CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE for:

APPLICATION NUMBER: 020611

TRADE NAME: Dovonex Scalp Solution 0.005%

GENERIC NAME: Calcipotriene solution

SPONSOR: Bristol-Myers Squibb Pharmaceutical Research Institute

APPROVAL DATE: 03/03/97

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAR 03 1997

NDA 20-611

Bristol-Myers Squibb Pharmaceutical Research Institute
Attention: David Silberstein
100 Forest Avenue
Buffalo, New York 14213-1091

Dear Mr. Silberstein:

Please refer to your June 30, 1995, new drug application (NDA) submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act for Dovonex (calcipotriene solution) Scalp Solution, 0.005%.

Reference is also made to our not approvable letter dated July 3, 1996.

We acknowledge the receipt of your correspondence and amendments dated July 8, August 5, September 4 and 30, October 30, 1996, and January 17, 20, 28, 29, and 31, and February 25, 1997.

This new drug application provides for topical treatment of chronic, moderately severe psoriasis of the scalp.

We have completed the review of this application, as amended, including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed revised draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed revised draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

The carton and bottle labeling will include the following: "Avoid sunlight" will appear after the temperature declaration, and the warning section will state in bold face type "Drug Product Is Flammable. Keep Away From Open Flame".

Please submit twenty copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-611. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We acknowledge your Phase 4 commitments specified in your submission dated September 4, 1996. These commitments are described below:

Conduct photodegradation studies under current ICH guidelines:

Protocols, data, and final reports should be submitted to your IND for this product, and a copy of the cover letter sent to this NDA. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitment."

In addition, we acknowledge your commitment, dated March 28, 1996, to conduct dermal and photocarcinogenicity studies using a clinical formulation of calcipotriene.

We acknowledge your correspondence dated February 25, 1997, stating your understanding that the storage statement "Avoid sunlight" will be included in the labeling until 24 months data from the photostability studies has been received and found acceptable by the Agency. At that time you will be allowed to delete this storage statement from the labeling, if the Agency finds that the product remains within specifications at that time.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug when its available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Robin Anderson, RN, MBA
Project Manager
(301) 827-2020

Sincerely yours,

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental
Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

JUL -3 1996

NDA 20-611

Bristol-Myers Squibb Pharmaceutical Research Institute
Attention: David L. Silberstein
100 Forest Avenue
Buffalo, New York 14213-1091

Dear Mr. Silberstein:

Please refer to your June 30, 1995, new drug application, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dovonex (calcipotriene solution) Solution, 0.005%.

We acknowledge receipt of your correspondence dated July 24 and 26, August 1, 18 and 30, September 15, October 25 and 26, and November 20, 1995; March 8, 15 and 28, May 31, and June 3, 7, 11, 12, 17, 18 and 25, 1996.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are as follows:

1. The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product do not comply with the current good manufacturing practice regulations in parts 210 and 211.

2. Under the product specifications, the identification test is unacceptable because it failed to provide a different Identity Test from the test used to assay calcipotriene (HPLC test). Therefore, an ID test, such as IR or UV, should be included in the finished product specifications.

3. It is understood that Bristol-Myers Squibb will use Leo Pharmaceutical Products' HPLC method (# 9-1004-3) for the assay of calcipotriene in Dovonex Solution as their regulatory method. It is also understood that all release and stability testing will be performed by Leo Pharmaceutical Products. The HPLC methods [# 9-1004-3 (2); without methyltestosterone as the internal standard] may be used by Bristol-Myers Squibb as the alternate method. If Bristol-Myers Squibb were to use this method as their regulatory method, it would have to be validated. Therefore the accuracy, precision, specificity

and linearity data should be provided to show that both HPLC methods are equivalent.

In addition, although not the basis for the non-approval of this application, the following areas should be addressed in any resubmission of this application:

1. Based on inspectional observation, only a 140 liter batch size has been validated in the existing Ballerup, Denmark, facility. The new manufacturing area, where production size lots are intended to be manufactured, is not yet available for production, and the process validation protocol has not been completed. The use of this new manufacturing facility will require a supplement to the application when approved.

2. Please provide a commitment to conduct the following Phase 4 study:

3. The excipients under the SPECIFICATIONS & METHODS FOR DRUG PRODUCT COMPONENTS should include the following information:

   a. An indication of whether the inactive ingredients are controlled by USP and/or NF monographs. These ingredients must meet the requirements as stipulated in the USP/NF monographs.

   b. A side-by-side comparison should be made of the European Pharmacopoeia, British Pharmacopoeia, USP and NF monographs for the inactive ingredients in order to demonstrate the differences in specifications for these ingredients.

4. The METHODS OF MANUFACTURING AND PACKAGING of the finished drug product should include the following information:

   a. A discrepancy was observed between the unexecuted batch record and the representative batch record for several of the inactive ingredients in the finished product (e.g., sodium citrate, and water); the calculations for these ingredients should be reconciled. Also, please submit an English translation

of these SOPs because it was submitted in Danish.

b. The manufacturing procedure describes the finished solution as being filtered into bulk containers (last step). In this regard, the following information is requested:

1. The bulk container/closure system for the finished product;

2. Storage conditions and a maximum time for storage of the bulk product before packaging.

c The manufacturing procedure failed to provide information on the packaging operations for the finished solution. This description should indicate the equipment used for filling the finished solution into the marketed container/closure system. The target fill weight specifications should also be included.

d. The in-process tests should be expanded to include microscopic examination and viscosity measurement to assure the quality of the drug product. In this regard, microscopic examination will show the absence of undissolved particles in the solution and assure total solubility of calcipotriene. The viscosity measurement will assure that the solution remains slightly viscous during manufacture.

5. Regarding the SPECIFICATIONS AND METHODS FOR THE DRUG PRODUCT:

a. A copy of Leo's testing specifications used in the stability of the finished product was inadvertently submitted on pg. 176, instead of submitting Leo's Regulatory Specifications for the finished product. In this regard, the description of the product should indicate the physical characteristics of the solution; e.g., clear, colorless, etc.

b. Under the product specifications, the specifications should be expanded to include a test for viscosity and weight loss because they are included in the stability specifications for Dovonex (calcipotriene) Solution. Their specification limits should also be included.

6. Under STABILITY of the finished drug product, the following information should be submitted:

a. The Test Specifications used by BMS in monitoring the stability of the finished product, specifically those reported in Stability Report KRAZ-RJ-95007, are different from those used by Leo Pharmaceuticals. These specifications should be identical to the specifications submitted by Leo.

b. There should be a formal written stability protocol as required by the Agency's stability guidelines for batches of drug product placed on the stability studies. This stability protocol should include a detailed plan of the studies to be performed and the methodology used to obtain acceptable stability data in support of the proposed expiration. The plan should include the test stations, storage conditions, sampling procedures, methods of testing at each test station, and the standard three point stability commitment.

The stability protocol should be common to both BMS and Leo Pharmaceutical Products'.

c. The specifications used in the stability studies on the finished product are inadequate as follows:

1. They do not include limits for viscosity and weight loss.
2. The appearance test does not indicate the physical attribute for odor and clarity of solution.
3. The calcipotriene related substances should contain the limits and test for 5,6-trans calcipotriene.
4. The established 10.0% total impurities limit is significantly higher than the observed values. A reduction in the limit is recommended.

7. Please provide the following information in the Environmental Assessment Section to complete the Environmental Assessment evaluation:

a. The exact location of both the drug substance and the drug product manufacturing facilities.
b. A brief, general description of the methods of disposal, including whether the facility is permitted to destroy hazardous or non-hazardous material. The responsible facility should be further identified by:

i. license or permit number
ii. issuing authorities identification number
iii. license or permit expiration dates and issuing

agent

c. Complete identification of chemical substances to include:

i. nomenclature:
   a. established name (U.S. Adopted Name-USAN)
   b. brand/proprietary name
   c. chemical names
ii. Chemical Abstract Service (CAS) registration number
iii. molecular formula
iv. molecular weight
v. structural (graphic) formula
vi. physical description
vii. additives
viii. impurities

d. Certification that each of the foreign manufacturing facilities are:

i. in compliance with local and national environmental laws,
ii. in compliance with emission requirements set forth in all permits, and
iii. that approval and subsequent increase in production at the facilities are not expected to affect compliance with current emission requirements or environmental laws.

The statement should be signed and dated by the responsible company official, and a certified English translation provided, if needed.

e. Provide a Material Data Safety Sheet (MSDS) for calcipotriene.

8. Please resubmit the Methods Validation package (vol. 1.3) because some of the information as required by the guidelines was not included. The Methods Validation package should contain the following:

a. A tabular list describing all the samples to be prepared by the applicant and to be collected by the investigator or analyst sent by the district office. Samples descriptions should include batch number, type of batch (e.g. bioequivalence, clinical, stability), scale of manufacturing (e.g. laboratory, pilot, commercial), item, quantity, etc.

b. Complete test results (Certificate of Analysis and raw data) for all samples that are to be collected by the field investigator or analyst.

c. A listing of all proposed regulatory specifications cross-referenced by application page numbers to the detailed descriptions of the respective analytical methods.

d. Information supporting the integrity of the reference standard and its ability to serve its intended purpose.

e. A statement of the composition of the finished dosage form.

f. Information supporting the suitability of the methodology for the new drug substance.

g. Information supporting the suitability of the methodology for the dosage form.

h. System suitability test for all liquid and gas chromatographic procedures and others where appropriate.

i. A summary of development data to demonstrate adequate precision, linearity, accuracy, sensitivity, and specificity for regulatory and stability-indicating purposes.

j. Material Safety Data Sheet (MSDS) or equivalent for any substance that will be supplied to the laboratories.

We acknowledge your commitment, dated March 28, 1996, to conduct dermal and photocarcinogenicity studies using a clinical formulation of calcipotriene.

Any resubmission of this application should also include an updated safety report as specified under 21 CFR 314.50(d)(5)(vi)(b).

Until the safety and effectiveness of this drug product have been established, we reserve comment on the proposed labeling.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intention to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as

a major amendment, nor will the review clock be reactivated until all deficiencies have been addressed.

Should you have any questions, please contact:

Mary Jean Kozma-Fornaro
Project Manager
Telephone: (301) 827-2023

Sincerely yours,

7/3/96

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:

NDA 20-611
HFD-550/DIV FILE
HFD-80
DO: SAN JUAN
HFD-222/New Drug Chemistry Division Director
HFD-540/Div Dir/Wilkin
HFD-540/Dep Dir/Katz
HFD-540/MO/Toombs/7/1/96
HFD-540/CHEM/Pappas
HFD-540/PHARM/Avalos
HFD-713/BIOSTAT TL/Srinivasan
HFD-880/BIOPHARM/Lee
HFD-160/MICRO/Hughes
HFD-540/PM/Fornaro

Concurrence:

HFD-540/CHEM TL/DeCamp/ 7/2/96
HFD-540/PHARM TL/Jacobs/
HFD-880/BIOPHARM TL/
HFD-713/BIOSTAT DIR/Harkins/
HFD-160/MICRO/Cooney/
HFD-540/SPM/CookR/7/1/96

file: 20611na

NOT APPROVABLE

cc:

NDA 20-611
HFD-550/DIV FILE
HFD-80
DO: SAN JUAN
HFD-222/New Drug Chemistry Division Director
HFD-540/Div Dir/Wilkin
HFD-540/Dep Dir/Katz
HFD-540/MO/Toombs/7/1/96
HFD-540/CHEM/Pappas
HFD-540/PHARM/Avalos
HFD-713/BIOSTAT TL/Srinivasan
HFD-880/BIOPHARM/Lee/7/2/96
HFD-160/MICRO/Hughes
HFD-540/PM/Fornaro

Concurrence:

HFD-540/CHEM TL/DeCamp/7/2/96
HFD-540/PHARM TL/Jacobs/7/1/96
HFD-880/BIOPHARM TL/
HFD-713/BIOSTAT DIR/Harkins/
HFD-160/MICRO/Cooney/
HFD-540/SPM/CookR/7/1/96

file: 20611na

NOT APPROVABLE

PATENT CERTIFICATION

Re: Patent #4,866,048

The patent cited above is the only patent which claims the drug that is the subject of this application.

To the best of my knowledge, the above patent claims the use of the drug designated by the patent holder as MC 903 or calcipotriol. This patent is assigned to Leo Pharmaceutical Products, Ltd., from whom Westwood-Squibb and Bristol-Myers Squibb have secured a license to market drug products in the United States using this active. Bristol-Myers Squibb has assigned this substance the internal code BMS 181161 (formerly BMY 30434). The International Nonproprietary Name (INN) for this compound is calcipotriol, and the USAN name is calcipotriene.

PATENT INFORMATION

MC 903 (calcipotriene) is the subject of U.S. Patent 4,866,048, which specifically claims the drug substance which has been variously identified as MC 903, BMY 30434 or BMS 181161. The rights to distribute dermatological products containing calcipotriene (MC 903) as the active principle for the treatment of psoriasis have been licensed, in the United States, to Bristol-Myers Squibb Company and its Westwood-Squibb subsidiary by Leo Pharmaceutical Products, Ltd., the manufacturer of the drug substance and drug product, and the patent holder. The relevant patent information is as follows:

1. U.S. Patent 4,866,048 — Expiration date: September 12, 2006

2. Type of patent: — Drug

3. Name of patent owner: — Leo Pharmaceutical Products, Ltd.

4. Applicant maintains a place of business in the United States.

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

(NDA)/PLA # 20-611 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-540 Trade (generic) name/dosage form: Dovonex (Calcipotriene Solution), Solution 0.005% Action: (AP) AE NA

Applicant Bristol Myers-Squibb Therapeutic Class psoriatic

Indication(s) previously approved plaque psoriasis - NDA 20-273 Dovonex Ointment
Pediatric labeling of approved indication(s) is adequate ___ inadequate ✓

Indication in this application chronic moderately severe psoriasis of the scalp
(For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

✓ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

✓ b. The applicant has committed to doing such studies as will be required.
___ (1) Studies are ongoing.
___ (2) Protocols were submitted and approved.
___ (3) Protocols were submitted and are under review.
X (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

___ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

Robin Anderson — 2/25/97
Signature of Preparer and Title (PM, CSO, MO, other) Date

cc: Orig (NDA)/PLA # 20-611
HFD-540 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

Janet Wilson, 2/28/97

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

5/95

2/25/97

Before pursuing a pediatric claim for Rovorex Solution, 0.005%, the sponsor will review worldwide data and potential need for pediatric use. However, sponsor agrees to perform pediatric protocols if needed. Sponsor requests clarification of need for additional pre-clinical work, as requested by M.O. for ointment formulation, prior to protocol submission.

per Mr Kozma Tornaro 6/14/96
Robin Anderson, Project Manager

2/28/97

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 20611 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD 540 Trade (generic) name/dosage form: Dovonex (calcipotriene solution), Solution 0.005% Action: AP AE NA

Applicant Bristol-Myers Squibb Therapeutic Class psoriatic

Indication(s) previously approved plaque psoriasis - NDA 20273 Dovonex ointment
Pediatric labeling of approved indication(s) is adequate ___ inadequate ✓

Indication in this application chronic moderately severe psoriasis of the scalp
(For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

✓ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

✓ b. The applicant has committed to doing such studies as will be required.
___ (1) Studies are ongoing.
___ (2) Protocols were submitted and approved.
___ (3) Protocols were submitted and are under review.
✓ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

___ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

Mary Jean Vienna Jones — 6/14/96

Signature of Preparer and Title (PM, CSO, MO, other) Date

cc: Orig NDA/PLA # 20611
HFD 540 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

Jennifer Willis, 7/3/96

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

5/95

6/14/90 Before pursuing a pediatric
claim for Dovonex Solution, 0.005%
the sponsor will review worldwide data
and potential need for pediatric use.
However, sponsor agrees to perform pediatric
protocols if needed. Sponsor requests
clarification of need for additional
preclinical work, as requested by M.O.
for ointment formulation, prior to protocol submission.
Kathleen Project Manager

Bristol-Myers Squibb
Pharmaceutical Research Institute

100 Forest Avenue Buffalo, NY 14213-1091 716 887-3400 Fax: 716 887-3638

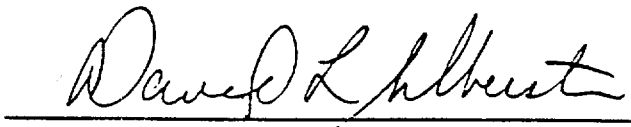
CERTIFICATION

This certifies that Bristol-Myers Squibb Company (including the Bristol-Myers Squibb Pharmaceutical Research Institute and Westwood-Squibb Pharmaceuticals) has not used in any capacity any persons identified by the United States Food and Drug Administration on any Debarment List, or identified as having been permanently debarred by publication in the Federal Register since March 8, 1993.

Further, we certify that Bristol-Myers Squibb Company will not use the services in any capacity of anyone debarred by the United States Food and Drug Administration.

We are not aware of any relevant convictions for which a person can be debarred as described in section 306 (a) and (b), for persons employed and/or affiliated with Bristol-Myers Squibb (including contractors) responsible for the development of data and information to support approval of this application for calcipotriene solution, 0.005%.

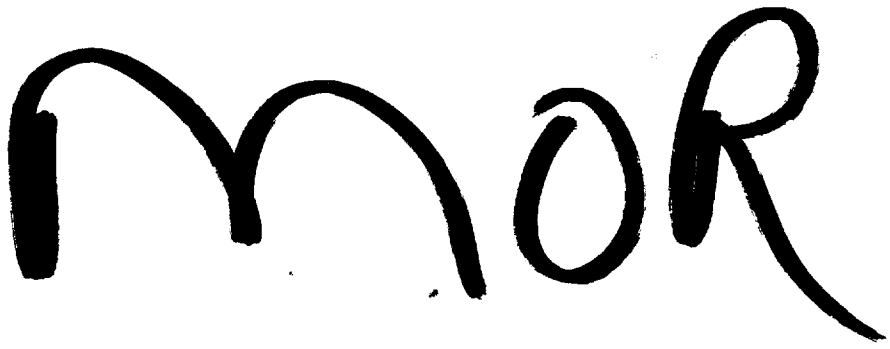
Name	David L. Silberstein
Title	Manager
Date	June 30, 1995
Company	Bristol-Myers Squibb Pharmaceutical Research Institute
Address	100 Forest Avenue
City	Buffalo, NY 14213
Telephone	(716) 887-3641



David L. Silberstein, Manager, Drug Regulatory Affairs

NDA 20-611 Dovonex (calcipotriene solution) Solution, 0.005%

DSI audits of pivotal clinical trials were not requested by the clinical team. Dovonex Ointment, NDA 20-273 is marketed for the treatment of moderate plaque psoriasis.


mor

JUL -3 1996

Medical Officer's Review of NDA 20-611

Submission Date:	June 30, 1995
Receipt Date:	July 11, 1995
First Draft:	June 7, 1996
Second Draft:	June 27, 1996
Third Draft:	July 2, 1996

Sponsor:

Bristol Myers Squibb PRI
100 Forest Avenue
Buffalo, New York 14213-1091

Drug:

Trade Name:
Calcipotriene Solution 0.005%
Generic Name:
Dovonex Solution 0.005%

Pharmacologic Category:

Vitamin D3 Analogue

Proposed Indication:

Psoriasis of the Scalp

Dosage Form and Route of Administration:

Topical Solution

Proposed Dosage:

Twice Daily

Chemical Name:

24 cyclopropyl-9,10-secocola-5,7,10(19),22-tetraene 1,3,24-triol-(1 alpha, 3 beta, 5 zeta, 7E, 22E, 24S)

Related NDA:

20-554 Calcipotriene Cream 0.005%
20-273 Calcipotriene Ointment 0.005%

Related INDs:

Table of Contents

Background:

Psoriasis is a chronic, relapsing, incurable skin disorder with a prevalence approximating 2% worldwide. The scalp is one of the most frequently involved sites of the disease. Furthermore, the scalp is often the first area of psoriatic activity.

Therapy is usually palliative and can include combinations of: topical- tars (with or without UVB light), keratolytics, emollients, corticosteroids, anti-infectives and/or psoralens with UVA light. Anthralin is currently the only FDA approved product specifically indicated for treatment of psoriasis affecting the skin of the scalp.

Calcipotriene Ointment 0.005% was approved in December, 1993, by the Food and Drug Administration for the treatment of plaque type psoriasis. It is also approved and marketed in over 51 foreign countries including: Canada, Germany, Sweden, Denmark, United Kingdom and Ireland. The NDA filed in the United States for Calcipotriene Cream 0.005% was found to be "approvable". As of May, 1995, Calcipotriene Cream has been approved and marketed in 5 foreign countries including Canada, Denmark, Switzerland, the United Kingdom, and Sweden. A solution in the same formulation as proposed in this NDA is approved and marketed in The United Kingdom, Iceland, Ireland, New Zealand, and Finland.

The post-marketing surveillance data received by the FDA on Dovonex Ointment 0.005% has revealed a small number of adverse events similar to those reported in the clinical studies submitted under NDA 20-273. The majority of these events cutaneous. Specifically, there have been no reports of abnormalities related to calcium metabolism, bone abnormalities or renal dysfunction.

Manufacturing and Controls:

The active drug ingredient is manufactured in Denmark by Leo Laboratories. Leo Laboratories supplies the final product to Bristol-Myers Squibb Company, (NDA applicant in the United States).

Manufacturer:

Leo Pharmaceutical Products, Ltd.
55, Industriparken
DK-2750 Ballerup
Ballerup, Denmark

Formulation: **mg/ml**

Calcipotriene

Propylene Glycol
Hydroxypropyl Cellulose
Sodium Citrate
Menthol
Purified Water

Calcipotriene hydrate is a white crystalline powder which is freely soluble in methanol, ethanol and 2-propanol. The formulation submitted in this NDA contains calcipotriene hydrate in an amount equivalent to calcipotriene 0.005% in a hydroalcoholic solution.

This submission contains manufacturing and clinical information on two concentrations of calcipotriene: a 0.005% and 0.0025% solution. The chemical difference is a decrease in the concentration of calcipotriene hydrate from mg/ml in the 0.0025% formula. **The sponsor states that the only formula to be marketed at this time is the calcipotriene solution 0.005%.**

The sponsor plans to market the product in bottles containing 8, 30 and 60cc of drug. The 8cc bottles will be used as physician sample sizes.

Pharmacology-Toxicology:

Approximately thirty pre-clinical trials were assessed in support of NDA 20-273 for Calcipotriene Ointment 0.005%. (Refer to Pharmacology Review of NDA 20-273) Additional preclinical trials were submitted in support of the application for the cream formulation (20-554). Although, the sponsor did not submit any new animal toxicity data in support of this application, previous applications have included the results of two (rabbit) dermal irritancy studies, which revealed that calcipotriene solution is a mild dermal irritant in rabbits. Mild dermal irritancy following application of the solution was confirmed in minipig and rat dermal toxicity studies.

Oral animal toxicity studies showed changes in the metabolism of calcium and or phosphorous only at the highest dosage levels; amounts which are far in excess of the proposed human dosage.

Carcinogenicity studies for the solution are underway and will be submitted as amendments to this NDA. The sponsor will submit the results to this NDA. Those results will also become incorporated into lables for the cream and ointment formulations of Dovonex.

BIOPHARMACEUTICS

Background data from NDA 20-273 (Calcipotriene Ointment 0.005%)
The sponsor submitted the results from 3 percutaneous absorption studies which were reviewed in NDA 20-273. Two of these studies were completed in patients without psoriasis; one was in psoriatic patients. The results of all of these studies suggested that topical absorption of calcipotriene ointment 0.005% is approximately 5.8% of the applied dose.

Pharmacokinetic Studies in Humans, Calcipotriene Solution 0.005%:

Protocol DE127-030 **"Percutaneous Absorption of Calcipotriene Solution Applied to Normal Scalp"**

Chief Investigator:

This single dose, open label trial was designed to assess the extent of percutaneous absorption of calcipotriene solution 0.005% when applied to the "normal" scalp skin of five healthy subjects. One hundred twenty micrograms of radiolabeled calcipotriene solution 0.005% was applied to a 160cm square area of scalp and allowed to remain in contact with the subject areas for twelve hours. Following removal of the study preparation; samples of blood, urine and feces were collected for 21 days.

Results: Percutaneous absorption ranged from % of the applied dose. Recovery from the application site was 71.3% of the applied dose.

Conclusion: Percutaneous absorption of calcipotriene solution 0.005% averages 0.40% of the applied dose.

Reviewer's Comments: Percutaneous absorption of calcipotriene solution is extremely low (much lower than for the ointment described above).

Protocol DE127-028 **"Percutaneous Absorption of Calcipotriene Solution Applied to Psoriatic Scalp"**

Chief Investigator:

Methods: This single dose, open label trial was designed to assess the extent of percutaneous absorption of calcipotriene solution 0.005% when applied to psoriasis of the scalp in otherwise healthy subjects. Five patients were enrolled and instructed to avoid use of antipsoriatic medicines for one week prior to study commencement. One hundred micrograms of radiolabeled calcipotriene solution 0.005% was applied and allowed to remain in contact with the subject areas (160 square centimeters) for twelve hours. Following removal of the study preparation; samples of blood, urine and feces were collected for 21 days.

