapy to the head and neck, allowing patients with negative KOH on direct examination is not appropriate because radiation therapy, similar to OPC, can result in oral erythema, mucositis, burning/soreness, xerostomia, and modified taste. In addition, a positive culture may indicate colonization, and is not specific for infection. Thirty-nine (39) patients with negative KOH smear were enrolled, 17 to receive MBT and 22 to receive the gel. These patients could not be identified in the datasets to be excluded from the analysis.*

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*The prohibition of the concomitant medications was based on the French prescribing information compendium for the oral gel.*

*Miconazole oral gel is not approved or available in the United States.*

Patients could withdraw their consent to participate in the trial at any time. Investigators could terminate the participation of any patient in the trial early for any reason. The sponsor reserved the right to request the early withdrawal of patients who had serious protocol violations.

Reasons for early withdrawal were documented in the CRF.

Major Protocol amendments

The original protocol approved on April 11, 2002 was amended 12 times, seven related to the inclusion of new study centers. The other amendments were to

- Initiate blind evaluation on day 14
- Increase the number of patients enrolled to 227
- Allow patients who had received prior antifungal treatment if not within 2 weeks of study
- Define hepatic failure as LFTs > 5 times UNL instead of 2 times UNL
- Exclude patients receiving drugs likely to interact with miconazole

**8.4.7 Data quality**

The sponsor contracted an independent company ( (b) (4) ) to audit four study sites, one site in Tunisia (site 42), one site in Morocco (site 22), and two sites in France (sites 17 and 60).

*Reviewer’s comments: The sponsor did not state the reasons for choosing these sites for audit. Because of higher enrollment (14% of patients), and lower efficacy of miconazole buccal tablet compared to the study as a whole (25% vs. 56%), this reviewer chose site 22 for DSI inspections. Because of higher enrollment (19% of patients), and higher efficacy of both treatments at this site compared to the study as a whole (85 and 88% vs. 56 and 49% for MBT and comparator respectively), this reviewer chose site 42 for inspections.*

*Inspection of sites 22 and 42 revealed minor protocol, informed consent, and recordkeeping violations. The inspector concluded that the audited sites adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations, and that the violations identified should not have any significant impact on data integrity or subject safety. The data submitted by Bioalliance Pharma Inc. may be used in support of the indication.*

**8.4.8 Study events**

The study duration was up to two months, with five scheduled visits.

**Table 87 Summary of study events – BA2002/01/02**

	Day -7 to -10 Screening	Treatment period			Post-treatment	
		Day 1 Randomization	Day 7	Day 14 EOT	Day 30	Day 60
History and	X					

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physical						
ECOG	X	X				
Informed consent	X					
Labs	X				X	
Oral exam	X	X	X	X	X	X
Mycology direct exam	X					
Fungal culture	X		X if score 0	X	X If relapse or progression	X If relapse or progression
Patient questionnaire	X		Collected	Collected		

Adapted from study report page 38

The primary endpoint was Clinical Success (complete or partial clinical response) at day 14. Complete clinical response was defined as complete resolution of oral lesions. Partial clinical response was defined as at least 2 points decrease of oral lesions score obtained on day 1.

Candida oral lesions scores were according to the Murray scale:

0 = none

1= single, localized

2= multiple, localized

3 = extensive, confluent

*Reviewer's comments: The primary endpoint was complete or partial resolution of oral lesions at EOT in the mITT population, regardless of symptoms. The primary endpoint for study BA2004/01/04 (miconazole tablet vs. clotrimazole troches for the treatment of OPC in HIV infected adults) was complete resolution of oral lesions and symptoms on day 17-22 (3-8 days after EOT). Not including symptom resolution in the definition of response is appropriate for this study, since OPC and radiation therapy can cause overlapping symptoms of altered taste, oral soreness/burning, pharyngeal irritation and dry mouth.*

Secondary endpoints were

- Clinical success (complete or partial response) on day 7
- Improvement of symptoms of OPC (decrease of at least 1 point in the symptom score) and lesions of OPC (decrease of at least 1 point in lesion score) on day 14 compared to the rating on day 1. Lesions scores were according to the Murray scale. Symptoms scores were as follows: 0 = absence, 1= mild, 2 = moderate, 3 = severe
- Clinical cure defined as complete resolution of oral lesions and symptoms on days 7 and 14
- Relapse rate on day 60 (45 days after end of therapy). Relapse was defined as reappearance of oral lesions in a patient whose lesions had previously resolved.
- Mycologic cure defined as complete eradication or less than 10 colonies per plate on day 14

In addition to the above endpoints, duration of tablet adhesion and local safety were assessed by a patient questionnaire. Compliance was determined by patient questionnaire, and by the number of tablets remaining in the returned bottles at the end of therapy. In case of discrepancy, the smaller of the two values was used.

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*Reviewer’s comments: Clinical cure as an endpoint was not planned in the protocol. It was added after discussion with “European and US experts” after the database was locked.*

## 8.4.9 Efficacy evaluation

### 8.4.9.1 Patient Disposition

Thirty-six (36) centers across France, Tunisia, Morocco, and Algeria enrolled 308 patients, 154 to receive miconazole buccal tablet (MBT), and 154 to receive miconazole gel.

The mITT population as defined by the sponsor included all randomized patients who received at least one dose of study drug and had at least one efficacy evaluation visit.

Of the 154 patients enrolled into the miconazole tablet group, six patients did not take the study medication, one patient received miconazole gel instead (this patient was included in miconazole gel group), and six patients did not have an assessment of efficacy. The mITT population thus included 141 patients.

Of the 154 patients enrolled into the miconazole gel group, one patient was randomized before signing an informed consent, one patient was randomized after the end of the inclusion period, six patients did not take the study medication, six patients did not have at least one assessment of efficacy, and one patient was added from the tablet group. The mITT population thus included 141 patients.

**Table 88 Patients enrolled and excluded from mITT population – study BA2002/01/02**

	MBT N = 154	Gel N = 152
Excluded from mITT	13 (8.4%)	12 (7.9%)
▪Did not take study med	6	6
Negative fungal cultures	3	2
Withdrew consent	1	1
Did not come back	1	2
Drug not available at site	1	1
▪Received other assigned med	1 (added to gel group)	0
▪Did not have at least one efficacy assessment		
Lost to follow up	2	0
Withdrew consent	1	2
Negative fungal cultures	3	3
Died	0	1
MITT	141 (91.6%)	141 (92.1%)

Adapted from study report page 52, derived from Figure 1, page 52 and from data listings 16.2.1.3.1 and 16.2.3.4

*Reviewer’s comment: The sponsor defined the mITT population to include all randomized patients who received at least one dose of study drug and had one efficacy visit. Since that exclusion is based on post-*

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*randomization information that could bias the results, the reviewer also calculated clinical success in all randomized patients who received at least one dose of treatment.*

The PP population included those who

- completed minimum of 10 days of therapy
- had a blind clinical efficacy evaluation on day 14-16
- did not take any prohibited medications
- did not have a major protocol violation

The PP population included 107 patients in the MBT arm, and 106 in the Gel arm.

**Table 89 Patients excluded from PP - BA2002/01/02**

	MBT N = 141	Gel N = 141
No blind assessment	18 (12.8%)	19 (13.5%)
No efficacy evaluation on day 14-16	14 (9.9%)	15 (10.6%)
Major protocol deviation		
Took another antifungal during treatment	1 (0.7%)	0
Less than 2 weeks after end of radiation	1 (0.7%)	1 (0.7%)
<b>Total excluded</b>	<b>34 (24.1%)</b>	<b>35 (24.8%)</b>

Derived from study report listing 16.2.3.5.2.

If a patient had more than one reason for exclusion, this reviewer used the following hierarchy for classification: no documented efficacy evaluation on day 14-16 > no blind assessor > other reasons

### 8.4.9.2 Patient Demographics

Patient demographics in the ITT and PP populations are summarized in the tables below.

**Table 90 Patient demographics – mITT and PP population comparison BA2002/01/02**

	mITT		PP	
	MBT N = 141	Gel N = 141	MBT N = 107	Gel N = 106
Age (mean), years	51	53	49	50
< 65	115 (81.6%)	113 (80.1%)	90 (84.1%)	93 (87.7%)
≥ 65	26 (18.4%)	28 (19.9%)	17 (15.9%)	13 (12.3%)
Gender				
Male	103 (73.0%)	109 (77.3%)	72 (67.3%)	79 (74.53%)
Female	38 (27.0%)	32 (22.7%)	35 (32.7%)	27 (25.5%)
Country				
France	63 (44.6%)	65 (46.1%)	37 (34.6%)	36 (34.0%)
Tunisia	41 (29.1%)	40 (28.4%)	34 (31.8%)	37 (34.9%)
Morocco	29 (20.6%)	29 (20.6%)	29 (27.1%)	26 (24.5%)
Algeria	8 (5.7%)	7 (4.9%)	7 (6.5%)	7 (6.6%)

Adapted from study report p. 58-62 and derived from datasets

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*Reviewer's comments: In the mITT population, age, gender, and country of origin were balanced between the two treatment arms. Almost half of the patients were from France, and half from North Africa. Males outnumbered females by 3:1, reflecting the epidemiology of head and neck cancer, which is more common in males.*

*Males were enrolled equally between France and North Africa, whereas 76% (53/70) of females were enrolled in North Africa. Head and neck cancer is globally more common in males than in females. However, the ratio of males:females is lower in developing countries than in more developed countries, indicating that head and neck cancer is more common among women in developing countries than in more developed countries<sup>16</sup>.*

