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:	12999	NCT00781820
Study Phase:	III	
Official Study Title:	A double-blind, randomized, multicenter, placebo controlled phase 3 trial to prove the superiority of bifonazole vs placebo after 4 weeks of onychomycosis treatment (as a follow-up of a 2 weeks treatment of non-surgical nail ablation of diseased nail matrix with a 40% urea paste)	
Therapeutic Area:	Anti-Infectives	
Test Product		
Name of Test Product:	Bifonazole (Mycospor/Canesten Extra, BAYH4502)	
Name of Active Ingredient:	Bifonazole	
Dose and Mode of Administration:	Group 1 Bifonazole 1% cream and Urea 40% paste Mode of Administration: Urea: Topical application once daily on infected nail areas (14 days up to 28 days) Bifonazole: Topical application once daily on infected nail areas (28 days)	
Reference Therapy/Placebo		
Reference Therapy:	Placebo cream	
Dose and Mode of Administration:	Group 2 Urea 40% paste and Placebo Mode of Administration: Urea: Topical application once daily on infected nail areas (14 days up to 28 days) Placebo cream: Topical application once daily on infected nail areas (28 days)	
Duration of Treatment:	The overall treatment duration per subject was 42 days up to 56 days: 1st treatment phase (nail ablation): 14 days (up to 28 days) 2nd treatment phase (antifungal treatment): 28 days	
Studied period:	Date of first subjects' first visit:	23 OCT 2008
	Date of last subjects' last visit:	21 JAN 2010
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	Amendment no. 1 (dated 21 AUG 2008) specified the following changes: • The exclusion criteria "Uncontrolled diabetes mellitus assessed by HbA1c-level (>8.5)" and "Arterial circulatory disorders" were changed to "Uncontrolled diabetes mellitus" and "Peripheral arterial disease".	

	• In case of incomplete ablation at Visit 2 (V2) the treatment with urea paste could be prolonged for up to 14 days (up to V2a). Amendment no. 2 (dated 28 NOV 2008) specified the following changes: • Extension of the washout period prior to screening from 12 weeks to 6 - 9 months. • Removal of subjects from the trial: The following two reasons were added: ▪ "In case of a substantial worsening of the clinical signs and symptoms of onychomycosis" ▪ "In case of an intolerability of the study medication" Amendment no. 3 (dated 20 MAY 2009) specified the following changes: • With an estimated screening failure rate (40%) and an estimated dropout rate (30%) about 1200 subjects were screened to ensure randomization of about 700 subjects and 500 evaluable subjects (250 subjects per treatment arm). • Subjects with psoriasis at head/neck and torso, Fontaine stage I (no symptoms), no signs of venous disease or presenting with only ecstatic or reticular veins or with varicose veins (Widmer stage I-II), known rheumatic disease not requiring any treatment, known history of Hepatitis C in the past not requiring any treatment, and basalioma or actinic keratodermia could be included in the study. • Disinfection of nails with alcohol prior to sampling was not to be performed • Consistent description of the photo documentation to be performed at all study visits has been introduced and the photo documentation was included in the flow chart. • Primary efficacy analysis was based on the Intention-To-Treat (ITT)1 population. As a sensitivity analysis, the per protocol (PP) population was analyzed. The ITT1 population was defined as all subjects of the safety population with complete data for the primary efficacy variable. • Procedures scheduled for the last follow-up visit (V5) were also performed in subjects who discontinued the study prematurely. • Adverse Event (AE) documentation: The start of the AE documentation was more precisely described. AE documentation was to start already after study medication had been dispensed to the subject. Therefore, at each visit after enrollment, the investigator was to ask the subject about the occurrence of any AEs.
Study Centre(s):	The study was conducted at 51 active centers, i.e., centers which screened at least one subject, in Germany (35), Poland (6), and the Czech Republic (10).
Methodology:	This trial was designed as a double-blind, randomized, multicenter, two-arm, placebo-controlled, parallel group phase 3 study. This study comprised of screening period, treatment phase, and post-treatment period. Visit 1 (V1) was for baseline charactersitic measurements. Treatment phases were: First treatment phase (nail ablation), and second treatment phase (antifungal treatment). During the first 14 days of treatment (day 0 to day 13; first treatment phase) all subjects applied once daily urea 40% paste on the infected nail areas and covered the nail(s) with a standardized patch after each application. The investigator checked ablation of infected parts of the nail at day 14 (V2). In case of incomplete ablation the treatment with urea paste