Results: Percutaneous absorption ranged from % of the applied dose. Recovery from the application site was 67.1% of the applied dose.

Conclusion: Percutaneous absorption of calcipotriene solution 0.005% when applied to psoriatic scalp approximates 0.14% of the applied dose. This compares to a percutaneous absorption of 5.8% from the ointment preparation.

Reviewer's Comments: The limited amount of cutaneous surface occupied by the scalp in concert with minimal percutaneous absorption of calcipotriene solution should result in limited systemic toxicity.

HUMAN SAFETY AND EFFICACY STUDIES

Clinical safety and/or efficacy studies submitted in support of this application consisted of which are reviewed in subsequent pages include:

I) 4 Human dermal toxicity studies

II) 2 multicentered, double blind safety and efficacy trials which were completed in the United States comparing calcipotriene solutions 0.005% and 0.0025% with vehicle

III) 4 supportive European trials

I Dermal Toxicity Studies

Investigator for 4 dermal toxicity studies:

Dermatotoxicity Scale

0 = no signs of irritation
1 = slight erythema
2 = erythema and slight induration
3 = erythema with marked edema
4 = erythema with edema and blistering

A) Study # DE118-019-008 21 Day Cumulative Irritation Test

Introduction: Thirty healthy adult subjects (26 females, 4 males) were enrolled in this single center, open label study in order to determine the incidence of cutaneous irritancy, following topical application of calcipotriene solutions 0.005% and 0.0025% compared to calcipotriene vehicle and sodium lauryl sulfate. Twenty-eight subjects completed the study and were evaluable. One subject experienced a serious adverse event ("nervousness" requiring an overnight hospitalization). A second subject changed employers which prevented completion of study visits.

Methods: Each of the test products: calcipotriene solution 0.005%, vehicle and 0.05% sodium lauryl sulfate (0.04cc per square centimeter) were applied under occlusive patches to square centimeter area (one site per product) of the skin of the backs of the subjects daily for 21 days. Sundays were excluded. Twenty-four hours after application, the patches were removed, sites were evaluated for irritation, cleansed and new patches were applied. Irritation was measured according to the standard 5-point scale used in dermal toxicity studies (see scale above).

Results:

	Mean Score
0.5% sodium lauryl sulfate in petrolatum	3.72
Calcipotriene solution 0.005%	2.65
Calcipotriene solution 0.0025%	2.50
Vehicle	1.13

Reviewer's Comment: The results of this study demonstrate that calcipotriene solution is a mild-moderate topical irritant when applied to normal skin; which does not seem to be related to the concentration of active drug. (The significance of these results can not be extrapolated to psoriatic skin, however, as **psoriatic skin is not necessarily more reactive** than normal skin). The effects on "koebnerization" are unknown. The safety results from the clinical studies will help determine whether or not cutaneous irritancy is a problem in the clinical setting.

B) Study DE118-018-008 Repeated Insult Patch Test (Modified Draize Skin Sensitization Test)

Introduction: This open label, single center/investigator study enrolled 230 subjects (188 female, 42 male) in order to determine the allergic contact sensitization potential of calcipotriene solutions 0.005% and 0.0025% compared to vehicle.

Methods: Each test material was applied (0.04cc - 0.1cc/cm^2 patch) to a specific site on the skin of the subjects back under an occlusive patch three times weekly for three weeks. Following this three week induction and a two week rest period, a challenge application was applied to a previously spared site. Evaluations for allergic sensitization were completed 48-72 hours later using the standard 5 point dermatotoxicity scale.

Results: Two-hundred thirty subjects were enrolled. Eleven subjects were dropped by the investigator for lack of compliance: five subjects were dropped for protocol violations (using restricted medications), two subjects were dropped for missing more than two study visits. The following adverse events were reported: pharyngitis, whiplash, swollen eyes, myalgia, automobile accident, hypertension and pelvic infection. These adverse events were not considered to be drug related. Two-hundred twelve subjects completed the study and were evaluable.

Table 1. Induction

Product	Number of Subjects Per Grade During Induction Phase					Dropped
	Grade 4	Grade 3	Grade 2	Grade 1	Grade 0	
0.005% sln.	82	42	95	6	1	4
0.025% sln.	65	35	115	10	1	4
vehicle	10	26	101	84	5	4

Table 2. Challange

Product	Number of Subjects Per Grade During Challenge Phase				No shows
	Grade 4	Grade 3	Grade 2	Grade 0 or 1	
0.005% sln.	6	11	38	155	2
0.025% sln.	5	12	33	160	2
vehicle	1	3	17	189	2

Reviewer Comments: During the induction phase greater than 94% of the calcipotriene treated subjects had positive reactions of grade 3 or 4 as opposed to 16% of the vehicle sites. On re-challenge the numbers of significant reactors significantly decreased. The results suggest that calcipotriene solution is a mild to moderate skin irritant at both concentrations.

C) Study DE118-021-008 Phototoxicity Study

Introduction: Twelve healthy, adult subjects (11 female/1 male) were enrolled in this open label, vehicle controlled study designed to assess the phototoxic potential of calcipotriene solutions in 0.005% and 0.0025% concentrations. All 12 subjects who were enrolled completed the study.

Methods: Cellophane tape stripping of four specified sites on the back skin of each of the subjects was followed the by application of calcipotriene solution 0.005% or 0.0025% concentrations or vehicle to a 2 um/cm sq area. An untreated, tape stripped control site was included. These sites were subsequently occluded followed by irradiation with UVA and UVB.

Evaluations of all sites were made: immediately, 3 and 24 hours after irradiation. Signs and symptoms of phototoxicity were evaluated using the dermatotoxicity grading scale previously outlined.

Results: Twelve subjects completed the study and were evaluable. At the immediate evaluation ten subjects ~~in each group~~ had a +1 reading at the irradiated site; the remaining two study participants had readings of zero (0). At the 3 and 24 hour evaluations all subjects had readings of zero.

Safety: No adverse events were reported.

Conclusion: Neither calcipotriene solution at concentrations of 0.005% nor 0.0025% appear to be phototoxic drugs based on these test results.

II Domestic Efficacy and Safety Studies

Introduction: Two multicenter United States studies enrolling a total of four hundred adult patients with stable plaque type scalp psoriasis were submitted by the sponsor to assess the safety and efficacy of calcipotriene 0.005% and 0.0025% solutions as compared to vehicle in the treatment of scalp psoriasis. The protocols were identical.

Methods: Patients who met the study entry criteria were given 60 cc of study product weekly and instructed to apply the preparation twice daily to psoriatic areas of the scalp for eight weeks.

Efficacy evaluations were made at baseline and after weeks 1, 2, 4, 6 and 8 for the following efficacy parameters: erythema, scaling, induration, overall disease severity and a physicians global assessment. Urinalysis, complete blood counts and serum chemistries were monitored at weeks 1, 2, 4, and 8 as part of the safety assessment.

Inclusion Criteria: 18 years of age or older

Stable scalp psoriasis of at least grade 4

Willingness and ability to sign informed consent as well as comply with the study requirements

Exclusion Criteria: Use of any hair treatment within 1 week prior to study entry

Use of systemic or photo antipsoriatic therapy within 8 weeks prior to study

Use of any topical scalp psoriasis treatment within one week prior to study entry

Pregnancy, lactation or females of childbearing age not using effective contraception

Participation in an investigational study currently or within the previous 4 weeks

History of erythrodermic, extensive (greater than 20% body psoriasis) or pustular psoriasis

History of other scalp disease, hypercalcemia, renal or hepatic disease

Intention to have prolonged scalp sun exposure

D) Study DE118-020-008 Photocontact Allergy Test

Introduction: This was a single center, open label, vehicle controlled study which enrolled 30 healthy, adult subjects (27 females/3 males) in order to assess the photoallergic potential of topically applied calcipotriene 0.005% and 0.0025% solutions.

Methods: The induction phase consisted of application of each test material (0.04 - .1cc /cm2 of calcipotriene solution 0.005%, 0.0025% or vehicle) to two areas of each subject's upper back skin under occlusive patches twice weekly for three weeks. Areas of skin with scars or moles were avoided. Twenty four hours after the test material applications, the occlusive patches were removed and the sites were irradiated with 3 MED (minimal erythema dose). An unpatched, untreated area of skin was also irradiated.

The challenge phase consisted of test product application to previously untreated, non-irradiated areas with 24 hour occlusion followed by irradiation with ten (10) times the MED.

Twenty-nine subjects completed the five week study and were considered fully evaluable. One subject was dropped due to traveling and an inability to attend study visits.

Results: During the induction, 3 calcipotriene treated subjects (numbers, 4, 8 and 20) had readings of grade 2 or higher. Following the challenge, all were grade 0 or 1 except subjects number 8 and 20 who continued to have grade 2 readings. There were no significant increases in cutaneous reactions in the active vs vehicle vs control irradiated sites.

Conclusion: The results of this study indicate that calcipotriene solutions 0.005% or 0.0025% are not photosensitizing drugs.

Table 3. Clinical Efficacy Measures

Scaling	Erythema	Plaque Elevation	Overall Disease Severity
0 = no evidence of scaling on the lesions	0 = no evidence of erythema	0 = no evidence of plaque above normal skin level	0 = no evidence of disease (except possible residual discoloration)
2 = mild; mainly fine scales; some lesions at least partially covered	2 = pink coloration	2 = slight definite elevation above normal skin level	2 = mild; approximately 5% involvement, e.g., 5 plaques each of 1% body surface area or equivalent; average plaque elevation in the region of Grade 4; scaling and/or erythema in the region of Grade 2
4 = moderate; somewhat coarser scales; most lesions at least partially covered	4 = red coloration	4 = moderate elevation with rounded or sloped edges to plaque	4 = moderate; approximately 10% involvement, e.g., 10 plaques each of 1% body surface area or equivalent; average plaque elevation in the region of Grade 4; scaling and/or erythema in the region of Grade 4
6 = severe; coarse, thick scales; virtually all lesions covered; rough surface	6 = very red coloration	6 = marked elevation, with hard sharp edges to plaque	6 = severe: approximately 15% involvement, e.g. 15 plaques each of 1% body surface area or equivalent; average plaque elevation in the region of Grade 6; scaling and/or erythema in the region of Grade 6
8 = very severe: coarse, very thick scales; all lesions covered; very rough surface	8 = extreme red coloration	8 = very marked elevation with very hard sharp edges to plaque	8 = very severe; approximately 20% involvement, e.g., 20 plaque each of 1% body surfaces area or equivalent; average plaque elevation in the region of Grade 8; scaling and/or erythema in the region of Grade 8

Table 4. Physician's Global Assessment

Grade	
1	Completely Clear: Except for possible residual discoloration
2	Almost Clear: Very significant clearance (about 90%); however, slight degree of scaling and elevation as well as some erythema may be present
3	Marked Improvement: Significant improvement (about 75%); however, some disease remaining
4	Moderate Improvement: Intermediate between slight and marked, representing about 50% improvement
5	Slight Improvement: Some improvement about (25%); however, significant disease remaining
6	No Change
7	Worse

A) **Study DE127-031 "A Randomized, Double-blind, Parallel Group Dose Ranging Comparison of the Efficacy and Safety of Calcipotriene Solution in the Treatment of Scalp Psoriasis."**

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Study Design: This eight center, double-blind, vehicle controlled parallel group study enrolled 225 subjects with stable scalp psoriasis of at least grade 4. The patients were randomized into one of three treatment groups: 78 in calcipotriene 0.0025% solution, 78 in calcipotriene solution 0.005% or 75 in vehicle.

Demographics of Enrolled Patients Who Were Evaluable at Day 1 - Study DE127-031

	Calcipotriene Solution 0.005%	Calcipotriene Solution 0.0025%	Vehicle
Number of Patients	78	77	75
Mean Age (range years)	45	47	47
Mean Height (in)	67.34	67.71	67.13
Mean Weight (lb)	173.94	185.60	182.13
Duration of Current Psoriatic Episode (yrs)	15.05	14.41	17.80
Sex			
Female	41 (53%)	38 (49%)	39 (52%)
Male	37 (47%)	39 (51%)	36 (48%)
Race			
Caucasian	70 (90%)	66 (86%)	72 (96%)
Hispanic	4 (5%)	3 (4%)	1 (1%)
Black	1 (1%)	4 (5%)	1 (1%)
Oriental	2 (3%)	3 (4%)	1 (1%)
Other	1 (1%)	1 (1%)	0 (0%)

Two hundred and thirty-five subjects were enrolled, 204 completed the 8 week study, 195 of whom were evaluable. Thirty-one subjects discontinued, (13 vehicle treated/12 calcipotriene 0.005% and 6 calcipotriene 0.0025%) 10 of these discontinuances were considered treatment failures (including worsening of psoriasis):

Table 5. Number of Discontinuances

	Calcipotriene 0.005%	Calcipotriene 0.0025%	Vehicle
Administrative	6	2	1
Adverse Reaction	6	4	12
Total	12	6	13

Table 6. Results Clinical Efficacy Measures Study DE127-031

	CALCIPOTRIENE SOLUTION 50 µg/mL		CALCIPOTRIENE SOLUTION 25 µg/mL		VEHICLE				PAIRWISE COMPARISONS		
	N	MEAN	N	MEAN	N	MEAN	F	OVERALL P-VALUE[1]	50 µg/mL VS. VEHICLE P-VALUE[2]	25 µg/mL VS. VEHICLE P-VALUE[2]	50 µg/mL VS. 25 µg/mL P-VALUE[2]
DAY 1											
SCALING	78	4.96	77	5.14	75	5.27	0.788	0.4559	---	---	---
ERYTHEMA	78	4.71	77	4.78	75	4.88	0.367	0.6933	---	---	---
PLAQUE ELEVATION	78	4.17	77	4.32	75	4.31	0.472	0.6247	---	---	---
OVERALL SEVERITY	78	4.83	77	5.05	75	5.13	2.229	0.1102	---	---	---
PRURITUS	78	3.56	77	3.57	75	3.71	0.557	0.5740	---	---	---
DAY 4											
SCALING	74	4.73	71	4.62	72	5.10	2.427	0.0910	---	---	---
ERYTHEMA	74	4.39	71	4.46	72	4.78	1.952	0.1448	---	---	---
PLAQUE ELEVATION	74	3.97	71	4.08	72	4.17	0.592	0.5545	---	---	---
OVERALL SEVERITY	74	4.57	70	4.70	72	5.01	2.798	0.0634	---	---	---
PRURITUS	74	3.12	71	3.21	72	3.35	0.502	0.6059	---	---	---
WEEK 1											
SCALING	75	4.16	73	4.30	73	4.75	3.082	0.0481	0.0147	0.1304	0.3512
ERYTHEMA	75	3.89	73	4.14	73	4.60	4.940	0.0081	0.0022	0.0451	0.2853
PLAQUE ELEVATION	75	3.49	73	3.70	73	4.05	4.214	0.0161	0.0044	0.0778	0.2742
OVERALL SEVERITY	75	4.13	73	4.45	73	4.86	7.432	0.0008	0.0002	0.0512	0.0611
PRURITUS	75	2.57	73	2.75	73	3.22	2.713	0.0688	---	---	---
WEEK 2											
SCALING	74	3.89	74	4.01	71	4.48	2.753	0.0662	---	---	---
ERYTHEMA	74	3.58	74	3.84	71	4.28	4.053	0.0189	0.0055	0.0638	0.3407
PLAQUE ELEVATION	74	3.19	74	3.43	71	3.76	3.006	0.0518	---	---	---
OVERALL SEVERITY	74	3.74	74	4.09	71	4.52	5.235	0.0061	0.0014	0.0772	0.1406
PRURITUS	74	2.28	74	2.42	71	2.63	0.932	0.3956	---	---	---
WEEK 4											
SCALING	73	3.48	71	3.68	65	4.46	5.795	0.0036	0.0013	0.0108	0.4875
ERYTHEMA	73	3.11	71	3.58	65	4.29	8.115	0.0004	0.0001	0.0131	0.1253
PLAQUE ELEVATION	73	2.81	71	3.04	65	3.69	5.180	0.0065	0.0021	0.0211	0.4163
OVERALL SEVERITY	73	3.34	71	3.70	65	4.51	8.156	0.0004	0.0001	0.0127	0.1259
PRURITUS	73	1.78	71	1.92	65	2.63	3.664	0.0275	0.0086	0.0623	0.4276
WEEK 6											
SCALING	67	3.19	69	3.39	66	4.33	6.701	0.0016	0.0009	0.0037	0.6335
ERYTHEMA	67	2.76	69	3.33	66	4.12	8.412	0.0003	0.0001	0.0081	0.1571
PLAQUE ELEVATION	67	2.45	69	2.78	66	3.58	8.832	0.0002	0.0001	0.0041	0.2148
OVERALL SEVERITY	67	2.96	69	3.46	66	4.32	10.617	0.0000	0.0001	0.0013	0.2095
PRURITUS	67	1.54	69	1.72	66	2.53	6.202	0.0025	0.0010	0.0085	0.4673
WEEK 8											
SCALING	65	2.94	68	3.19	62	4.37	7.291	0.0009	0.0005	0.0027	0.5567
ERYTHEMA	65	2.65	68	3.18	62	4.21	9.603	0.0001	0.0001	0.0022	0.2096
PLAQUE ELEVATION	65	2.22	68	2.54	62	3.65	10.254	0.0001	0.0001	0.0007	0.3508
OVERALL SEVERITY	65	2.86	68	3.22	62	4.27	7.204	0.0010	0.0003	0.0059	0.3400
PRURITUS	65	1.45	68	1.59	62	2.39	5.219	0.0063	0.0028	0.0114	0.5912

Reviewer Comments: A statistically significant advantage favoring calcipotriene 0.005% solution over vehicle was evident for scaling, erythema, plaque elevation and overall disease severity beginning at week one. No comparable significance for demonstrated for the 0.0025% concentration except for erythema. Pairwise analysis of the difference between the two concentrations suggests no statistical advantage for either.

Table 7. Physicians Global Assessment Study 127-031

0.005 = Calcipotriene 0.005%
0.0025 = Calcipotriene 0.0025%
V = Vehicle

(Numbers of Subjects)

	Week 1	Week 2	Week 4	Week 6	Week 8
	.005/.0025/V	.005/.0025/V	.005/.0025/V	.005/.0025/V	.005/.0025/V
Completely Clear	0/0/0	0/0/0	2/0/0	5/1/1	8/8/2
Almost Clear	0/0/0	1/2/0	6/9/1	10/12/3	11/9/2
Marked Improvement	4/5/2	5/7/4	11/8/3	9/8/4	9/8/6
Moderate Improvement	15/8/4	19/15/8	14/16/8	16/17/7	11/13/4
Slight Improvement	27/30/20	29/32/29	23/24/21	15/15/16	12/18/17
No Change	27/30/40	17/16/24	14/12/26	10/13/27	12/10/24
Worse	2/2/7	3/2/6	3/2/6	2/2/8	2/2/7

p-values

0.005%/vehicle	0.004	0.023	0.003	0.001	0.001
0.0025%/vehicle	0.006	0.005	0.001	0.001	0.001
0.005%/0.0025%	0.431	0.607	0.608	0.741	0.936

note: a p-value of <0.05 was considered statistically significant

Reviewer Comments: Calcipotriene 0.005% was significantly better than vehicle at all time points. The lower concentration 0.0025% was significantly better than vehicle at all time points except week 1. Analysis of the parallel comparison data suggests that there is no significant advantage of the higher concentration product.

Safety Evaluation

Results

Abnormal Laboratory Values: There were seven reported incidences of elevated serum calcium levels. Two minor elevations (10.3 and 10.2) occurred in the calcipotriene 0.005% group, at day 1 and week 1, respectively. One patient in the calcipotriene 0.0025% treated group had an elevation of serum calcium (10.3) at week 4. Four patients in the vehicle group had similarly mild elevations in their serum calcium levels. With the exception of one of the vehicle treated patients; all serum calcium elevations reverted to within normal range (normal calcium laboratory values 8.6 - 10)by the end of the study.

Seven patients in the calcipotriene 0.005% group and 6 in the calcipotriene 0.0025% and 6 in the vehicle groups had slight, insignificant, depressions (.1 - .5) of their serum phosphorous levels.

Creatinine levels were mildly elevated (2 - 4 tenths of a point) in eight subjects enrolled in the calcipotriene 0.005% group, 12 subjects in the calcipotriene 0.025% and 8 subjects in the vehicle group. The results of the blood urea nitrogen abnormalities were similar,ie. 11 minor elevations in the 0.005% group, 14 eleven minor elevations in the calcipotriene 0.0025% group and 14 elevations in the vehicle group.

Reviewer's Comments: The minor laboratory elevations were not of clinical relevance.

Signs and Symptoms: One-hundred thirty-five (non-serious) adverse clinical events were reported; of these, 51 occurred in the calcipotriene 0.005% group, 37 occurred in the calcipotriene 0.0025% group and 47 were reported in the vehicle group. The majority of these were cutaneous and occurred equally throughout the groups.

Table 8. Numbers of subjects with adverse events by organ system DE127-031

	Calcipotriene 0.005%	Calcipotriene 0.0025%	Vehicle
Skin and appendages erythema, stinging rash, xerosis, acne	44	33	47
Body as a Whole headache, infection	27	14	30
Cardiovascular vasodilation	0	0	0
Digestive dyspepsia, nausea	2	3	5
Hematopoietic system thrombocytopenia	1	0	1
Metabolic hyperlipemia, hyperglycemia	4	5	3
Musculoskeletal arthritis	1	4	3
Nervous system dizziness nervousness	1	2	3
Respiratory dyspnea, pneumonia, cough	9	8	7
Special Senses tinnitus conjunctivitis	2	1	4
Urogenital system hematuria, dyspareunia	3	4	5
Endocrine diabetes, hypothyroidism	1	0	0

Reviewer's Comments: The number and type of adverse reactions reported in this study was low. There were no differences between the two active treatment groups or vehicle. These results suggest that calcipotriene solution in either concentration is a safe drug used under the conditions described.

B) Study DE127-032 "A Randomized, Double-blind, Parallel Group Dose Ranging Comparison of the Efficacy and Safety of Calcipotriene Solution in the Treatment of Scalp Psoriasis."

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Study Design: This multi-centered, double-blind trial enrolled 239 adult patients with stable plaque psoriasis, of at least grade 4, affecting the skin of the scalp. The study was designed in order to assess the efficacy and safety of calcipotriene solutions in concentrations of 0.005% and 0.0025% as compared to vehicle. Two hundred ten subjects completed the study.

Methods: Patients who met the study entry criteria were given 60 cc of study product weekly and instructed to apply the preparation twice daily to psoriatic areas of the scalp for eight weeks.

Efficacy evaluations were made at baseline and after weeks 1, 2, 4, 6, and 8 for the following efficacy parameters: erythema, scaling, induration, overall disease severity, and a physicians global assessment. Urinalysis, complete blood counts and serum chemistries were monitored at weeks 1, 2, 4, and 8 as part of the safety assessment.

