ABBREVIATED CLINICAL STUDY REPORT

FINAL VERSION

A Randomized, Double-blind, Placebo and Active Treatment-Controlled Study in Psoriatic Patients to Assess the Tolerability, Pharmacokinetics and Efficacy of a Cream Formulation Containing 3% of P32/98

Clinical Phase	IIa
Probiodrug Study No.:	PBD-0313
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Last Medication:	14 May 2007 (Part B)

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SIGNATURE PAGE

This is to confirm that to the best of our knowledge the study has been performed in accordance with the requirements of this clinical study protocol and also in accordance with "good clinical practice" (GCP) and all applicable regulatory requirements, including, where applicable, the 1996 version of the Declaration of Helsinki.

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25-June 2008
Date

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Date

2 SYNOPSIS

Name of Sponsor/Company: Probiodrug AG Name of Finished Product: Name of Active Ingredient: P32/98	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)

Title of Study:

A Randomized, Double-blind, Placebo and Active Treatment Controlled Study in Psoriatic Patients to Assess the Tolerability, Pharmacokinetics and Efficacy of a Cream Formulation Containing 3% of P32/98

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According to Amendment No. 1, dated 23 Jan 2007

Publication (reference): None at the time of this abbreviated report	
Study Period (years): Mar 2007 – Jul 2007	Clinical Phase: IIa

Objectives:

Primary:

- To assess the efficacy of a 3% cream formulation of P32/98 compared to placebo

Secondary:

- To assess the local and systemic tolerability and safety of a 3% cream formulation of P32/98 after application to healthy and psoriatic skin (according to Amendment No. 1, dated 23 Jan 2007)
- To assess the pharmacokinetics of a 3% cream formulation of P32/98 after application to healthy and psoriatic skin (according to Amendment No. 1, dated 23 Jan 2007)

Methodology:

This was a single-center, randomized, placebo and active treatment controlled, single and multiple-dose proof-of-concept study with two sequential cohorts in patients with psoriasis to assess the tolerability, pharmacokinetics and efficacy of a cream formulation containing 3% of P32/98. In Cohort A, the study consisted of a screening visit within −21 to −1 day before Day 0, an ambulatory

experimental part (Days 0 to 4) and a study completion evaluation >5 days after the last dosing day (according to Amendment No. 1, dated 23 Jan 2007). In this cohort P32/98 or placebo was applied

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in a double-blinded fashion on non-lesional (healthy) skin over five days for the assessment of safety and pharmacokinetics after application of P32/98 (ratio verum:placebo 3:1). In Cohort B the study consisted of a screening visit within 21 to 4 days before Day 0, an ambulatory experimental part (Days –3 to 28) and a study completion evaluation >5 days after the last dosing day. In this cohort the study was double-blind for P32/98 and placebo treatment and open for the active comparator within each patient. A single topical dose of P32/98, placebo and active comparator was applied onto three different lesional skin sites selected by a dermatologist. After a single application of investigational products a dermatologist examined the treated skin sites for local tolerability. As no safety concerns were raised, a 28-day multiple, once-daily, placebo-controlled topical treatment commenced on the selected target lesions treated with 3% P32/98, placebo and active comparator.

The planned study duration was approximately 35–47 days for each patient.

Number of Patients (planned and analyzed):

Part A		Part B	
Number of patients screened:	12	Number of patients screened:	26
Number of patients failed:	0	Number of patients failed:	5
Number of patients included:	8	Number of patients included:	15
Number of patients withdrawn:	0	Number of patients withdrawn:	14
Number of patients completed:	8	Number of patients completed:	1

Diagnosis and Main Criteria for Inclusion:
Male and female patients with stable plaque-type psoriasis, aged between 18 and 60 years (both inclusive), with a Body Mass Index (BMI) between 20 and 30 kg/m² (both inclusive).

