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:	13069	NCT00859196
Study Phase:	IV Interventional	
Official Study Title:	A randomized, double-blind, single centre, placebo-controlled pilot study to assess on a molecular level the influence of a 5% dexpanthenol ointment in subjects with previously injured skin by investigation of skin biopsies	
Therapeutic Area:	Dermatology	
Test Product		
Name of Test Product:	Dexpanthenol (Bepanthen, BAY 81-2996) ointment	
Name of Active Ingredient:	Dexpanthenol	
Dose and Mode of Administration:	30 µL of 5% dexpanthenol applied topically on 3 cm^2 skin	
Reference Therapy/Placebo		
Reference Therapy:	Matching placebo: Bepanthen® (Bepanthen Wund-und Heilsalbe) ointment	
Dose and Mode of Administration:	30 µL of matching placebo applied topically on 3 cm^2 skin	
Duration of Treatment:	Group I: One (1) application 12 ± 1 hours after wounding on first day Group II: Five (5) applications every 12 ± 1 hours after wounding Group III: Eleven (11) applications every 12 ± 1 hours after wounding	
Studied period:	Date of first subjects' first visit:	05 FEB 2009
	Date of last subjects' last visit:	03 MAR 2009
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	None	
Study Centre(s):	This study was conducted at a single center in Germany.	
Methodology:	Each subject received both dexpanthenol (dextrorotatory [D] isomer of pantothenic acid) and placebo, each applied to one predefined test area on the lower/outer back. At the first day (d1) test areas were defined. Two 4 mm biopsies were taken from each subject at the lower/outer back (buttock) in order to induce wounds at test areas (minimal distance of at least 8 cm between the 2 test areas). Afterwards, wounds were covered with a protective bandage and the subjects left the study center. Approximately 12 ± 1 hours after wounding, subjects returned to the study center for the first application of the study treatments. The procedures for the 3 study groups are described separately below:	

	Group I • d1 wounding of two test areas with a 4 mm biopsy • Twelve hours after wounding application of dexpanthenol or the respective placebo • Twenty-four (24) hours after wounding 2 additional 8 mm biopsies taken from injured and treated skin for efficacy analysis Group II • d1 wounding of two test areas with a 4 mm biopsy • Product application every 12 hours after wounding of the test areas (dexpanthenol or the respective placebo; a total of 5 treatments) • Seventy-two (72) hours after wounding 2 additional 8 mm biopsies taken from injured and treated skin for efficacy analysis Group III • d1 wounding of two test areas with a 4 mm biopsy • Product application every 12 hours after wounding of the test areas (dexpanthenol or the respective placebo; a total of 11 treatments) • One hundred-and-fourty four (144) hours after wounding two additional 8 mm biopsies taken from injured and treated skin for efficacy analysis The 8 mm skin biopsies were sent for gene expression analysis and histology. The healing of the wounds was followed up. Five (5) days after the 8 mm punch biopsies a control visit took place, and 10 to 12 days after the 8 mm punch biopsies the stitches were taken out. At each visit, adverse events and concomitant medication were carefully monitored. Overall, the total duration of this study was approximately 3 weeks including the time needed for screening and follow-up of injured and treated test areas.
Indication/ Main Inclusion Criteria:	Indication: Wound healing Main Inclusion Criteria: Healthy male and female Caucasian subjects 18 to 45 years of age and with a skin type stage I to IV.
Study Objectives:	<u>Overall:</u> To analyze the efficacy of pantothenate on wound healing by investigation of gene expression in dermal fibroblasts and keratinocytes on a molecular level involved in skin proliferation after wounding of the skin and three different numbers of applications.
Evaluation Criteria:	<u>Efficacy (Primary):</u> Analyses of the proliferative effect of pantothenate on induced wounds via investigation of gene expression in dermal fibroblasts and keratinocytes. Comparison of active versus placebo treatment in 3 groups differing in the number of applications and analyses of the different expression pattern at each point of time. <u>Efficacy (Secondary):</u> Not applicable

	Safety: Documentation and analysis of adverse events, and documentation of concomitant medication. Baseline safety assessments included pregnancy test for women of childbearing potential, human immunodeficiency virus (HIV) and hepatitis test, vital signs measurement, medical history records, physical examination (focused on skin examination) and skin classification.
Statistical Methods:	Efficacy (Primary): Gene expression analysis was performed. Total Ribonucleic Acid (RNA) was isolated and gene expression was analyzed using GeneChip® Human Exon 1.0 ST arrays. Data analysis was performed using the Bioconductor packages under integrated suite of software facilities for data manipulation, calculation and graphical display (R). The whole dataset were normalized with PLIER. Low expressed genes were filtered before RankProduct was involved to distinguish differentially expressed genes. Genes exceeded a fold-change threshold of 1.5 and met a significance criterion of $P < 0.01$ were considered as differentially expressed. Efficacy (Secondary): Not applicable Safety: Demographic and safety data were listed and described in summary tables by treatment group. Frequency tables for qualitative data were provided. Adverse events were summarized based on Medical Dictionary for Regulatory Activities (MedDRA) version 12.0. The incidence of treatment-emergent adverse events was tabulated by treatment group and by left or right site dexpanthenol application, using MedDRA. Frequency tables of concomitant medication were provided.
Number of Subjects:	Planned: 15 subjects, 5 per study group Analyzed: Safety: 15 subjects, 5 per study group Efficacy: 9 subjects, 3 per study group