Demographics of Enrolled Patients - Study DE127-032

	Calcipotriene Solution 0.005%	Calcipotriene Solution 0.0025%	Vehicle
Number of Subjects	79	80	79
Mean Age (range years)	47.41	47.95	44.18
Height (in)	67.11	67.13	66.99
Weight (lbs)	171.73	171.69	171.88
Duration of Current Psoriatic Episode (yrs)	14.83	14.80	14.09
Sex (%)			
Female	42 (53%)	43 (54%)	45 (57%)
Male	37 (47%)	37 (46%)	34 (43%)
Race (%)			
Caucasian	73 (92%)	77 (96%)	75 (95%)
Hispanic	3 (4%)	1 (1%)	1 (1%)
Black	2 (3%)	1 (1%)	0 (0%)
Oriental	1 (1%)	0 (0%)	2 (3%)
Other	0 (0%)	1 (1%)	1 (1%)

Discontinuances

	Calcipotriene 0.005%	Calcipotriene 0.0025%	Vehicle
Administrative	5	7	2
Adverse Reactions	2	4	9

Table 9. Results Clinical Efficacy Measures 127-032

	CALCIPOTRIENE SOLUTION 50 µg/mL		CALCIPOTRIENE SOLUTION 25 µg/mL		VEHICLE				PAIRWISE COMPARISONS		
	N	MEAN	N	MEAN	N	MEAN	F	OVERALL P-VALUE[1]	50 µg/mL VS. VEHICLE P-VALUE[2]	25 µg/mL VS. VEHICLE P-VALUE[2]	50 µg/mL VS. 25 µg/mL P-VALUE[2]
DAY 1											
SCALING	79	4.71	80	5.23	79	4.94	2.763	0.0654	---	---	---
ERYTHEMA	79	4.44	80	4.84	79	4.53	3.270	0.0399	0.4668	0.0807	0.0137
PLAQUE ELEVATION	79	4.46	80	4.66	79	4.61	0.451	0.6378	---	---	---
OVERALL SEVERITY	79	4.73	80	5.06	79	4.94	2.195	0.1139	---	---	---
PRURITUS	79	4.11	80	4.33	79	3.97	0.300	0.7409	---	---	---
DAY 4											
SCALING	74	4.12	74	4.53	70	4.36	1.982	0.1406	---	---	---
ERYTHEMA[3]	74	4.27	74	4.30	70	4.31	0.020	0.9803	---	---	---
PLAQUE ELEVATION	74	4.08	74	4.22	70	4.23	0.204	0.8154	---	---	---
OVERALL SEVERITY	74	4.34	74	4.64	70	4.51	1.287	0.2786	---	---	---
PRURITUS	74	3.35	74	3.58	70	3.47	0.148	0.8626	---	---	---
WEEK 1											
SCALING	78	3.68	78	4.09	74	4.01	0.808	0.4470	---	---	---
ERYTHEMA[3]	78	3.85	78	3.71	74	4.20	5.906	0.0032	0.0133	0.0011	0.4112
PLAQUE ELEVATION	78	3.60	78	3.69	74	3.91	1.156	0.3167	---	---	---
OVERALL SEVERITY	78	3.87	78	4.05	74	4.28	1.835	0.1622	---	---	---
PRURITUS	78	3.06	78	3.13	74	3.27	0.425	0.6540	---	---	---
WEEK 2											
SCALING	76	3.25	77	3.83	72	3.96	2.343	0.0986	---	---	---
ERYTHEMA[3]	76	3.44	77	3.35	72	4.03	9.058	0.0002	0.0004	0.0002	0.8853
PLAQUE ELEVATION	76	3.14	77	3.27	72	3.82	4.394	0.0136	0.0073	0.0158	0.7730
OVERALL SEVERITY	76	3.39	77	3.69	72	4.04	3.823	0.0235	0.0063	0.1916	0.1392
PRURITUS	76	2.71	77	2.75	72	2.92	0.506	0.6035	---	---	---
WEEK 4											
SCALING	73	3.00	73	3.22	71	3.58	2.207	0.1128	---	---	---
ERYTHEMA[3]	73	3.01	73	2.89	71	3.91	16.112	0.0001	0.0001	0.0001	0.4626
PLAQUE ELEVATION	73	2.66	73	2.86	71	3.52	6.711	0.0015	0.0007	0.0050	0.5380
OVERALL SEVERITY	73	3.03	73	3.14	71	3.83	6.349	0.0021	0.0013	0.0044	0.6928
PRURITUS	73	2.21	73	2.41	71	2.56	1.267	0.2841	---	---	---
WEEK 6											
SCALING	73	2.55	72	2.89	70	3.24	1.895	0.1531	---	---	---
ERYTHEMA[3]	73	2.55	72	2.60	70	3.49	10.918	0.0001	0.0001	0.0001	0.8369
PLAQUE ELEVATION	73	2.33	72	2.51	70	3.21	5.539	0.0046	0.0030	0.0062	0.8114
OVERALL SEVERITY	73	2.45	72	2.75	70	3.54	8.047	0.0004	0.0002	0.0034	0.3801
PRURITUS	73	1.74	72	2.18	70	2.59	4.055	0.0188	0.0050	0.1112	0.2115
WEEK 8											
SCALING	71	2.59	67	2.70	66	3.09	1.835	0.1626	---	---	---
ERYTHEMA[3]	71	2.41	67	2.25	66	3.30	11.134	0.0001	0.0003	0.0001	0.4068
PLAQUE ELEVATION	71	2.28	67	2.12	66	2.94	4.461	0.0129	0.0284	0.0047	0.4865
OVERALL SEVERITY	71	2.44	67	2.48	66	3.26	5.175	0.0065	0.0052	0.0062	0.9874
PRURITUS	71	1.75	67	1.70	66	2.26	2.370	0.0964	---	---	---

note: a p-value of <0.05 was considered statistically significant

Reviewer's Comments: Analysis of the pairwise comparison results suggests a statistically significant ($p = 0.013$) of calcipotriene at both concentrations over vehicle for scalp erythema at week 1. There was no advantage of calcipotriene 0.005% over calcipotriene 0.0025% ($p = 0.4$).

As the study progressed, week 2 results demonstrated significant advantages of the active agents; (calcipotriene 0.005% ($p = 0.0004$) and calcipotriene 0.0025% ($p = 0.0002$) over vehicle for erythema. Between drug comparisons revealed no significant advantage to the higher concentration, calcipotriene 0.005%. The trends for plaque elevation and overall severity tended toward greater improvement in the higher concentration group; however, there was no statistically demonstrable difference between the calcipotriene concentrations.

Table 10. Physicians Global Assessment Study 127-032

0.005 = Calcipotriene 0.005%
0.0025 = Calcipotriene 0.0025%
V = Vehicle

(Numbers of Subjects)

	Week 1	Week 2	Week 4	Week 6	Week 8
	.005/.0025/V	.005/.0025/V	.005/.0025/V	.005/.0025/V	.005/.0025/V
Completely Clear	0/0/0	0/0/0	3/2/1	8/8/2	11/10/2
Almost Clear	2/3/2	6/9/4	13/10/5	15/10/2	12/9/6
Marked Improvement	3/4/0	5/5/2	6/9/0	11/6/5	9/15/7
Moderate Improvement	12/11/8	18/11/4	11/20/14	14/25/17	13/13/14
Slight Improvement	25/32/25	26/30/26	26/17/34	17/12/25	16/11/18
No Change	35/28/37	20/20/26	13/13/25	7/11/17	9/9/18
Worse	1/0/2	3/2/6	1/2/2	1/0/2	1/0/1
p-values					
0.005%/vehicle	0.178	0.016	0.005	0.001	0.008
0.0025%/vehicle	0.006	0.010	0.001	0.001	0.001
0.005%/0.0025%	0.157	0.864	0.672	0.763	0.414

Note: a p-value of <0.05 was considered statistically significant

Reviewer Comments: Calcipotriene 0.005% was significantly better than vehicle after the first week of treatment. The lower concentration 0.0025% was significantly better than vehicle at all time points. Analysis of the parallel comparison data suggests that there is no significant advantage of calcipotriene 0.005%.

Safety Evaluation 127-032

Results

Abnormal Laboratory Values: There were eleven patients with elevated serum calcium levels; 2 minor elevations (10.3 and 10.2) occurred in the calcipotriene 0.005% group. Five patients in the calcipotriene 0.0025% treated group and 4 patients in the vehicle group had similarly mild elevations in their serum calcium levels.

Five patients in the calcipotriene 0.005% group and 9 in the calcipotriene 0.0025% and vehicle groups had slight depressions (.1 - .5) of their serum phosphorous levels.

Creatinine levels were mildly elevated (2 - 4 tenths of a point) in eleven subjects enrolled in the calcipotriene 0.005% group, 10 subjects in the calcipotriene 0.025% and 14 subjects in the vehicle group. The results of the blood urea nitrogen abnormalities were similar: 18 minor elevations in the 0.005% group, 12 eleven minor elevations in the calcipotriene 0.0025% group and 16 elevations in the vehicle group.

Reviewer's Comments: The minor laboratory elevations were not of clinical relevance.

Signs and Symptoms: One-hundred thirty-five (non-serious) adverse clinical events were reported; of these, fifty-one occurred in the calcipotriene 0.005% group, 37 occurred in the calcipotriene 0.0025% group and forty-seven were reported in the vehicle group. The majority of these were cutaneous and considered non-serious.

Table 10. Numbers of subjects with adverse events by system DE127-032

	Calcipotriene 0.005%	Calcipotriene 0.0025%	Vehicle
Skin and appendages erythema, stinging rash, xerosis, acne	39	50	30
Body as a Whole headache, infection	28	16	32
Cardiovascular vasodilation	4	3	1
Digestive dyspepsia, nausea	5	0	2
H opoietic system thrombocytopenia	0	1	1
Metabolic hyperlipemia, hyperglycemia	4	5	3
Musculoskeletal arthritis	1	4	3
Nervous system dizziness nervousness	1	2	2
Respiratory dyspnea, pneumonia, cough	9	8	7
Special Senses tinnitus conjunctivitis	2	1	4
Urogenital system hematuria, dyspareunia	3	4	5

Reviewer's Comments: There were no serious adverse events reported in this study. There were no differences between the two active treatment groups or vehicle except in the number of cutaneous reactions. Calcipotriene appears to be mildly irritating as was suggested in the dermal toxicity studies. Similar responses were noted with the cream and ointment formulations. The reactions observed in this trial were not serious enough to suggest a safety risk.

Conclusion: As in the previous study, 127-031, there was a statistically significant improvement in the signs and symptoms of scalp psoriasis in the calcipotriene 0.005% and 0.0025% treated groups. The results of the physician's assessment and grading of the individual parameters correlate well. Improvement was described early in the treatment course and continued throughout the eight week trial. No serious adverse reactions were described. Although there was a slight increase in the incidence of cutaneous adverse events occurring in the calcipotriene group as compared to the vehicle treated group, the overall good clinical response that was demonstrated by treatment with calcipotriene solution is supportive of its efficacy and safety in the treatment of adults with stable psoriasis of the scalp. Although the sponsor submitted the results of two concentrations of the test product, plans are to market calcipotriene solution in the 0.005% concentration.

II.) European Supportive Trials

Introduction: The sponsor submitted the results of four studies which were not performed in the United States as supportive of their application for calcipotriene solution:

Study 890 - Single investigator	- open label	- 11 subjects	- 6 weeks
Study 490 - Multi center	- blinded/vehicle	- 46 subjects	- 4 weeks
Study 1190- Multi center	- blinded/vehicle	- 46 subjects	- 4 weeks
Study 290 - Multi center	- blinded/active	- 274 subjects	- 4 weeks

*** Note: The formulation used in these supportive studies (calcipotriol 0.005%) differs from the one used in the United States trials in having a higher concentration of menthol (1.0 mg/ml compared to 0.8 mg/ml).**

Study 890: Eleven subjects were enrolled, in this open label, single investigator 6 week study which was designed to assess the safety and efficacy of calcipotriol solution 0.005% in the treatment of scalp psoriasis. Six subjects completed the trial; 5 withdrew (3 of whom were unable to comply with study requirements, 1 experienced deterioration of disease and 1 described discomfort of application as well as lack of benefit). Efficacy and safety were monitored using parameters similar to the US studies (erythema, scaling, induration - lab abnormalities, signs and symptoms).

Efficacy results: Total sign score (composite of erythema, scaling and induration) at the end of the study decreased by a mean of 2.7; based on a range of (

Safety results: Thirty percent of the subjects described a sensation of "burning" following application of the test product. There were no serious adverse events reported.

C sion: This results of this small open label study suggests calcipotriol may improve the signs a mptoms of scalp psoriasis in some patients. Cutaneous irritation and stinging is the most frequently reported side effect.

Reviewer's Comments: This study adds little to the application as the dermal toxicity studies and clinical safety trials showed calcipotriene to be an efficacious drug with a moderate risk of cutaneous irritancy.

Study 490: Ten investigators participated in this multicenter, double blinded, vehicle controlled 4 week study which enrolled 46 patients; all of whom were evaluable. The safety and efficacy of calcipotriol solution 0.005% as compared to vehicle was measured using parameters similar to the US trials (erythema, scaling, induration) additionally a patient self-assessment was included.

Results efficacy: Although both groups improved; no statistically significant differences were found between calcipotriol and vehicle for investigator's overall assessment ($p = 1$), total sign score ($p = 0.9$), induration ($p = 0.26$) or scaling ($p = 0.9$). Calcipotriol demonstrated a statistically significant advantage over vehicle in decreasing erythema ($p < 0.001$) and decreasing the extent of disease ($p < 0.001$). The patients assessment of itching also tended toward supporting an advantage of calcipotriol; decreasing significantly from baseline with a p-value less than 0.001.

Results safety: Seventeen cutaneous adverse events (itching, stinging, burning) were reported in the calcipotriol group and 10 were reported in the vehicle group. There were no overall differences in laboratory parameters between the two groups.

Conclusion: Calcipotriol was more effective than vehicle in decreasing the erythema, extent, and itching of psoriasis. However, more burning and stinging was reported than with vehicle.

Reviewer's comments: The results of this study do not demonstrate significant superiority overall of calcipotriol over vehicle in the treatment of scalp psoriasis.

Study 1190: This 5 center study enrolled 49 patients; 46 of whom are included in the final tabulations, 3 withdrew (2 - vehicle for inadequate response and 1 - calcipotriol for itching and stinging). The study conduct was the same as **Study 490**: the safety and efficacy of calcipotriol solution 0.005% as compared to vehicle was measured using parameters similar to the US trials (erythema, scaling, induration) additionally a patient self-assessment was included as a secondary parameter.

Results efficacy: Statistical significance ($p < 0.001$) of calcipotriol solution over vehicle was obtained for **all** parameters assessed (erythema, extent of disease, scaling, induration and patient assessment of treatment response.

Results safety: The adverse event profile was similar to other studies with a slight increase in cutaneous signs or symptoms as the only significant adverse event reported.

Conclusion: The results of this blinded trial clearly shows an advantage of calcipotriol over vehicle in the treatment of scalp psoriasis for all of the parameters assessed.

Reviewer's comments: Calcipotriol solution 0.005% was effective in the treatment of scalp psoriasis, the incidence of cutaneous side effects is greater, however these side effects were non-serious.

Study 290: The trial randomized 274 patients in 68 centers (Denmark, Finland, Vorway, Sweden, United Kingdom and the Netherlands) with scalp psoriasis to be treated with either calcipotriol solution or betamethasone 17 valerate solution 0.1% for 4 weeks. **Note:** It is not clear whether the formulation of betamethasone 17 valerate used in this study is the same formulation of betamethasone available in the United States. Efficacy of the two drugs was compared using the smae parameters as in the other studies: induration, scaling, erythema and a patient assessment. Safety was monitored by laboratory testing and the recording of adverse events.

Results efficacy: The sum of the scores for the primary efficacy parameters decreased (from baseline) by 45.2% in the calcipotriol treated group and by 61.6% (from baseline) in the betamethasone treated group. At the end of the study, betamethasone was significantly ($p < 0.001$) more effective than calcipotriol in the reducing the scaling, erythema, induration, itching and flaking associated with scalp psoriasis is this study.

Results safety: Sixty-two patients in the calcipotriol group reported cutaneous irritation; 19 patients in the betamethasone treated groups reported cutaneous irritation. Serum calcium levels did not differ between the two groups, nor did other laboratory parameters.

Conclusion and reviewer's comment: Betamethasone seems to be a safer and more effective treatment for scalp psoriasis than calcipotriol solution according to the results of this study.

Overall Conclusion: The sponsor submitted the results of: 1) two bioavailabilty studies, 2) four human dermal toxicity studies, 3) two domestic 8 week, multi-center, double blind, vehicle controlled efficacy and safety studies and 4) non-US clinical safety and efficacy trials to support the safety and efficacy of calcipotriene 0.005% solution for the treatment of mild to moderately severe scalp psoriasis in adults patients when applied twice daily for eight weeks. Calcipotriene solution 0.005% overall showed slightly more efficacy than the 0.0025% concentration. Both formulations are cutaneous irritants. There were no other significant adverse events reported.

Recommendation: The approval of this NDA is recommended.

Ella L. Toombs, MD
Medical Officer

cc:
HFD-540/CSO/Kozmas
HFD-540/CHEM/Pappas
HFD-540/PHARM/
HFD-540/Katz 3/3/96
HFD-540/Wilkin
HFD-713/Harkins/Srinivasan 3/96

Clin/Stat

Clinical/Statistical Review and Evaluation(Supplement)

APR 8 1996

NDA #/Drug Class:	20-611/3S
Applicant:	Bristol Myers Squibb
Name of the Drug:	Calcipotriene Solution 0.005%
Documents ro be reviewed:	Volumes 1.1 and 28 through 50 dated July 3, '95 and the data diskettes provided by the sponsor
Indication:	Psoriasis
Type of Report:	Clinical/Statistical
Clinical Input:	Ella Toombs, M.D. (HFD-540)

I. Introduction: The sponsor has submitted two studies (DE127-031 and DE127-032) that comprise the primary efficacy database for calcipotriene solutions 50 μg/mL and 25 μg/mL. These two studies were double-blind, vehicle-controlled, dose-ranging studies in subjects with moderate-to-severe scalp psoriasis. Calcipotriene solution 50 μg/mL, Calcipotriene solution 25 μg/mL, or vehicle was applied twice daily for 8 weeks for both studies. The subjects were evaluated at Day 1, Day 4, and Weeks 1,2,4,6, and 8. To be eligible for entry into the studies, subjects must have had scalp psoriasis with overall disease severity of at least moderate (Grade 4 on the Psoriasis Grading Scale for overall disease severity). Efficacy in the treatment of scalp psoriasis was assessed using nine-point (0-8) ordinal scales for the characteristics of erythema, scaling, plaque elevation, overall disease severity, and pruritus. Clinical significance would be achieved if a 1-unit difference between treatment group means was noted in any of the clinical parameters. For the measures erythema, scaling, plaque elevation, and overall disease severity, investigators were instructed to consider the condition of all treated sites at the time of the evaluation in relation to their knowledge of the disease, not in relation to the subject at a previous visit. For the measure pruritus, subjects assessed and reported the degree of pruritus they experienced, based on a nine-point pruritus scale. In the following sections, I will present a synopsis of sponsor's results and conclusions followed by my review and conclusions. According to the reviewing medical officer, to gain approval, statistical superiority should be established for Calcipotriene over Vehicle for all the primary efficacy measures, erythema, plaque elevation, scaling and overall severity, at the end of study (Week 8), so adjustment on the p-values is made.

2. Efficacy Analyses of Psoriasis Studies

A. Study DE127-031

1. Study Description, Patient Enrollment and Subject Demographics:

Calcipotriene solution 50 μg/mL (formulation #181161-M-25-A) and 25 μg/mL (formulation #181161-M-26-A), and matching vehicle (181161-M-27-A), applied twice daily in the treatment of scalp psoriasis, were evaluated for efficacy and safety in a randomized, double-blind, parallel-group, vehicle-controlled study. Subjects with overall disease severity of at least moderate (Grade 4 on a 0-8 scale) entered this study. Two hundred thirty-five subjects were enrolled.

Of the 235 subjects enrolled in the study, 230 were evaluable at baseline, of whom 204 completed the study. Of the 230 evaluable subjects, 78 received calcipotriene solution 50 μg/mL, 77 received calcipotriene solution 25 μg/mL and 75 received vehicle. There were 112 males (49%) and 118 females (51%) in the Evaluable Subject data set at baseline with a mean age of 46.8 years (range, years). Most subjects (90%) in the Evalauble Subject data set were white, while 3% each were Hispanic, Asian, and black, and 1% were classified as "other." No statistically significant differences existed among treatment groups in baseline demographic characteristics ($p > 0.05$).

There were no statistically significant baseline differences among the treatment groups in any of the clinical response measures ($p \geq 0.110$). All subjects scored at least "moderate" (grade 4 on a 0-8 scale) for overall disease severity, as required in the protocol. Thirty-one subjects did not complete the study. From the calcipotriene solution 50 μg/mL treatment group, five subjects withdrew because of adverse events, and seven subjects discontinued because of protocol violations. From the calcipotriene solution 25 μg/mL, three discontinued because of protocol violations and three subjects withdrew because of adverse events. From the vehicle group, seven subjects withdrew because of adverse events, and six subjects withdrew due to protocol violations. Ten of these subjects were considered treatment failures, so data for their last visits were extrapolated through Week 8 so as not to bias the Intent-to-treat analyses. Discontinued subjects were judged treatment failures by the clinical monitor after assessing the reason for discontinuation, adverse events, and the physician's global assessment.

2. Efficacy Results of Evaluable-Subject Data (by the sponsor and checked by the reviewer)

a. Analysis for differences among treatments for Scaling, Erythema, Plaque Elevation, Overall Disease Severity, and Pruritus:

The statistical plan provided for separately analyzing all subjects randomized into the study ("Intent-to-treat" analysis) and Evaluable subjects as a check against bias. To ensure that the data from all investigators could be appropriately combined, treatment-investigator interactions for all clinical response measures were examined to document the presence or absence of qualitative differences among investigational sites. The sponsor's results of the two-way analysis of variance on data ranked within investigator, showed there were no significant treatment-investigator interactions ($p \geq 0.140$), indicating that the data were poolable.

The sponsor employed a two-way analysis of variance procedure on ranked data to analyze the data for each response measure evaluation. Pairwise comparisons were performed at the 0.05 level only if the overall treatment effect was statistically significant ($p \leq 0.05$). In addition, orthogonal polynomial contrasts were conducted to evaluate the presence of linear or quadratic trends.

For all the five response measures (scaling, erythema, plaque elevation, overall disease severity and pruritus) beginning at Week 1 (with the exception of Week 2 pruritus measure), a statistically significant ***linear trend*** ($p < 0.0219$) existed without a statistically significant quadratic trend. It is inferred that a linear relationship existed between the dose applied and the response score: the higher the dose (concentration), the more effective the treatment. Calcipotriene solution 50 μg/mL was consistently more effective in reducing the characteristics of scalp psoriasis than either calcipotriene solution 25 μg/mL or vehicle.

The baseline (Day 1) mean scores for scaling, erythema, plaque elevation, and overall disease severity denoted moderate-to-severe disease for all three groups. The baseline pruritus mean score indicated severity that was somewhat less than moderate. No statistically significant difference among treatment groups existed at baseline ($p \geq 0.110$), which demonstrated the comparability of test groups prior to beginning treatment. The results of the two-way analysis of variance test on data ranked within investigator indicated statistically significant overall treatment differences at Week 1 for scaling, erythema, plaque elevation and overall disease severity ($p \leq 0.048$). At Week 2, overall treatment group differences were noted only for erythema and overall disease severity ($p \leq 0.019$). By Week 4, all five response measures demonstrated a statistically significant overall treatment group difference ($p \leq 0.028$), which was sustained through Weeks 6 and 8 ($p \leq 0.006$). For the response measures that demonstrated significant overall treatment group

differences, pairwise comparisons were conducted to identify the sources of differences.

For the response measures that demonstrated significant overall treatment group differences, pairwise comparisons were conducted to identify the sources of differences. Al significant pairwise comparisons favored calcipotriene solution over vehicle. All pairwise comparisons between calcipotriene solution 50 μg/mL and vehicle were statistically significant ($p \leq 0.015$). The pairwise comparisons between calcipotriene solution 25 μg/mL and vehicle were statistically significant in all response measures except these:

WEEK 1	WEEK 2	WEEK 4
Plaque elevation	Erythema	Pruritus
Scaling	Overall Severity	
Overall Severity		

No pairwise comparisons between calcipotriene solution 50 μg/mL and calcipotriene solution 25 μg/mL were statistically significant ($p > 0.05$).

For the Intent-to-Treat data set, the sponsor's results were virtually identical.

Based on trend analysis, calcipotriene solution 50 μg/mL is more effective in reducing the symptoms of scalp psoriasis than either calcipotriene solution 25 μg/mL or vehicle. The implications of the significant linear relationship between dose and response are that, from Week 1 through Week 8, calcipotriene solution 50 μg/mL was consistently better at reducing the clinical signs of scalp psoriasis than either calcipotriene solution 25 μg/mL or vehicle.

b. Physician's Global Assessment:

Overall treatment group differences were detected beginning at Week 1 ($p = 0.001$) and remained significant during the remaining 8 weeks of treatment ($p \leq 0.014$). Pairwise comparisons at Weeks 1-8 indicated that both the calcipotriene solution 50 μg/mL vehicle contrasts were statistically significant in favor of calcipotriene solution ($p \leq 0.023$). Table 1 gives the linear and quadratic trend p-values for Physicians's Global Assessment.

Table 1
Linear and Quadratic Trend p-values for Physician's Global Assessment[1,2]

	Linear	Quadratic
Day 4	***0.0197***	0.6038
Week 1	***0.0004***	0.2667
Week 2	***0.0230***	0.0553
Week 4	0.0002	***0.0058***
Week 6	0.0001	***0.0166***
Week 8	0.0001	***0.0104***

1 P-values are from the ESTIMATE statement in PROC GLM. P-values ≤0.05 were considered statistically significant and appear in bold/italic type.

2 If both the linear and quadratic trend p-values are significant, only the p-value for the quadratic trend is in bold type because the quadratic test demonstrates an incrementally better fit than the linear test.

As can be seen in Table 1, trend analysis indicted a statistically significant linear trend from Day 4 through Week 2, from which it can be inferred that early in the study, calcipotriene solution 50 μg/mL was more effective than either calcipotriene solution 25 μg/mL or vehicle. Statistically significant linear and quadratic trends were evident from Week 4 through Week 8, from which a variable rate of improvement based on dose can be inferred: both calcipotriene solutions 50 μg/mL and 25 μg/mL have similar patters of global assessments from physicians at Weeks 4, 6 and 8. The superiority of treatment with calcipotriene solution versus its vehicle is reflected in the results of the physician's global assessment. By Week 8, only 4 subjects (6%) were rated "completely clear" or "almost clear" in the vehicle group, compared with 19 (29%) in the calcipotriene solution 50 μg/mL group and 17 (25%) in the calcipotriene solution 25 μg/mL group.

