SYNOPSIS

Name of Sponsor: TopoTarget A/S

Name of Finished Product/Active Ingredient:
Baceca® (2-propyl pentanoic acid (2-PPA), also known as valproic acid)
Zorac® (tazarotene)

Title of Study:
A randomised, double-blinded parallel group study to compare efficacy and tolerability of topically applied Baceca and Tazarotene against placebo and Tazarotene in patients with basal cell carcinoma

Protocol : Baceca-030-BCC with amendment 1.

Investigators:
H.C.Wulf

Study Centers:
Dept. of Dermatology,
Bispebjerg Hospital, Copenhagen, Denmark

Publication (reference):
Not applicable

Study Period: **First subject visit to last subject visit**
19 oct 2005 to 11 apr 2008

Phase of Development:
IIa

Objectives
Primary objective was estimation and comparison of the rate of complete remission in two treatment regimens in patients with BCC accrued from one center, Bispebjerg University Hospital, Copenhagen.
Secondary objectives: Evaluation of safety and tolerability of repeated topical applications of Tazarotene and Baceca® or of Tazarotene and placebo in patients with BCC

Methodology:
The study was carried out in one centre as a double-blind, randomized study. In both treatment groups patients would have to treat the dry and clean skin of one BCC lesion once daily prior to bedtime with one of the following topical treatment combinations:

Treatment group 1: Week 1 – 8: placebo gel followed by Tazarotene gel 15 to 30 min later
Treatment group 2: Week 1 – 8: Baceca® followed by Tazarotene gel 15 to 30 min later
Group 1 + 2 (extension phase): Week 10 – 17 Baceca® followed by Tazarotene gel 15 to 30 min later
Patients with a biopsy-confirmed diagnosis of BCC for the selected lesion were randomly assigned to one of the above mentioned treatment groups. After clinical assessment and documentation of the baseline disease characteristics, the patients were provided with medication for the randomized treatment.
All subjects would return to the clinic at specified intervals for assessment of the efficacy and tolerability of the treatment and blood sampling. After 8 weeks of treatment all treated lesions would be clinically evaluated at a visit taking place one week after the end of treatment. In case of complete clearance a biopsy would be performed to confirm complete remission. All other patients would continue treatment with Baceca® and Tazarotene for another 8 weeks (extension phase). 18 weeks after start of treatment another biopsy of the lesion already examined at the screening visit would be performed in all patients taking part in the extension phase. The treatment efficacy was to be evaluated by means of the histological examination, by measuring the size of the lesion and by assessment of the clinical profile.

Number of Subjects/Patients:
A total of 50 patients were randomized, 25 patients in each group. All patients are included in the safety population, two patients had no response values given.

Diagnosis and Main Inclusion Criteria:
1. Men and women aged 18 years and older
2. Informed consent signed by the patient
3. Patients with at least one BCC tumor could be included if the lesion met the following criteria:
    - macroscopically (clinically) consistent with BCC
    - histological confirmed diagnosis of BCC for the tumor lesion to be treated.
    - tumor at least 0.5 cm^2 in size, but not more than 4 cm^2
    - exhibits clearly defined borders
    - easily identifiable and treatable
    - located anywhere on the body except on eye lids, nose, lips, mucosa or in anogenital area
    - A tumor biopsy within the last 6 months is usuable according to protocol. The BCC must not have been treated, neither with a drug nor a non-drug treatment which could have a direct influence on the tumor.

Test Products, Dose, Route of Administration & Batch Number:
Baceca® 3% gel for topical administration was supplied as a clear off-white to yellow, semi-solid gel containing 30 mg/ml 2-PPA, soybean lecithin, phosphatidylglycerol, and 0.2% sorbic acid. Batch numbers 04M1001 and 06C31002A.