**Table 91 Patient demographics – age and gender – mITT and PP populations- BA2002/01/02**

	mITT		PP	
	MBT N = 141	Gel N = 141	MBT N = 107	Gel N = 106
Males	103 (73.0%)	109 (77.3%)	72 (67.3%)	79 (74.5%)
< 65	80 (56.7%)	87 (61.7%)	58 (54.2%)	70 (66.0%)
> 65	23 (16.3%)	22 (15.6%)	14 (13.1%)	9 (8.5%)
Females	38 (27.0%)	32 (22.7%)	35 (32.7%)	27 (25.5%)
< 65	35 (24.8)	26 (18.4%)	32 (29.9%)	23 (21.7%)
> 65	3 (2.2%)	6 (4.3%)	3 (2.8%)	4 (3.8%)

*Derived from datasets*

**Table 92 Patient demographics – country and gender – mITT and PP- BA2002/01/02**

	mITT		PP	
	MBT N = 141	Gel N = 141	MBT N = 107	Gel N = 106
Males	103 (73.0%)	109 (77.3%)	72 (67.3%)	79 (74.5%)
France	55 (39.0%)	56 (39.7%)	31 (29.0%)	31 (29.2%)
North Africa	48 (34.0%)	53 (37.6%)	41 (38.3%)	48 (45.3%)
Females	38 (27.0%)	32 (22.7%)	35 (32.7%)	27 (25.5%)
France	8 (5.7%)	9 (6.4%)	6 (5.6%)	5 (4.7%)
North Africa	30 (21.3%)	23 (16.3%)	29 (27.1%)	21 (19.8%)

*Derived from datasets*

*There was an imbalance of patients excluded from mITT by country. 55/69 (79.7%) patients lost from the mITT population were from France, where the study was initiated before a blind assessment was required. Slightly more than 40% of the French patients were excluded from the mITT population in each treatment arm. In addition, numerically more females and patients older than 65 years of age were lost from the mITT Gel group than from the mITT MBT group.*

<sup>16</sup>Curado MP et al. Recent changes in the epidemiology of head and neck cancer. Current opinions in Oncology 2009;21:190-200

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**Table 93 Distribution of patients by country – mITT and PP BA2002/01/02**

	<i>MITT</i> N = 282	<i>PP</i> N = 213
<i>France</i>	128 (45.4%)	73 (34.3%)
<i>Tunisia</i>	81 (28.7%)	71 (33.3%)
<i>Morocco</i>	58 (20.6%)	55 (25.8%)
<i>Algeria</i>	15 (5.3%)	14 (6.6%)

*Derived from datasets*

**Table 94 Patients excluded from PP population by country- BA2002/01/02**

	<i>MBT</i> N = 141	<i>Gel</i> N = 141
<i>France</i>	26/63 (41.3%)	29/65 (44.6%)
<i>Tunisia</i>	7/41 (17.1%)	3/40 (7.5%)
<i>Morocco</i>	0/29 (0%)	3/29 (10.3%)
<i>Algeria</i>	1/8 (12.5%)	0 (0%)

*Derived from datasets*

**Table 95 Patients excluded from PP by age and gender- BA2002/01/02**

	<i>MBT</i> N = 141	<i>Gel</i> N = 141
<i>Males</i>	31/103 (30.1%)	30/109 (27.5%)
<i>Females</i>	3/38 (7.9%)	5/32 (15.6%)
< 65	25/115 (21.7%)	20/113 (17.7%)
≥ 65	9/26 (34.6%)	15/28 (53.6%)

*Derived from datasets*

*Because of the above, the distribution of patients by age, gender, and country of origin was different in the PP population compared to the mITT population. In the PP population, numerically more women received miconazole tablet than women who received the gel. Males outnumbered females by approximately 2:1 in the MBT arm, and 3:1 in the gel arm. Approximately a third of the patients were from France, and two-thirds from North Africa.*

Sites 17 (France), 22 (Morocco), and 42 (Tunisia) collectively enrolled 119/282 (42.2%) of patients in the mITT population, and 101/213 (47.4%) of patients in the PP population.

**Table 96 Patient distribution by site – mITT and PP populations BA2002/01/02**

	<i>mITT</i>		<i>PP</i>	
	<i>MBT</i> N = 141	<i>Gel</i> N = 141	<i>MBT</i> N = 107	<i>Gel</i> N = 106
<i>Site 17 (France)</i>	12 (8.5%)	15 (10.6%)	7 (6.5%)	11 (10.4%)
<i>Site 22 (Morocco)</i>	20 (14.2%)	20 (14.2%)	20 (18.9%)	18 (17%)
<i>Site 42 (Tunisia)</i>	27 (19.1%)	25 (17.7%)	23 (21.5%)	22 (20.7%)
<i>Total</i>	59 (41.8%)	60 (52.6%)	50 (46.7%)	51 (48.1%)

### 8.4.9.3 Patient Characteristics

Patients characteristics according to ECOG grade, tumor location, history of prior OPC, salivary gland function, severity of OPC lesions, and positive fungal culture were presented.

**Table 97 Patient characteristics - mITT BA2002/01/02**

	mITT		PP	
	MBT N = 141	Gel N = 141	MBT N = 107	Gel N = 106
ECOG				
0	89 (63.1%)	95 (67.4%)	73 (68.2%)	74 (69.8%)
1	47 (33.3%)	39 (27.7%)	31 (29%)	28 (26.4%)
2	5 (3.6%)	7 (4.9%)	3 (2.8%)	4 (3.8%)
Tumor location				
Cavum	65 (46.1%)	62 (44%)	58 (54.2%)	56 (52.8%)
Oropharynx	11 (7.8%)	13 (9.2%)	7 (6.5%)	8 (7.5%)
Larynx	9 (6.4%)	13 (9.2%)	5 (4.7%)	6 (5.7%)
Not specified	56 (39.7%)	53 (37.6%)	37 (34.6%)	36 (34%)
Treatment				
Surgery	45 (31.9%)	53 (37.6%)	30 (28.04%)	30 (28.3%)
Chemotherapy	93 (66%)	95 (67.4%)	72 (67.3%)	77 (72.6%)
Radiotherapy	141 (100%)	141 (100%)	107 (100%)	106 (100%)
History of prior antifungal treatment				
Local	47 (33.3%)	49 (34.7%)	34 (31.8%)	41 (38.7%)
Systemic	24 (17%)	21 (14.9%)	21 (14.9%)	13 (12.3%)
Salivary secretion				
Absent	30 (21.2%)	19 (13.5%)	22 (20.6%)	15 (14.2%)
Partial	105 (74.5%)	116 (82.3%)	80 (74.8%)	87 (82.1%)
Normal	6 (4.3%)	5 (3.5%)	5 (4.7%)	3 (2.8%)
Hyper	0	1 (0.7%)	0	1 (0.9%)
Oral Lesions score				
1	49 (34.7%)	57 (40.4%)	31 (29.0%)	44 (41.5%)
2	75 (53.2%)	64 (45.4%)	61 (57.0%)	51 (48.1%)
3	17 (12.1%)	20 (14.2%)	14 (14.0%)	11 (10.4%)
Positive fungal culture	136 (96.5%)	136 (96.5%)	104 (97.2%)	103 (97.2%)

Adapted from study report page 58-66, and derived from datasets

*Reviewer's comments: In both the mITT and PP populations, patient distribution was balanced as to ECOG functionality grade, tumor location, receipt of chemotherapy, and history of prior antifungal therapy. Numerically more patients in the MBT group had absent salivary secretion, while numerically more patients in the gel group had mild OPC at baseline (candida score 1).*

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*In patients with history of prior antifungal therapy, those patients who received systemic antifungal therapy within 14 days of the study were excluded. It is not clear if the same exclusion applied to patients who received local antifungal therapy.*

Thirty-nine (39) patients with negative KOH smear were enrolled, 17 received MBT and 22 received miconazole gel. 136 patients in each treatment arm had positive fungal cultures.

**Table 98 *Candida* species at baseline – mITT BA2002/01/02**

	MBT N = 141		Gel N = 141	
	<i>Candida albicans</i> only	92	65.2%	86
<i>Candida albicans</i> with other species	8	5.7%	15	10.6%
Non-albicans <i>Candida</i> species	36	25.5%	35	24.8%
Negative cultures	3	2.1%	2	1.4%
Missing value	2	1.4%	3	2.1%

Adapted from study report page 66

**Table 99 *Candida* species isolated at baseline – mITT and PP BA2002/01/02**

	mITT		PP	
	MBT N = 141	Gel N = 141	MBT 107	Gel 106
<i>C. albicans</i>	100 (70.9%)	101 (71.6%)	79 (73.8%)	73 (68.9%)
<i>C. tropicalis</i>	15 (10.6%)	22 (15.6%)	10 (9.3%)	20 (14.2%)
<i>C. krusei</i>	12 (8.5%)	14 (9.9%)	9 (8.4%)	9 (8.5%)
<i>C. glabrata</i>	6 (4.3%)	7 (5.0%)	3 (2.8%)	5 (4.7%)
<i>C. kefyr</i>	5 (3.5%)	6 (4.3%)	3 (2.8%)	6 (5.7%)
<i>C. parapsilosis</i>	7 (5.0%)	1 (0.7%)	3 (2.8%)	1 (0.9%)
Negative cultures	3 (2.1%)	2 (1.4%)	0	0
Missing value	2 (1.4%)	3 (2.1%)	0	0

Derived from datasets

#### 8.4.9.4 Primary endpoint

The primary efficacy endpoint was clinical success (complete or partial resolution of oral lesions) on day 14 in the mITT population.