The sponsor's results of the Intent-to-Treat group produced similar results.

3. Examination of Sub-groups

The effects of age, gender, race (dichotomized into white and non-white) and extent of overall disease severity at baseline were independently evaluated for their association with overall disease severity at Week 8. For the qualitative characteristics (race and gender) an analysis of variance was employed using the

overall disease severity score (Week 8) ranked within investigator as the dependent variable. For the quantitative characteristics (age and baseline overall disease severity), a step-wise regression analysis using backward elimination was undertaken using the Week 8 overall disease severity score ranked within investigator as the dependent variable. There were no significant differences between gender or between categories of race in overall disease severity (ranked) at Week 8. The interactions were also nonsignificant.

The results of the sponsor's analysis between age and Week 8 overall disease severity indicated that homogeneity of slopes was not rejected ($p > 0.05$, dropped from step-wise regression model) for the calcipotriene solution 50 μg/mL vs. Vehicle analysis, indicating that both calcipotriene solution 50 μg/mL and vehicle groups had a common slope. However, for the calcipotriene solution 25 μg/mL and vehicle groups, homogeneity of slopes was rejected ($p = 0.014$), so a separate regression line for calcipotriene solution 25 μg/mL was tested. This test indicated that the parameter estimate was negative but not statistically significant ($p = 0.066$).

B. Study DE127-032

1. Study Description, Patient Enrollment and Subject Demographics

This was a double-blind, parallel-group, vehicle-controlled, dose ranging study of subjects with scalp psoriasis with an overall disease severity of at least moderate (Grade 4). Calcipotriene solutions 50 μg/mL and 25 μg/mL and the matching vehicle were assigned by blocked randomization. After a 1-week washout period, study subjects were treated twice daily for 8 weeks. The inclusion/exclusion criteria, efficacy endpoints, statistical methodology used and efficacy measurement time points are the same as in Study DE127-031.

Two-hundred thirty-nine subjects were enrolled at eight sites. Two hundred ten subjects completed the trial, of whom 204 were evaluable. 29 subjects who prematurely discontinued the study (seven subjects, calcipotriene solution 50 μg/mL group; 11 subjects, calcipotriene solution 25 μg/mL; and 11 subjects, vehicle group). Nine of these subjects are considered treatment failures, so data for their last visits were extrapolated through Week 8 so as not to bias the Intent-to-Treat analyses. Discontinued subjects were judged treatment failures by the clinical monitor after assessing the reasons for discontinuation, adverse events, and the physician's global assessment.

No statistically significant differences among treatment groups existed in any of the demographic characteristics ($p > 0.05$) Of the 238 subjects deemed evalauble at Day 1, 45% were male and 55% were female; 95% were white, 2% were

Hispanic, 1% were black, 1% were Asian, and 1% were "other". The mean age was 46.5 years (range, years). There were no statistically significant baseline differences among the treatment groups in any of the clinical response measures except for erythema ($p=0.040$). The mean erythema scores at Day 1 showed that the calcipotriene solution 50 μg/mL and vehicle group scores were similar (calcipotriene solution 50 μg/mL group mean score, 4.44; vehicle group mean score, 4.53), but the calcipotriene solution 25 μg/mL score was higher (4.84, indicating more severe disease). Pairwise comparison analyses at baseline showed that the calcipotriene solution 50 μg/mL vs. 25 μg/mL comparison was statisticaliy significant ($p=0.014$). The nature of the statistical difference in the treatment groups suggested that the most appropriate analysis of the post-baseline data was a covariance analysis. Thus, for all post-baseline erythema analyses (Day-4 Week 8) a two-way analysis of covariance was performed on the data ranked within investigator, with the ranked baseline (Day 1) erythema score as covariate.

To ensure that the data from all invesitgators could be appropriately combined, treatment-investigator interactions for all clinical response measures were examined to document the presence or absence of qualitatitive differneces among investigational sites. The sponsor's results of the two-way analysis of variance on data ranked wihtin investigator showed that ***Plaque Elevation*** at Week 8 was the only response measure for which a statistically significant treatment-investigator interaction was evident ($p=0.085$).

To investigate this interaction, it was first necessary to determine the investigator(s) associated with the interaction. The central issue was whether an investigator diverged in kind from the collective remaining seven investigators (that is, the remaining investigators considered as a totality). Examination of these investigator contrasts revealed that Investigators 5 (Koo) and 8 (Krusinski) were associated with a statitically significant treatment-investigator interaction and that the interaction was qualitative. The treatment differences for the Week 8 plaque elevation scores of Dr. Krusinski arise because he rated the calcipotriene solution 50 μg/mL group two units higher than the calicpotriene solution 25 μg/mL. Dr. Koo rated the calcipotriene solution 50 μg/mL group over 2 units lowere than calcipotriene solution 25 μg/mL, and he rated the vehicle group 1.5 units lower than the calcipotriene solution 25 μg/mL group.

This was the only interaction found to be significant out of the 42 separate tests for interaction (by chance alone, up to one in 10 would be expected). It was not part of a consistent or widespread pattern. Removing Dr. Koo and Dr. Krusinski from the analysis did not change the conclusions drawn from the analysis of investigators (calcipotrine solution 50 μg/mL vs. Vehicle and calcipotrine solution 25 μg/mL group vs. vehicle are statistically significant). Both of these investigators rated plaque elevation consistently across the three treatment groups

throughout the study (Day 1 through Week 8). Moreover, since overall disease severity was defined as the primary efficacy response measure, it was concluded that the efficacy results would not be compromised by pooling the plaque elevation data.

2. Efficacy Results of Evaluable-Subject Data (by the sponsor and checked by the reviewer)

a. Analysis for differences among treatments for Scaling, Erythema, Plaque Elevation, Overall Disease Severity and Pruritus.

The sponsor did a ***trend analysis*** for the response measures scaling, erythema, plaque elevation, overall disease severity, and pruritus. For ***overall disease severity*** at Weeks 2 through 8, a statistically significant linear trend existed without a statistically significant quadratic trend ($p = 0.0063, 0.0013, 0.0002$ and 0.0052, respectively). It is inferred that a linear relationship exists between the dose applied and the scores for overall disease severity: the higher the dose (concentration), the more effective the treatment. Calcipotriene solution 50 μg/mL was more effective in reducing the overall disease severity of scalp psoriasis (the primary response measure) than either calcipotriene solution 25 μg/mL or vehicle.

For plaque elevation at Weeks 2 through 6, a statistically significant linear trend existed without a statistically significant quadratic trend, indicating that calcipotriene solution 50 μg/mL was more effective in reducing plaque elevation than the other treatments during these weeks. At Week 8, however, a significant quadratic trend was detected, indicating that at Week 8, plaque elevation scores varied based on dose.

To perform the trend analysis for erythema, adjusted ranked means (adjusting for baseline ranked erythema scores) were used instead of raw ranked means. At Weeks 1 through 8, a statistically significant quadratic trend was detected for erythema, indicating a variable rate of improvement based on dose. Although a statistically significant linear trend was also noted for erythema, the presence of a statistically significant quadratic trend suggests an incrementally better fit was found with the quadratic test than with the linear test.

For scaling and pruritus, no consistent pattern of trends emerged.

The sponsor's results of the ***analyses of response measures*** indicated lack of significant differences at baseline in four of the five response measures (scaling, plaque elevation, overall disease severity and pruritus). The results of the response measures analyses indicated that throughout the study, erythema, plaque elevation, and overall disease severity maintained a consistent pattern of statistically

significant overall treatment differences from Week 2 through Week 8 ($p \leq 0.024$). At Week 6, all response measures except for scaling demonstrated statistically significant overall treatment group differences ($p \leq 0.019$). At Week 8, however, overall treatment group differences were again noted only for erythema, plaque elevation, and overall disease severity ($p \leq 0.013$).

For the response measures that demonstrated a significant overall treatment group difference, pairwise companions were conducted to identify the source(s) of the treatment group difference. All significant pairwise comparisons favored calcipotriene solution over vehicle. In all cases, the calcipotriene solution 50 μg/mL vs. vehicle pairwise comparisons were statistically significant ($p \leq 0.028$). The calcipotriene solution 25 μg/mL vs. vehicle pairwise companions were statistically significant for all response measures except Week 2 overall disease severity and Week 6 pruritus. No pairwise comparisons between calcipotriene solution 50 μg/mL and calcipotriene solution 25 μg/mL were statistically significant.

The results of the sponsor's Intent-to-treat analyses are similar to that of the results of the Evaluable data set analysis.

Based on trend analysis, calcipotriene solution 50 μg/mL is more effective than either calcipotriene solution 25 μg/mL or vehicle in reducing most of the symptoms of scalp psoriasis. The implications of the significant linear relationship between dose and overall disease severity from Week 2 through 8 are that calcipotriene solution 50 μg/mL was consistently better at reducing the overall disease severity of scalp psoriasis (the primary response measure) than either calcipotriene solution 25 μg/mL or vehicle. Calcipotriene solution 50 μg/mL was also found to be better at reducing plaque elevation than either calcipotriene solution 25 μg/mL or vehicle from Weeks 2 through 6.

b. Physician's Global Assessment:

Relative to ***physician's global assessment***, overall treatment group differences were detected beginning at Week 1 ($p = 0.024$) and remained highly significant during the remaining 8 weeks of treatment ($p \leq 0.018$).

Pairwise comparisons at Weeks 2-8 indicated that both the calcipotriene solution 50 μg/mL vs. vehicle contrast and calcipotriene solution 25 μg/mL vs. vehicle contrast were statistically significant in favor of calcipotriene solution ($p \leq 0.017$). At Week 1, the calcipotriene solution 25 μg/mL vs. vehicle contrast was statistically significant ($p = 0.0065$).

The sponsor's trend analysis indicated statistically significant linear and quadratic trends (suggesting an incrementally better fit with the quadratic test than with he

linear test) beginning at Week 4 and continuing through Week 8. It is inferred that there is a variable rate of improvement based on dose. Both calcipotriene solutions 50 μg/mL and 25 μg/mL have similar patters of global assessments from physicians at Weeks 4, 6, and 8.

The superiority of treatment with calcipotriene solution versus its vehicle is reflected in the results of the physician's global assessment. By Week 8, only eight subjects (12%) in the vehicle group were rated "completely clear" or "almost clear", compared with 23 subjects (32%) in the calcipotriene solution 50 μg/mL group and 19 subjects (28%) in the calcipotriene solution 25 μg/mL.

3. Examination of Subgroups

Pre-existing characteristics of the subjects were examined to see if these attributes might be associated with response to treatment. The effects of age, gender, race (dichotomized into white and non-white) and extent of overall disease severity at baseline were independently evaluated for their association with overall disease severity at Week 8. For the qualitative characteristics (race and gender) an analysis of variance was employed using the overall disease severity score (Week 8) ranked within investigator as the dependent variable. For the qualitative characteristic (age and baseline overall disease severity), a stepwise regression analysis using backward elimination was undertaken using the Week 8 overall disease severity score ranked within investigator as the dependent variable.

Statistically significant differences were found between the main effect of gender and overall disease severity both at baseline and at Week 8 ($p = 0.0011$ and $p = 0.0326$, respectively). The gender effect at Week 8 was present even though the ranked Week 8 overall disease severity means were adjusted for the baseline gender/treatment differences in overall disease severity.

The results of stepwise regression with age as the quantitative independent variable eliminated all the terms in the model except the key terms (which it was forced to retain); thus, the assumptions of a common slope and no quadratic trend are supported. Age was not associated with overall disease severity at Week 8, and subjects of all ages responded similarly to treatment.

The results of the stepwise regression with overall disease severity at baseline, ranked within investigator, as the quantitative independent variable eliminated all the terms in the model except the key terms (which it was forced to retain); thus, the assumptions of a common slope and no quadratic trend are supported. The common linear term for baseline overall disease severity was significantly related to overall disease severity at Week 8 ($p < 0.05$). The sign of the slope coefficient was positive (0.516), from which it can be inferred that within each treatment there

was a direct relationship between the baseline overall disease severity and overall disease severity at Week 8. Because the data are expressed as ranks (consistent with efficacy analysis), the results are not readily interpretable. For each 1-unit increase in ranked overall disease severity at baseline, there was a 0.516-unit increase in ranked overall disease severity at Week 8, meaning that subjects who entered the study with higher scores tended to leave the study with higher scores. However, regardless of the condition at baseline, improvement was seen at Week 8.

3. Safety Analyses of Psoriasis Studies *(by the sponsor and checked by the reviewer)*

A. Study DE127-031

Two hundred thirty-five subjects (79 in the calicpotriene solution 50 μg/mL group, 78 in the calcipotriene solution 25 μg/mL group, and 78 in the vehicle group) received study medication and were part of the Intent-to Treat population. The sponsor performed all safety analyses on this population.

1. Extent of Exposure:

The average total consumption for all treatment groups was 201.9 grams of solution per subject. The average weekly consumption was 27.0 grams of solution per subject. No statistical difference in consumption among treatment groups was found (p = 0.322) (range of total consumption, grams per subject).

2. Adverse Events:

Fifty-one subjects (65%) in the calcipotriene solution 50 μg/mL, 37 subjects (47%) in the calcipotriene solution 25 μg/mL group, and 47 subjects (60%) in the vehicle group were reported to have experienced at least one adverse event (whether or not the event was related to treatment).

The majority of the related adverse events occurred in the ***Skin and Appendages*** category. The most frequently reported related adverse event was ***Burning, Stinging, Tingling*** in all three treatment groups (calcipotriene solution 50 μg/mL rate. 24.1; calcipotriene solution 25 μg/mL rate, 17.9; vehicle rate, 20.5.

Because facial irritation has appeared in studies of other calcipotriene dosage forms, the number of subjects who experienced facial irritation was calculated for this study. A total of 26 subjects (11% of the subjects enrolled) experienced facial irritation: 12 subjects in calcipotriene solution 50 μg mL group, eight subjects in the calcipotriene solution 25 μg/mL group, and six subjects in the vehicle group.

Adverse events of ***Skin and Appendages*** were compiled for the survival analysis of treatment differences. The results of the survival analysis (SAS-PROC LIFETEST Wilcoxon Test) revealed no statistically significant treatment differences in the time to onset and frequency of adverse event ($p = 0.832$).

3. Subgroup Analyses

Statistical analyses were undertaken to explore possible associations between ***gender, race and age*** in the proportion of subjects experiencing skin-related adverse events. Weighted-least-squares were employed (using the marginal probabilities as the response function) for the qualitative independent variables (gender and race) with treatment and interaction included in the model. Stepwise logistic regression was performed for the quantitative independent variable (age). No statistically significant relationships were observed between the proportion of subjects manifesting skin-related adverse events and any of the subgroup variables (***Gender***: $p = 0.7910$, ***race***: $p = 0.0991$ and ***age***: $p > 0.05$).

4. Laboratory Results:

Because of the similarities between calcipotriene and vitamin D in physical structure and potential physiologic effects, and because vitamin D is most likely to show effects on kidney function, laboratory tests that would show changes in kidney function were selected for detailed statistical analyses. These tests are ***serum calcium, creatinine, phosphorus, and blood urea nitrogen (BUN).***

Additionally, the four tests were statistically analyzed for trends over time with a repeated measures analysis of variance of differences among the three treatment groups and among time points. Tests were conducted to detect a linear and quadratic trend over time for each analysis. Tests to detect differences among treatments in trends were also evaluated. Additionally, a test was performed to evaluate the equality of the changes in laboratory values at 8 weeks relative to baseline. Due to limitations of the statistical procedures, only subjects who had completed laboratory observations at Day 1 and Weeks 1, 4, and 8 were analyzed as "non-interpolated".

a. Analysis of Calcium

The mean calcium concentration across treatments remained within the normal range (8.6 to 10.2 mg/dL). Both the linear trend averaged across treatments and the contrast between Day 1 and Week 8 averaged across treatments were statistically significant ($p \leq 0.044$). The analysis of the mean concentration of all three treatment groups through time shows a decrease in average calcium concentration from Day 1 to Week 8. The average decreases in calcium

concentration were 0.04 mg/dL for the calcipotriene solution 50 μg/mL group, 0.11 mg/dL for the calcipotriene solution 25 μg/mL group, and 0.01 mg/dL for the vehicle group. The quadratic trend test was not statistically significant for either analysis ($p>0.05$). No statistically significant treatment differences in trends were observed, and thus the changes appear to be independent of treatment. The differences in calcium concentrations over time within treatments were small compared to the range of normal values and are not considered to be clinically significant.

b. Analysis of Creatinine

The mean creatinine concentration across treatments remained within the normal range (0.8 to 1.5 mg/dL). No trends nor the contrast between Day 1 and Week 8 were statistically significant ($p\geq0.060$). The average change in creatinine concentration was <0.02 mg/dL for all treatment groups. The quadratic trend test was not statistically significant for either analysis ($p>0.05$). No statistically significant treatment differences in trends were observed.

c. Analysis of Phosphorus

The mean phosphorus concentration across treatments remained within the normal range (2.2 to 4.8 mg/dL). Both the linear trend averaged across treatments and the contrast between Day 1 and Week 8 averaged across treatments were statistically significant ($p\leq0.012$). The analysis of the mean concentration of all three treatment groups through time shows an increase in average phosphorus concentration from Day 1 to Week 8. The average increases in phosphorus concentration were 0.08 mg/dL for the calcipotriene solution 50 μg/mL group, 0.17 mg/dL for the calcipotriene solution 25 μg/mL and 0.13 mg/dL for the vehicle group. The quadratic trend test was not statistically significant for either analysis. No statistically significant treatment differences in trends were observed, and thus the changes appear to be independent of treatment. The differences in phosphorus concentrations over time within treatments were small compared to the range of normal values and are considered to be clinically significant by the sponsor.

d. Analysis of Blood Urea Nitrogen

The mean BUN concentration across treatments remained within the normal range (6 to 25 mg/dL). With the exception of one test, the linear and quadratic trend tests were not statistically significant nor was the contrast between Day 1 and Week 8 concentrations. A statistically significant quadratic trend treatment interaction was detected, indicating that the treatments differed in quadratic terms. Testing pairwise comparisons to identify the source of this interaction revealed that only the calcipotriene solution 50 μg/mL vs. vehicle comparison was statistically

significant (p = 0.005). For the calcipotriene solution 50 μg/mL group, BUN concentration decreased from baseline to Week 4 and then increased from Week 4 to Week 8. For the calcipotriene solution 25 μg/mL group, BUN concentration decreased from baseline to Week 1, increased from Week 1 to Week 4, and then decreased from Week 4 to Week 8. For the vehicle group, BUN concentration increased from baseline to Week 4 and t hen decreased from Week 4 to Week 8. All three treatments had Week 8 concentrations that were comparable to baseline concentrations (≤0.27 mg/dL difference). The differences in BUN concentrations among treatments over time were small compared to the range of normal values and are not considered to be clinically significant by the sponsor.

B. Study DE127-032

Two hundred thirty-nine subjects (80 in the calcipotriene solution 50 μg/mL group, 80 in the calcipotriene solution 25 μg/mL group, and 79 in the vehicle group) received study medication and were part of the Intent-to Treat population. All safety analyses were performed on this population.

1. Extent of Exposure

The average weekly consumption was 26.8 grams of solution per subject. So statistically significant difference in consumption among treatment groups was found (p = 0.391) (total consumption range, grams per subject).

2. Adverse Events

Forty-seven subjects (59%) in the calcipotriene solution 50 μg/mL, 51 subjects (64%) in the calcipotriene solution 25 μg/mL, and 50 subjects (63%) in the vehicle group were reported to have experienced at least one adverse event (whether or not the event was related to treatment).

The majority of the related adverse events occurred in the ***SKIN AND APPENDAGES*** category. The most frequently reported related adverse event was ***BURNING, STINGING AND TINGLING*** in all three treatment groups (calcipotrine solution 50 μg/mL rate, 21.3; calcipotriene solution 25 μg/mL rate, 28.8; vehicle rate, 22.8).

Because facial irritation has appeared in studies of other calcipotriene dosage forms, the number of subjects who experienced facial irritation was calculated. A total of 24 subjects (10% of the subjects enrolled) experienced facial irritation: 14 subjects in the calcipotriene solution 50 μg/mL group, nine subjects in the calcipotriene solution 25 μg/mL, and one subject in the vehicle group.

Adverse events of SKIN AND APPENDAGES were compiled for the survival analysis

of treatment differences. The results of the survival analysis (SAS-PROC LIFETEST Wilcoxon Test) revealed no statistically significant treatment differences in the time to onset and frequency of adverse events ($p = 0.258$).

3. Subgroup Analyses

Statistical analyses were undertaken to explore possible associations between gender, race, and age in the proportion of subjects experiencing skin-related adverse events. Weighted-least-squared analyses were employed (using the marginal probabilities as the response function) for the qualitative independent variables (gender and race) with treatment and interaction included in the model. Stepwise logistic regression was performed for the quantitative independent variable (age). No statistically significant relationships were observed between the proportion of subjects manifesting skin-related adverse events and any of the subgroup variables (***Gender:*** $p = 0.8066$; ***Race:*** $p = 0.6867$ and ***Age:*** $P > 0.05$).

4. Laboratory Results

Because of the similarities between calcipotriene and vitamin D in physical structure and potential physiologic effects, and because vitamin D is most likely to show effects on Kidney function, laboratory tests that would show changes in kidney function were selected for detailed statistical analyses. These tests are ***serum calcium, creatinine, phosphorus, and blood urea nitrogen (BUN).***

Additionally, the four tests were statistically analyzed for trends over time with a repeated measures analysis of variance for differences among the three treatment groups and among time points. Tests were conducted to detect a linear and quadratic trend over time for each analysis. Tests to detect differences among treatments in trends were also evaluated. Additionally, a test was performed to evaluate the equality of the changes in laboratory values at 8 weeks relative to baseline. Due to limitations of the statistical procedures, only subjects who had completed laboratory observations at Day 1 and Weeks 1, 4, and 8 were analyzed as "non-interpolated."

a. Analysis of Calcium:

The mean calcium concentration remained within the normal range (8.6 to 10.2 mg/dL). Both the linear trend averaged across treatments and the contrast between Day 1 and Week 8 averaged across treatments were statistically significant ($p \leq 0.001$). The analysis of the mean concentration of all three treatment groups through time shows a decrease in average calcium concentration from Day 1 to Week 8. The average decreases in calcium concentration between Day 1 and

Week 8 were 0.10 mg/dL for the calcipotriene solution 50 μg/mL group, 0.12 mg/dL for the calcipotriene 25 μg/mL group, and 0.09 for the vehicle group. The quadratic trend test was not statistically significant ($p>0.05$). No statistically significant treatment differences in trends were observed, and thus the changes were independent of treatment. The differences in calcium concentrations over time within treatments were small compared to the range of normal values and are not considered to be clinically significant.

b. Analysis of Creatinine

The mean creatinine concentration remained within the normal range (0.8 to 1.5 mg/dL). No trends nor the contrast between Day 1 and Week 8 were statistically significant ($p\geq0.102$). The average changes in creatinine concentration between Day 1 and Week 8 were 0.01 mg/dL for both active solution groups and 0.02 mg/dL for the vehicle group. The quadratic trend was not statistically significant for either analysis ($p>0.4822$). No statistically significant treatment differences in trends were observed ($p>0.05$).

c. Analysis of Phosphorus

The mean phosphorus concentration remained within the normal range (2.2 to 4.8 mg/dL). Neither the linear trend nor the contrast between Day 1 and Week 8 were statistically significant ($p>0.05$). The average changes in phosphorus concentration between Day 1 and Week 8 were 0.03 mg/dL for the calcipotriene solution 50 μg/mL group, 0.02 mg/dL for the calcipotriene solution 25 μg/mL group, and 0.01 mg/dL for the vehicle group. The quadratic trend test was not statistically significant ($p>0.05$).

d. Analysis of Blood Urea Nitrogen (BUN)

The mean BUN concentration remained within the normal range (6 to 25 mg/dL). With the exception of one test, the linear and quadratic tests were not statistically significant nor was the contrast between Day 1 and Week 8 concentrations. Statistically significant patterns of curvature, however, were detected by the test for quadratic trend averaged across treatments ($p=0.0412$). Since the test for differences among treatments in trends was not significant ($p=0.376$), these changes appear to be independent of treatment. All three treatments had Week 8 concentrations that were comparable to baseline concentrations (≤0.67 mg/dL difference). No other statistically significant treatment differences were observed. The differences in BUN concentrations within treatments over time were small compared to the range of normal values and are not considered to be clinically significant.

