2 SYNOPSIS

Title of study: Antifungal shampoo for the treatment of pityriasis capitis and scalp seborrhoeic dermatitis.		
Investigators: Dr Terrina Dickson		
Study Centre(s): Alba Science Ltd., 24 Broughton Street, Edinburgh, EH1 3RH		
Publication (reference): Not applicable		
Study period : *Date of first enrolment:* *Date of last completed:*	*8 months* *11/09/2012* *14/05/2013*	**Phase of development:** II
Objectives: To determine whether TBSH shampoo is significantly more effective than placebo in treating pityriasis capitis (severe dandruff) and seborrhoeic dermatitis of the scalp, when used to wash patients' hair twice weekly. To confirm the safety of TBSH shampoo in this indication.		
Methodology: The trial was a randomised placebo-controlled, double blind, parallel group evaluation in patients aged 14 years and over, presenting with pityriasis capitis (severe dandruff) or seborrhoeic dermatitis of the scalp.		
Number of patients planned and analysed: 250 patients were screened in order to randomise the required 114. In total 116 patients were randomised into the treatment phase.		
Diagnosis and main criteria for inclusion: Male and female patients aged 14 years and over, presenting with pityriasis capitis (severe dandruff) or seborrhoeic dermatitis of the scalp were eligible for inclusion provided that they: • had a history of severe dandruff for a minimum of the last two months. • had an overall dandruff severity score of 35 or more (out of a maximum of 80) • were prepared to attend the clinic twice a week for a total of 7 weeks and to have their hair washed by a technician at each study centre visit • were not subject to any of the exclusion criteria		
Test product, dose and mode of administration, batch number: Terbinafine shampoo (TBSH) batch TS29/6. Sufficient shampoo applied to wet hair to produce an abundant lather, massaged vigorously into the scalp, left for 1 to 2 minutes, rinsed off, and then the whole process repeated.		
Duration of treatment: During the 4 week treatment period the patients attended the clinic twice a week to have their hair washed by the technician using their allocated shampoo (TBSH or placebo)		
Reference therapy, dose and mode of administration, batch number: Placebo, batch TSP19/6. Dose and mode of administration as for test product.		

Criteria for evaluation:

Efficacy:

Primary efficacy variable:

- *Investigator assessed Overall Dandruff Severity Score (ODSS)*
  ODSS was assessed by the Investigator at screening, randomisation, at the end of the 4 week treatment period. ODSS assessment is based on the severity and area of flaking and scaliness of the scalp divided into 4 quadrants, resulting in a score range of 0-80. The primary efficacy variable was the improvement in ODSS from baseline 4 weeks of treatment.

Secondary efficacy variables:

- *Investigator assessed erythema*
  The severity of erythema was assessed by the Investigator at the start of the treatment period and after 2 and 4 weeks of treatment, using a 5 point scoring system (0 to 4). The analysis variable was the percentage of patients with improved investigator assessed erythema score at the end of the 4 week treatment period.
- *Patients' self-assessed improvement in dandruff severity*
  Patients were asked to assess their condition at the 2 and 4 week visits compared to the start of the treatment period, in terms of dandruff severity using an 8 point scoring system (0-7). The analysis variable was the percentage of patients with self-assessed significant improvement (i.e. score of 2, 1 or 0) at the end of the 4 week treatment period.
- *Patients' self-assessed pruritus*
  At baseline, 2 weeks and 4 weeks, patients were asked to score how itchy their scalp felt, on a scale of 0-4. The analysis variable was the percentage of patients with improved pruritus score at the end of the 4 week treatment period.

Safety:

Adverse events were monitored throughout the study and for two weeks following the patient's last visit to the test centre. Patients were given a section in their Treatment Diary in which to record any health problems that occurred during their participation in the study. Staff at the study centre questioned patients at each visit about any changes in health or adverse events.

Statistical methods:

Statistical analysis of the results was planned and performed by a consultant Chartered statistician appointed by the Sponsor.

The principal analyses are those performed on the Full ITT Analysis Set, but a decision to perform Per Protocol analyses, as provided for in the study Protocol, was confirmed in the Statistical Analysis Plan during blinded review. Analysis of covariance was used to analyse the primary outcome analysis variable of change from baseline ODSS, with baseline ODSS and the stratification factor of presence/absence of erythema at baseline included in the model and the treatment by baseline erythema interaction was investigated. Estimated treatment effects were presented with 95% confidence intervals and all statistical testing was two-sided using a 5% level of significance.

Summary

a) Efficacy results:

Primary Efficacy Variable - ODSS

Full ITT Analysis Set: Whilst both the Placebo and TBSH groups showed significant improvement in ODSS from baseline, the improvement for the TBSH group was not statistically significantly different from that of the Placebo group (TBSH group adjusted mean improvement of 18.9 units, 95% CI 15 to 23 units versus Placebo group 13.9 units, 95% CI 10 to 18 units, TBSH-Placebo difference 5.1 units, 95%CI –0.3 to +10.4 units). , The estimated TBSH treatment effect at 5 units was smaller than the expected treatment effect (8 units) used for the sample size determination in this study.

Per Protocol Analysis Set: In the Per Protocol analysis, the TBSH treatment effect was a little larger then in the ITT analysis (6.6 units, 95% CI 0.9 to 12.1 units) and was statistically significant. The confidence intervals demonstrate that the TBSH treatment effects in the ITT and Per Protocol analyses are not contradictory.