	could be continued for up to another 14 days (until V2a) at the discretion of the investigator. The time needed for nail ablation was assessed. During second treatment phase, from day 15 to day 42, subjects applied once daily bifonazole cream 1% (bifonazole group) or placebo cream (placebo group) on the infected nail bed(s) without covering with a patch. Assessment of clinical signs and symptoms and photography of all affected/treated nails was done on screening, baseline and from V3 – V5 (14 - 168 days after the end of treatment; post-treatment period). Iin addition, photography of all affected/treated nails was also done on Day 14 (between the 2 treatment phases). Microscopy and mycological culture were assessed on screening and from V3 – V5. Healthy re-growth of the nail was assessed on V4 and V5. Monitoring of AEs was done throughout the treatment period.
Indication/ Main Inclusion Criteria:	Indication : Onychomycosis Main Inclusion Criteria: Subjects of either sex aged at least 18 years with positive clinical and mycological findings of onychomycosis (positive microscopy and positive culture with identification of pathogen). Nail mycosis in not more than 3 nails (each nail not more than 50% infected area, in the target nail between 20% and 50%).
Study Objectives:	Primary: The primary objective of the trial was to demonstrate superiority of bifonazole vs placebo after 28 days of onychomycosis treatment as a follow-up of non-surgical nail ablation with a 40% urea paste over 14 days (up to 28 days) by assessing complete cure (mycological and clinical cure) 2 weeks after the end of treatment with bifonazole or placebo (Visit 3). Secondary: Secondary objectives included comparison of clinical signs and symptoms and mycological culture and microscopy between bifonazole and placebo: For the main analysis 2 weeks after the end of treatment (Visit 3), for the follow-up analysis 3 months (Visit 4) and 6 months (Visit 5) after the end of treatment. Further secondary objective of the trial was to compare safety and tolerability of bifonazole vs placebo with respect to the incidence of AEs during the trial.
Evaluation Criteria:	Efficacy (Primary): The primary endpoint of the trial was the overall cure rate comprising clinical cure and mycological cure rate (microscopy + culture negative) assessed 14 days after the end of treatment with bifonazole compared to placebo (V3). Efficacy (Secondary): Secondary endpoints for the main analysis at 14 days after the end of treatment (V3) were: • Clinical cure rate • Mycological cure rate • Clinical improvement rate and overall evaluation rate

	• Mycological culture • Microscopy Secondary endpoints for the follow-up analysis at 3 months and 6 months after the end of treatment (V4 and V5, respectively) were: • Overall cure rate • Relapse rate • Clinical cure rate • Mycological cure rate • Clinical improvement rate and overall evaluation rate • Mycological culture • Microscopy Safety: Safety (main analysis and follow-up analysis): Safety and tolerability of the study medication was assessed by incidence and type of AEs that occurred during the whole trial.
Statistical Methods:	Population: Demographic and baseline characteristics were summarized descriptively for the safety population as well as for the ITT0, ITT1 and PP populations. Efficacy (Primary): The study results were analyzed in two steps: The main analysis was performed after V3, i.e., the database was locked after all data for V3 were entered. The follow-up analysis was performed after V5, i.e., at the end of the trial. The primary efficacy variable of the trial was the overall cure rate of the target nail. For the main analysis, the overall cure rate at 2 weeks after the end of treatment (V3) was compared between the treatment groups. The following hypothesis was tested in a confirmatory manner using two-sided Fisher's exact test at the significance level of 0.05: H_0: $p_B = p_P$ H_1: $p_B \neq p_P$ with p_B as the expected overall cure rate under bifonazole and p_P as the expected overall cure rate under placebo. The primary efficacy analysis was based on the ITT1 population. As sensitivity analysis, the PP and ITT0 populations were analyzed. On demand of the Medicines and Healthcare products Regulatory Agency (MHRA) the analysis of the primary efficacy variable was also performed as a worst case analysis using the safety population (SP). Efficacy (Secondary): The secondary efficacy analysis was conducted on the ITT1 population as well as on the PP population. As sensitivity analysis, the ITT0 population was evaluated. In addition, follow-up analysis at V5 was performed for the ITT2 population as to account for subjects with incomplete data at V3 (e.g., due to missing nail specimen) but complete data at V5. For all rates with binary outcome the two-sided Fisher's exact test at a

significance level of α = 0.05 was used.