C. Integarated Safety Summary Analysis

1. Adverse Events

This evaluation of the safety of twice-daily treatment with calcipotriene solution is based on the combined data (Studies DE127-031 and DE127-032) from 159 subjects treated with calcipotriene solution 50 μg/mL, 158 subjects treated with calcipotriene solution 25 μg/mL, and 157 subjects treated with vehicle. Statistically similar durations of exposure were noted in all three treatment groups ($p = 0.769$).

No statistically significant differences among the treatment groups existed in any of the demographic characteristics (***$p > 0.217$***). The overall incidence of adverse events was statistically comparable in the active and vehicle treatment groups (***$p = 0.453$***).

The two most frequently reported adverse events considered related to treatment were the event BURNING/STINGING/TINGLING and the event RASH. The rates of BURNING/STINGING/TINGLING were similar among treatment gorups (calcipotriene solution 50 μg/mL rate, 22.6; calcipotriene solution 25 μg/mL rate, 23.4; vehicle rate, 21.7). The rate of RASH was highest in the calcipotriene solution 50 μg/mL group (rate, 11.3) and lowest in the vehicle group (rate, 4.5). The rate of RASH in the calcipotriene solution 25 μg/mL group was 7.6.

Because facial irritation has been reported in studies of other calcipotriene dosage forms, the number of subjects who experienced fcial irritation was calculated for Studies DE127-031 and DE127-032. There Is a statistically significant difference between the three treatment groups relative to the number of subjects who experienced facial irritation (50 μg/mL: 26 (16.4%); 25 μg/mL: 17 (10.8%) and Vehicle: 7 (4.5%); ***$p = 0.003$***).

For Studies DE127-031 and DE127-032, skin-related adverse events were compiled for a survival analysis of treatment differences. The results of the survival analysis revealed no statistically significant treatment differences in the time to onset and frequency of adverse events (***$p = 0.751$***).

2. Adverse Events and Their Relationship to Age, Sex, or Race

For studies DE127-031 and DE127-032, a statistical analysis was performed to determine the possible associations between gender, race, and age in the proportion of subjects reporting at least one SKIN AND APPENDAGES adverse event. The results of these analyses indicated a significant association between gender and proportion of subjects experiencing at least one SKIN AND

APPENDAGES adverse event (p=0.011). Since the treatment-by-gender interaction was not significant (p=0.957), these differences in gender (43% of females reporting at least one SKIN AND APPENDAGES adverse event compared with 31% of males) were consistent among all three treatment groups. This suggests that the differences in gender were independent of (or not associated with) treatment. Neither race (p=0.7274) nor age (p=0.7783) analysis showed significant effects.

3. Laboratory Results

In the two pivotal studies, calcium, creatinine, phosphorus, and BUN concentrations were statistically analyzed for trends over time, differences among the three treatment groups, and change from baseline to Week 8, with a repeated measures analysis of variance.

1. Analysis of Calcium:

The mean ***calcium*** concentrations (both non-interpolated and interpolated) remained within the normal range (8.6 to 10.2 mg/dL). Both the linear trend averaged across treatments were statistically significant (p=0.0001). The **quadratic trend test** was **not statistically significant.** No statistically significant treatment differences in trends were observed, and thus the changes appear to be independent of treatment. The differences in calcium concentrations over time within treatments were small compared to the range of normal values and are not considered to be clinically significant.

2. Analysis of Creatinine

The mean ***creatinine*** concentrations remained within the normal range (0.8 to 1.5 mg/dL). The analysis of the mean concentration of all three treatment groups through time shows an increase in average creatinine concentration from Day 1 to Week 8. No statistically significant treatment differences in trends (Linear and Quadratic) were observed (p>0.07), and thus the changes apppear to be independent of treatment. The differences in creatinine concentrations over time within treatments were small compared to the range of normal values and are not considered to be clinically significant.

3. Analysis of Phosphorus

The mean phosphorus concentrations remained within the normal range (2.2 to 4.8 mg/dL). The analysis of the mean concentration of all three treatment groups through time shows an increase in average phosphorus concentration from Day 1 to Week 8. No statistically significant treatment differences in linear trend is

observed, and thus the changes appear to be independent of treatment ($p > 0.1999$). The differences in phosphorus concentrations over time within treatments were small compared to the range of normal values and are not considered to be clinically significant.

4. Analysis of Blood Urea Nitrogen (BUN)

The mean BUN concentrations remained within the normal range (6 to 25 mg/dL). No statistically significant treatment differences in linear trend was observed, and thus the changes appear to be independent of treatment ($p > 0.2509$). The differences in BUN concentrations over time within treatments were small compared to the range of normal values and are not considered to be clinically significant.

4. Conclusions (which may be conveyed to the sponsor):

a. Study DE127-031

In summary, for the ***twice-daily treatment of moderate-to-severe scalp psoriasis***, the results of this study show that there is a significant relationship between dose and response, indicating that calcipotriene solution 50 µg/mL is superior to calcipotriene solution 25 µg/mL and its vehicle, as demonstrated by the following:

- At Weeks 1 through 8, ***trend analysis*** indicated a significant linear relationship between increasing dose and improved signs and symptoms ($p \leq 0.028$) for all response measures (except Week 2 pruritus), from which it can be inferred that calcipotriene solution 50 µg/mL consistently reduced the signs and symptoms of scalp psoriasis better than calcipotriene solution 25 µg/mL or vehicle.

- Week 1 pairwise comparisons showed that calcipotriene solution 50 µg/mL group achieved statistically significant lower mean scores than the vehicle group for scaling, erythema, plaque elevation, and overall disease severity ($p \leq 0.015$). The calcipotrine solution 25 µg/mL group achieved a statistically significant lower mean score than the vehicle group only for erythema ($p = 0.045$).

- Week 2 pairwise comparisons showed that the calcipotriene solution 50 µg/mL group achieved statistically significant lower mean scores than the vehicle group for erythema and overall disease severity ($p \leq 0.005$), while the calcipotriene solution 25 µg/mL group achieved no statistically significant lower mean scores compared with the vehicle group ($p \geq 0.064$).

- From Week 4 through Week 8, pairwise comparisons showed that the calcipotriene solution 50 μg/mL group achieved statistically significant lower mean scores than the vehicle group for all signs and symptoms of psoriasis (scaling, erythema, plaque elevation, overall disease severity, and pruritus; $p \leq 0.009$). From Week 4 through Week 8 for the calcipotriene solution 25 μg/mL group, the mean scores for all response measures were significantly better than the mean scores for the vehicle group ($p \leq 0.021$), except for Week 4 pruritus.

- For the physician's global assessment, a significant linear relationship between dose and response was noted from Day 4 through Week 2 ($p \leq 0.023$), from which it can be inferred that early in the study, calcipotriene solution 50 μg/mL was more effective than either calcipotriene solution 25 μg/mL or vehicle. Statistically significant pairwise differences in favor of calcipotriene solution 50 μg/mL and 25 μg/mL over vehicle were observed by Week 1 ($p \leq 0.007$) and were sustained through Week 8 ($p \leq 0.023$). By Week 8, 29% of the calcipotrine solution 50 μg/mL subjects were rated "completely clear" or "almost clear." compared with 25% of the calcipotriene solution 25 μg/mL subjects and only 6% of the vehicle subjects.

- Calcipotriene solution was well tolerated. No statistically significant differences were found in the time to onset and frequency of skin-related adverse events among treatment groups. The principal related adverse event was ***BURNING, STINGING, TINGLING***. Adverse events of SKIN AND APPENDAGES were compiled for survival analysis of treatment differences. The results of the ***survival analysis*** done by the sponsor, revealed no statistically significant treatment differences in the time to onset and frequency of adverse events ($p = 0.832$)

b. Study DE127-032

In summary, for the ***twice-daily treatment of moderate-to-severe scalp psoriasis***, the results of this study show that there is a significant relationship between dose and extent of the primary response measure, indicating that calcipotriene solution 50 μg/mL is superior to calcipotriene solution 25 μg/mL and its vehicle.

- ***Trend analysis*** indicated a linear relationship between dose and the extent of overall disease severity (the primary response measure, $p \leq 0.006$) from Week 2 through Week 8, from which it can be inferred that calcipotriene solution 50 μg/mL was consistently more effective in reducing the ***overall disease severity*** of scalp psoriasis compared with both calcipotriene 25 μg/mL and vehicle. Also, from Weeks 2 through 6, there was a linear relationship between dose and the extent of ***plaque elevation*** ($p \leq 0.007$), from which it

can again be inferred that calcipotriene solution 50 μg/mL was more effective in reducing plaque elevation than calcipotriene solution 25 μg/mL or vehicle.

- Calcipotriene solution 50 μg/mL vs. vehicle comparisons for erythema, plaque elevation, and overall disease severity were statistically significant ($p \leq 0.028$) in favor of calcipotriene solution 50 μg/mL from Week 2 through Week 8. Calcipotrine solution 50 μg/mL was also significantly more effective than vehicle in reducing pruritus at Week 6 ($p = 0.005$), while calcipotriene solution 25 μg/mL was not.

- The physician's global assessment pairwise comparisons from Week 2 through Week 8 indicated statistically significant differences favoring both calcipotriene solutions 50 μg/mL and 25 μg/mL over vehicle ($p \leq 0.017$). No statistically significant differences between calcipotriene solutions 50 μg/mL and 25 μg/mL were found ($p > 0.05$). By Week 8, only eight subjects (12%) in the vehicle group were rated "completely clear" or "almost clear," compared with 23 subjects (32%) in the calcipotriene solution 50 μg/mL group and 19 subjects (28%) in the calcipotriene solution 25 μg/mL group.

- Calcipotriene solution was well tolerated, although the calcipotriene solution 25 μg/mL had a somewhat higher rate (number of events per 100 subjects) of skin-related adverse events considered related to treatment than the other groups. The principal related adverse event was BURNING, STINGING, TINGLING. No statistically significant differences were found in the time to onset and frequency of skin-related adverse events among treatment groups. Laboratory test results were similar in the three treatment groups and were not associated with treatment-related changes.

Thus, for the ***twice-daily treatment of moderate-to-severe scalp psoriasis***, the results of the ***two studies, Study DE127-031 and DE127-032*** show that there is a ***statistically significant relationship between dose and extent of the primary response measure, indicating that Calcipotriene solution 50 μg/mL is superior to Calcipotrine solution 25 μg/mL and it vehicle.*** Further, Calcipotriene solution is well tolerated. ***No statistically significant differences*** were found in the time to **onset and frequency of skin-related adverse events among treatment groups.** ***Laboratory test results were similar in the three treatment groups and were not associated with treatment-related changes.*** The **Integrated Safety Summary** of the two studies also reveal ***statistically similar*** results. Because the Safety profiles of calcipotriene solution 50 μg/mL and calcipotriene solution 25 μg/mL so similar, and because the efficacy results for calcipotriene solution 50 μg/mL, reveal that it tended to be statistically more effective than calcipotriene solution 25 μg/mL, the sponsor wishes to gain approval for Calcipotriene solution 50 μg/mL in the treatment of Scalp Psoriasis.

April 8, '96
R. Srinivasan, Ph.D.
Acting Team Leader, Biometrics IV

Concur: Ralph Harkins, Ph.D.
Acting Division Director, Biometrics IV

cc:
Archival NDA 20-611
HFD-540
HFD-540/Mr. Cross
HFD-540/Dr. Toombs
HFD-540/Dr. Wilkin
HFD-725/Dr. Harkins
HFD-725/Dr. Srinivasan
HFD-344/Dr. Pierce

Chron

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CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA:	20-611	**SUBMISSION DATES:**	06/30/95
PRODUCT:	Dovonex® (Calcipotriene) Scalp Solution 0.005%		10/26/95 06/07/96
SPONSOR:	Bristol-Myers Squibb Pharmaceutical Research Institute 100 Forest Avenue, Buffalo, NY 14213		06/28/96
TYPE OF SUBMISSION:	Original NDA, 3S	**REVIEWER:**	Sue-Chih Lee, Ph.D.

I. BACKGROUND:

Calcipotriene was synthesized by Leo Pharmaceutical Products of Denmark. It is a vitamin D_3 derivative which retains the anti-hyperproliferative activity with reduced hypercalcemic activity when compared to 1,25-dihydroxy D_3. Dovonex Ointment 0.005% has been approved under NDA 20-273 for the treatment of plaque psoriasis and the solution is intended for the treatment of scalp psoriasis. The solution of a similar formulation (different only in the amount of menthol) has been marketed outside the US by Leo Pharmaceutical Products under the same trade name.

II. FORMULATION:

Component	mg/mL	Kg/140 L
Calcipotriene hydrate equiv. to Calcipotriene anhyd.		
✓ Isopropyl alcohol		
✓ Propylene glycol		
✓ Hydroxypropyl cellulose		
✓ Sodium citrate		
✓ Menthol		
✓ Purified water	q.s.	L

III. DOSAGE REGIMEN:

Apply the solution only to the scalp lesions and rub in gently and completely.

IV. METABOLISM OF CALCIPOTRIENE:

The proposed metabolic pathway of calcipotriene involves oxidation at side chain and formation of water as well as conjugation to form glucuronides and sulfates.

V. IN VIVO PERCUTANEOUS ABSORPTION STUDIES:

Two single-dose studies were conducted to assess the percutaneous absorption of calcipotriene from the proposed scalp solution in healthy subjects (DE127-030) and patients with scalp psoriasis (DE127-028). In either study, a 2.0 mL dose was applied to the scalp (160 cm^2) of each subject for 12 hours. The extent of systemic exposure was 0.12 ± 0.17% of the applied dose in psoriatic patients and 0.40 ± 0.38 % in healthy subjects.

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VI. IN VITRO PERCUTANEOUS ABSORPTION STUDY:

A study (Study MC 92-03 NM-21) was conducted to investigate the in vitro percutaneous absorption and distribution of calcipotriene in human cadaver skin for various calcipotriene preparations (ointment, cream and solution) using modified Franz diffusion cells. The distribution of calcipotriene in the skin layers was determined 6 days after application of the test formulations and, therefore, the data are considered of no value because the skin is expected to have deteriorated. The amount of calcipotriene in the receptor fluid at 54 hrs in descending order is: ointment > solution > cream.

VII. COMMENTS:

1. In the original submission, any BQL values observed for the samples were taken as zero. The sponsor later readjusted BQL values as shown below. This amendment yielded slightly higher results but the changes do not impact on this reviewer's decision.

Adjusted mean total recovery from urinary residues (in % of applied dose):

$0.044 \pm 0.037\%$ (psoriatic patients)

$0.11 \pm 0.06\%$ (healthy subjects)

Adjusted mean total recovery from fecal residues (in %dose):

$0.118 \pm 0.128\%$ (psoriatic patients)

$0.22 \pm 0.13\%$ (healthy subjects)

Readjustment of BQL values:

a. Serum and urine samples;

The first BQL value after a detectable value was readjusted to the actual cpm detected if the value was greater than one-half the LOQ. One half the LOQ was used to calculate recovery if the actual cpm detected was less than one-half the LOQ.

b. Fecal samples:

All BQL samples for collection interval between 24 hours and 168 hours were readjusted to the value of one-half the LOQ.

2. In a previous study with calcipotriene ointment (DE127-029), the total cumulative excretion of radioactivity in urine and fecal residues (U+F) for each individual subject was obtained by fitting the data from Days 1-7 to the following equation:

$$\text{Total excretion (up to day D)} = A \times [1 - \exp(-B \times D)],$$

where A is the maximum total excretion (in urine and fecal residues) and B is the elimination rate constant. The data fitting yielded a 17% higher value in total excretion. (Note that this approach did not necessarily result in a more accurate estimate due to the assumptions involved in the equation. However, the difference should be kept in mind for comparing different studies. In this case, a 17% difference is not considered significant to affect this reviewer's decision.

3. The extent of in vivo percutaneous absorption for the scalp solution (<0.5% of the applied dose) was much less than that observed for the ointment (5-6%). The difference in the dosing area (4x) alone does not fully explain the observed difference in percutaneous absorption (>10x). Other possible contributing factors are:

a. The scalp hair may adsorb calcipotriene from the applied dose and result in less percutaneous absorption. However, the sponsor did not examine this factor.

b. The occlusive nature of the ointment promotes hydration of skin and may facilitate the percutaneous absorption.

c. The method of calculation used for the scalp solution may somewhat underestimate the result.

d. In the case of the scalp solution, evaporation of the solvent may result in the precipitation of calcipotriene, and hence reduces the percutaneous absorption.

e. The formulation and skin at the application site (scalp vs. back of trunk) also may affect the percutaneous absorption of the drug.

4. The in vitro skin permeation studies were conducted for 7 days. The skin is expected to deteriorate during the experiment and, therefore, the results are not meaningful except for the 54-hr in vitro percutaneous absorption data.

5. This reviewer does not consider it necessary to request a multiple-dose study for the scalp solution based on the following reasons:

a. With one single topical application, the percutaneous absorption from the scalp solution is less than that from the approved ointment formulation.

b. Studies with calcipotriene ointment indicates that the extent of absorption from an ointment dose remains the same after 2 weeks of topical applications when compared to one single topical application.

Labeling Comments:

1. The extent of percutaneous absorption should be given along with the dose, dosing surface area and dose exposure time. Therefore, the labeling should read as follows:

VIII. RECOMMENDATION:

From the biopharmaceutics standpoint, the application is acceptable. Labeling Comment #1 should be conveyed to the sponsor.

Sue-Chih Lee, Ph.D.
Division of Pharmaceutical Evaluation III

RD Initialed by Dennis Bashaw, Pharm.D. 7/2/96

FT Initialed by Dennis Bashaw, Pharm.D. 7/2/96

Biopharm Day (Date: 7/1/96; Attendees: Drs. Fleischer, Lazor, Hunt, Mehta, Shah, Bashaw and Lee)

CC:
NDA 20-611
✓ HFD-540 (2 copies)
HFD-880 (TL - Bashaw)

HFD-340 (Viswanathan)
HFD-205 (FOI)
✓ Drug File (Clarence Bott, HFD-870, Pkln 13B31)
HFD-880 (DPE3)
HFD-880 (Reviewer - Lee)

1) **Study DE127-028:**

PERCUTANEOUS ABSORPTION OF ^{3}H-BMS-181161 (MC 903) SOLUTION VIA PSORIATIC SCALP

INVESTIGATOR AND LOCATION:

OBJECTIVES:
To estimate the extent of percutaneous absorption of calcipotriene from a solution (50 μg/mL) via the psoriatic scalp.

FORMULATION:
The formulation is the same as the to-be-marketed formulation but contains ^{3}H-calcipotriene.

STUDY DESIGN:
This is a single-dose study in 5 female patients (age: 55$\pm$8.3 yrs., wt: 75.2$\pm$15.4 Kg) with large stable psoriatic lesions on the scalp. After a 1-week washout period, a 2.0 mL (100 μg calcipotriene) dose of tritium labeled calcipotriene solution (~170 μCi) was applied to the psoriatic scalp (160 cm^2) of each patient and the test site was covered by a non-occlusive surgical cap. After 12 hours, the medication was removed with gauze pads soaked with 70% isopropanol/30% water followed by a hairwash with shampoo and water. All 5 subjects completed the study.

Sample collections - Samples were collected over a 3-week period.

Blood:	pre-dose, 1, 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, 168, 288 (or 312) and 456 (or 480) hours post-dose.	
Urine:	Day -1:	50 mL
	Day 1:	0-4 hr, 4-8 hr, 8-12 hr, 12-16 hr, 16-24 hr
	Days 2 to 8:	0-24 hrs
	Days 13/14 and 20/21:	0-24 hrs
Feces:	Daily collections from Days 1 to 8, Day 13/14 and Day 20/21 and spot sample on Day -1	

ASSAY:
The radioactivity in each sample was determined by liquid scintillation counting method following appropriate sample preparation.

Serum samples:
For determining the total radioactivity in serum samples, samples were digested with Soluene, neutralized with acid, and then mixed with scintillation cocktail for scintillation counting.
For determining the non-volatile radioactivity in serum samples, samples were evaporated to

dryness, three water washes were used to reconstitute the residue and the above procedures were followed for determining the radioactivity. The difference in radioactivity in the original samples and the dried residues is attributed to the ^3H_2O in the sample.

Urine samples:
Samples were evaporated to dryness and five water washes were used to reconstitute the residue, which was then mixed with scintillation cocktail for determining the radioactivity.

Fecal samples:
Samples were homogenized with water. A portion of the homogenate was transferred onto a combustion cone and allowed to dry. The dried samples were oxidized and the ^3H_2O trapped was counted for radioactivity. The recovery of the spiked fecal homogenates ranging from dpm/g was %.

Comment:
Upon the request of this reviewer, the sponsor provided the assay sensitivity (LOQ) for all types of biological samples as shown below:

Urine:	8 dpm/mL
Urine residue:	4 dpm/mL
Serum:	40 dpm/mL (11 pg/mL)
Serum residue:	16 dpm/mL (4.7 pg/mL)
Fecal residue:	40 dpm/g

DATA ANALYSIS:
The extent of percutaneous absorption was calculated based on the following equation:

$$D_0 = W+U+F,$$

where,

D_0 = total absorbed ^{3}H-calcipotriene (as % of dose);
W = total ^3H_2O formed;
U = cumulative recovery of radioactivity in urinary residue after evaporation
F = cumulative recovery of radioactivity in fecal residue after evaporation

Formation of tritiated water is regarded as the result of metabolism of calcipotriene. This approach considers that the elimination of tritiated water follows first order kinetics and that its formation is not rate limiting.

The total ^3H_2O formed, W, was calculated according to the following equation:

$$W = Cl_{(3H2O)} * AUC_{(3H2O)} = V_d * K_{el} * AUC_{inf.\,(3H2O)}.$$

In this analysis, it was assumed that the elimination of tritiated water followed first order kinetics and its formation was not rate-limiting. The volume of distribution of ^3H_2O was assumed to be 60% of the body weight, and values of K_{el} were obtained from the beta phase of the serum ^3H_2O concentration-time curves. The serum concentration of ^3H_2O was obtained by taking the difference in serum sample radioactivity before and after evaporation.

Since the tritiated water content in the urine was accounted for in W, only the cumulative recovery in urinary residue (U), the radioactive non-water portion after the evaporation of the urine collections, was included in the calculation of D_0. The same applied to fecal samples and only the cumulative recovery in fecal residue (F) was included in the calculation of D_0.

RESULTS:

i) Dose Administered:
The mean dose applied was 1.83 ± 0.02 g with the mean total active drug of 99.7 μg and mean total radioactivity of 179.3 μCi per subject. This is equivalent to a mean dose of 12.08 mg (solution) per cm^2.

Comment:
It is unclear whether the radioactivity remaining in the bottle/dropper and on the gloves used for dose application was taken into account in the calculation of dose administered.

ii) Recovery of Administered Dose From Application Site:
The total recovery of administered dose from application site (gauze pads, tape, hair washings and caps) was 67.1% (range: %) of the applied dose.

Comments:
The low recovery may be contributed by the following factors:
1. The dose actually applied to the scalp might be smaller than was intended since some drug might remain in the bottle/dropper after dosing.
2. Radioactivity remaining in the skin and hair was not determined.

iii) Excretion of Radioactivity in Urine and Feces (After Evaporation):

Urine sample residues - Radioactivity was detected on Day 1 in all 5 subjects and no subject had detectable radioactivity after Day 5. The mean cumulative excretion of radioactivity in urine was 0.037 ± 0.038% of the applied dose.

Fecal sample residues - No subjects had detectable radioactivity in the fecal samples collected on Day 1 or after Day 6 and no radioactivity was detected in any fecal samples of 2 subjects (#3 and 4). The mean cumulative excretion of radioactivity in feces was 0.088 ± 0.133% of the applied dose.

iv) Serum samples:
The mean radioactivity in serum samples was below LOQ in all samples except two in 2 subjects, indicating the amount of tritiated water in serum is negligible.

v) Extent of percutaneous absorption:
The mean tritiated water formed was shown to be negligible and was set to zero for the purpose of calculating the extent of percutaneous absorption. The extent of percutaneous absorption was, therefore, equal to the mean cumulative recovery of radioactivity in the

urinary and fecal residue and amounted to 0.12±0.17% of the applied dose. The mean total amount applied was estimated to be 99.7 μg of calcipotriene and, therefore, the amount absorbed from an area of 160 cm^2 was approximately 0.12 μg.

Statistics	U	F	D_0
Mean	0.037	0.088	0.12
SD	0.038	0.13	0.17
N	5	5	5
CV%	102.7	153.2	141.7

Comments:

1. There appears to be no correlation between psoriatic grade (See Table 1) and percutaneous absorption.

2. It is noted that the extent of percutaneous absorption for the solution formulation when applied to the psoriatic scalp was much less than that for the ointment formulation when applied to the psoriatic skin in the trunk.

In this study, a single dose of 2 mL (1.84 g) of the 0.005% solution was applied to the psoriatic scalp (160 cm^2) for 12 hours and 0.12±0.17% of the dose (equivalent to about 0.12 μg of calcipotriene) was absorbed into systemic circulation.