In the mITT population, the difference in either clinical success or complete resolution of lesions was 7.1% (95% CI -4.5%, 18.7%). In the PP population, difference in clinical success was 3.2% (95% CI -10.1%, 16.5%), and the difference in complete resolution of lesions was 1.4% (95% CI -12.0-14.8%).

**Table 100 Clinical Success at day 14 – mITT and PP BA2002/01/02**

mITT	MBT N = 141	Gel N = 141	difference	95% CI
Complete + partial Response	79 (56.0%)	69 (48.9%)	7.1%	-4.5%, 18.7%

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Complete	74 (52.5%)	64 (45.4%)	7.1	-4.5%, 18.7%
Partial	5	5		
PP	MBT N = 107	Gel N = 106		
Complete + partial Response	62 (57.9%)	58 (54.7%)	3.2%	-10.1%, 16.5%
Complete	57 (53.3%)	55 (51.9%)	1.4%	-12.0-14.8%
Partial	5	3		

Adapted from study report page 68 and derived from datasets

*Reviewer’s comments: The non-inferiority margin for complete resolution of lesions was defined at 12.5%. MBT is non-inferior to miconazole gel for the treatment of OPC in patients with head and neck cancer who had received radiation therapy as defined.*

*The mITT population included all randomized patients who received at least one dose of study drug and had one efficacy visit. Since that exclusion is based on post-randomization information which could bias the results, clinical success was recalculated in all randomized patients who received at least one dose of treatment). The conclusions regarding miconazole tablet efficacy compared to miconazole gel are unchanged.*

**Table 101 Clinical success at day 14 – all randomized patients who received at least one dose of treatment**

mITT	MBT N = 148	Gel N = 146	difference	95% CI
Complete + partial Response	79 (53.4%)	69 (46.6%)	6.1%	-5.3%, 17.5%
Complete	74 (50.0%)	64 (43.2%)	6.2	-5.2, 17.6
Partial	5	5		

*One patient (02-042-3208) did not have source documents available for DSI inspection. This patient received MBT and had a complete response. If this patient is discounted, the results remain unchanged.*

**8.4.9.4.1 Clinical success by age**

*Clinical success was numerically higher in patients under 65 who received MBT compared to patients under 65 who received the gel. The numerically higher response in patients under 65 who received miconazole tablet was not explained by differences in salivary gland function or severity of OPC.*

**Table 102 Clinical success by age - mITT and PP BA2002/01/02**

	mITT		PP	
	MBT N = 141	Gel N = 141	MBT N = 107	Gel N = 106
< 65 years	68/115 (59.1%)	56/113 (49.6%)	54/90 (60.0%)	51/93 (54.8%)
≥ 65 years	11/26 (42.3%)	13/28 (46.4%)	8/17 (47.1%)	7/13 (53.8%)

Derived from datasets

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**Table 103 Salivary gland function by age - mITT BA2002/01/02**

	<i>Age &lt; 65</i>		<i>Age ≥65</i>	
	<i>MBT</i> <i>N = 115</i>	<i>Gel</i> <i>N = 113</i>	<i>MBT</i> <i>N = 26</i>	<i>Gel</i> <i>N = 28</i>
<i>Absent</i>	27 (23.5%)	17 (15.0%)	3 (11.5%)	2 (7.1%)
<i>Partial</i>	82 (71.3%)	92 (81.4%)	23 (88.5%)	24 (85.7%)
<i>Normal</i>	6 (5.2%)	4 (3.5%)	0	1 (3.6%)
<i>Hyper</i>	0	0	0	1 (3.6%)

*Derived from datasets*

**Table 104 OPC severity by age - mITT BA2002/01/02**

	<i>Age &lt; 65</i>		<i>Age ≥65</i>	
	<i>MBT</i> <i>N = 115</i>	<i>Gel</i> <i>N = 113</i>	<i>MBT</i> <i>N = 26</i>	<i>Gel</i> <i>N = 28</i>
<i>Score 1</i>	38 (33.0%)	47 (41.6%)	11 (42.3%)	10 (35.7%)
<i>Score 2</i>	63 (54.8%)	52 (46.0%)	12 (46.2%)	12 (42.9%)
<i>Score 3</i>	14 (12.2%)	14 (12.4%)	3 (11.5%)	6 (21.4%)

*Derived from datasets*

#### **8.4.9.4.2 Clinical success by gender**

*Clinical success was numerically higher in male patients who received MBT compared to male patients who received the gel. This was not explained by differences in salivary gland function or OPC severity.*

**Table 105 Clinical success by gender day 14 – mITT and PP BA2002/01/02**

	<i>mITT</i>		<i>PP</i>	
	<i>MBT</i> <i>N = 141</i>	<i>Gel</i> <i>N = 141</i>	<i>MBT</i> <i>N = 107</i>	<i>Gel</i> <i>N = 106</i>
<i>Male</i>	59/103 (57.3%)	52/109 (47.7%)	44/72 (61.1%)	43/79 (54.4%)
<i>Female</i>	20/38 (52.6%)	17/32 (53.1%)	18/35 (51.4%)	15/27 (55.6%)

*Derived from datasets*

**Table 106 Salivary function by gender - mITT BA2002/01/02**

	<i>Males</i>		<i>Females</i>	
	<i>MBT</i> <i>N = 103</i>	<i>Gel</i> <i>N = 109</i>	<i>MBT</i> <i>N = 38</i>	<i>Gel</i> <i>N = 32</i>
<i>Absent</i>	21 (20.4%)	12 (11.0%)	9 (23.7%)	7 (21.9%)
<i>Partial</i>	76 (73.8%)	93 (85.3%)	29 (76.3%)	23 (71.9%)
<i>Normal</i>	6 (5.8%)	4 (3.7%)	0	1 (3.1%)
<i>Hyper</i>	0	0	0	1 (3.1%)

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**Table 107 Oral lesions score by gender - mITT BA2002/01/02**

	Males		Females	
	MBT N = 103	Gel N = 109	MBT N = 38	Gel N = 32
Mild, Score 1	42 (40.8%)	40 (36.7%)	7 (18.4%)	17 (53.1%)
Moderate, Score 2	50 (48.5%)	51 (46.8%)	25 (65.8%)	13 (40.6%)
Severe, Score 3	11 (10.7%)	18 (16.5%)	6 (15.8%)	2 (6.2%)

#### 8.4.9.4.3 Clinical success by country of origin

There was considerable variation in clinical efficacy among patients from different countries. Efficacy was lower in Moroccan patients who received MBT compared to Moroccan patients who received the gel, and compared to patients from other countries who received either treatment. The reverse pattern occurred in French patients, where efficacy was lower in patients who received the gel. Efficacy was higher in patients from Tunisia and Algeria regardless of treatment compared to patients from Morocco or France.

**Table 108 Clinical success by country at day 14 –BA2002/01/02**

	mITT			PP		
	MBT N = 141	Gel N = 141	Difference %	MBT N = 107	Gel N = 106	Difference %
France	30/63 (47.6%)	19/65 (29.2%)	18.4	19/37 (51.3%)	11/36 (30.5%)	20.8
Tunisia	34/41 (82.9%)	30/40 (77.5%)	5.4	29/34 (85.3%)	29/37 (78.4%)	6.9
Morocco	7/29 (24.1%)	15/29 (51.7%)	-27.6	7/29 (24.1%)	13/26 (50%)	-25.9
Algeria	8/8 (100%)	5/7 (71.4%)	28.6	7/7 (100%)	5/7 (71.4%)	28.6
Overall	79/141 (56.0%)	69/141 (48.9%)	7.1	62 (57.9%)	58 (54.7%)	3.2

Patients from Morocco who received MBT had more severe OPC at baseline compared to patients from Morocco who received gel, or patients from other countries who received either treatment. Patients from France who received the gel had more severe disease compared to French patients who received the tablet. However, severity of OPC did not correlate with clinical success in patients who received the gel (please refer to table 113)

**Table 109 OPC Severity by country at baseline - mITT BA2002/01/02**

	MBT N = 141			Gel N = 141		
	Mild 1	Moderate 2	Severe 3	Mild 1	Moderate 2	Severe 3
France	32/63 (50.1%)	23/63 (36.5%)	8/63 (12.7%)	29/65 (44.6%)	23/65 (35.4%)	13/65(20%)
Tunisia	12/41 (29.3%)	27/41 (65.9%)	2/41(4.8%)	13/40 (32.5%)	24/40(60%)	3/40(7.5%)

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Morocco	1/29(3.4%)	21/29 (72.5%)	7/29 (24.1%)	11/29 (37.9%)	14/29 (48.3%)	4/29 (13.8%)
Algeria	4/8(50%)	4/8(50%)	0	4/7(57.1%)	3/7(42.9%)	0

Derived from datasets

Salivary gland function did not explain the differences in response rates in Morocco or France.

**Table 110 Salivary gland function by country – mITT BA2002/01/02**

	MBT N = 141				Gel N = 141			
	Absent	Partial	Normal	Hyper	Absent	Partial	Normal	Hyper
France	14/63(22.2%)	47/63(74.6%)	2/63(3.2%)	0	8/65(12.3%)	52/65(80%)	4/65(6.2%)	1/65(1.5%)
Tunisia	5/41(12.2%)	34/41(83.0%)	2/41(4.9%)	0	3/40 (7.5%)	37/40(85.0%)	0	0
Morocco	9/29(31.0%)	20/29 (69%)	0	0	8/29(27.6%)	21/29(72.4%)		0
Algeria	2/8(25.0%)	4/8(50.0%)	2/8(25.0%)	0	0/7	6/7(85.7%)	1/7(14.3%)	0

Derived from datasets

## 8.4.9.5 Exploratory analyses

### 8.4.9.5.1 Clinical success by salivary gland function at baseline

Clinical success in either treatment arm was numerically higher in patients with better salivary gland function.

