Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer HealthCare AG	
Study Number:	13957	NCT01013909
Study Phase:	II	
Official Study Title:	An investigator-blind, randomized, multicenter, 5-arm, placebo- and active controlled parallel group pilot trial to explore the efficacy and tolerability of topical bifonazole liquid spray in patients with athlete's foot.	
Therapeutic Area:	Dermatology	
Test Product		
Name of Test Product:	Bifonazole (Mycospor/Canesten Extra, BAYH4502)	
Name of Active Ingredient:	Bifonazole	
Dose and Mode of Administration:	Bifonazole OD group: Bifonazole 1% liquid spray, applied topically once daily (OD) on infected foot areas. Bifonazole BID group: Bifonazole 1% liquid spray, applied topically twice daily (BID) on infected foot areas.	
Reference Therapy/Placebo		
Reference Therapy:	Terbinafine film forming solution (FFS) (Lamisil Once®) Placebo liquid spray	
Dose and Mode of Administration:	Terbinafine group: Terbinafine FFS 1% solution, single topical application on both feet. Placebo OD group: Placebo liquid spray, topical application OD on infected foot areas. Placebo BID group: Placebo liquid spray, topical application BID on infected foot areas.	
Duration of Treatment:	The overall treatment duration per subject was 1 day (Terbinafine group) or 6 days (Bifonazole and placebo groups), followed by a follow-up period of 36 days.	
Studied period:	Date of first subjects' first visit:	03 DEC 2009
	Date of last subjects' last visit:	26 MAY 2010
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	Amendment no. 1 (dated 12 OCT 2009) specified the following changes: • Change of exclusion criteria wherein four additions made were as follows: ▪ Long-term consequences of diabetes mellitus (i.e., diabetic foot syndrome) ▪ Peripheral artery disease	

	▪ Topical treatment with potent corticosteroids (i.e., all corticosteroids except hydrocortisone) 4 weeks prior to screening as well as during the trial ▪ Patients who were committed to an institution by virtue of an order issued either by the judicial or the administrative authorities (according to § 40 (1) 4 AMG) • Removal of subjects from the trial: ▪ Worsening of athlete's foot (AF) symptoms after start of treatment with respect to the athlete's foot severity score (AFSS) as assessed at screening; ▪ New symptoms like erythema, scaling, maceration, pain, burning etc. rated at least moderate (=2) in the AFSS scoring. • The subjects were not centrally randomized but instead individually by each center. • The list of prohibited medication prior to screening and during the trial was extended to include topical use of potent corticoids (i.e., all corticoids except hydrocortisone) within 4 weeks prior to screening as well as during the trial. • The review and assessment of the subject's entries in the diary was not performed to keep the investigator blind. • An antifungal effect of less than 42.5% for the new Bifonazole formulation (60%-17.5%) would be regarded as a negative study outcome. Amendment no. 2 (dated 08 JUN 2010) specified the number of planned subjects on the basis of the estimated drop-out rate. The drop-out rate due to microbiological assessment raised to 47%. Together with the general drop-out rate of 2%, 220 subjects were planned to be randomized into the trial in order to achieve 120 evaluable subjects.
Study Centre(s):	The study was conducted at 4 active centers in Germany.
Methodology:	This trial was designed as an investigator-blind, randomized, multicenter, 5-arm, placebo- and active controlled, parallel group phase 2 study. The study comprised of three phases: Screening and baseline period (visit 1 [V1]), treatment periods (V2 and V3), and post-treatment periods (V4 through V7). Assessment of specific clinical signs and symptoms like itching/burning were done by subjects in their diaries (Day 2 through Day 6) and by investigator at V1 and V4 through V7. Assessment of the 5 clinical signs and symptoms (Athlete's Foot Severity Score), overall cure rates, clinical cure rates, mycological cure rates, "culture negative" rates, and "microscopy negative" rates were done at V4, V5, and V7. Daily assessment of AEs was done by subjects in their diaries (Day 2 through Day 6) and by investigator at V2, V3 and V4 through V7. The trial duration for an individual subject was approximately 6 weeks.
Indication/ Main Inclusion Criteria:	Indication: Moderate athlete's foot Main Inclusion Criteria: Subjects of either sex aged between 18 and 70 years with positive clinical findings of athlete's foot, limited to interdigital spaces, with a total athlete's foot severity score of at least 5 and not exceeding 10 points for the signs and symptoms of athlete's foot, and no sign or symptom scoring "severe".