In previous studies, 2.5 g of the ointment formulation (0.005%) was applied to the psoriatic skin in trunk, arms and legs (625 cm^2) as a single dose or at a bid regimen, the extent of absorption was 6±3% in the single dose study and 6.1±3.6% in the multiple dose study (equivalent to an absorption of about 7.5 μg of calcipotriene).

The differences in the dosing area (3.9x) alone does not explain the difference in the extent of systemic absorption (40x) between the solution and ointment formulations. Possible reasons include differences in skin, hair and formulation.

vi) Adverse events:

There were 2 adverse events considered to be related or possibly related to the drug treatment. Subject [redacted] reported having mild burning sensation on scalp which lasted less than 10 minutes during drug application. Subject [redacted] had slightly elevated SGPT on Day 13 which resolved when measured on Day 20.

There were 5 marked laboratory abnormalities in 4 subjects including elevated triglycerides (1 subject), elevated urinary WBC (3 subjects) and elevated urinary blood (1 subject). These events were considered not related to the study drug by the investigator.

TABLE 1

SUBJECT DEMOGRAPHY

Treatment=All Subjects

	Subject Number	Age (yr)	Height (cm)	Weight (kg)	Gender	Build	Race	Psoriasis Plaque Grade
	[redacted]	41	135.3	55.9	Female	Small	White	2
		58	163.8	79.5	Female	Large	White	4
		53	160.0	83.2	Female	Medium	White	7
		62	160.0	63.6	Female	Medium	White	2
		59	165.0	94.0	Female	Large	White	3
N		5	5	5				
MEAN		55	156.8	75.2				
STD		8.3	12.24	15.35				
MIN		41	135.3	55.9				
MAX		62	165.0	94.0				

Table 2 : Dose Administered 3H-BMS-181161 Solution

Subject #	Volume of Solution Applied (mL)	Weight of Solution Applied (g)	Calcipotriene Applied (ug)	Surface Density (uL/cm2)*	Surface Density (mg/cm2)	Radioactivity uCi Applied**
[redacted]	2.00	1.84	100.00	12.50	11.50	179.80
	2.02	1.86	101.00	12.70	11.63	181.60
	1.99	1.83	99.50	11.44	11.44	178.90
	1.98	1.82	99.00	11.38	11.38	178.00
	1.98	1.82	99.00	12.38	11.38	178.00
Mean	**1.99**	**1.83**	**99.70**	**12.08**	**11.46**	**179.26**
SD	**0.02**	**0.02**	**0.84**	**0.63**	**0.10**	**1.50**

*Over scalp area selected for dose application

**Specific activity 89.9 uCi/mL solution

50 ug/mL BMS-181161; 1.84 g/2 mL

Table 3 : Total Percent (%) Recovery of Administered Dose from Application Site after 12 Hours (Hair Wash, Gauze, Tape, Cap)

Subject #	Hair Wash	Container A (gauze, tape, cap)	Total
	14.7	56.0	70.7
	5.6	63.5	69.1
	9.6	57.9	67.6
	3.1	65.4	68.5
	13.1	46.5	59.5
Mean	**9.2**	**57.9**	**67.1**
SD	**4.9**	**7.4**	**4.4**

Table 4: Individual and Mean Percent Cumulative Excretion of Radioactivity In Urine and Fecal Residue

Cumulative Fecal Residue

	Subjects						
Day	1	2	3	4	5	Mean	SD
1	NS	0	0	0	0	0.000	0.000
2	0.00	0.02	0.00	0.00	0.00	0.004	0.009
3	0.00	0.19	0.00	0.00	0.09	0.056	0.083
4	0.02	0.32	0.00	0.00	0.09	0.085	0.135
5	0.02	0.32	0.00	0.00	0.09	0.085	0.135
6	0.03	0.32	0.00	0.00	0.09	0.088	0.133
7	0.03	0.32	0.00	0.00	0.09	0.088	0.133
13	0.03	0.32	0.00	0.00	0.09	0.088	0.133
20	0.03	0.32	0.00	0.00	0.09	0.088	0.133

Cumulative Urine Residue

	Subjects						
Day	1	2	3	4	5	Mean	SD
1	0.01	0.04	0.00	0.00	0.03	0.019	0.017
2	0.01	0.07	0.01	0.01	0.05	0.029	0.029
3	0.01	0.08	0.01	0.01	0.07	0.037	0.038
4	0.01	0.08	0.01	0.01	0.07	0.037	0.038
5	0.01	0.08	0.01	0.01	0.07	0.037	0.038
6	0.01	0.08	0.01	0.01	0.07	0.037	0.038
7	0.01	0.08	0.01	0.01	0.07	0.037	0.038
13	0.01	0.08	0.01	0.01	0.07	0.037	0.038
20	0.01	0.08	0.01	0.01	0.07	0.037	0.038

Table ~~Tabel~~ 5: Mean Percent of Total Cumulative Excretion of Radioactivity (Urine Residue + Fecal Residue)

	Subjects						
Day	1	2	3	4	5	Mean	SD
1	0.01	0.04	0.00	0.00	0.03	0.019	0.017
2	0.01	0.09	0.01	0.01	0.05	0.033	0.037
3	0.01	0.27	0.01	0.01	0.16	0.093	0.120
4	0.03	0.40	0.01	0.01	0.16	0.122	0.168
5	0.03	0.40	0.01	0.01	0.16	0.122	0.168
6	0.04	0.40	0.01	0.01	0.16	0.124	0.166
7	0.04	0.40	0.01	0.01	0.16	0.124	0.166
13	0.04	0.40	0.01	0.01	0.16	0.124	0.166
20	0.04	0.40	0.01	0.01	0.16	0.124	0.166

Table 6: **Serum Radioactivity and Formation of Tritiated Water (pg/mL, 3H-BMS-181161 Equivalents)**

Subject [redacted]

Time (hr)	Radioactivity Total	Radioactivity in Residue	Radioactivity in Tritiated Water
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	26.9	10.5	16.4
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0

Subject [redacted]

Time (hr)	Radioactivity Total	Radioactivity in Residue	Radioactivity in Tritiated Water
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0

Subject [redacted]

Time (hr)	Radioactivity Total	Radioactivity in Residue	Radioactivity in Tritiated Water
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	34.6	9.9	24.7
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0

Subject [redacted]

Time (hr)	Radioactivity Total	Radioactivity in Residue	Radioactivity in Tritiated Water
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0

Subject [redacted]

Time (hr)	Radioactivity Total	Radioactivity in Residue	Radioactivity in Tritiated Water
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0
	0	0.0	0

BQL: below quantifiable level
N/S: no sample

Figure 1: Mean Daily and Cumulative Excretion of Radioactivity in Urinary and Fecal Residue After Evaporation of Water (as % of Applied Dose)

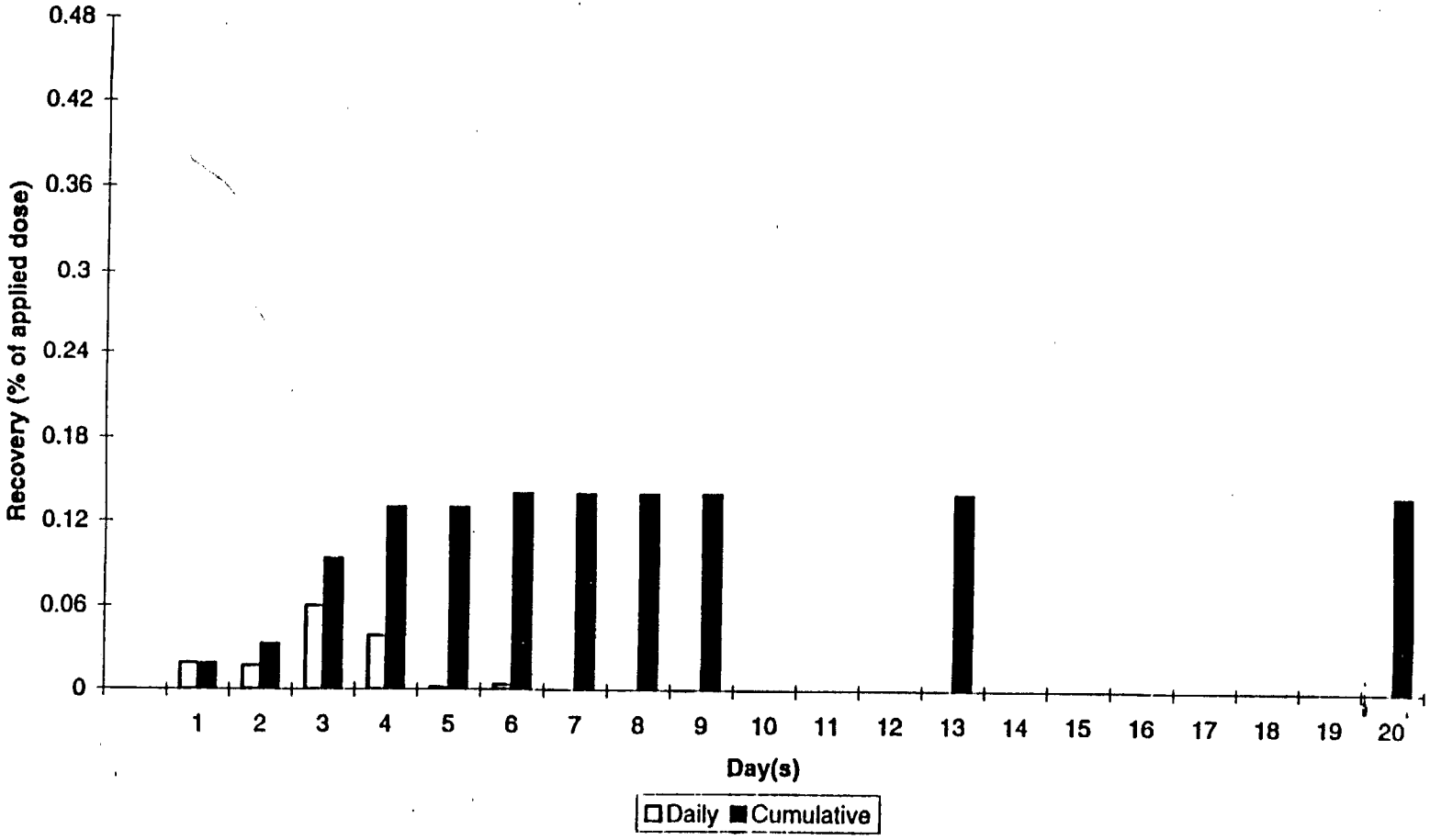
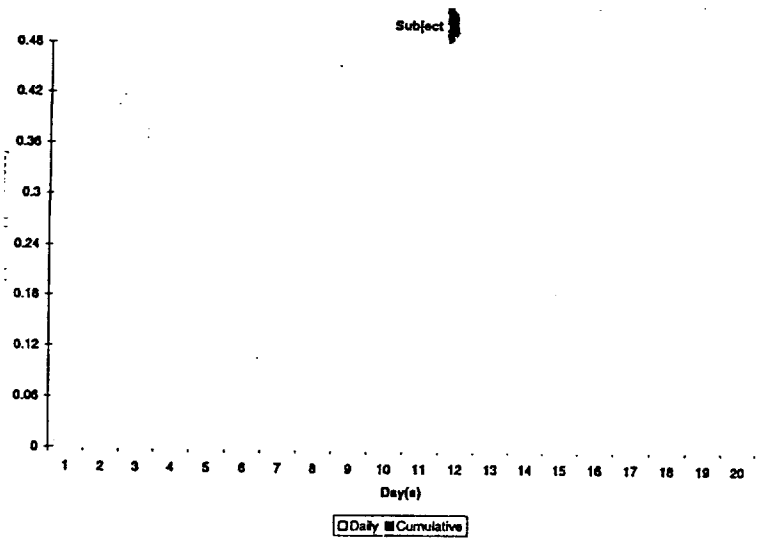
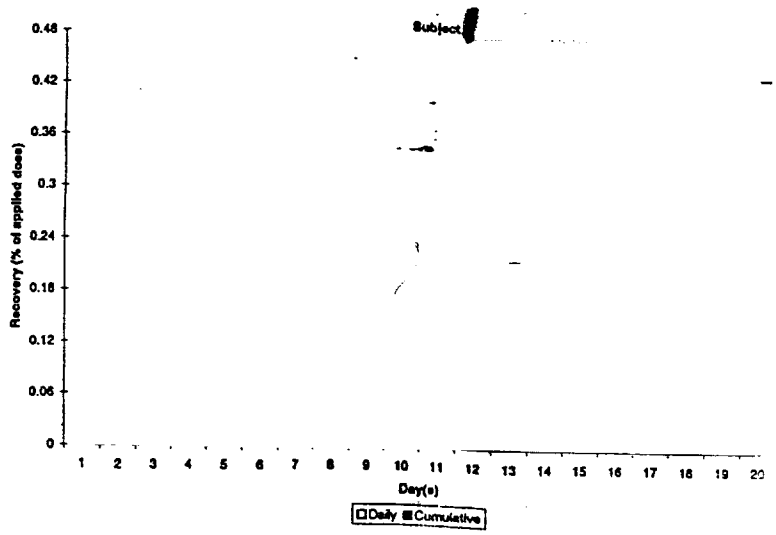
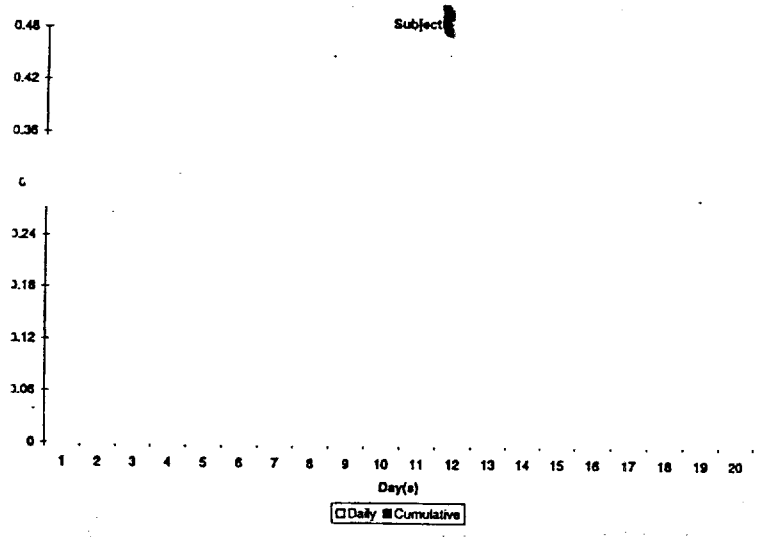
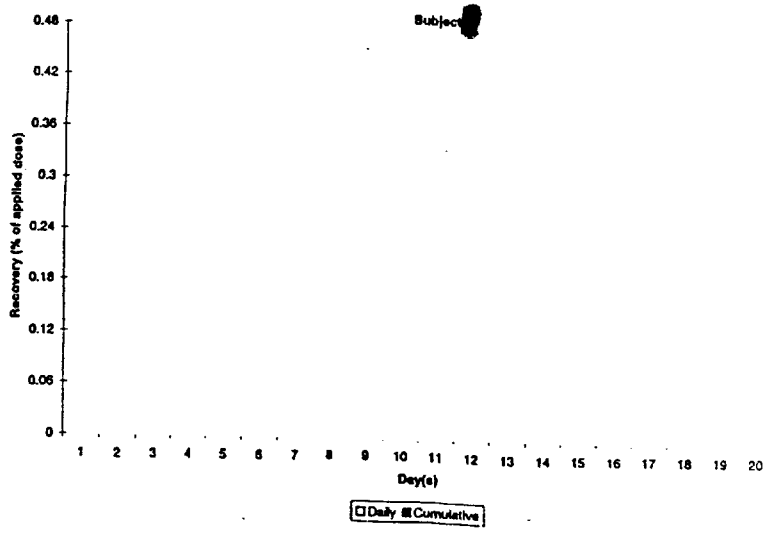


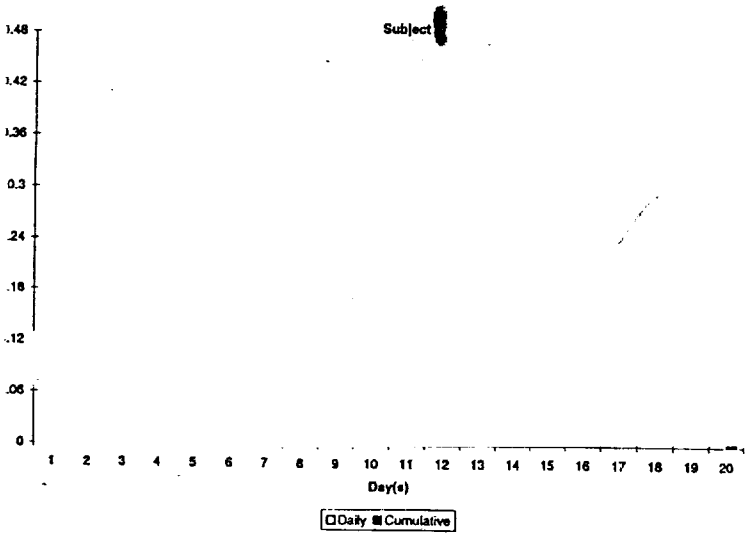
Figure 2: Individual Daily and Cumulative Excretion of Radioactivity in Urine and Fecal Residue After Evaporation of Water (as % of Applied Dose)











2) **Study DE127-030:**

PERCUTANEOUS ABSORPTION OF ^{3}H-BMS-181161 (MC 903) SOLUTION APPLIED TO NORMAL SCALP

INVESTIGATOR AND LOCATION:

OBJECTIVES:
To estimate the extent of percutaneous absorption of calcipotriene from a solution (50 μg/mL) via normal scalp.

FORMULATION: #181161-M-28-A

STUDY DESIGN:
The design of this study is similar to the above study in psoriatic patients.

This is a single-dose study in 5 normal male subjects (age: 36.0$\pm$10.3 yrs., wt: 79.5$\pm$8.9 kg). After a 1-week washout period, a 2.0 mL (100 μg calcipotriene) dose of tritium labeled calcipotriene solution (~150 μCi) was applied to the scalp (160 cm^2) of each subject and the test site was covered by a non-occlusive surgical cap. After 12 hours, the dose was removed with gauze pads soaked with 70% isopropanol/30% water followed by a hairwash with shampoo and water. All 5 subjects completed the study.

Sample collections - Samples were collected over a 3-week period.

Blood:	pre-dose, 1, 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, 168, 288 (or 312) and 456 (or 480) hours post-dose.	
Urine:	Day -1:	50 mL
	Day 1:	0-4 hr, 4-8 hr, 8-12 hr, 12-16 hr, 16-24 hr
	Days 2 to 8:	0-24 hrs
	Days 13/14 and 20/21:	0-24 hrs
Feces:	Daily collections from Days 1 to 8, Day 13/14 and Day 20/21 and spot sample on Day -1 (a total of 11 samples)	

ASSAY:
The radioactivity in each sample was determined by liquid scintillation counting method as described for the above study (Study DE127-028).

DATA ANALYSIS:
Same as for the above study (Study DE127-028).

RESULTS:

i) Dose Administered:
The mean dose applied was 1.84±1.01 g with the mean total active drug of 98.9±0.5 μg and mean total radioactivity of 150.2±0.7 μCi per subject. This is equivalent to a mean dose of 11.49±0.05 mg (solution) per cm^2.

ii) Recovery of Administered Dose From Application Site:
The total recovery of administered dose from application site (gauze pads, tape, hair washings and caps) was 71.3±2.1% of the applied dose.

iii) Excretion of Radioactivity in Urine and Feces (After Evaporation):
Urine sample residues - Radioactivity was detected on Day 1 in all 5 subjects and no subject had detectable radioactivity after Day 5. The mean cumulative excretion of radioactivity in urine was 0.10±0.06% of the applied dose.

Fecal sample residues - No subjects had detectable radioactivity in the fecal samples collected on Day 1 or from Day 13/14. The mean cumulative excretion of radioactivity in feces was 0.21±0.14% of the applied dose.

iv) Serum samples:
Radioactivity was only detected in the serum of Subject [redacted]. All serum samples from the remaining subjects were below the LOQ. Since the serum data in this study was insufficient to calculate a reliable K_{el} for tritiated water, the mean value of K_{el} (0.0044 hr^{-1}) obtained in a previous study in healthy subjects was used to calculate $AUC_{t-\infty}$. The contribution to percutaneous absorption from total ^3H_2O formed in Subject [redacted] was 0.44%. The total ^3H_2O (W) was not calculated for the remaining subjects.

v) Extent of percutaneous absorption:
The mean total percutaneous absorption was 0.40±0.38% of the applied dose. Estimated from a total applied dose of 98.9 μg of calcipotriene, the amount absorbed after a 12-hour exposure was approximately 0.40 μg from an area of approximately 160 cm^2.

Statistics	U	F	D_0
Mean	0.10	0.21	0.40
SD	0.06	0.14	0.38
CV (%)	59.4	65.4	95.2
N	5	5	5
95% CI	(0.03, 0.18)	(0.04, 0.38)	(-0.07, 0.87)

(Note: U represents the % dose recovered from the urine residue; F is the %dose recovered from the fecal residue; D_0 is the extent of percutaneous absorption.)

Comments:
In this study, the mean total percutaneous absorption was found to be 0.40±0.38% of the applied dose. The highest value observed was 1.08% for Subject no. 2. The sponsor stated that this subject had extremely short hair.

In a previous study with the 0.005% ointment formulation, a single dose of 2.5 g was applied to the trunk, arms and legs (625 cm^2) of 5 healthy subjects, the mean systemic absorption was 5.0±1.2% of the applied dose.

A comparison of these two studies in healthy subjects indicates that the difference in the dosing area (3.9x) does not fully explain the difference in the extent of systemic absorption (12.5x) between the solution and ointment formulations. This study suggests that scalp hair may be an important factor since Subject no. 2 had extremely short hair and was found to have the highest systemic absorption of calcipotriene.

vi) Adverse events:
There was 1 laboratory value meeting the criteria for marked abnormalities. On Day 14, Subject 1 had a hemoglobin level which was a greater than 3 g/dl decrease from his baseline level of 17.1 g/dl, although still within the normal range.

TABLE 1

SUBJECT DEMOGRAPHY

Treatment=All Subjects

	Subject Number	Age (yr)	Height (cm)	Weight (kg)	Gender	Build	Race
		27	175.0	82.0	Male	Large	White
		23	183.5	82.5	Male	Large	Black
		40	191.0	87.0	Male	Large	White
		45	187.0	82.0	Male	Large	White
		45	167.0	64.0	Male	Medium	White
N		5	5	5			
MEAN		36	180.7	79.5			
STD		10.3	9.67	8.92			
MIN		23	167.0	64.0			
MAX		45	191.0	87.0			

Table 2: Dose of [^{3}H]BMS-181161 Solution Administered

Subject No.	Solution Applied (g)	Calcipotriene Applied (µg)	Surface Density (mg/cm^2)*	Radioactivity Applied (µCi)
	1.85	99.54	11.56	151.1
	1.83	99.46	11.44	149.5
	1.83	99.46	11.44	149.5
	1.84	99.00	11.50	150.3
	1.84	99.00	11.50	150.3
Mean	1.84	98.89	11.49	150.2
SD	1.01	0.45	0.05	0.7

* Over scalp area selected for dose application

Table 3: Recovery of Administered Dose From the Application Site After 12 Hours (cap, wipes, tape, hairwash solution)

Subject No.	% of Dose Recovered
	68.21
	71.41
	72.79
	73.60
	70.61
Mean	71.32
SD	2.09

Table 4:

Cumulative Excretion of Non-Volatile Radioactivity In the Urine of Individual Subjects Following Application Of [^{14}C]BMS-181161 To Normal Scalp

Time (hr)	Subject No.	Subject No.	Subject No.	Subject No.	Subject No.
	0.00	0.01	0.01	0.00	0.00
	0.01	0.03	0.02	0.00	0.03
	0.01	0.06	0.04	0.01	0.04
	0.02	0.09	0.07	0.02	0.05
	0.03	0.11	0.08	0.03	0.05
	0.04	0.17	0.11	0.04	0.06
	0.04	0.18	0.13	0.05	0.07
	0.05	0.19	0.14	0.06	0.07
	0.05	0.19	0.14	0.06	0.07
	0.05	0.19	0.14	0.06	0.07
	0.05	0.19	0.14	0.06	0.07
	0.00	0.00	0.00	0.00	0.00
	0.00	0.00	0.00	0.00	0.00

[a] Percent of dose recovered during the collection interval

Table 5:

Excretion of Non-Volatile Radioactivity In the Feces of Individual Subjects Following Application Of [^{14}C]BMS-181161 To Normal Scalp

Time (hr)	Subject No.	Subject No.	Subject No.	Subject No.	Subject No.
	NS	0.00	0.00	0.00	0.00
	0.00	0.03	0.00	0.05	NS
	0.04	0.16	0.06	0.09	0.05
	NS	0.18	0.06	0.02	0.07
	0.04	NS	0.01	0.01	0.03
	0.03	0.06	0.03	0.00	0.00
	0.03	0.02	0.01	0.00	0.01
	0.00	0.00	0.00	0.00	0.00
	0.00	0.00	NS	0.00	0.00

NS - No sample

Table 6: Mean (SD) Excretion of Radioactivity in Urine Residue Following Application of [^{3}H]BMS-181161 To Normal Scalp

Collection Interval (hr)	Percent of Dose Collected in Urine Residue	
	Collection Interval	Cumulative
0-4	0.00 (0.00)	0.00(0.00)
4-8	0.02 (0.01)	0.02 (0.01)
8-12	0.01 (0.01)	0.03 (0.02)
12-16	0.02 (0.01)	0.05 (0.03)
16-24	0.01 (0.01)	0.06 (0.04)
24-48	0.02 (0.02)	0.09 (0.06)
48-72	0.01 (0.00)	0.09 (0.06)
72-96	0.01 (0.01)	0.10 (0 .06)
96-120	0.00 (0.00)	0.10 (0.06)
120-144	0.00 (0.00)	0.10 (0.06)
144-168	0.00 (0.00)	0.10 (0.06)
312-336	0.00 (0.00)	0.10 (0.06)
480-504	0.00 (0.00)	0.10 (0.06)

Table 7: Mean (SD) Excretion of Radioactivity in Fecal Residue Following Application of [^{3}H]BMS-181161 To Normal Scalp

Collection Interval (hr)	Mean (SD) Percent of Dose Collected in Fecal Residue	
	Collection Interval	Cumulative
0-24	0.00 (0.00)	0.00 (0.00)
24-48	0.01 (0.02)	0.01 (0.02)
48-72	0.08 (0.05)	0.09 (0.06)
72-96	0.07 (0.07)	0.16 (0.12)
96-120	0.02 (0.01)	0.18 (0.11)
120-144	0.02 (0.03)	0.20 (0.14)
144-168	0.01 (0.01)	0.21 (0.14)
312-336	0.00 (0.00)	0.21 (0.14)
480-504	0.00 (0.00)	0.21 (0.14)

Table 8 : Serum Radioactivity and Formation of Tritiated Water (pg-equivalents of [^{3}H]BMS-181161/mL) in Subject No.