**Table 111 Clinical success by salivary gland function – mITT BA2002/01/02**

	MBT N = 141	Gel N = 141
Absent	13/30 (43.3%)	6/19 (31.6%)
Partial	59/105 (56.2%)	60/116 (51.7%)
Normal	6/6 (100%)	2/5 (40%)
Hyper	0/0	1/1

Derived from datasets

### 8.4.9.5.2 Clinical success by OPC severity at baseline

In the MBT group, patients with severe OPC lesions at baseline had a lower response to therapy compare to patients with mild or moderate disease. In the Gel group, severity of disease did not correlate with clinical success.

**Table 112 Clinical success day 14 by severity at baseline - mITT BA2002/01/02**

	MBT N = 141	Gel N = 141
OPC Score 1 (mild)	28/49 (57.1%)	33/57 (57.9%)
OPC Score 2 (moderate)	44/75 (58.7%)	24/64 (37.5%)

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<i>OPC Score 3 (severe)</i>	7/17 (41.2%)	12/20 (60%)
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Derived from datasets

#### 8.4.9.5.3 Clinical success by ECOG

Clinical success was similar across ECOG grades, in contrast to the study in HIV infected patients where patients with higher ECOG grade had a lower response rate compared to patients with lower ECOG grade.

**Table 113 Clinical success by ECOG - mITT BA2002/01/02**

	<i>MBT</i> <i>N = 141</i>	<i>Gel</i> <i>N = 141</i>
<i>ECOG 0</i>	48/89 (53.9%)	46/95 (48.4%)
<i>ECOG 1</i>	28/47 (59.5%)	21/39 (53.8%)
<i>ECOG 2</i>	3/5 (60.0%)	2/7 (28.6%)

Derived from datasets

#### 8.4.9.5.4 Clinical success by study site

Study site variation in efficacy corresponded to the country variation.

**Table 114 Clinical success by site day 14 - mITT BA2002/01/02**

	<i>MBT</i> <i>N = 141</i>	<i>Gel</i> <i>N = 141</i>
<i>All sites</i>	79 (56.0%)	69 (48.9%)
<i>Site 17 (France)</i>	4/12 (33.3%)	4/15 (26.7%)
<i>Site 22 (Morocco)</i>	5/20 (25.0%)	12/20 (60.0%)
<i>Site 42 (Tunisia)</i>	23/27 (85.1%)	22/25 (88.0%)
<i>Sites 17, 22 and 42</i>	32/59 (54.2%)	38/60 (63.3%)
<i>All other sites</i>	47/82 (57.3%)	31/81 (38.2%)

Derived from datasets

#### 8.4.9.5.5 Clinical success by Candida species isolated at baseline

The two treatments achieved similar clinical success in patients with *C. albicans* and *C. tropicalis*. Clinical success was numerically higher in patients with *C. krusei* who received the tablet compared to patients with *C. krusei* who received the gel.

**Table 115 Clinical success by Candida species isolated at baseline – mITT and PP – BA2002/01/02**

	<i>mITT</i>		<i>PP</i>	
	<i>MBT</i> <i>N = 141</i>	<i>Gel</i> <i>N = 141</i>	<i>MBT</i> <i>N = 107</i>	<i>Gel</i> <i>N = 106</i>
<i>C. albicans</i>	58/100 (58.0%)	52/101 (51.5%)	45/79 (57.0%)	42/73 (57.5%)

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<i>C. tropicalis</i>	10/15 (66.7%)	14/22 (63.6%)	7/10 (70%)	13/20 (65%)
<i>C. krusei</i>	6/12 (50%)	2/14 (14.3%)	5/9 (55.6%)	1/9 (11.1%)
<i>C. glabrata</i>	3/6 (50%)	3/7 (42.9%)	1/3 (33.3%)	2/5 (40%)
<i>C. kefyr</i>	1/5 (20%)	2/6 (50%)	1/3 (33.3%)	2/6 (33.3%)
<i>C. parapsilosis</i>	4/7 (57.1%)	1/1 (100%)	1/3 (33.3%)	1/1 (100%)

#### 8.4.9.6 Secondary Endpoints

Secondary endpoints were clinical success at day 7, clinical cure at days 7 and 15, relapse rate, and mycologic cure.

**Table 116 Secondary endpoints – mITT and PP BA2002/01/02**

	mITT		PP	
	MBT N = 141	Gel N = 141	MBT N = 107	Gel N = 106
Clinical Success day 7	20 (14.2%)	28 (19.9%)	14 (13.1%)	23 (21.7%)
Complete resolution of lesions	17 (12.0%)	21 (14.9%)	11 (10.3%)	17 (16.0%)
Partial resolution of lesions	3	7	3	6
Clinical cure day 7	17 (12.0%)	21 (14.9%)	11 (10.3%)	17 (16.0%)
Clinical cure day 15	55 (39.1%)	55 (39.1%)	43 (40.2%)	45 (42.4%)
Relapse 30 days	14/74 (18.9%)	8/64 (12.5%)	12/57 (21.0%)	6/55 (10.9%)
Relapse 60 days	16/74 (21.6%)	11/64 (17.2%)	14/57 (24.6%)	8/55 (14.5%)
Mean time to relapse (days)	18.8	20.6	20.3	21.3
Mycologic cure day 14	64 (45.4%)	77 (54.6%)	53 (49.5%)	65 (61.3%)

Adapted from study protocol page 70, 74, 80 and derived from datasets

*Reviewer's comments: clinical success and clinical cure at day 7 were numerically higher in the gel group, implying a more rapid clinical response in patients who received miconazole gel.*

*Clinical cure (complete resolution of lesions and symptoms) was not a planned endpoint in this study, but was added after the data was locked. This is the primary endpoint for study BA2004/01/04 (miconazole tablet vs. clotrimazole troches for the treatment of OPC in HIV infected patients). In both treatment arms, resolution of lesions occurred at a higher frequency than resolution of lesions and symptoms. In patients who received the tablet, complete resolution of lesions on day 15 was 52.5% (74/141), and complete resolution of lesions and symptoms was 39.1%. In patients who received the gel, resolution of lesions on day 15 occurred in 45.4% (64/141), and resolution of lesions and symptoms occurred in 39.1% (55/141). In this population of patients with head and neck cancer who had received radiation therapy, resolution of lesions did not necessarily accompany resolution of symptoms, probably because OPC symptoms can overlap with symptoms of radiation exposure.*

*Similar to clinical success, there was country variability in clinical cure rates, with Moroccan patients having the lowest cure rate in the MBT arm, and French patients having lower cure rate in gel arm. In*

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*the MBT treatment arm, the cure rate was numerically higher in males than females. In the gel arm, the cure rate was numerically higher in females than males.*

**Table 117 Clinical cure rate by country – mITT – BA2002/01/02**

	<i>MBT</i> N = 141	<i>Gel</i> N = 141
<i>France</i>	21/63 (33.3%)	13/65 (20%)
<i>Tunisia</i>	26/41 (63.1%)	27/40 (67.5%)
<i>Morocco</i>	5/29 (17.2%)	13/29 (44.8%)
<i>Algeria</i>	3/8 (37.5%)	2/7 (28.6%)

*Derived from datasets*

**Table 118 Clinical cure rate by gender – mITT – BA2002/01/02**

	<i>MBT</i> N = 141	<i>Gel</i> N = 141
<i>Male</i>	42/103 (40.8%)	41/109 (37.6%)
<i>Female</i>	13/38 (34.2%)	14/32 (43.7%)

*Derived from datasets*

*Relapse rate was numerically higher (18.9% vs. 12.5%) and the time to relapse shorter (18.8 days vs. 20.6 days) in patients who received MBT compared to patients who received oral gel.*

*Mycologic cure was numerically higher in patients who received the gel compared to patients who received the buccal tablet (61.3 % vs. 49.5%). Combined mycologic cure and clinical cure was also numerically higher in patients who received the gel (25.5% vs. 21.3%).*

*Miconazole tablet achieved a numerically lower rate of eradication of the three most common isolated Candida species (C. albicans, C. tropicalis and C. krusei), but numerically higher clinical success rates. Mycologic cure did not correlate with clinical success.*

**Table 119 Mycologic cure by Candida species – mITT and PP- BA2002/01/02**

	<i>mITT</i>		<i>PP</i>	
	<i>MBT</i> N = 141	<i>Gel</i> N = 141	<i>MBT</i> N = 107	<i>Gel</i> N = 106
<i>Candida albicans</i>	47/100 (47.0%)	59/101 (58.4%)	40/79 (50.6%)	47/73 (64.4%)
<i>C. tropicalis</i>	7/15 (46.6%)	14/22 (63.6%)	5/10 (50%)	12/20 (60%)
<i>C. krusei</i>	2/12 (16.7%)	5/14 (35.7%)	2/9 (22.2%)	5/9 (55.6%)
<i>C. glabrata</i>	2/6 (33.3%)	2/7 (28.6%)	1/3 (33.3%)	1/5 (20%)
<i>C. kefyr</i>	1/5 (20%)	3/6 (50%)	1/3 (33.3%)	4/6 (66.7%)
<i>C. parapsilosis</i>	3/7 (42.9%)	0/1 (0%)	1/3 (33.3%)	0/1 (0%)