Tazarotene was provided as a 0.1% gel in form of the marketed product Zorac®. Batch numbers 24982 and 40949.
The *placebo* was supplied as a gel for topical administration of the same type and outer appearance as Baceca®. The placebo gel is optically identical to Baceca® and can only be identified by means of the randomization list and the emergency code envelopes. Batch number was 05E18004.
The patients were provided with tubes containing the appropriate amount of gel for 8 weeks of treatment according to randomization. Patients were instructed to apply Baceca® or the placebo gel of tube A thinly in the evening before bedtime to the target lesion. Fifteen to thirty minutes thereafter the tazarotene gel of tube B was applied thinly. This procedure was repeated every day for the full 8 weeks. For the following 8 weeks (extension phase) placebo was replaced by Baceca® for group 1. Patients of group 2 who did not show a complete clearance after the first 8 weeks of treatment would continue the treatment of the BCC lesion.
During the study the supplies were provided by KLIFO A/S (Copenhagen) for a total of 50 patients, packed according to the randomization list.

Reference Therapy, Dose, Route of Administration & Batch Number:
Tazarotene and placebo, see above

Criteria for Evaluation:
Safety: Assessments included adverse events (AEs) evaluated using the National Cancer Institute Common Toxicity Criteria (NCI-CTC), physical exam results, and clinical lab results (including hematology, coagulation parameters, serum chemistry). Furthermore patient observations were noted in a personal diary. The MedDRA dictionary was used for assigning system organ classes and preferred terms.
Efficacy: Response rate as proportion of patients showing complete remission with no histological evidence for BCC in the posttreatment biopsy performed after 8 or 16 weeks of treatment, respectively, proportion of patients with partial remission, change in the size of the BCC lesion, change in the clinical profile of the target BCC lesion. The response rate at the 3-month follow-up was furthermore included.

Statistical Methods:
The primary analysis was on an intention to treat basis. The response rates, using the endpoints described above, were tested using Fishers exact test. P-values less than 5% are considered significant.
Demographic data were summarized for all patients by treatment and overall using descriptive statistics (N, mean, standard deviation, minimum, median, and maximum). Randomization and performance of the study in a double-blind manner is considered sufficient to ensure the comparability of the treatment groups regarding possible disruptive factors.
The adverse event incidence (proportion of patients who experienced an adverse event) were calculated by dividing the number of subjects who experienced an adverse event

by the total number of subjects exposed to the respective treatment. Lesional and nonlesional adverse events were analysed separately. The summary tables for lesional and non-lesional adverse events were broken down by treatment and system organ class. Additional tables were generated by treatment for the relationship of AEs to study medication (related/not related) and for the severity of AEs. If a subject experienced more than one adverse event in any body system group he/she was counted once in that group and also once only in the overall total of subjects experiencing adverse events in any body system group..
Laboratory data were presented in the measured units. Values outside the investigator's normal range were flagged as H (above the normal range) or L (below the normal range) in the listings. Shift tables for all parameters were generated (i.e. tables with descriptive statistics of differences of post-dose assessments vs. the corresponding screening result).
Frequency tables by treatment were generated for patient's assessment of tolerability.

Summary:
Safety Results:
No drug related SAEs were reported. The most frequent adverse events (AE), all grades, were lesional events such as erythema (17/25 vs. 20/25 patients in the two treatment groups), itching (18 vs 15 patients), ulceration (11 vs 16 patients) and local pain (8 vs 6 patients). There were no statistically significant differences between the two groups with respect to safety results.

Efficacy Results:
Both treatment regimens induced tumor regression within the first 8 weeks and tumor regressions continued during the following treatment and during the 3-months follow-up. While the complete remission rates at 8 weeks were non-different and below 15 %, the frequency increased with time and at the 3-month follow-up 69% achieved CR in the Baceca® arm versus 48% in the control arm (with small numbers the difference is not statistically significant, p=0.32). Further follow-up at 6 months and at 12 months is carried out.

Conclusion:
The combination of Baceca® (2-propyl pentanoic acid) and Zorac® (tazarotene) demonstrated antineoplastic effect against basal cell carcinoma. The frequency of complete remissions increased with time up to the 3-month follow-up time point, where it reached 69% in the Baceca®+Zorac® group versus 48 % in the group treated with Zorac®+ placebo for 8 weeks followed by 8 weeks of Baceca®+ Zorac®. With small numbers the difference is not statistically significant(p=0.32). Both regimens were well tolerated with only moderate lesional adverse events.

Date of Report:
May 7, 2008