For rates with tertiary outcome such as overall evaluation the two-sided Mantel-Haenszel Chi-Square test at a significance level of α = 0.05 was used instead. All inferential analyses for the secondary efficacy parameters were to be interpreted in the exploratory manner. No adjustment of p-values was necessary.

Frequency tables stratified by treatment group were conducted for all secondary efficacy variables. Supplemental, for all efficacy assessments collected for target and non-target nails (such as mycological culture and microscopy), frequency tables or descriptive statistics (whatever was appropriate) stratified by treatment were presented comprising the total of all efficacy nails (target and non-target nails).

Safety:

The safety analysis was performed on the safety population. Safety was mainly assessed from the incidence of AEs and the rate of premature withdrawals. AEs were displayed in summary tables using descriptive statistics. They were grouped by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (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 was tabulated by reason for discontinuation. No statistical tests were performed.

For all efficacy and safety analyses data were used as documented (i.e., missings were not replaced).

Number of Subjects:

Number of subjects in various analysis population are described in Table 1.

Table 1: Total number of subjects in the analysis populations

	Bifonazole	Placebo	Total
Randomized	347	345	692
Safety	347	345	692
ITT0	325	327	652
ITT1 (all parameters for overall cure at V3)	299	296	595
ITT2 (all parameters for overall cure at V5)	295	310	605
PP	282	265	547

Study Results

Results Summary — Subject Disposition and Baseline

Out of 692 subjects who were randomised, 653 subjects completed both treatment phases of the study, 325/347 subjects (93.7%) in the bifonazole group and 328/345 subjects (95.1%) in the placebo group. A total of 629 subjects completed the whole study period, i.e., until visit V5, 311/347 subjects (89.6%) in the bifonazole group and 318/345 subjects (92.2%) in the placebo group.

Of the total of 692 subjects in the safety population, 384 (55.5%) were male and 308 (44.5%) were female. Both treatment groups had a slightly higher proportion of male subjects. All subjects were Caucasians except for four subjects in the bifonazole group who were Negroid, Arab, or of Asian origin and one subject in the placebo group who was Hispanic.

Results Summary — Efficacy

Main analysis
Analysis of the primary efficacy variable of the study (the overall cure rate comprising clinical and mycological cure in the target nail assessed 14 days after the end of treatment (V3) in the ITT1 population) resulted in a distinctly higher effect in the bifonazole group (54.8%) as compared to the placebo group (42.2%). The difference between the treatment groups of 12.6% was statistically significant (p=0.0024, two-sided Fisher's exact test). Therefore it could be concluded that the treatment with urea followed by bifonazole is superior to the treatment with urea followed by placebo.

Analysis of the SP and PP populations yielded a similar result, also significant in both populations, which confirmed the results of the ITT1 analysis.

Regarding the secondary efficacy parameters in the ITT1 population, the clinical cure rate was high in both treatment groups. The clinical cure rate at V3 was slightly better in the bifonazole group as compared to the placebo group (86.6% vs 82.8%, respectively). This difference between the two treatment groups of 3.9% was statistically not significant (p=0.2109, two-sided Fisher's exact test). In contrast, the mycological cure rate at V3, however, was distinctly higher in the bifonazole group (64.5% vs 49.0% in the placebo group). The difference between the two treatment groups of 15.6% was statistically significant (p=0.0001, two-sided Fisher's exact test). Thereby, both parameters contributing to the mycological cure, i.e., negative mycological culture and microscopy, showed similar results: The difference between the two treatment groups in favor of bifonazole was 16.4% and 15.9%, respectively.

Results of the PP population were very similar.

Follow-up analysis
Regarding the overall cure rate, the statistically significant difference between the two treatment groups, observed at V3, could also be observed at V4 (9.8%, p=0.0260, two-sided Fisher's exact test) but no longer at V5 (-1.1%, p=0.8581, two-sided Fisher's exact test). At this time point the overall cure rate was 33.6% in the bifonazole group and 34.6% in the placebo group.

Correspondingly, the relapse rate, similar between the two treatment groups at V4 (39.1% vs 35.5% in the bifonazole and placebo groups, respectively) was distinctly higher in the bifonazole group than in the placebo group at V5 (64.7% vs 42.0%, respectively).