*Derived from datasets*

*Progression (defined as an increase of at least one point in oral lesions score in patients who did not have a complete response on day 14) was not an endpoint in this study.*

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**Table 120 Progression – mITT – BA2002/01/02**

	mITT		PP	
	MBT N = 141	Gel N = 141	MBT N = 107	Gel N = 106
Progression at day 30	6 (4.2%)	10 (7.1%)	5 (3.5%)	5 (3.5%)
Progression at day 60	2 (1.4%)	2 (1.4%)	2 (1.4%)	2 (1.4%)

*Derived from datasets*

#### **8.4.10 Efficacy conclusions:**

*The primary endpoint was clinical success (complete or partial resolution of lesions) at end of therapy. The sponsor considered an NI margin of 20%. However, the reviewer considered an NI margin for complete resolution of lesions of 12.5% to be more appropriate (please refer to NI margin justification section). The sponsor used the mITT population (defined as patients who received at least three days of study medication and had at least one efficacy evaluation visit) as the primary population for efficacy analysis. The reviewer calculated the efficacy rate in the mITT population as defined by the sponsor, and in the population of patients who received at least one dose of study medication regardless of efficacy evaluation. In both populations, MBT 50 mg daily for 14 days was non-inferior to miconazole gel 125mg 4 times a day for 14 days for the treatment of OPC in patients with head and neck cancer who had received radiation therapy.*

*The study was conducted in France, and three North African countries (Tunisia, Morocco, and Algeria). More males than females were enrolled in the study, consistent with the epidemiology of head and neck cancer, which is more common in men. The ratio of males to females enrolled was higher in France than in North Africa, also consistent with the epidemiology of head and neck cancer, where the ratio of males to females is lower in developing countries than in more developed Western countries.*

*Initially, an evaluator aware of the patient’s allocated therapy assigned clinical outcome. A blind evaluator assigned outcome after 59 patients were randomized and treated. The mITT population included all patients who received 3 days of therapy and had an efficacy evaluation performed, while the PP population included patients who had a blind evaluation. Because the study was initiated in France, most of the patients excluded from PP population were French. In addition, numerically more females and patients older than 65 years of age were excluded from the PP Gel group than from the PP MBT group. Therefore, age, gender and country of origin demographics were different in the mITT population compared to the PP population.*

*Although mITT and PP populations were not similar in demographics, within each population the two treatment arms were balanced as to age, gender, country of origin, ECOG grade, tumor location, receipt of chemotherapy, history of prior antifungal treatment, and Candida species at baseline. Numerically more patients in the MBT arm had absent salivary secretion, while numerically more patients in the gel arm had mild OPC at baseline.*

*Efficacy conclusions were similar in the mITT and PP populations. In each treatment arm, clinical success was lower in patients with absent salivary function. In the MBT arm, patients with more severe disease had a lower response rate than patients with less severe disease, but there was no correlation*

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*between severity and clinical success in the gel arm. In contrast to the study in HIV infected patients, ECOG grade did not correlate with treatment success in patients with head and neck cancer.*

*There was considerable variation in clinical efficacy among patients from different countries. Efficacy was lower in Moroccan patients who received MBT compared to Moroccan patients who received the gel, and to patients from other countries who received either treatment. The reverse pattern occurred in French patients, where efficacy was lower in patients who received the gel. Regardless of treatment, efficacy was higher in patients from Tunisia and Algeria compared to patients from Morocco or France. The country difference was not explained by differences in OPC severity or salivary gland function.*

*Clinical success and clinical cure on day 7 were numerically higher in the gel group, implying a more rapid clinical response in patients who received miconazole gel. Within each treatment arm, complete resolution of lesions was higher than complete resolution of lesions and symptoms indicating that symptom relief did not necessarily accompany resolution of lesions. In contrast, resolution of lesions and resolution of lesions and symptoms were similar in the HIV study. This is probably because OPC symptoms can be similar to radiation symptoms.*

*Relapse rate was numerically higher, and time to relapse shorter, in patients who received the buccal tablet. Mycologic cure was also numerically higher in patients who received the gel despite the fact that the PK study (BA2000/01/01) indicated that salivary concentrations of miconazole were higher and more sustained following the application of the tablet compared to the gel. Mycologic cure did not correlate with clinical success.*

*Although almost half of the patients in either treatment arm did not respond to treatment, few patients progressed.*

#### **8.4.11 Safety Evaluation**

The safety population included all patients who received at least one treatment dose, 147 patients in miconazole buccal tablet group and 147 patients in the miconazole gel group.

##### **8.4.11.1 Compliance**

The sponsor did not calculate compliance with the gel. Compliance with the tablet was calculated from the number of tablets returned by the patient at EOT visit. Percent compliance was calculated as  $\{1 - \{(P-A)/A\} \} \times 100$ , where

P = the number of tablets scheduled = number of days on study x dosing regimen

A = the number of tablets actually taken = number of tablets dispensed – number of tablets returned

Compliance was also calculated from patient questionnaire. In case of discrepancy, the smaller of the numbers was reported.

Mean compliance was 96.4% in the mITT population, and 98.1% in PP population.

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#### 8.4.11.2 Drug exposure

Duration of tablet adhesion was determined from the patient questionnaire.

The tablet adhered for at least 6 hours in 117 patients, for at least 12 hours in 112 patients, and until bedtime in 97 patients. Thirty-nine (39) patients swallowed 121 tablets, and 17/39 had to replace the tablet at least once. 71 patients spat out 239 tablets, 50/71 replaced the tablet at least once. Among patients who swallowed the tablet, 18.9% swallowed it within the first 6 hours, and among patients who expectorated the tablet, 55.5% expectorated it within the first 6 hours.

**Table 121 Tablet adhesion – BA2002/01/02**

	Safety N = 147
Number of tablets taken	1829
Number of tablets swallowed	121 (6.6%)
Number of tablets spat out	293 (16.0%)
Number of tablets adhering 6 hours	1362 (74.5%)
Number of tablets adhering 12 hours	1029 (56.3%)
Number of tablets adhering at bedtime	788 (43.1%)
Patients with tablets adhering for at least 6 hours	117 (79.8%)
Patients with tablets adhering for at least 12 hours	112 (76.2%)
Patients with tablets adhering until bedtime	97 (66.0%)

Adapted from study report and derived from datasets

*Reviewer's comment: the proportion of tablets adhering for 6 hours was around 75%. In contrast, the proportion of tablets adhering for at least 6 hours in HIV infected patients in study BA2004/01/04 was 91%. The lower adhesion rate in this study probably reflects radiation-induced xerostomia in patients with head and neck cancer. 95.7% of patients in this study were classified by the investigator as having absent or partial salivary secretion, compared to 27.6% of HIV infected patients classified as having moderate or severe dry mouth, and 53% of HIV infected patients who reported "too little" saliva production.*

#### 8.4.11.3 Adverse Events

In the MBT group, 43 patients experienced at least one adverse event, 26 patients experienced at least one drug related AE, and one patient experienced a serious AE. None of the SAEs was considered drug related. Three patients discontinued the study due to an AE, and one patient due to a drug related AE. There were no deaths.

In the Gel group, 40 patients experienced at least one AE, 20 patients experienced at least one drug related AE, and seven patients experienced a serious AE. None of the SAEs was considered drug related. Six patients discontinued the study due to an AE, and two patients due to a drug related AE. There were three deaths. None of the deaths was considered drug related.

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**Table 122 Summary of AE – safety population BA2002/01/02**

	MBT N = 147	Gel N = 147
Patients with at least one AE	43 (29.2%)	40 (27.2%)
Patients with at least one drug related AE	26 (17.7%)	20 (13.6%)
Patients with serious AE	1 (0.7%)	7 (4.7%)
Patients with drug related serious AE	0	0
Study discontinuation due to AE	3 (2.0%)	6 (4.1%)
Drug discontinuation due to AE	1 (0.7%)	2 (1.4%)
Deaths	0	3 (2.0%)

Adapted from study report page 87 and Derived from datasets

*Reviewer’s comments: The proportion of patients experiencing an adverse event was lower in this study compared to study BA2004/01/04 in HIV infected adults, probably reflecting the higher level of systemic immunocompromise in HIV infected patients. The incidence of AEs was similar in both treatment arms regardless of gender or age.*

**Table 123 All causality AE by age and gender BA2002/01/02**

	MBT N = 147		Gel N = 147	
< 65	37/120	30.8%	32/116	27.6%
> = 65	6/27	22.2%	8/31	25.8%
Male	32/109	29.4%	31/113	27.4%
Female	11/38	28.9%	9/34	26.5%

Adapted from study report page 87 and Derived from datasets

#### **8.4.11.3.1 Serious AEs and deaths**

Eight patients developed a serious AE (including three deaths), one in the MBT group, and seven in the gel group. No serious AE was considered drug related.

*Reviewer’s comments: The case report forms and narratives of the patients who died or had a serious AE were reviewed. The SAEs were cerebrovascular accident (2), progressive cachexia (2), metastatic cancer (2), local invasion of cancer into the pharyngeal cavity (1), and cardiac arrest (1). The reviewer agrees that the serious AEs and deaths were not related to the study drugs, but were related to progression and complications of the underlying cancer and its therapy.*

#### **8.4.11.3.2 Adverse Events leading to discontinuation of the drug**

Three patients discontinued the study drug due to an adverse event, one in the MBT group, and two in the gel group.