Time (hr)	Total	Residue	Tritiated Water
	<LLQ	<LLQ	0
	<LLQ	<LLQ	0
	<LLQ	<LLQ	0
	<LLQ	6	0
	<LLQ	6	0
	7	3	4
	6	<LLQ	6
	15	<LLQ	15
	13	<LLQ	13
	7	<LLQ	7
	<LLQ	<LLQ	0
	6	<LLQ	6
	<LLQ	<LLQ	0
	<LLQ	<LLQ	0
	<LLQ	<LLQ	0
	<LLQ	<LLQ	0

<LLQ - Lower limit of quantitation

Table 9 : Estimation of the Extent of Percutaneous Absorption of [^{3}H]BMS-181161 From a 12-Hour Application

Subject No.	F (% of Dose)	U (% of Dose)	W (% of Dose)	D_0 (% of Dose)
Mean	0.21	0.10	---	0.40
SD	0.14	0.06	---	0.19

ND - None Detected
D_0 - total absorbed [^{3}H]BMS-181161
W - total ^3H_2O formed
U - cumulative recovery of radioactivity in urinary residue after evaporation (non-^3H_2O amounts)
F - cumulative recovery of radioactivity in fecal residue after evaporation (non-^3H_2O amounts)

3) Study MC 92-03 NM-21:

^{3}H-CALCIPOTRIENE DISTRIBUTION IN HUMAN SKIN IN VITRO: COMPARISON OF OINTMENT, CREAM II AND LOTION

OBJECTIVE:
To investigate the distribution of calcipotriene in human skin layers and the permeation through human skin after topical application of ^{3}H-calcipotriene ointment, cream and lotion in vitro.

FORMULATIONS:
The lotion was actually a solution which differs from the proposed formulation in the menthol content (mg/mL rather than mg/mL). The cream formulation is quite different from that of NDA 20-554 while the ointment formulation is exactly the same as that under NDA 20-273.

EXPERIMENTAL:
Human cadaver skin was mounted in the modified Franz diffusion cells with an available diffusion surface area of 3.14 cm^2 and a recipient chamber volume of 8.3 to 9.9 ml. An appropriate amount of the preparation (15 mg of the cream or ointment; 15 μl of solution) was applied to the skin to give 4.7 mg/cm^2 (twice daily during weekdays and once daily on weekends). The receptor fluid consisted of isopropanol and pH 7.3, 0.05M phosphate buffer (30/70). The water bath was maintained at 36.5°C and the resulting temperature of the skin was 32°C.

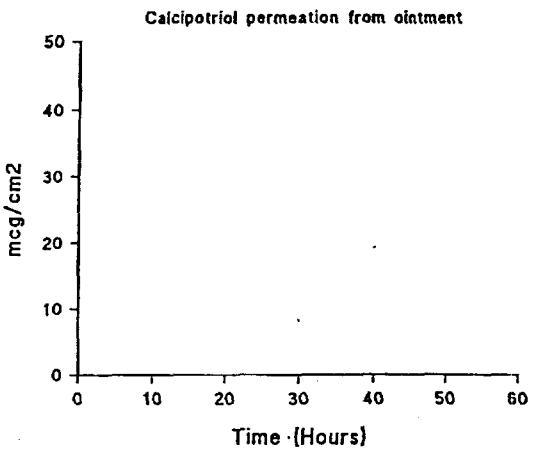
After one week, the skin was wiped with cotton plugs wetted with solvent (n-heptane for the ointment and isopropanol for the cream and solution). The residual formulation was then washed off the skin (using heptane and then isopropanol for ointment, and isopropanol only for the cream and solution).

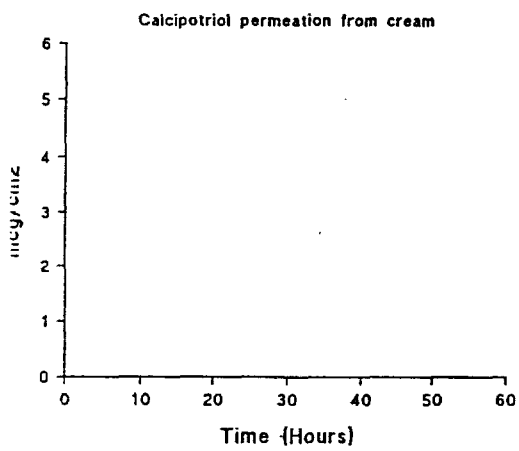
The skin was then wiped with a dry cotton plug and stripped 6-10 times using adhesive tape to remove the upper layers of stratum corneum. The epidermis was collected using forceps or by punch biopsies followed by heat separation of epidermis layer.

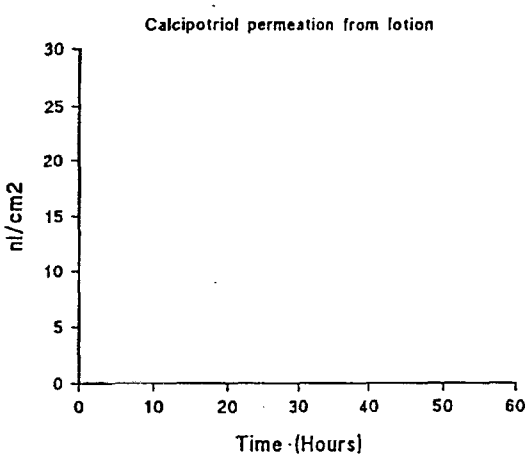
Samples were digested with Soluene or extracted with an isopropanol/water mixture (3:1) as appropriate. All samples were analyzed for radioactivity by liquid scintillation counting after addition of scintillation cocktail.

RESULTS:
The receptor fluid was assayed at 5, 25, 30, 48 and 54 hours and several more time points thereafter for up to 7 days. The distribution of calcipotriene in the skin was determined after 6 days of application of test formulations. The results (in %dose) are as follows:

Component	Ointment	Cream	Lotion
Stratum corneum (% Dose)	2.4	1.7	10.2
Epidermis (% Dose)	2.2	0.3	3.5
Dermis (% Dose)	9.9	0.3	1.7
Receptor fluid - a. after 54 hrs. (% Dose) b. after 6 days	0.19 38.1	0.014 0.9	0.066 10.2







COMMENT:

1. The in vitro skin permeation studies were conducted for 6 days. The skin is expected to deteriorate during the experiment and, therefore, the data on drug distribution in the skin is not reliable.

2. An examination of the 54-hr data shows that the extent of in vitro percutaneous absorption is: ointment > solution > cream. The in vivo studies also indicate a greater percutaneous absorption from the ointment than from the solution.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020611

PHARMACOLOGY REVIEW(S)

10/13/95

Review and Evaluation of Pharmacology and Toxicology Data
Division of Topical Drug Products, HFD-540

NDA#: 20-611 (000)

Date Submitted, CDER Received: 6/30/95, 7/3/95
Date Assigned: 7/12/95
Date Review Completed: 10/13/95

Sponsor: Bristol-Myers Squibb
Pharmaceutical Research Institute
100 Forest Avenue
Buffalo, NY 14213
716-887-3400

Name of Drug: Dovonex 0.005% Solution

Chemical Name: Calcipotriene (USAN), calcipotriol (INN)

Code Names: MC903, BMY 30434, BMY 181161

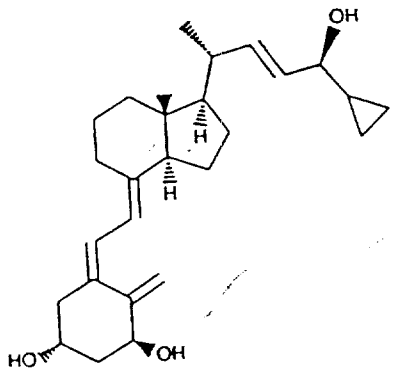
Pharmacological Category: Vitamin D_3 Analog

Indication: Psoriasis

Route of Administration: Topical dermal

Recommended Dosage: Solution is to be applied twice/day to scalp lesions. (Note length of exposure and amount applied is not specified.)

Structure:

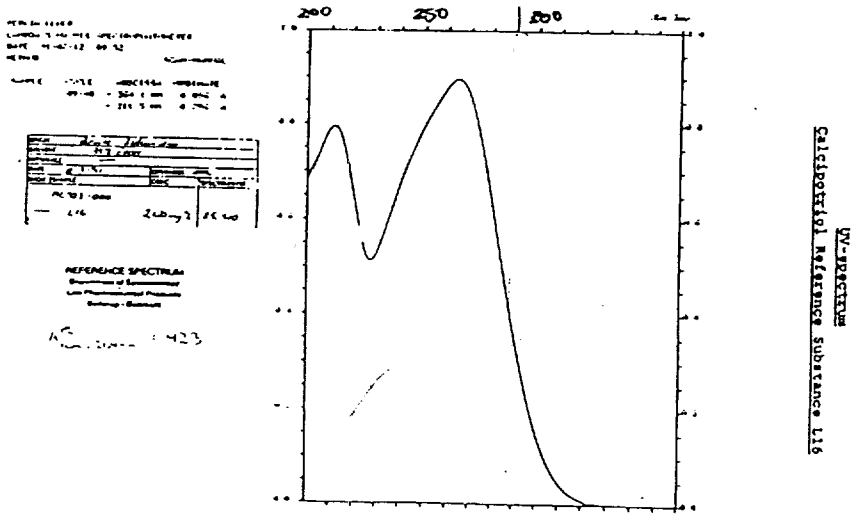


Formulation:

For the sake of completion, all formulations are shown below. The solution ingredients are in bold.

Ingredient:	solution (mg/ml)	cream (mg/g)	(ointment mg/g)
Calcipotriene	**0.05**	0.05	0.05
Isopropyl alcohol			
Propylene glycol			
Hydroxypropyl cellulose			
Sodium citrate			
Menthol			
Purified water	**q.s.**	q.s.	
White soft paraffin	----	----	q.s.
Cetearyl alcohol	----		---
Ceteth-20	----		----
Mineral oil	----		----
Disodium phosphate dihydrate	----		
Diazolidinyl urea	----		
Dichlorobenzyl alcohol	----		
Edetate disodium	----		
Glycerin	----		
White petrolatum	----		
Sodium hydroxide	----	μl	
DLα-tocopherol	----	----	
Liquid paraffin	----	----	
Polyoxyethylene-(2)-stearyl ether	----	----	

UV Spectra: The UV maximum for Dovonex is 264 nm. The UV spectrum is shown below.



Related INDs/NDA: cream: IND and NDA 20-554; ointment: IND and NDA 20-273

Index of Review:

Journal Articles

Non-Clinical Studies:
Solution formulation:
One-Month Dermal Irritation and Toxicity Study in Rats (cream and solution tested)
Six-Week Skin Irritation Test in the Rabbit
Solution formulations different from the final clinical formulation:
Dermal Absorption of ^{3}H-Calcipotriol in Mice
4-Week Dermal Toxicity Study in Mice
Cream formulation:
One-Month Dermal Irritation and Toxicity Study in Rats (cream and solution tested)
Primary Skin Irritation Study in Rabbits
Ointment formulation:
(Complete index and review of the ointment NDA are presented in Appendix A; the following studies, which appear particularly germane to this NDA, are summarized below.)
Six-Month Dermal Study in Minipigs
52-Week Dermal Study in Minipigs
Six-Month Oral Study in Minipigs
Four Reproduction Studies
Mutagenicity Studies
ADME Study in the Rat
Pharmacokinetics in the Rat
Autoradiography in the Rat

Introduction

This NDA for calcipotriene 0.005% solution is the third formulation of calcipotriene (DOVONEX) submitted to the FDA. Calcipotriene 0.005% ointment was approved for marketing in 1994 (NDA 20-273) with an 8-week maximum dosing regimen, and is currently in supplemental review for a 1-year dosing regimen. The 0.005% cream formulation also is in review, the NDA (20-554) for calcipotriene cream includes a chronic dosing regimen of up to 1 year. The clinical reviews of the solution and the extended ointment dosing regimen are not yet completed. The clinical review of the cream recommended approval for an 8-week dosing regimen. The final pharmacology recommendation for the cream also was approval for 8 weeks and not approvable for the extended dosing of one year. Pharmacology also recommended that the extended dosing not be approved for the ointment formulation. (The pharmacology recommendations were based on a 12-month mini-pig study using the ointment formulation that revealed mineralizations in the lung. The study is summarized below. The sponsor has been asked to re-examine this study and attempt to explain the lung

findings; this re-examination has not yet been submitted.)

In this solution application, just two preclinical studies were completed with the final solution formulation. Four preclinical studies were performed with the cream formulation; all other preclinical data were collected using the ointment formulation. Ointment and cream studies that are germane to the safety of calcipotriene solution are summarized within the body of this review.

Background

Calcipotriene is a vitamin D_3 analog that appears to have anti-hyperproliferative and perhaps an anti-inflammatory effect when applied topically to psoriatic skin. Endogenous vitamin D is normally activated by UV radiation to vitamin D_3. When systemic vitamin D_3 is hydroxylated in the liver or kidney it forms 1α,25-dihydroxy vitamin D_3. The hormone binds a nuclear vitamin D_3 receptor in intestine, bone, and kidney to transcriptionally activate genes encoding calcium binding proteins, which leads to absorption and reabsorption of calcium and phosphorous. Thus, the classically recognized effects of Vitamin D are stimulation of intestinal absorption of calcium and phosphorous, mineralization of bone matrix, resorption of bone, and reabsorption of calcium. High doses of vitamin D (10-100 times the RDA) result in hypercalcemia, metastatic calcifications, bone demineralization and reabsorption, and calculi in the soft tissue and the kidneys. Over the past decade, other areas and tissues beyond the classic targets have been found to contain receptors for the active vitamin D metabolite; functionality has also been demonstrated in many of the new sites of action. Included are the hematopoietic and immune system; cardiac, skeletal, and smooth muscle; brain; liver; breast endothelium; endocrine glands; thyroid; ovary; testis; pituitary; parathyroid; and the skin--including keratinocytes, melanocytes, and fibroblasts.

Summary of Submitted Journal Articles

The sponsor submitted 27 journal articles or book chapters with this NDA. They generally provide background information or support of efficacy; most concentrate on the natural form of Vitamin D_3. Three articles appear to be particularly relevant to this submission. In one article (Binderup, L and Bremme, E. Effects of a novel vitamin D analogue MC 903 (1988) *Biochemical Pharm.* 37, 5:889-895), calcipotriene *in vitro* induced cell differentiation, inhibited cell proliferation, and inhibited DNA-synthesis similar to natural vitamin D. *In vivo* rat studies indicated that oral and IP calcipotriene was 100 times less potent than natural vitamin D in causing hypercalciuria, hypercalcemia, and calcium bone mobilization. (This article is supportive of label claims made by the sponsor.) In an article entitled "Vitamin D Metabolism in the Pig" (Engstrom GW, and Littledike, ET (1986) IN: *Swine in Biomedical Research*, Plenum Press, pp 1091-1112) the pig is shown to metabolize vitamin D similar to humans. Many of the same changes and responses occur in pigs and humans as diet changes during development. This publication appears to be germane in that the sponsors pivotal nonclinical chronic studies were performed in pigs. In the single article that deals with safety, rats were treated with vitamin D_3 for up to 30 days (Makita, T. et al. (1976)

Toxicologic studies of the hormonal form of Vitamin D_3; *Tox. Appl. Pharm.* 36:323-329). Rats receiving 12.5 μg/kg/day or more showed severe signs of hypercalcemia; 2.5 μg/kg day was considered the NOEL. The data support findings in several of the sponsor's rat toxicity studies, which also indicated that rats were sensitive to calcipotriene.

Solution Formulation Studies

One-Month Dermal and Irritation Study (Study No. 93020, Batch No. B93G003 and B93F005, Nov. 1993)

Rats (20/group, one-half with abraded skin) dosed with calcipotriene solution (50 μg/ml) or cream (50 μg/g) daily under occlusion exhibited slight, intermittent scab formation. Rats treated with calcipotriene solution had increased hemoglobin and mean corpuscular hemoglobin concentration in males and decreased plasma prothrombin time and activated partial thromboplastin time in males and females. Rats treated with the calcipotriene cream had decreased hematocrit and mean corpuscular volume in females and decreased plasma prothrombin time and activated partial thromboplastin time in males. Rats treated with calcipotriene cream had increased ALT and AST values in males and increased calcium and phosphorus levels in females. Females treated with calcipotriene solution also had increased calcium and phosphorous levels. Animals treated with calcipotriene cream exhibited increased water consumption, urine output, and urine calcium excretion; as well as decreased urine specific gravity, urine pH, urine protein concentration, and urobiligin. Rats treated with calcipotriene solution exhibited the same findings, although only females had increased calcium excretion and decreased specific gravity. In the group treated with calcipotriene solution, absolute and relative kidney weights were decreased in males. Yellow discoloration at the application site was noted in animals treated with the cream vehicle and calcipotriene cream. Histopathology was not evaluated in this report.

Six-Week Skin Irritation Test (Study No. 9106121, Batch No. 9028911, October 1991)

Six female rabbits were treated with 100 mg 0.005% calcipotriene daily for a total of six weeks. Skin erythema was evaluated daily prior to topical application and skin thickness was measured weekly. Erythema was noted in treated and vehicle-control rabbits, although the BMS-18116-treated skin exhibited more severe erythema. Skin thickening, superficial ulceration, hair growth in tufts was noted in both groups. BMS-18116-treated rabbit skin developed the reactions more quickly than the vehicle control skin, although by 3 weeks and up to 6 weeks there was little difference in the magnitude of the reactions. Rabbits were sacrificed after six weeks of treatment and skin samples were evaluated histopathologically. Histopathological changes, including thickened epidermis and mononuclear/eosinophilic cell accumulation in the corium, were noted in both treated and control areas.

Studies of solutions using non-clinical formulations

Dermal Absorption of ^{3}H-Calcipotriol in Mice (Study No. AE/94/01, Lot no. CAL9125, Sept. 1994) *Not a GLP study. This study was submitted with this NDA and has not been previously reviewed.*

Male and female CD-1 mice (1/sex/group) were given calcipotriene as single dermal doses (10, 30, or 90 μg/kg). Dermally dosed animals were collared and exposed for 5 hours, and the treated skin was than wiped clean and then washed with an ethanol/water mix. The test compounds were formulated in a propylene glycol and citrate buffer vehicle. Levels of ^{3}H were measured at 72 hours in the excreta, liver, kidneys, and the treated skin. Based on levels in the feces, absorption was calculated at 46-71% (percent of the administered dose) for both sexes. Urine excretion levels were generally less than 2%. Treated skin residual radioactivity was 9% with 26 ± 9% removed at 5 hours with ethanol and water; liver radioactivity level was 60 ± 5%, and kidneys were 58 ± 6%. Dermal absorption was independent of dose, and no difference was noted between males and females. Mice given a single IV dose (30 μg/kg) had levels approximately twice the dermally dosed animals in the assayed tissues.

4-Week Dermal Toxicity Study in Mice (Study No. 940411T7, Batch No. 9411462 and 9411463, September 1994)

Mice (6/sex/group; 0, 60, 120, or 180 μg/kg/day) were dosed dermally on clipped backs (50 μl/mouse over a 4 cm^2 area) with an alcohol-based formulation (calcipotriol, μg; citric acid monohydrate, μg; isopropyl alcohol, mg; sodium citrate dihydrate, mg; water, q.s. ml). High-dose male body weights lagged below control values on days 8 and 10 for the high-dose group. Erythema was noted in all treated groups; incidence and severity increased with dose. Thickened skin and transverse wrinkling were noted in the mid- and high dose groups. Significant increases in serum calcium and inorganic phosphate were noted for all drug-treated groups for both males and females. Male mean kidney (all treated males) and heart (mid- and high-dose males) values were significantly less than control values. Organ weight values in females were comparable. Only the skin and kidneys were evaluated histopathologically. Basophilic cortical tubules of the kidney were noted in 1 mid- and 1 high-dose male and in 1 mid-dose female. One low-dose female was noted with chronic inflammatory infiltration of the kidney. In the skin, acanthosis, hyperkeratosis, and parakeratosis was noted in all treated groups; incidence and severity increased with dose level.

Cream and/or Ointment formulation studies

Primary skin irritation study (Study No. 92692, Batch No. not given, October, 1992)

Rabbits were dosed with 6 different formulations of 0.005% Calcipotriene (cream or ointment) on intact and abraded skin under 24-hour patch occlusion. Observations were made

at 24 and 72 hours and primary skin irritation was determined. At 24 hours, the three cream formulations exhibited slight to well-defined erythema (grades 1-2) and edema (grades 1-2). Somewhat less irritation was noted with the ointment formulations. At 72 hours, irritation decreased: the primary irritation index indicated moderate and mild to moderate irritation potential for the cream and ointment formulations, respectively.

Six-Month Dermal Toxicity Study in Minipigs (Study No. 425A-601-242-91, Sponsor ID no. 91-001, Lot no. 253006, March 1992)

minipigs (5/sex/group) were dosed topically for 3 or 6 months with 0.2, 0.5, or 1.0 g/kg/day of 0.005% calcipotriene ointment. The study included a 3-month interim sacrifice of 2 animals/sex/group. Skin was non-occluded, and remaining test materials were gently scraped off the skin at the end of the daily 5-6 hour exposure. No significant changes were noted in mortality, body weights, food consumption, and skin, outside of minimal local irritation (minimal acanthosis and hyperkeratosis). No statistically significant changes were noted in hematology or urinalysis at 3 or 6 months, although increases in serum calcium and kidney weights were noted in high dose males and females at 3 and 6 months, and at 6 months in the mid-dose animals. In the histopathological evaluation 1 low dose, 3 mid-dose, and 6 high-dose animals had minimal to moderate chronic nephrosis with focal tubular dilatation, focal tubular epithelial cellular degeneration and regeneration, and areas of interstitial fibrosis. In one low-dose, 4 mid-dose, and 6 high-dose animals minimal-to-slight mineralized deposits were found in the collection tubules and ducts in the medullary areas of the kidney. Other mineralizations were noted in the lumen of the urinary bladder (2 low-dose and one high-dose animal) wall of the coronary artery (one high-dose minipig), and in the submucosa of the stomach (one high-dose minipig). These histopathology findings support the finding of hypercalcemia as evidenced by mineralization in the kidney and other soft tissues.