Study Objectives:	Overall: This explorative pilot trial was to assess efficacy and safety of the new bifonazole liquid spray compared to placebo and the active comparator terbinafine film forming solution (Lamisil Once®). Various endpoints were assessed in order to select the most appropriate primary endpoint for a confirmatory trial.
Evaluation Criteria:	Efficacy (Primary): Overall cure rate (clinical cure and mycological cure). Assessment of erythema/desquamation, scaling, vesiculation, maceration/fissuring, and pruritus/burning based on a categorical scale (0=absent to 3 =severe), assessment of mycological cure based on cultures and microscopy (after 6 applications [7 and 42 days after start of treatment]). Efficacy (Secondary): • Clinical cure (after 6 applications [7, 14, and 42 days after start of treatment]) • Mycological cure (after 6 applications [7, 14, and 42 days after start of treatment]) • Rate of negative culture (after 6 applications [7, 14, and 42 days after start of treatment]) • Rate of microscopy negative (after 6 applications [7, 14, and 42 days after start of treatment]) • Rate of absence of itching and burning (during treatment period) and 7, 14, and 42 days after start of treatment. Safety: • Incidence and severity of adverse event (from V2 [day 3] till V7 [day 42]) • Vital Signs (V1 [day 1] and V7 [day 42]) • Local side effects (from V2 [day 3] till V7 [day 42])
Statistical Methods:	Population: Demographic data and baseline characteristics were summarized descriptively for the safety population (SP) as well as for the full analysis set (FAS) and per protocol set (PPS) and displayed per treatment group. Efficacy (Primary): The efficacy analysis was conducted on the FAS and PPS and displayed per treatment group. The statistical analysis was exploratory. The treatment effects within the groups and between the groups were presented by 95% confidence intervals. The primary efficacy variable (overall cure rate) was analyzed using Fischer's two-sided exact test at a significance level of $\alpha = 0.05$. For the efficacy analysis of the FAS the observed data of all regular visits without replacement as well as V7 data with replacement (denoted as V7_rep) were used. Efficacy (Secondary): The secondary efficacy variables (clinical cure, mycological cure, rate of negative culture, rate of negative microscopy, and the rate of absence of itching and burning) were analyzed using Fischer's two-sided exact test at a significance level of $\alpha = 0.05$. In addition to the

	statistical analysis for primary efficacy variable, Wilcoxon 2-sample test was used for continuously distributed variables. Safety: The safety analysis was performed on the SP using descriptive statistics. No statistical tests were performed for safety data. Safety was mainly assessed from the incidence of AEs and the measurement of vital signs. The AEs were displayed in summary tables by treatment groups. They were grouped by Medical Dictionary for Regulatory Activities System organ class (MedDRA SOC) and preferred term (PT) and analyzed with regard to their severity and relationship to study treatment. The number of subjects who discontinued the study prematurely were tabulated by reason for discontinuation. For the safety analysis the observed values were used without replacement.
Number of Subjects:	Table 1 summarizes the number of subjects in various treatment groups. **Table 1: Number of subjects**

	Bifona-zole OD	Bifona-zole BID	Terbi-nafine	Placebo OD	Placebo BID	Total
Planned	55	55	55	28	27	220
Randomized	54	56	55	28	27	220
Analysis populations:*						
Safety	54	56	55	28	27	220
FAS	24	34	29	14	10	111
PP	22	30	27	12	10	101

Study Results

Results Summary — Subject Disposition and Baseline

All 220 screened subjects were randomized for treatment with bifonazole OD (54), bifonazole BID (56), terbinafine (55), placebo OD (28), or placebo BID (27). A total of 179 subjects completed the study, 43/54 subjects (79.6%) in the bifonazole OD group, 51/56 subjects (91.1%) in the bifonazole BID group, 46/55 subjects (83.6%) in the terbinafine group, 19/28 subjects (67.9%) in the placebo OD group, and 20/27 subjects (74.1%) in the placebo BID group.