*Reviewer’s comments: The case report forms for patients who discontinued the drug due to an adverse event were reviewed. The patient in the MBT group (subject 041-2258) developed local edema and itching at site of tablet application on day 7 of therapy. He had no respiratory symptoms. No specific*

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work up was reported and no treatment given. His symptoms resolved 2 days after the drug was discontinued.

One patient in the gel group (subject 007-2165) developed local mouth burning and dyspnea associated with gel application. He stopped the drug on day 3 with resolution of symptoms. No specific workup for causes of dyspnea was reported. The other patient in the gel group (subject 006-2205) developed burning of the oral cavity associated with application of the gel. He stopped therapy on day 7. The adverse event resolved upon drug discontinuation.

Given the temporal relationship between drug administration and occurrence of the events and between drug discontinuation and resolution of the events, the reviewer agrees that these adverse events are probably drug related.

### 8.4.11.3.3 All Causality Adverse Events

**Table 124 All causality treatment emergent AEs occurring in  $\geq 2\%$  of patients– BA2002/01/02**

System Organ Class/Preferred term MedDRA version 9.1	MBT N = 147	Gel N = 147
<b>Patients with at least one AE</b>	<b>43 (29.2%)</b>	<b>40 (27.2%)</b>
<b>GI disorders</b>	<b>13 (8.8%)</b>	<b>20 (13.6%)</b>
Abdominal pain, upper	2 (1.4%)	3 (2.0%)
Oral discomfort	4 (2.7%)	4 (2.7%)
Nausea	1 (0.7%)	4 (2.7%)
Vomiting	1 (0.7%)	3 (2.0%)
Glossodynia	0	3 (2.0%)
<b>Nervous system</b>	<b>8 (5.4%)</b>	<b>2 (1.4%)</b>
Dysgeusia	(4.1%)	0
Ageusia	1 (0.7%)	1(0.7%)
<b>Infections and infestations</b>	<b>7 (4.8%)</b>	<b>8 (5.4%)</b>
<b>General disorders</b>	<b>6 (4.1%)</b>	<b>5 (3.4%)</b>
<b>Skin</b>	<b>5 (3.4%)</b>	<b>1 (0.7%)</b>
Pruritis	3 (2.0%)	1 (0.7%)
<b>Musculoskeletal and connective tissue</b>	<b>5 (3.4%)</b>	<b>2 (1.4%)</b>
<b>Respiratory</b>	<b>2 (1.4%)</b>	<b>6 (4.1%)</b>

Derived from datasets

*Reviewer's comments: the most common all causality adverse events were nausea, upper abdominal pain, oral discomfort and dysgeusia. Dysgeusia was more frequent in patients in patients who received the tablet, however, one center (22, Morocco) reported all nine patients with dysgeusia in the MBT arm.*

### 8.4.11.3.4 Local Adverse events

The sponsor considered adverse events local if they occurred at the application site of the study drug, or were due to the local diffusion of the study drug from its site of application into the oral and nasopharyngeal areas without systemic ingestion. Local AE were sub-classified as follows:

L1: Oral event definitely at the site of drug application

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L2: Oral event possibly related to the site of drug application.

L3: Other local event possibly related to the local diffusion of the drug to the pharynx, to the ear or to the digestive tract.

**Table 125 Local adverse events – BA2002/01/02**

	MBT N = 147	Gel N = 147
Overall AEs	69 events	61 events
Systemic	33/69 (47.8%)	22/61 (36.1%)
Local	36/69 (52.2%)	39/61 (63.9%)
L1 At site of application	3	4
L2 Oral disorder	18	16
L3 Pharynx	15	19

Adapted from study report page 98

*Reviewer's comment:* The sponsor reported frequencies in events, rather than in patients. Local events as classified by the sponsor were numerically less frequent in the MBT arm.

As derived from the adverse events dataset, the frequency of oral and application site AEs (oral discomfort, oral pain, dry mouth, glossodynia, loss of taste, altered taste, tongue ulceration, mouth ulceration, tooth disorder, or application site discomfort or pain) was similar in patients who received the tablet (14/147, 9.5%) compared to patients who received the gel (16/147, 10.9%).

#### 8.4.11.3.5 Laboratory values

**Table 126 Laboratory value changes (increase in CTC class by 2 or 3 points) BA2002/01/02**

	MBT N = 147	Gel N = 147
Hematology	14 (9.5%)	9 (6.1%)
Decreased lymphocytes	12 (8.2%)	7 (4.8%)
Decreased HB	1 (0.7%)	0
Decreased PMN	1 (0.7%)	2 (1.4%)
Liver	1 (0.7%)	6 (4.1%)
Increased ALT	0	1 (0.7%)
Increased AST	0	3 (2.0%)
Increased GGT	1 (0.7%)	2 (1.3%)
Increased Alkphos	0	0

Adapted from study report page 106

None of the lab abnormalities was considered by the sponsor to be drug related, but considered related to underlying cancer and its treatment, or underlying alcohol intake (a risk factor for head and neck cancer).

*Reviewer's comments*

Abnormalities of liver enzymes were similar between the two treatment arms.

**Table 127 Changes in LFTs - BA2002/01/02**

	<i>MBT</i> N = 147	<i>Gel</i> N = 147
<i>ALT increase &gt; 3x baseline</i>	3 (2.0%)	6 (4.1%)
<i>ALT increase &gt; 5x baseline</i>	0	0
<i>AST increase &gt; 3x baseline</i>	2 (1.4%)	3 (2.0%)
<i>AST increase &gt; 5x baseline</i>	0	2 (1.4%)
<i>Alkph increase &gt; 3x baseline</i>	1 (0.7%)	1 (0.7%)
<i>Alkph increase &gt; 5x baseline</i>	0	0
<i>GGT increase &gt; 3x baseline</i>	2 (1.4%)	4 (2.7%)
<i>GGT increase &gt; 5x baseline</i>	1 (0.7%)	1 (0.7%)

*Derived from datasets*

#### **8.4.11.4 Safety conclusions**

*Around 75% of the tablets adhered for at least 6 hours, 56% adhered for at least 12 hours, and 43% adhered until bedtime. Tablet adherence was lower in this study compared to BA2004/01/04, probably due to radiation-induced xerostomia in patients with head and neck cancer compared to HIV infected patients.*

*The incidence of all causality AEs were similar in the two treatment arms. The most common AEs occurring in more than 2% of patients were upper abdominal pain, oral discomfort, nausea, headache and dysgeusia. Dysgeusia occurred more frequently in patients who received the tablet, but almost all instances of dysgeusia were reported from a single center. As derived from the dataset, the frequency of oral and application site AEs was similar in patients who received MBT or miconazole gel. There were no serious AEs or deaths related to the drug. One patient who received the tablet discontinued the drug due to a local oral adverse event.*

## **9 Integrated review of efficacy**

### **9.1 Comparison of efficacy of MBT across clinical trials in different patient populations:**

The clinical studies used different primary endpoints to evaluate treatment efficacy. Studies BA2000/01/03 (non-comparative study of miconazole buccal tablet for the treatment of OPC in HIV infected adults) and BA2002/01/02 (miconazole buccal tablet vs. miconazole gel for the treatment of OPC in patients with head and neck cancer who had received radiation therapy) defined efficacy as clinical success: complete or partial resolution of oral lesions at EOT. Study BA2004/01/04 (miconazole tablet vs. clotrimazole troches for the treatment of OPC in HIV infected adults) defined efficacy as clinical cure: complete resolution of oral lesions and symptoms on day 21.

Relapse rates were assessed in HIV infected patients who had a complete or partial reponse, and in head and neck cancer patients who had a complete response.

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Studies BA2000/01/03 and BA2004/01/04 were both conducted in HIV infected individuals. Although these studies were different in design and endpoints, the results were combined to provide an overall efficacy in this population.

**Table 128 Integrated efficacy – all studies combined – mITT population**

	MBT 50 mg		Clotrimazole	Miconazole gel
	HIV infected N = 315	H&N cancer N = 141	HIV infected N = 287	H&N cancer N = 141
Resolution of lesions and symptoms	189 60%	55 39%	187 65.2%	55 39.0%
Resolution of lesions	201 63.8%	74 52.5%	198 69%	64 45.4%
Mycologic cure	86 27.3%	64 45.4%	71 24.7%	77 54.6%

Derived from datasets

**Table 129 Integrated efficacy – all studies combined – PP population**

	MBT 50 mg		Clotrimazole	Miconazole gel
	HIV infected N = 259	H&N cancer N = 107	HIV infected N = 236	H&N cancer N = 106
Resolution of lesions and symptoms	176 68.0%	43 40.2%	175 74.2%	45 42.5%
Resolution of lesions	186 71.8%	57 53.3%	184 78%	55 51.9%
Mycologic cure	79 30.5%	53 49.5%	64 27.1%	65 61.3%

Derived from datasets

**Table 130 Relapse rate – all studies combined**

	MBT 50 mg			Clotrimazole	Miconazole Gel	
	HIV infected N = 315	H&N cancer N = 141		HIV infected N = 287	H&N cancer N = 141	
	21 day after EOT	15 days after EOT	45 days after EOT	21 days after EOT	15 days after EOT	45 days after EOT
Relapse	59 (18.7%)	14 (9.9%)	16 (11.3%)	53 (18.5%)	8 (5.7%)	11 (7.8%)

Derived from datasets

Resolution of lesions occurred more frequently in HIV infected patients compared to patients with head and neck cancer regardless of the treatment administered. The lower cure rate in patients with head and neck cancer is consistent with literature reports. Patients with head and neck cancer treated with fluconazole experience a lower cure rate compared to HIV infected patients, attributed to lower

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penetration of the drug into salivary tissues in head and neck cancer patients due to radiation-induced xerostomia (cure rate 21-73% vs. 87-100%)<sup>1, 6, 7, 16</sup>.