The same tendency as for overall cure was observed for the mycological cure rate and the two components contributing to mycological cure, i.e., negative culture and microscopy: After a significant difference between the treatment groups at V4 (p-values <0.05, two-sided Fisher’s exact test) the differences were distinctly smaller at V5 (i.e., 52.1% vs 48.1% in the bifonazole and placebo groups, respectively, for mycological cure and negative microscopy, and 65.2% vs 58.5%, respectively, for negative culture) with no significant difference between the treatments.

The clinical cure rate was still high in both treatment groups at V4 (about 74%) and also at V5 (about 57%). However, there was no difference between the two treatment groups at any time point (p-values >0.05, two sided Fisher's exact test). This was already the case at V3.

Results of the PP, ITT2 and ITT0 populations were similar.

However subgroup analyses performed in order to identify factors which contributed to the results at V5 showed that certain subject groups still benefited from treatment with bifonazole at V5, namely subjects with only 1 affected nail, male subjects and subjects older than 64 years.

Results Summary — Safety

The assessment of the AEs that occurred after the start of treatment yielded that during the urea treatment (treatment phase 1) a total of 10 AEs in 10/347 subjects (2.9%) in the bifonazole group and 15 AEs in 14/345 subjects (4.1%) in the placebo group occurred.

During treatment phase 2 (antifungal therapy) a total of 14 AEs in 12/328 subjects (3.7%) in the bifonazole group and 19 AEs in 18/330 subjects (5.5%) in the placebo group were reported. During the follow-up phase a total of 46 AEs in 35/325 subjects (10.8%) in the bifonazole group and 53 AEs in 43/328 subjects (13.1%) in the placebo group were reported.

This means that in both treatment phases as well as in the follow-up phase the frequency of AEs was slightly higher in the placebo group as was the percentage of subjects who experienced AEs (incidence).

Except for MedDRA SOCs "skin and subcutaneous tissue disorders" and "infections and infestations", which were reported most frequently in both treatment groups, there were no SOC or PT categories showing a particular frequency of events.

The incidence of subjects with AEs considered related to study medication (defined as definite, probable, or possible) was very low and similar between the two groups, i.e., 0.6% in the bifonazole group versus 0.9% in the placebo group during treatment phase 1, and 0.3% vs 0.9%, respectively, during treatment phase 2.

The respective AEs were commonly observed events under treatment with Canesten® Extra Nagelset, nail ointment (phase 1 AEs, Summary of Product Characteristics [SPC] 2006) and Canesten® Extra Bifonazole, 1% cream (phase 2 AEs, SPC 2006).

The number of subjects withdrawn due to AEs or serious adverse events (SAEs) were also low. During the treatment phase two subjects in the placebo group prematurely terminated the trial due to bronchitis and contact dermatitis, respectively. During follow-up, 1 subject in the bifonazole group and 3 subjects in the placebo group terminated the trial prematurely due to subdural hematoma, tinea pedis, upper limb fracture and eczema, respectively. Except for contact dermatitis, the investigators assessed all of these AEs as not related to study medication.

No subject died in this trial until V3. During the follow-up phase, 1 subject of the bifonazole group died due to "cardiac failure" following non-occlusive mesenterial ischemia and multi organ failure as a result of extended malignant disease. The event was assessed by the investigator as not related to study medication.

Apart from the death, 1 SAE was documented in one subject of the placebo group during screening, 1 SAE in one subject of the placebo group during treatment phase 2, as well as 11 SAEs in 4 subjects of the bifonazole group, and 5 SAEs in 4 subjects of the placebo group during follow-up. In addition, 1 SAE was reported for a subject who dropped out during the screening phase, i.e., who received no study medication.

None of the SAEs was judged by the investigator as related to study medication.

Conclusion(s)
In this study, treatment with urea followed by bifonazole is a safe, well-tolerated and efficient antifungal therapy. The results show that treatment with bifonazole after successful nail ablation with urea adds a significant and clinically relevant benefit to onychomycosis therapy. This benefit, present at 3 months post-treatment, could no longer be observed at 6 months post-treatment in the whole study population. Subgroup analyses, however, revealed benefit of bifonazole until 6 months after treatment end in particular subject groups, namely subjects with only 1 affected nail, male subjects, and subjects older than 64 years.

Publication(s):	None		
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