In addition, the Per Protocol analysis provided evidence, in a pre-specified analysis, that the effect of TBSH was significantly greater for patients with erythema at baseline than for patients without. For the TBSH group, the improvement from baseline was considerably greater for patients with erythema at baseline (24.9 units) than for patients without erythema at baseline (16.2 units) and this 8.7 unit difference in means was statistically significant, while for the Placebo group, the improvement from baseline was similar for the patients with erythema at baseline and for patients without. Consequently, the TBSH treatment effect for patients with erythema at baseline (11.0 units) was more than three times that for patients without erythema at baseline (3.1) The TBSH treatment effect for patients with erythema at baseline was statistically significant (11.0 units, 95% CI 2.4 to 19.6, p = 0.012), whilst that for patients without erythema at baseline (3.1 units, 95% CI –4.5 to +10.7, p = 0.42) was not statistically significant.

Secondary variables

Investigator assessed Erythema

Full ITT Analysis Set: Of the 53 patients with erythema at baseline, 11 of 28 patients (39%) in the TBSH group had improved erythema at their final assessment compared to only 5 of 25 (20%) in the Placebo group although this difference was not statistically significant due to the small number of patients involved.

Per Protocol Analysis Set: Of the 45 patients from the Per Protocol dataset with erythema at baseline, 10 of 24 patients (42%) in the TBSH group and 5 of 21 patients (24%) in the Placebo group had improved erythema at their final assessment but again this difference was not statistically significant due to the very small number of patients involved.

Patient self-assessed improvement in severity

Full ITT Analysis Set: The percentage of patients with self-assessed significant improvement in their dandruff severity at the final visit was 24.1% (14/58) for the TBSH group and 22.4% (13/58) for the Placebo group. The difference between the two groups was not statistically significant.

Per Protocol Analysis Set: As for the ITT analysis, the difference in the percentage of patients with self-assessed significant improvement in their dandruff severity was not statistically significant (TBSH group 25.5% and Placebo group 23.1%).

Patient self-assessed improvement in pruritus

Full ITT Analysis Set: Of the 70 patients with itching at baseline, 26 (79%) patients in the TBSH group had less itching at the final visit compared to 22 (59%) in the Placebo group. Although substantial in magnitude this difference was not statistically significant due to the relatively small number of patients involved. In a pre-specified analysis, there was evidence of an interaction between presence/absence of erythema at baseline and treatment with respect to this outcome. For those patients without erythema at baseline, there was a statistically significant difference between the TBSH and Placebo groups, with 94% of TBSH patients without erythema at baseline having reduced itching at the final visit compared to only 61% for Placebo patients without erythema at baseline despite the number of patients involved being very small (34 in total). For patients with erythema at baseline, the difference between the TBSH and Placebo groups was much smaller and not statistically significant.

Analysis of the ordinal outcome of the degree of improvement in itching showed a statistically significant difference in improvement in itching between the TBSH and Placebo treatment groups with the TBSH group showing better improvement in itching scores than the Placebo group.

Per Protocol Analysis Set: Of the 63 patients from the Per Protocol dataset with pruritus at baseline, 26 (84%) patients in the TBSH group and 20 (62%) patients in the Placebo group had improved pruritus at their final assessment. As for the ITT analysis, the difference between the two groups was large but just failed to achieve statistical significance at the 5% level due to the small number of patients involved. Analysis allowing for the presence/absence of erythema at baseline also just failed to show a statistically significant difference between the two treatment groups.

As for the ITT set, analysis of the ordinal outcome of the degree of improvement in itching showed a statistically significant difference between the TBSH and Placebo treatment groups with the TBSH group showing better improvement in itching scores than the Placebo group.

b) Safety results:

There were two serious adverse events, both from a single patient in the Placebo group that were considered to be not related to the study treatment. All of the other adverse events reported by patients were classed as mild, two of which led to discontinuation of the patient in the study (one during the washout phase, the other during the treatment phase). There were 56 in total, of which 26 were from the TBSH group and 24 in the placebo group (and 6 were during the washout period for patients not randomised into the treatment phase of the study). Of these, 26 reports were considered as possibly or probably related to the test products (mainly related to perceived lack of efficacy), 15 in the TBSH group and 11 in the placebo group.

Conclusion:

This study was designed to determine whether TBSH shampoo is significantly more effective than its placebo in treating pityriasis capitis (severe dandruff) and seborrhoeic dermatitis of the scalp, when used to wash patients' hair twice weekly.

Both the TBSH and Placebo groups showed statistically significant improvement from baseline for the primary efficacy parameter, ODSS, however, the estimated TBSH treatment effect was smaller than the expected effect size used for the sample size determination in this study, and consequently the TBSH treatment effect was not statistically significant in the ITT analysis. In the Per Protocol analysis, the improvement in the TBSH group was a little larger than in the ITT analysis and this led to it being statistically significantly greater than that of the Placebo group, although again the magnitude of the TBSH treatment effect was a little smaller than expected. In addition, the Per Protocol analysis showed that the effect of TBSH in improving ODSS was statistically significantly greater for patients with erythema at baseline than for patients without erythema at baseline. In both the full ITT analysis and the Per Protocol analysis, there is little evidence of the effectiveness of TBSH in patients without erythema at baseline and since more than half of the randomised patients did not have erythema at baseline, this effectively gives a considerably reduced sample size for providing evidence of the effectiveness of TBSH. For erythema as a secondary efficacy parameter, the TBSH treatment was effective in improving erythema in almost twice as many patients than the placebo, although the reduced sample size meant that this difference was not significant in either ITT or Per Protocol analysis.

There were no differences between TBSH and placebo for patient self assessed dandruff severity, but the TBSH did give a statistically significantly greater improvement than placebo in self assessed pruritus.

As an antifungal shampoo, TBSH would be expected to show particular efficacy in cases of pityriasis capitis (severe dandruff) and seborrhoeic dermatitis of the scalp with active fungal infection, and generally it is these cases which show a higher degree of erythema.

Date of report: 01 May 2014