The lower rate of resolution of lesions in head and neck cancer patients compared to HIV infected patients treated with topical miconazole is probably due to differences in salivary gland function. 97.5% of patients with head and neck cancer had absent or partial salivary secretion compared to 53% of HIV infected patients, and patients with decreased salivary gland function responded less frequently regardless of the treatment administered (please refer to individual study analyses: cure by salivary gland function). In addition, patients with head and neck cancer had a lower percentage of tablets adhering to the oral mucosa at least 6 hours (91% vs. 75%), probably resulting in lower salivary concentrations/drug exposure.

Resolution of lesions and resolution of lesions and symptoms were similar in HIV infected patients, indicating that resolution of symptoms accompanied lesion resolution. In contrast, resolution of lesions occurred more frequently than resolution of lesions and symptoms in patients with head and neck cancer, indicating that resolution of symptoms did not necessarily accompany lesion resolution, probably reflecting the fact that symptoms of OPC are similar to symptoms of radiation therapy.

Relapse rates in HIV infected patients were in the range reported in the literature for other antifungal agents: 44% for HIV infected patients treated with nystatin, around 50% for patients treated with clotrimazole, and around 20% for patients treated with fluconazole.

Mycologic cure was lower in HIV infected patients compared to patients with head and neck cancer, despite higher frequency of tablet adhesion and better salivary function (thus probably higher local drug exposure). In addition, HIV infected patients were more likely to relapse and to have a shorter time-to-relapse regardless of treatment. The lower mycologic cure and rate of relapse probably reflect the higher degree of underlying systemic immunosuppression of HIV infected patients compared to patients with head and neck cancer.

## 10 Integrated review of safety

### 10.1 Combined safety information from all submitted studies

The safety population included all patients who received at least one dose of study drug. Four hundred and eighty individuals (480) received at least one 50 mg dose of miconazole buccal tablet: 18 healthy subjects, 315 HIV infected patients (290 in BA2004/01/04 and 25 in BA2000/01/03), and 147 patients with head and neck cancer. Two hundred and eight seven (287) HIV infected patients received at least one dose of clotrimazole. One hundred and sixty-five (165) individuals received miconazole gel: 18 healthy subjects and 147 patients with head and neck cancer.

**Table 131 Subjects with Treatment Emergent adverse events - all studies combined**

	MBT 50 mg N = 480	Clotrimazole N = 287	Miconazole Gel N = 165
Patients with At least one AE	206 (42.9%)	146 (50.9%)	43 (26%)

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Patients with Serious AE (including deaths)	11 (2.3%)	9 (3.1%)	7 (4.2%)
Patients with Drug related AE	98 (20.4%)	65 (22.6%)	23 (13.9%)
Patients with Serious drug related AE	0	0	0
Study discontinuation due to AE	5 (1.0%)	3 (1.0%)	6 (3.6%)
Drug discontinuation due to AE	3 (0.6%)	0	2 (1.2%)
Deaths	5 (1.0%)	6 (2.1%)	3 (1.8%)

Derived from datasets

**Table 132 Treatment Emergent Adverse events occurring in  $\geq 2\%$  of subjects**

System Organ Class/Preferred term MedDRA version 9.1	MBT N = 480	Clotrimazole N = 287	Miconazole gel N = 165
<b>Gastrointestinal disorders</b>	<b>99 (20.6%)</b>	<b>68 (23.7.7%)</b>	<b>25 (15.1%)</b>
Diarrhea	29 (6.0%)	23 (8.0%)	1
Nausea	22 (4.6%)	22 (7.7%)	4 (1.2%)
Abdominal pain upper	12 (2.5%)	8 (2.8%)	3 (1.8%)
Vomiting	12 (2.5%)	9 (3.1%)	3 (1.8%)
<b>Infections and infestations</b>	<b>57 (11.9%)</b>	<b>49 (17.1%)</b>	<b>8 (4.8%)</b>
URI	6 (1.2%)	7 (2.4%)	0
<b>Nervous system disorders</b>	<b>52 (10.8%)</b>	<b>24 (8.4%)</b>	<b>5 (3.0%)</b>
Headache	23 (4.8%)	19 (6.6%)	1 (0.6%)
Dysgeusia	14 (2.9%)	3 (1.0%)	1 (0.6%)
<b>General and admin site</b>	<b>26 (5.4%)</b>	<b>23 (8.0%)</b>	<b>6 (3.6%)</b>
<b>Skin</b>	<b>23 (4.8%)</b>	<b>12 (4.2%)</b>	<b>1 (0.6%)</b>
<b>Musculoskeletal</b>	<b>20 (4.2%)</b>	<b>18 (6.3%)</b>	<b>2 (1.2%)</b>
<b>Respiratory</b>	<b>17 (3.5%)</b>	<b>22 (7.7%)</b>	<b>6 (3.6%)</b>
<b>Blood</b>	<b>21 (4.4%)</b>	<b>24 (8.4%)</b>	<b>0</b>
<b>Investigations</b>	<b>16 (3.3%)</b>	<b>18 (6.3%)</b>	<b>0</b>

Derived from datasets

**Table 133 Laboratory abnormalities – all studies combined**

Liver function test elevations (all studies combined)	MBT N = 480	Clotrimazole N = 287	Miconazole gel N = 165
ALT > 3x baseline	5 (1.0%)	7 (2.4%)	6 (3.6%)
ALT > 5x baseline	0	1 (0.3%)	0
AST > 3x baseline	2 (0.4%)	3 (1.0%)	3 (1.8%)
AST > 5x baseline	0	1 (0.3%)	2 (1.2%)
Alkph > 3x baseline	0	0	1 (0.6%)
Alkph > 5x baseline	0	0	0
GGT > 3x baseline	8 (1.7%)	6 (2.1%)	4 (2.4%)
GGT > 5x baseline	3 (0.6%)	1 (0.3%)	1 (0.6%)

Five patients (1.0%) who received MBT died. None of the deaths was determined by the sponsor or the reviewer to be related to the drug. Eleven patients (2.3%) had a serious AE, none was determined by the

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sponsor or the reviewer to be related to the drug. Three patients (0.6%) discontinued the drug due to an adverse event: one HIV positive patient developed dysphagia on day 8, one HIV positive patient developed nausea on day 12, and one patient with head and neck cancer developed local edema at the site of the tablet application on day 7 of therapy.

All causality adverse events were more frequent in HIV infected patients compared to patients with head and neck cancer regardless of treatment. Among HIV infected patients, adverse events were more frequent in females compared to males, probably due to more frequent receipt of concomitant medications and greater debility (higher ECOG) in females enrolled in the study. There were no gender differences in the rate of adverse events among patients with head and neck cancer.

The most common adverse events in patients who received MBT were diarrhea (6.0%), nausea (4.6%), headache (4.8%), dysguesia (2.9%), vomiting (2.5%) and upper abdominal pain (2.5%). The frequency of all local oral adverse events (oral discomfort, oral pain, oral burn, dry mouth, glossodynia, loss of taste, altered taste, tongue ulceration, mouth ulceration, tooth disorder, and application site discomfort or pain) was 10.4% in patients who received MBT, 9.4% of patients who received clotrimazole and 10.8% of patients who received the miconazole gel.

Elevations of liver function tests were infrequent, consistent with the lack of systemic absorption of miconazole. None of the laboratory abnormalities was attributed to the drug.

## 11 Postmarketing safety

Miconazole buccal tablet gained market authorization in France on October 10, 2006 and was launched in September 2007. It is currently marketed in Denmark, Finland, Germany, Sweden, and the UK.

The sponsor submitted postmarketing safety reports for the period of October 10, 2006 to October 9, 2008. Based on sales units dispensed during that period, (b) (4) patients were exposed to the drug with an average length of therapy of 10 days. No adverse events were reported to the sponsor, to the French regulatory agency (AFSSAPS), to European regulatory authorities, or in the literature.

The sponsor also submitted post marketing safety reports for the period of October 10, 2008 to April 9, 2009. An estimated (b) (4) additional patients were exposed to the drug, with an average length of therapy of 10 days. Sixteen (16) AE occurring in 10 patients were reported to the sponsor. Eleven AE were already reflected in the European product label (vomiting, abdominal pain, bitter taste, nausea, rash, application site burning/pain/irritation), and six were not (application site ulcer, oral blister, gingival bleeding, diarrhea and flatulence). Of the six unexpected events, 5 were reported as possibly related to the drug and one as unlikely related to the drug (application site ulcer in a patient concomitantly receiving oral radiation therapy). None of the adverse events was serious.