Test Product, Dose and Mode of Administration, Batch Number:

Test product/ formulation:	P32/98 / cream
Strength:	3% of P32/98
Planned Doses:	3% once daily (Cohorts A and B)
Mode of Administration:	topical
Batch No.:	Cohort A:150207/3%; Cohort B: 230307/3% and 260407/3%

Reference/Comparator Therapy, Dose and Mode of Administration, Batch Number:

Reference product/ formulation:	Placebo matching P32/98 cream
Strength / Dose:	n/a
Mode of Administration:	topical
Batch Number:	Cohort A: 150207; Cohort B: 010307
Comparator product/ formulation:	Silikis ® 3µg/g / ointment (Cohort B, only)
Strength:	3 µg/g
Dose:	3 µg/g once daily
Mode of Administration:	topical
Batch Number:	6100049

Pre-Treatment Therapy, Dose and Mode of Administration:

Pre-treatment product/ formulation:	Salicylvaseline 5% / ointment
Strength:	5%
Dose:	5% once daily
Mode of Administration:	topical

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Duration of Treatment:
Treatment in Cohort A took 5 days and the planned treatment period of Cohort B was 28 days.

Criteria for evaluation:

Primary:

1. Thickness of psoriatic epidermis assessed by high-frequency ultrasound

Secondary:

1. Echo density of the psoriatic skin assessed by high-frequency ultrasound
2. Scoring of target lesions by a dermatologist (PGA)
3. Thickness of psoriatic epidermis, assessment of inflammation and proliferation parameters and T-cell counts by skin punch biopsy
4. Local and systemic tolerability after application to healthy and psoriatic skin
5. Safety laboratory, vital signs, 12-lead ECG, adverse events monitoring after application to healthy and psoriatic skin
6. Pharmacokinetics: Plasma concentrations of P32/98 after application to healthy and psoriatic skin

According to Amendment No. 1, dated 23 Jan 2007

Statistical Methods:
Although not planned in the protocol, an interim analysis was introduced according to an interim statistical analysis plan (SAP) after the study was stopped prematurely due to several unexpected adverse events. The primary aim of this interim analysis was to check whether any effect was seen with the active treatment and positive control as well as to explore the reason(s) for the observed safety issues (skin blisters). The outcome of this interim analysis is described in this abbreviated report.

The primary endpoint was to assess the epidermal thickness after a 3% cream formulation of P32/98 compared to placebo by high-frequency ultrasound. Secondary endpoints included the differences between P32/98-treated and placebo-treated target lesions in the change of echodensity of the skin as assessed by high-frequency ultrasound, in the scoring of target lesions by a dermatologist, in the thickness of epidermis, assessment of inflammation and proliferation parameters, and T-cell counts as assessed by skin punch biopsy, and in local and systemic tolerability. Additionally, secondary analyses included safety laboratory, vital signs, 12-lead ECG, adverse events monitoring and plasma concentrations of P32/98.

All demographic, tolerability and efficacy variables were listed and summarized by descriptive statistics, as appropriate. Plasma concentrations were listed only. All statistical tests were performed using a two-sided significance level of 5%. However, all statistical analyses were interpreted in an exploratory manner only. All evaluable data were accounted for in this interim analysis.

SUMMARY OF RESULTS:

Efficacy:

- Sonography results did not show the desired effect of P32/98, i.e. a decrease in average thickness of infiltrate and a corresponding increase in intensity (density) after application to lesional skin sites. In contrast, there was a mean increase in average (thickness) of infiltrate

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(p<0.05) and a corresponding mean decrease in its intensity (density; p<0.01), which were both statistically significant on Day 15.