52-Week Dermal Toxicity and Irritancy Study in Minipigs (Study No. HWI 6108-183, Sponsor ID no. 92613; Lot no's IBR B91L020, B91L008, B91F003; April 1994)

minipigs (5/sex/group) were dosed topically for 52 weeks with 0.02, 0.1, or 0.3 g/kg/day of Dovonex ointment (which the sponsor stated is equivalent to 0.5, 1, or 2.5 times the clinical dose). Animals were exposed on the dorsal area of the trunk. (The skin was clipped, abraded in 3 animals/sex/group, unoccluded, exposed for 6 hours, and wiped following exposure.) One high-dose male was hypoactive and one high-dose female was hunched with slow movements. Observations of the skin included scabs, alopecia, red skin, and broken skin. Dermal abnormalities appeared in both the control and treated groups, although at a slightly greater incidence (but not severity) in Dovonex-treated groups. Desquamation also was noted in all groups. One mid-dose male had pustules/papules at the dose site. Sporadic changes in clinical hematology/chemistry values were noted throughout the study. Sporadic changes in albumin and globulin (and corresponding A/G ratios) were noted in treated groups. Increases in serum calcium were noted in several individual animals, although these differences were not statistically significant. One high-dose female and two mid-dose males had increased calcium levels, although these values had normalized by the

end of the study. Mineralization was noted in the lung in males for 0, 2, 2, and 4 and in females for 2, 4, 2, and 2 animals in the control, low, mid, and high dose groups, respectively. For kidneys, mineralization was noted in 1, 0, 1, and 0 males and 1, 0, 1, and 1 in the control, low, mid, and high dose groups, respectively. Other sporadic observations in the kidney included lymphohistiocytic infiltrate, cysts, and chronic active inflammation. Because of the sporadic nature of the lesions that indicate hypercalcemia, i.e. the lung and kidney findings, and the fact that control animals were being moved to different rooms to avoid cross exposure to treated compound (as noted in the methods section), it is quite likely that the animals were consuming the compound. A recent FDA compliance visit to the laboratory confirmed the fact that animals did indeed consume Dovonex across different treatment groups. The amount of compound taken orally is impossible to ascertain, and thus the dose levels in this study can not be accurately determined.

Six-Month Oral Toxicity Study in the Minipig (Study No. 880111T1, Batch No. EB9283 and 9311, August 1988)

minipigs (3/sex/group) were given 1, 3, or in the high-dose group, a combination of 6 (weeks 1-20), 9 (weeks 21-24), and 18 (weeks 25-26) μg/kg/day calcipotriene orally by gavage in a propylene glycol vehicle. The animals showed no signs of toxicity until the dose was increased to 18 μg/kg/day. During these last two weeks of the study, the high-dose group became inactive, lost weight, and had decreased food consumption. The kidneys of all high dose animals were affected as evidenced by increased serum calcium, gross necropsy findings, higher organ weights, tubular nephrosis and renal calcification.

Fertility and General Reproductive Performance in the Rat (Study No. 870727 T 7, Batch No. CAL 6109, February 1989)

Rats were dosed orally prior to and during mating, and in females during pregnancy and lactation (at 6, 18, or 54 μg/kg/day calcipotriene). High-dose animals had significantly lower body weight gains prior to mating, and during gestation a dose-related lower weight gain was seen in all treated dams. All treated offspring had incomplete development of skull bones and a higher number of wavy ribs and small hyoid bones; observations did not occur in a dose-related manner. Mating, pregnancy, and development of the F1 and F2 generations of rats were not affected.

Teratology Studies in the Rat and the Rabbit (Study No. 870824T8, Batch No. PC 11351A, February 1988; and Study No. 339/503, Batch No. CAL 6045, March 1988; respectively)

Rats were dosed orally on days 6-15 of gestation (6, 18, or 54 μg/kg/day calcipotriene). High-dose females had significantly lower body weight gains. No major malformations were noted; a higher incidence of skeletal abnormalities (enlarged fontanelles and increased extra ribs) were noted in the high-dose.

Rabbits were dosed orally on days 6-18 of gestation (4, 12, or 36 μg/kg/day calcipotriene). One, 2, and 5 females were found dead in the low-, mid-, and high-dose groups, respectively. High dose-females showed body weight losses and decreased food consumption. At scheduled sacrifice, high-dose and mid-dose groups were noted with lesions in the stomach (red pyloric region) and kidneys (white streaks in the cortex). Two low-dose animals also had the stomach changes. The high-dose animal had significantly increased post-implantation loss, and the mid- and high-dose had statistically reduced fetal weights. A major abnormality was a very high incidence of retinal detachment; the finding was also noted in controls and is likely an artifact.
High-dose fetuses had a significant increase in the number of incomplete ossification of the sternebrae, pubic bones, forelimb phalanges, and incomplete skull bone ossification.

Peri- and Post-Natal Study in the Rat (Study No. 880415T3, Batch No. EB 9302, Nov., 1988)

Pregnant rats were orally dosed with 6, 18, or 54 μg/kg/day calcipotriene from pregnancy day 15 to day 20 postpartum. No drug induced abnormalities were noted in the dams, litters, or fetuses.

Genotoxicity Studies [Study No's LOP 46/871637 (Mouse Lymphoma), LOP 47/88113 (human lymphocytes), April 1988; Study No. 870211N1 (Ames), April 1987; Study No. 870406N1 (mouse micronucleus) in May 1987]

Calcipotriene was negative in the Ames mutagenicity assay with and without S-9 activation at 0.01- 1.0 mg/plate. Calcipotriene was also negative in the mouse lymphoma TK locus assay (an *in vitro* mammalian cell mutation assay) with and without metabolic activation at up to 40 μg/plate (>20 μg was toxic). To determine if Calcipotriene could induce chromosome aberration in human lymphocytes *in vitro*, Calcipotriene was exposed to cells at up to 11 μg/ml both with and without metabolic activation. Without activation, there was a statistically significant increase (2%) in chromosomal aberrations. In the *in vivo* mouse micronucleus bone marrow assay, no increase in micronucleated polychromatic erythrocytes was noted at 1 mg/kg given I.P.

ADME Study in the Rat (File No. 35-89/12, Lot No. CAL7111X, April, 1989)
Not a GLP study.
Female rats were administered radiolabeled calcipotriene or a metabolite (MC 1080) at 0.10 mg/kg IV or 0.20 mg/kg PO. Radioactivity was measured in plasma (n=3), major organs (N=3), and excreta (N=6). Half life of calcipotriene was 12 minutes; half life of the metabolite was 54 minutes. These results indicate that calcipotriene is very rapidly metabolized in the rat. The metabolite was noted even in the first plasma sample, 5 minutes after IV administration. Vd was 1.1 L/kg. The levels of drug and metabolite were much lower following oral administration than IV administration. Bioavailability was calculated by the sponsor to be approximately 60%, based on renal excretion (i.e. a rough estimate.) Highest concentrations were found in the liver, kidneys, and intestine with smaller

concentrations found in the fat, muscle, and spleen. Approximately 16 and 20% was excreted in the urine, 43 and 40% in the feces, after oral and IV dosing, respectively.

ADME Study in the Minipig (File No. 35-89/15, Lot No. CAL7111X, September, 1989) *Not a GLP study.*

minipigs were dosed with 200 or 100 μg/kg calcipotriene by oral or IV administration, respectively. Following oral administration, Tmax was 30-40 minutes, and Cmax was 70-98 ng/ml. Plasma half-life was approximately one hour. The main metabolite (MC 1080), had a half life of approximately 1.8 hours. Bioavailability following oral calcipotriene was approximately 40%. After 10 days of dosing, highest concentrations were found in the liver and kidneys.

Administration Studies in the Rabbit and Rat after Topical Administration (Study No. 35-89/13, Batch No. 890551101, August 1989)

Rats (12-25 μg/kg) and rabbits (9-10 μg/kg) were exposed to a single topical dose of tritiated Calcipotriene on the back without occlusion for 6 hours. Percutaneous absorption was 10% of administered dose in the rabbit and 17 -27% for male and female rats, respectively.

Whole-Body Autoradiography in the Rat (File no. 35-89/19, lot no. CAL7111X, September, 1989)

Rats were dosed orally (0.2 mg/kg) or by IV (0.1 mg/kg) for tritiated Calcipotriene. A generally uniform distribution level was noted in all tissues, with highest levels noted in the kidney, intestine, liver, and bile duct (excretory organs). The radiolabeled drug crossed the blood-brain barrier.

Summary

Calcipotriene solution and calcipotriol cream are under current NDA review, although only the solution is indicated for scalp psoriasis. Calcipotriol ointment has already been approved (NDA 20-273) for an 8-week dosing regimen; a one-year dosing regimen is undergoing review. Only two of the submitted animal studies were performed using the solution. The sponsor also submitted all studies performed for the cream and ointment; the germane studies for this NDA are summarized below.

All three of the calcipotriene formulations applied to the skin affect calcium absorption, as might be expected with a Vitamin D_3 analogue. In a **one-month dermal irritation and toxicity study**, rats dosed with Calcipotriene solution (50 μg/ml) or cream (50 μg/g) daily under occlusion exhibited slight intermittent scab formation. Treatment-related findings included increased ALT and AST values in males and increased calcium and phosphorus levels in females, increased water consumption, urine output, and urine calcium excretion; as well as decreased urine specific gravity, urine pH, urine protein concentration, and urobilogin. Neither formulation appeared to be more potent in terms of side effect.

In a **six-week skin irritation test,** six female rabbits treated with 100 mg 0.005% calcipotriene daily were noted with slightly more erythema in the treated animals compared to the controls, although the histopathological changes, which included thickened epidermis and mononuclear/eosinophilic cell accumulation in the corium, were noted in both treated and control areas.

In a **4-Week Dermal Toxicity Study in Mice**, animals were dosed dermally (60-180 μg/kg/day; 50 μl/mouse over a 4 cm^2 area) with an alcohol-based solution. Treatment-related effects included body weight decreases in high-dose males, erythema in all treated groups (incidence and severity increased with dose), and thickened skin and transverse wrinkling in the mid-and high dose groups. Significant increases in serum calcium and inorganic phosphate were noted for all drug-treated groups. Other effects included decreased kidney weights in all treated males and heart weights in mid- and high-dose males. In the skin and kidney histopathological evaluation, basophilic cortical tubules were noted (3 animals) and in the skin, acanthosis, hyperkeratosis, and parakeratosis was noted in all treated groups; incidence and severity increased with dose level. Utilizing the cream formulation in a **primary skin irritation study in rabbits**, slight-to-well defined erythema was noted. The assay support earlier tests of the ointment that indicate that calcipotriene is not a severe irritant.

Studies of greatest interest from the ointment NDA primarily include the minipig studies. The sponsor performed a **6-month dermal toxicity study in minipigs.** minipigs (5/sex/group) were dosed topically for 3 or 6 months with 0.2, 0.5, or 1.0 g/kg/day of 0.005% calcipotriene ointment. Non-statistically significant increases in serum calcium and kidney weights were noted in mid- and high-dose animals. Histopathological evaluation revealed moderate chronic nephrosis with focal tubular dilatation, focal tubular epithelial

cellular degeneration and regeneration, and areas of interstitial fibrosis; minimal to slight mineralized deposits were found in the collection tubules and ducts in the medullary areas of the kidney. Other mineralizations were noted in the lumen of the urinary bladder (2 low-dose and one high-dose animal), the wall of the coronary artery (one high-dose minipig), and in the submucosa of the stomach (one high-dose minipig). These histopathology findings support the finding of hypercalcemia as evidenced by mineralization in the kidney and other soft tissues.

In the **52-week dermal toxicity and irritancy study in minipigs,** minipigs (5/sex/group) were dosed topically for 52 weeks with 0.02, 0.1, or 0.3 g/kg/day of Dovonex ointment (equivalent to 0.5, 1, or 2.5 times the clinical dose). Observations of the skin included scabs, alopecia, red skin, and broken skin. Dermal abnormalities appeared in both the control and treated groups, although at a slightly greater incidence in the calcipotriene-treated groups. Desquamation also was noted in all groups. Sporadic changes in clinical hematology/chemistry values were noted throughout the study. Increases in serum calcium were noted in several individual animals, although these differences were not statistically significant. One high-dose female and two mid-dose males had increased calcium levels, although these values had normalized by the end of the study. Mineralization was noted in the lung in males for 0, 2, 2, and 4 and in females for 2, 4, 2, and 2 animals in the control, low, mid, and high dose groups, respectively. For kidneys, mineralization was noted in 1, 0, 1, and 0 males and 1, 0, 1, and 1 in the control, low, mid, and high dose groups, respectively. Other sporadic observations in the kidney included lymphohistiocytic infiltrate, cysts, and chronic active inflammation. Because of the sporadic nature of the lesions that indicate hypercalcemia, i.e. the lung and kidney findings, and the fact that control animals were being moved to different rooms to avoid cross exposure to treated compound, it is likely that the animals were consuming the compound. In a recent conversation with Mr. Davis from FDA compliance, a recent audit of this study at the laboratory confirmed that the pigs were consuming product across groups. Mr. Davis pointed out that the animals heads fit through the cage bars, and thus the animals may have easily consumed compound across groups. (Memo to follow from FDA compliance.) The amount of compound that may have been taken orally is impossible to ascertain, and thus the study is fundamentally flawed and cannot be used to support the systemic safety of chronic clinical exposure in humans. In support of this study, however, is that the skin findings do not appear to be compromised in this study. Over a one-year exposure, the skin of all treated animals did not appear different in the histopathological evaluation.

In the **six-month oral toxicity study in the minipig,** minipigs (3/sex/group) were given 1, 3, or in the high-dose group, a combination of 6 (weeks 1-20), 9 (weeks 21-24), and 18 (weeks 25-26) μg/kg/day orally by oral gavage in a propylene glycol vehicle. The animals showed no signs of toxicity until the dose was increased to 18 μg/kg/day. During the last two weeks of the study, the high-dose group became inactive, lost weight, and had decreased food consumption. The kidneys of all high dose animals were affected as evidenced by increased serum calcium, gross necropsy findings, higher organ weights, and tubular nephrosis and calcifications seen in the kidneys. PK and ADME data indicate that the

uptake and bioavailability of calcipotriene following oral administration is quite low--close to 40%.

The **reproduction or teratology studies** performed in rats or rabbits did not have any findings of major concern, with the possible exception of the rabbit teratology study in which high-dose fetuses had a significant increase in the number of incomplete ossification of the sternebrae, pubic bones, forelimb phalanges, and incomplete skull bone ossification. The reproduction studies were all performed with oral administration. As already noted, PK and ADME data indicate that the uptake and bioavailability of calcipotriene following oral administration is low. **Genotoxicity studies** were negative except for the human lymphocyte *in vitro* study, where without activation, there was a statistically significant increase (2%) in chromosomal aberrations.

In the **ADME study in rats**, animals administered radiolabeled calcipotriene or the metabolite MC 1080 (0.10 mg/kg IV or 0.20 mg/kg PO) had half lives of 12 or 54 minutes, respectively. Calcipotriene appears to be rapidly metabolized; the metabolite was noted in the 5-minute plasma sample after IV administration. The levels of drug and metabolite were much lower following oral administration than IV administration. Bioavailability was estimated at approximately 60%. Highest concentrations were found in the excretory organs, including the liver, kidneys, and intestine. In the **ADME study in the minipig**, minipigs were dosed with 200 or 100 μg/kg calcipotriene by oral or IV administration, respectively had a plasma half-life was approximately one hour. The main metabolite (MC 1080), had a half life of approximately 1.8 hours. Bioavailablility following oral calcipotriene was approximately 40%. After 10 days of dosing, highest concentrations were found in the liver and kidneys. In **Dermal Administration Studies,** rats (12-25 μg/kg) and rabbits (9-10 μg/kg) were exposed to a single topical dose of tritiated calcipotriene on the back without occlusion for 6 hours. Percutaneous absorption was 10% of administered dose in the rabbit and 17 -27% for male and female rats, respectively. Mice were given single dermal doses of calcipotriene (10, 30, or 90 μg/kg) for 5 hours (collared) and exposed for 5 hours. Based on levels in the feces (biliary excretion is expected), absorption was calculated at 46-71% (percent of the administered dose). Dermal absorption was independent of dose, and no difference was noted between males and females. Mice given a single IV dose (30 μg/kg) had levels approximately twice the dermally dosed animals in the assayed tissues. **PK** studies indicated that calcipotriene is equally distributed to most tissues and then found primarily in excretory organs. Findings were supportive of main elimination through the bile. Of possible relevance was the notation that the radiolabeled drug crossed the blood-brain barrier.

Discussion

Calcipotriene is a vitamin D_3 analog that appears to have anti-hyperproliferative and perhaps an anti-inflammatory effect when applied topically to psoriatic skin. The studies performed for the ointment had several significant findings: increased calcium excretion, increased mineral deposits in the kidney, and maternal and fetal toxicity. The findings, however, were not considered of great concern for a topical product with a proposed dosing duration of 8 weeks, and the pharmacologist's review of the NDA recommended approval of Calcipotriene ointment with no objections except for several labelling recommendations. For this new NDA however, several issues must be addressed.

First, the sponsor's increased dosing regimen from 8 weeks to one year is not supported by preclinical data. The 6-month and 52-week minipig studies revealed significant signs of hypercalcemia. Of greatest concern are the mineralizations noted in the lung in the 52-week study. The data are unclear on whether the lung mineralizations are treatment-related. The lung findings are particularly worrisome because they were at doses 0.5, 1.0, or 2.5 times the human doses, but only after 6-hour exposures; the clinical dose is administered for 24 hours. A further complication in the 52-week study is the likelihood (based on an FDA compliance lab. audit) that the minipigs were able to eat unknown amounts of drug treatment. Such a scenario would explain the sporadic occurrence of mineralizations in the lungs and kidneys, but would indicate that the study is flawed and cannot be used to support the systemic safety of calcipotriene. Additionally, there is no simple method to monitor for lung mineralization in humans (without lung biopsy or bronchoscopy), and thus the appearance of calcification in the lung is likely to go unnoticed until the effects are profound. Calcification of soft tissue is a known side effect of hypervitaminosis, and thus the lung mineralization is consistent with an expected side effect of Vitamin D or a Vitamin D analog. However, if the systemic concerns were addressed in the clinical data, the mini-pig study does appear to support safety of the drug on the skin for one year.

The PK and ADME data in all of the animals tested indicate that oral bioavailability is very low. This normally would not be a concern for a topical product. All of the reproductive studies, however, were done with oral administration. Bioavailability was measured in mini-pigs at approximately 40%, and in rats at 60%. All of the reproduction studies were performed using oral dose administration. Appropriate labelling changes that include the bioavailability data are recommended below.

No carcinogenicity studies were performed for calcipotriene. It is highly likely that the clinical use of the drug will be for multiple 8-week sessions. The data on Vitamin D and carcinogenicity is mixed: it has been reported as an anti-tumor agent stimulating cell differentiation (especially at high doses that would also be nephrotoxic), and Vitamin D has also been reported to stimulate cancer cell growth. At this time, the effect of calcipotriene over long periods has not been evaluated in systemic or dermal carcinogenicity studies.

This formulation is the first that is specifically indicated for an area of the body that will be

highly exposed to sunlight--the scalp. Thus, photocarcinogenicity is now of great concern for calcipotriene, and needs to be addressed. (Note: The sponsor has already been informed by telecon that they will likely be expected to perform a dermal carcinogenicity and a photocarcinogenicity study.)

Conclusions

Calcipotriene 0.005% cream has been shown in preclinical trials to be safe for short (e.g. up to 8 weeks) clinical courses in adults. The systemic safety of a 1-year dosing duration was not demonstrated in preclinical studies.

Recommendations

The NDA is approvable for 8-week clinical courses. The sponsor must also perform the following studies as Phase 3 or 4 studies, and must agree to such studies in writing prior to the approval of this NDA:

1) A dermal carcinogenicity study. [Although not previously noted in a Dovonex pre-clinical review, several conversations have been conducted with the sponsor addressing concerns over bone absorption associated with increased systemic levels of vitamin D or its analogs. The sponsor has agreed to measure bone density in the rodent carcinogenicity study.]
2) A photocarcinogenicity study.
3) The sponsor MAY need to repeat the 52-week minipig study; the recommendation will be dependent on submission of the histopathology re-evaluation and discussions with the medical officer.

It is suggested that the sponsor also perform a teratology study in rabbits with dermal dose administration. (See labelling changes that reflect the current gap in the teratology data.)

The following changes to the proposed label are recommended:

Should be changed to:

Hilary V. Sheevers, Ph.D.

cc:
HFD-340
HFD-540
HFD-540/PHARM/Sheevers
HFD-540/MO/Toombs
HFD-540/CHEM/Pappas
HFD-540/PM/Holmes

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Concurrence Only:
HFD-540/DD/Wilkin
HFD-540/SPHARM/Jacobs

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: OCT 17 1995

NDA's
20554
20273 - 9
20611

FROM: Dowell A. Davis
Pharmacologist, HFD-345

THROUGH: George W. James, Ph.D.
Chief, NCLSB, HFD-345

TO: Hilary V. Sheevers, Ph.D.
Pharmacologist, HFD-540

SUBJECT: Fifty-two Week Dermal Toxicity and Irritancy Study done with BMS 181161 (0.005% Ointment) in Minipigs by for Bristol-Myers Squibb.

In accordance with your request of July 18, 1995, a Good Laboratory Practice (GLP) data audit of the referenced study was implemented by the Nonclinical Laboratory Studies Branch of the Division of Scientific Investigations. The nonclinical testing facilities of were visited by Mr. Ronald R.Ruff, FDA investigator, HFR-MW3585, and myself during September 25-29, 1995. During that visit we reviewed all support study data, and interviewed the study director and the key laboratory technician.

We were told by Dr. Anthony L. Kiorpes, study director, that several problems occurred during the course of the study. The test material, a petroleum base concoction, was placed on clipped and, on some animals, abraded areas around the dorsal spine of the pigs' backs. Very early in the study the animals were observed licking and chewing the inner construction of the cages, possibly consuming test materials that had been left on the cages during the usual scratching and rubbing process, which is inherent in pigs. The question about the animals possibly consuming the test material was confirmed when some animal were found to have high plasma levels of calcium carbonate.

The study animals soon outgrew these cages, which were modified dog runs, and were moved to new roomier pens in the Although, these cages provided more space for the now, much larger pigs, the construction of the cages whose bars were about five inches apart allowed the pigs greater access to each others' backs. In the note that the pig that is lying down in the middle cage, his back is readily accessible to the animal in the adjoining cage.

According to Dr. Kiorpes, the pigs became even more difficult to handle after reaching sexual maturity. The males, in particular, became very aggressive towards the technicians and each other. A technician was bitten, with resulting lacerations and a fracture. One male pig was so aggressive that he jumped out of his and into and another's pen and severely injured the other pig.

Irrespective of the difficulties encountered during the conduct of this study, it was for the most part conducted in accordance with the study protocol and Good Laboratory Practice regulations. However, during the exit interview at the termination of the inspection, we informed the facility management that the final report may require an amendment to reflect the observations of the study animals consuming the test material from the cage construction and/or each others' backs.

Dowell A. Davis

cc:

HFA-224
HFC-230/Woollen
HFD-340/Kelsey/RF
HFD-341/Peters
HFD-540/Jacobs/NDA 20-554
HFR-MW3585/Ruff
HFR-MW350/Olson
HFD-502
HFD-345/James/Davis/Fujiwara(3)/CF
DSI.NCLSB.DAD.SHEEVERS
Final: 10/13/95

CFN: 2128592

FEB 28 1997

Memorandum

Date: February 28, 1997

To: Jonathan Wilkin, MD
Division Director, DDDDP (HFD-540)

Through: Abby Jacobs, Ph.D.
Team Leader, DDDDP (HFD-540)

From: Javier Avalos, Ph.D.
Pharmacologist/Toxicologist, DDDDP (HFD-540)

RE: Additional Changes to Dovonex 0.005% Solution Labeling
NDA 20-611

Several changes were made to the draft label which affect the Pregnancy section of the Dovonex Solution Label. As currently written, the Pregnancy section describes the exposure an individual would receive if that individual was being exposed to the cream formulation and not to the scalp solution. Following a treatment with the cream formulation, an individual would generally receive grams of cream (0.005%) a day. For the scalp solution, an individual would be treated with ml of the scalp solution (0.005%) per day. Pharmacokinetics studies have also determined that up to % of the applied dose for the cream is absorbed in humans while % of the applied dose is absorbed from the scalp solution. These differences would lead to lower exposure levels of calcipotriene in humans with the scalp solution than with the cream formulation. Thus, a 4 ml application of Dovonex scalp solution (0.005%) with a % absorption rate would represent a daily exposure of ug/m^2/day. Since the no-effect dose in rats and rabbits is $\mu g/m^2$/day and $\mu g/m^2$/day, respectively, these doses are 325 times and 132 times higher than the expected human systemic exposure.

The proposed change to the draft label is indicated in redline.

Javier Avalos 2/28/97

Javier Avalos, Ph.D.
Toxicologist

cc:
Orig NDA 20-611
HFD-540
HFD-540/Pharm/Jacobs
HFD-540/Pharm/Avalos
HFD-540/CSO/Anderson
HFD-540/MO/Toombs
HFD-540/Chem/Pappas

For Concurrence Only:
HFD-540/DD/JWilkin 2/28/97
HFD-540/Team Leader/Jacobs 2/28/97