In addition, the sponsor submitted AEs reported to the FDA's AERS database for miconazole from October 2008 thru March 2009. Five patients were reported to develop AEs (one from the US, two from the UK, and two from Japan). Only one patient was listed as having received the buccal tablet, a 4-year-old patient from the UK, although miconazole buccal tablet is not approved for use in children in the UK. The patient from the US was a 7-year-old female who received miconazole via an unknown route, and developed hemorrhage. No further details were provided. The two patients from the UK developed increased tacrolimus levels after oral administration of miconazole. Both patients were children (15

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*Reviewer's comments: Almost (b) (4) patients were exposed to miconazole buccal tablet post-marketing. No serious AEs were reported to the manufacturer or to European regulatory agencies. No new adverse events were noted. The adverse events reported to the AERS database pertained to other oral miconazole preparations, and reflect the potential for drug interactions as reported in the literature.*

*In addition to the sponsor's reports, this reviewer performed Pubmed search using the term "miconazole tablet" on October 5, 2009 and did not identify any additional reports that pertained to postmarketing safety of miconazole buccal tablet.*

## 12 Pediatric Assessment

The sponsor sought a waiver under Section 505B(a)(4)(B)(ii) of the Pediatric Research Equity Act (PREA), because there is significant risk that children under 3 years of age may aspirate the tablet. The sponsor also sought deferral for children above the age of 3 years under PREA Section 505B(a)(3)(A)(i); The approval for Oravig buccal tablet is anticipated before pediatric studies will be completed.

*Reviewer's comments: Pediatric assessment was discussed with the Pediatric Review Committee (PeRC) on March 17, 2010. A waiver for children  $\leq 5$  years of age will be granted because of concerns regarding the risk of choking, and inability to comply with use instructions.*

*The review committee agreed to deferral in children  $> 5$  years of age, and recommended studies to*

- evaluate the safety of miconazole buccal tablet*
- be initially conducted in children above the age of 12*
- identify an age group cognitively able to comply with use instructions*

## 13 Postmarketing Requirements

Pediatric studies as recommended by PeRC will be required to be submitted by March 31, 2014.

## 14 Labeling Review:

A copy of the sponsor's proposed label can be found at <\\Cdsesub1\evsprod\NDA022404\0008\m1\us\114-labeling\1141-draft-labeling>

A copy of the new label is attached in Appendix 1

19 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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## 16 Appendix 2

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Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22404

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ORIG-1

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BIOALLIANCE  
PHARMA

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Lauriad (miconazole (b) (4)  
tablet)

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/s/  
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HALA H SHAMSUDDIN  
04/12/2010

YULIYA I YASINSKAYA  
04/12/2010

**CLINICAL FILING REVIEW/CHECKLIST FOR NDA 22-404/ S-000  
(miconazole buccal tablet)**

**NDA/BLA Number: 22-404**

**Applicant: Bioalliance  
Pharma**

**Stamp Date: 02/06/2009**

**Review Date: 03/23/2009**

**Drug Name: Lauriad miconazole (b) (4) buccal tablet**    **NDA/BLA Type: 505 (b) (2)**

**Medical Reviewer: Hala  
Shamsuddin, M.D.**

On initial overview of the NDA/BLA application for filing:

**Studies submitted:**

- 1- BA 2000/01/01 – 18 subjects – 50 mg vs. 100 mg
- 2- BA 2002/01/02 – OPC head and neck cancer patients, compared to miconazole gel
- 3- BA 2002/01/03 – OPC in HIV + adults
- 4- BA 2004/01/04 – OPC in HIV + adults, compared to clotrimazole troches.

1- BA 2000/01/01 was a pharmacokinetic study comparing the safety, tolerability and pharmacokinetics of 50 mg miconazole (b) (4) buccal tablet to 100 mg tablet in 18 healthy subjects. On the basis of the data obtained from this study, a dose of 50 mg was chosen for subsequent trials.

2- BA 2002/01/02 was an open, randomized, 2 arm parallel-groups, multicenter phase III trial comparing the efficacy and safety of miconazole Lauriad 50 mg (b) (4) buccal tablet to that of miconazole gel in the treatment of oropharyngeal candidiasis in patients with head and neck cancer who had undergone radiation therapy. The study was conducted in centers in France and North Africa. 308 patients were randomized, 283 were in the MITT population.

3- BA 2002/01/03 was an open-label, non comparative study of miconazole (b) (4) buccal tablet in HIV positive adult patients who were receiving a stable HAART or no HAART regimen. The study was based on a group-sequential response adaptive design. If the efficacy was calculated at > 80% or < 60% after 20 patients were analyzed, enrollment would be halted. Otherwise, another 20 would be enrolled, and analysis performed with the same parameters on the 40 patients, then again on 60 patients if needed. 26 patients were enrolled. Efficacy was 90%.

4- BA 2004/01/04 was a multicenter, randomized, placebo-controlled, double-blind, double dummy study comparing Lauriad miconazole (b) (4) buccal tablet once daily for 14 days to clotrimazole troches 10 mg 5 times a day for 14 days in the treatment of oropharyngeal candidiasis in adult patients with HIV infection. 697 patients were enrolled. The study was conducted in centers in the US, Canada, and South Africa. This was the pivotal study.

The application was electronically submitted, indexed, paginated, and organized in a manner that would allow the clinical review to begin. An English translation was provided for all documents that were not in English. Draft labeling was submitted

Clinical Filing Review and Checklist for NDA 22-404, S000 (miconazole buccal tablet)

**CLINICAL FILING REVIEW/CHECKLIST FOR NDA 22-404/ S-000  
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consistent with CDER policies. Case report forms and case narratives for all deaths and serious adverse events were provided.

The application was submitted as 505 (b) 2, with miconazole as the reference drug Literature review; NDA 20-968 (miconazole cream 2%) and NDA 18-888 (miconazole suppository – Monistat 3) were used for non clinical studies reference. These references were appropriate and adequate.

The product is marketed in some countries in the European Union (France, Denmark, and Germany) and in the UK. Post marketing safety assessment was provided.

The sponsor is requesting pediatric waiver under section 505 B (a)(4)(B)ii of PREA for children under the age of 3 because of risk of choking on the product. Adequate documentation of the risk based on the size and shape of the product was provided. The sponsor is also requesting pediatric deferral under section 505 B (a)3Ai of PREA, as they anticipate approval of the product before completion of pediatric studies. <sup>(b) (4)</sup>

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
<b>LABELING</b>					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
<b>SUMMARIES</b>					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	x			Miconazole is the reference drug. Literature review, NDA 020-968 (miconazole cream

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(miconazole buccal tablet)**

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
					2%) and NDA 018888 (miconazole suppository – Monistat 3) were used for non clinical studies reference. These references were appropriate and adequate.
<b>DOSE</b>					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product ( <i>i.e.</i> , appropriately designed dose-ranging studies)? Study Number: Study Title: BA 2000/01/01 - Sample Size: 18 Arms: 50 mg vs. 100 mg tablets Location in submission: M5, 533-rep-human pk study	x			
<b>EFFICACY</b>					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?  Pivotal Study #1 BA2004/01/04 Lauriad compared to clotrimazole troches for treatment of oropharyngeal candidiasis in adult HIV + subjects.  Indication: Oropharyngeal candidiasis (OPC)  Pivotal Study #2 BA2002/01/02 Lauriad compared to miconazole gel for rx of OPC in patients with head and neck cancer who have received radiation therapy  Indication: OPC				1-study BA 2002/01/03 – non comparative study, Lauriad efficacy in rx of OPC in HIV + patients. 26 subjects enrolled.  2-Miconazole gel used as a comparator in study 02 is not approved or available in the US.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		x		
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product ( <i>e.g.</i> , QT interval studies, if needed)?			x	
20.	Has the applicant presented a safety assessment based on all	x			1-Safety data on 928 subjects included in the studies

**CLINICAL FILING REVIEW/CHECKLIST FOR NDA 22-404/ S-000  
(miconazole buccal tablet)**

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
	current worldwide knowledge regarding this product?				2-Product is available in France, UK, Germany and Denmark. Annual postmarketing reports are included.
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?			x	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?		x		Coding dictionary needed. Studies 02, 03, 04 coded with different versions of MedDRA. Study 01 coded with WHOART.
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included ( <i>e.g.</i> , label comprehension, self selection and/or actual use)?			x	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			pediatric waiver under section 505 B (a)(4)(B)ii of PREA for children under the age of 3 because of risk of choking on the product. Adequate documentation of the risk based on the size and shape of the product was provided. The sponsor is also requesting pediatric deferral under section 505 B (a) 3 Ai of PREA, as they anticipate

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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(miconazole buccal tablet)**

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
					approval of the product before completion of pediatric studies. (b) (4) 
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		x		
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?	x			Need to include subjects enrolled in study 01 in ISS safety analysis dataset
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? YES**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

**Although not fileability issues, the following are requested from the sponsor:**

- 1- Please submit a rationale for assuming the applicability of foreign data to US population for studies BA 2002/01/02, BA 2002/01/03, and BA 2004/01/04.*

**CLINICAL FILING REVIEW/CHECKLIST FOR NDA 22-404/ S-000  
(miconazole buccal tablet)**

- 2- *Please submit the coding dictionary used for mapping investigator verbatim terms to preferred terms for studies BA 2000/01/01, BA 2002/01/02, BA 2002/01/03, and BA 2004/01/04.*
- 3- *Please include the data of the 18 subjects enrolled in study BA 2000/01/01 in the ISS AE dataset. As the adverse events for these 18 subjects were coded using WHOART, please translate the data to MedDRA.*
- 4- *AE for studies 02, 03 and 04 were coded using different versions of MedDRA. If feasible, please provide coding using a unified version.*

Hala Shamsuddin, MD  
Reviewing Medical Officer

March 23, 2009  
Date

Yuliya Yasinskaya, MD  
Clinical Team Leader

March 23, 2009  
Date

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

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Hala Shamsuddin  
3/24/2009 11:05:40 AM  
MEDICAL OFFICER