- A treatment effect, i.e. a decrease in average (thickness) of infiltrate, which was statistically significant at EOT (p<0.05), and a corresponding not statistically significant increase in its intensity (density) was observed for the comparator, only.
- The average (thickness) of the entry echo decreased from baseline after all treatments, which reached statistical significance only after application of comparator and placebo on Day 15, but not after P32/98. Vice versa, the intensity (density) of the echo entry layer tended to decrease overall, which reached statistical significance only after P32/98 (p<0.05).
- The total skin thickness and intensity (density) showed only negligible changes from baseline after comparator or placebo, whereas a statistically significant increase (p<0.05) in thickness and decrease in density (p<0.05) was observed after P32/98 on Day 15.
- Skin punch biopsy revealed no statistically significant change in the epidermal thickness at the skin site treated with P32/98 (p>0.05), whereas a statistically significant decrease from Day −1 (baseline) was found after placebo treatment at EOT (p<0.05).
- The expected reduction in the number of T-cells and APCs was not observed after application of P32/98 to lesional skin sites. In contrast, there was rather an increase in the number of T-cells and APCs, which was statistically significant (p<0.05) for cells expressing CD3, CD8, CD11c and HLA-DR.
- There was also no reduced activation of T-cells and APCs after treatment with P32/98 as assessed by mRNA expression of IFN-gamma, interleukin-22 and CD69 and no reduction in the activation/proliferation of keratinocytes as assessed by mRNA expression of cytokeratin-16, CXCL-9 or interleukin-19. In contrast, a statistically significant increase was observed after treatment with P32/98 for the expression of CD69 from baseline at EOT (p<0.05).
- The PGA score at EOT showed slight improvements compared to baseline at skin areas treated with the comparator (−0.9 ±1.1), whereas almost no change was seen after placebo (−0.2 ±0.9) and a slight mean increase after P32/98 (0.5 ±1.0).

Pharmacokinetics:

- There were no quantifiable plasma concentrations of P32/98 in any patient.

Safety:

- Repeated application of a single topical dose of P32/98 (3%) on selected lesional skin sites for 6 to 29 days was not well tolerated in patients with psoriasis.
- A total of 9 of 15 patients were withdrawn due to adverse events that were localized at the P32/98-treated target sites. The study was, therefore, stopped prematurely.
- Most AEs occurred at the target skin sites treated with P32/98, all of which, except one, were considered at least possibly related to treatment by the Investigator. All the other AEs were considered unlikely related to treatment by the Investigator.
- There were no apparent differences in the AE profiles of patients treated with P32/98 in both cohorts and patients who were only treated with P32/98 in Cohort B.
- There were no deaths, no serious adverse events or significant adverse events in this study.
- The intensity of all 19 treatment-emergent AEs was mild (13) or moderate (6).

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Conclusions:

- Overall, P32/98 (3%) was not well tolerated in most of the patients with psoriasis when applied to lesional skin sites for 6 to 28 days.
- A total of 9 of 15 patients were withdrawn due to adverse skin reactions, which was the reason to stop the study in all patients.
- Sonography results revealed a statistically significant ($p<0.05$) increase in the average thickness and decrease ($p<0.01$) in intensity (density) of the infiltrate layer after treatment with P32/98 on Day 15, which was the opposite of the expected therapeutical effect.
- In contrast, application of a comparator (active control, calcipotriol) to the same patients led to a statistically significant decrease in the average thickness ($p<0.01$) and a not statistically significant increase in intensity (density) of the infiltrate layer at end-of-trial, thus indicating a therapeutical effect and, in addition, a proof-of-concept for the method of measurement.
- The PGA score supported the sonography results as it showed a slight mean increase from baseline after P32/98 (0.5 ±1.0), whereas a slight mean decrease was seen after the comparator (−0.9 ±1.1) and almost no change after placebo at EOT (−0.2 ±0.9).
- Skin punch biopsy data revealed that the number of T-cells and APCs after treatment with P32/98 increased statistically significantly ($p<0.05$) from baseline in the cells expressing CD3, CD8, CD11c and HLA-DR. Statistically not significant increases from baseline in the mRNA expression of interleukin-19 and CXCL-9 and a statistically significant increase in CD69 were also observed after application of P32/98 at EOT.
- These immunohistological observations support the assumption of an acute inflammatory immune response as a toxic or allergic reaction to the applied dose of P32/98. The true nature of this reaction remains undecided, although the experts' opinion tends to the assumption of an allergic reaction.
- No quantifiable plasma concentrations of P32/98 were observed in any patient.
- Based on the results of this study and based on the execution of the activities recommended by BfArM, it can be concluded that the project could continue in development and that the IMP may be a potential new drug candidate for the treatment of psoriasis.

Date of the Report: 06 Mar 2008