Study Results
Results Summary — Subject Disposition and Baseline
Fifteen Caucasian subjects, aged between 20.0 and 45.0 years (mean age: 34.7 years), with a BMI between 19.0 and 29.7 kg/m^2 (mean BMI: 23.40 kg/m^2), and skin type I to IV were enrolled into the study. In each study group, subjects were randomized to 1 of 2 different application conditions concerning the location of dexpanthenol and placebo applications: Treatment A: dexpanthenol right and placebo left site of lower/outer back (buttock) Treatment B: Placebo right and dexpanthenol left site of lower/outer back (buttock) The number of subjects per study group was as follows: In Group I: Treatment A: n=2 and Treatment B: n=3 In Group II: Treatment A: n=2 and Treatment B: n=3 In Group III: Treatment A: n=4 and Treatment B: n=1 All subjects complied with the inclusion and exclusion criteria with respect to age, BMI, and skin type. All 15 subjects enrolled were treated with both dexpanthenol and placebo according to the planned treatment schedule. No protocol deviation occurred. None of the subjects terminated the study prematurely. Thus, all 15 subjects completed the study according to protocol. Data analysis sets Safety Sample (SS): n = 15 Intent-to-treat (ITT) sample: n = 15 Per-protocol (PP) sample: n = 15 Sample for efficacy analysis: n = 9 (3 subjects per group)
Results Summary — Efficacy
Genes exceeding a fold-change threshold of 1.5 and meeting a significance criterion of P <0.01 were considered as differentially expressed. Significant effects of dexpanthenol on gene regulation in comparison to placebo treatment could be revealed in all samples from all 3 time-points analyzed, but especially in Group II (5 applications) an upregulation of 101 genes after dexpanthenol treatment was detected. These included genes coding for MMP23A, ketohexokinase, CXCL1, CCL18, CCR1, CXCR4, IL-1β and IL-6, CYP1B1, and HSPB3. Only the listed genes were analyzed by PCR. qRT-polymerase chain reaction (PCR) analysis revealed a 6-fold upregulation of messenger RNA (mRNA) regulation of CYP1B1, 5.5 fold upregulation of IL-1β, 6.7 fold upregulation of IL-6, 2.7 fold upregulation of CCL18, 3.4 fold upregulation of CCR1 and 3 fold upregulation of CXCL1 in skin samples from 1 subject of Group II treated with dexpanthenol 5 times within 72 h in comparison to placebo. In samples from Group III, strong upregulation of several keratin associated proteins such as KRTAP4-2 by dexpanthenol was detected, which could be confirmed by qRT-PCR analysis in dexpanthenol treated samples from all 3 subjects analyzed.
Results Summary — Safety
The study treatments (5% dexpanthenol and placebo) and the study procedures were well tolerated. Four subjects complained about adverse events during this study including 2 with hematoma, 1 with headache, and 1 with common cold. None of these 4 adverse events was treatment-related and all were of mild intensity. Headache and common cold occurred a few days after the last application of the study treatment and were therefore considered to be unrelated to the study treatments. Hematoma occurred 1 day after a biopsy was taken (either 1 day after the 4 mm biopsy for wound induction or after the 8 mm biopsy for gene investigation). Their occurrence was explained by the study procedures, i.e., biopsy and wound stitching. No death, other serious or significant adverse event occurred. No adverse event was of severe intensity. No subject discontinued due to an adverse event. All adverse

events were resolved by the end of this study.
Conclusion(s) • In this study, significant effects of dexpanthenol on gene regulation in comparison to placebo treatment could be revealed in all samples from all 3 time-points analyzed but especially in Group II, an upregulation of 101 genes was detected after dexpanthenol treatment. • This *in vivo* study showed strong correlations to previous *in vitro* data using cultured dermal fibroblasts. • Topical treatment of 30 µL 5% dexpanthenol on induced wounded areas over a time period of 1 to 6 days was considered safe and well tolerated.

Publication(s):	None		
Date Created or Date Last Updated:	14 MAY 2012	Date of Clinical Study Report:	11 FEB 2011

Investigational Site List

Marketing Authorization Holder in Germany	
Name	Bayer Vital GmbH
Postal Address	D-51368 Leverkusen, Germany
Sponsor in Germany	
Legal Entity Name	Bayer HealthCare AG
Postal Address	D-51368 Leverkusen, Germany

List of Investigational Sites						
No	**Investigator Name**	**Facility Name**	**Street**	**ZIP Code**	**City**	**Country**
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