Of the total of 220 subjects in the SP, 133 (60.5%) were male and 87 (39.5%) were female. All treatment groups had a higher proportion of male subjects. The mean age of the subjects was 50.2 years (range: 19 to 71), and was similar in all five treatment groups. All subjects were Caucasians except for one subject in the bifonazole BID group who was Latino.

Results Summary — Efficacy

For the evaluated parameters treatment with bifonazole was found considerably better than placebo treatment at study end (V7), particularly for the twice daily application. However, only in some cases the difference between the bifonazole and placebo treatment was statistically significant ($p<0.05$, two-sided Fisher's exact test).

The overall cure rate was 44.1% in the bifonazole BID group vs 10.0% in the placebo BID group. The difference (34.1%) was statistically not significant ($p=0.0670$, two-sided Fisher's

exact test). The difference between the bifonazole BID and terbinafine treatments (-16.6%) was also not significant (p=0.2134), but terbinafine was significantly different to bifonazole OD (p=0.0485).

Regarding clinical cure, the difference (54.2%) between bifonazole OD (69.6%) and placebo OD (15.4%) was statistically significant (p=0.0045). There was no difference between the bifonazole and terbinafine groups.

For the BID application the mycological cure rate was significantly higher for bifonazole (58.8%) than for placebo (10.0%) (p=0.0102). In this posology there was no significant difference between bifonazole and terbinafine (p=0.2811).

Both parameters contributing to the mycological cure, i.e., negative microscopy and culture, showed similar results. There was a distinct difference between the bifonazole BID and placebo BID groups which was, however, statistically not significant. This applied also to the comparison of the bifonazole BID and terbinafine groups.

Symptoms itching and burning were absent in 91.3% and 91.2% of subjects under bifonazole OD and BID, respectively, compared with 38.5% and 50.0% of subjects under placebo OD and BID, respectively. The differences of 52.8% and 41.2% were statistically significant (p=0.0013 and 0.0092, respectively). Comparison of the bifonazole groups with the terbinafine treatment yielded no relevant statistical differences.

Results of the PP population were very similar.

Results Summary — Safety

The assessment of the AEs that occurred during the study yielded that a total of 38 AEs in 28/220 subjects (12.7%) were reported: Twelve AEs in 7/54 subjects (13.0%) in the bifonazole OD group, 7 AEs in 6/56 subjects (10.7%) in the bifonazole BID group, 5 AEs in 4/55 subjects (7.3%) in the terbinafine group, 8 AEs in 7/28 subjects (25.0%) in the placebo OD group, and 6 AEs in 4/27 subjects (14.8%) in the placebo BID group. This means that the frequency of AEs was similar in all treatment groups as was the percentage of subjects who experienced AEs (incidence).

MedDRA SOCs "general disorders and administration site conditions" and "skin and subcutaneous tissue disorders" were reported most frequently in all treatment groups. Otherwise, there were no SOC or PT categories showing a particular frequency of events.

The percentage of subjects with AEs considered related to study medication was also similar between the groups, i.e., 9.3% under bifonazole OD, 7.1% under bifonazole BID, 3.6% under terbinafine, 10.7% under placebo OD, and 7.4% under placebo BID.

The respective AEs ("application site pain", "application site pruritus", "headache") were commonly observed events under treatment with Canesten® Extra Bifonazol, 1% cream (SPC, 2006) or Lamisil Once® terbinafine spray (product information, Novartis).

No subjects terminated the trial prematurely due to the occurrence of AEs.

There were no serious adverse events (SAEs) documented in the study and no subject died during the study.

Conclusion(s)			
In this study, the results indicate that treatment with bifonazole liquid spray is more effective than placebo treatment. Bifonazole BID has yielded better cure rates than bifonazole OD but the difference was not statistically significant. Terbinafine showed higher response rates compared to bifonazole BID which reached no significant difference. The modest mycological cure rates in both bifonazole groups suggest that the treatment duration of 6 days may be insufficient in subjects with moderate tinea pedis. However, small subject number per treatment group should also be taken into account. From safety results, it can be concluded that treatment of athlete's foot by bifonazole liquid spray is safe, well-tolerated, and adds clinical benefit to tinea pedis therapy.			
Publication(s):	None		
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Investigational Site List

Marketing Authorization Holder in Germany	
Name	Bayer Vital GmbH
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