CLINICAL STUDY REPORT

INVESTIGATION ON THE ACCEPTABILITY OF CALCIPOTRIOL OINTMENT (50 µg/g) UNDER OCCLUSION IN PATIENTS WITH FINGER NAIL PSORIASIS

A Multicentre, Open, Non Controlled, Pilot Study

The clinical study report has been redacted using the following principles: Where necessary, information is anonymised to protect the privacy of study subjects and named persons associated with the trial as well as to retain commercial confidential information.

Summary data are included but data on individual study subjects, including data listings, are removed. This may result in page numbers not being consecutively numbered.

Access to anonymised data on individual study subject may be obtained upon approval of a research proposal by the Patient and Scientific Review Board.

Appendices to the clinical study report are omitted.

Further details and principles for anonymisation is available in the document LEO PHARMA PRINCIPLES FOR ANONYMISATION OF CLINICAL TRIAL DATA

MCO9508 FR Study
Laboratoires Leo France
Medical Department

14 June 1999
COMPLIANCE WITH GOOD CLINICAL PRACTICE

This Clinical Study Report is designed to comply with the Good Clinical Practice (G.C.P.) Standards issued by the International Conference on Harmonisation (ICH) (topic E3 CPMP/ICH/137/95: Structure and Content of Clinical Study Reports).
AUTHENTICATION FORM

STUDY CODE: MCO 9508 FR
REPORT TITLE: INVESTIGATION ON THE ACCEPTABILITY OF CALCIPOTRIOL OINTMENT (50 μg/g) UNDER OCCLUSION IN PATIENTS WITH FINGER NAIL PSORIASIS
REPORT DATE: 14 June 1999

This study was performed in compliance with the Good Clinical Practice (GCP) standard issued by the International Conference on Harmonisation (ICH), the Declaration of Helsinki with subsequent amendments, and respecting national rules/regulations.

The study was performed in accordance with the approved Study Protocol and with Leo Pharmaceutical Products Standard Operating Procedures for GCP. The report provides a true and accurate record of the results obtained.

Authorised by: Medical Director, Leo DK

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CLINICAL STUDY REPORT APPROVAL FORM

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REPORT DATE: 14 June 1999

I confirm that I have read the Clinical Study Report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

APPROVAL BY INTERNATIONAL CO-ORDINATING INVESTIGATOR

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APPROVAL BY MEDICAL DIRECTOR, LEO DENMARK

[Signature]

APPROVAL BY HEAD OF MATHEMATICAL-STATISTICAL DEPARTMENT, LEO DENMARK (or BIOMETRIC DEPARTMENT in UK)

[Signature]

Distribution:
Original → Trial Master File
Copy → Study Report

Version: 210398
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APPROVAL BY INTERNATIONAL CO-ORDINATING INVESTIGATOR

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APPROVAL BY HEAD OF MATHEMATICAL-STATISTICAL DEPARTMENT, LEO DENMARK
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PRINTED NAME _____________________________ SIGNATURE _____________________________ Date DD MM YY

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Version: 210398
1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

1.1 ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.E.</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Classification</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>IRB/I.E.C.</td>
<td>Institutional Review Board/Independent Ethic Committee</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention To Treat</td>
</tr>
<tr>
<td>IU</td>
<td>International Unit</td>
</tr>
<tr>
<td>PASI</td>
<td>Psoriasis Area and Severity Index</td>
</tr>
<tr>
<td>PP</td>
<td>Per Protocol</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>UVB</td>
<td>Phototherapy with wave bands situated close 313 nm</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
</tbody>
</table>

1.2 DEFINITIONS OF TERMS

<table>
<thead>
<tr>
<th>Definition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Event</td>
<td>Any undesirable experience occurring to a subject during a clinical trial whether or not considered related to the investigational product.</td>
</tr>
<tr>
<td>End of study</td>
<td>Visit when the patient stopped the study treatment</td>
</tr>
<tr>
<td>Patient identification code or CRF code number</td>
<td>The unique number on each copy of each page in the Case Report Form assigned to an individual subject. It is not related in any manner to the randomisation code number.</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>An adverse experience that is fatal, life threatening, disabling or which results in inpatient hospitalisation or prolongation of hospitalisation. In addition, congenital abnormality and occurrence of malignancy are always considered serious adverse events.</td>
</tr>
</tbody>
</table>
2 SYNOPSIS

Study code: MCO9508 FR

Title:
Investigation on the acceptability of calcipotriol ointment (50 μg/g) under occlusion in patient with finger nail psoriasis.

Objectives:
The study objectives were to assess the acceptability and safety of calcipotriol ointment used under occlusion overnight for 4 weeks in the treatment of finger nail psoriasis.

Study design:
This study was a multicentre, open, non controlled pilot study with calcipotriol ointment (50 μg/g) used under occlusion once daily at night (at least 6 hours) for 4 weeks.

Duration of each study phase:
This study was performed with one phase of 4 weeks.

Total number of patients for inclusion in the study:
No sample size calculation was performed in this pilot study. Ten patients evaluable were required. Evaluable patients were defined as patients who completed the treatment period or withdrawn for adverse event related to study drug.

Source of patients:
Out patients were required.
Patient group studied:
The main inclusion criteria were:
- clinical diagnosis of nail psoriasis on at least one finger and present or previous experience of skin psoriasis,
- at least 18 years of age,

The main exclusion criteria were:
- clinical evidence of nail infection,
- patients who needed/used systemic treatment, PUVA or UVB during the study/with the 2-week period prior the study treatment started. Topical treatment for nail psoriasis was stopped at least 1 week before the study treatment started,
- current medication with vitamin D and/or any other medication (topical or systemic) that affected the course of the disease during the study period and/or on investigational drug within the 3 months prior the study treatment started,
- immunodeficiency state,
- hypercalcemia defined as serum calcium (albumin corrected) above the upper limit of reference range of the local laboratory,
- significant renal and/or hepatic disease.

Investigational products used:
All finger nails affected by psoriasis were treated with calcipotriol ointment (50 µg/g) overnight occlusion for 4 weeks. A small quantity of calcipotriol ointment was applied under occlusion with plastic gloves once daily in the evening and was kept the whole night (for at least 6 hours). No trial medication was applied on other regions. A maximum of 1 tube of 30 g of calcipotriol ointment was provided per week.

The primary efficacy, tolerability and safety parameter criteria:
The clinical assessment was performed in a target nail chosen by the investigators. The severity of pitting, discoloration, onycholysis and subungual hyperkeratosis was scored in 4 points (0=absent, 1=mild, 2=moderate, 3=severe) by the
investigators at each control visits. The severity of clinical aspect was calculated adding the score for each clinical items, above described at each visit.

The tolerability assessment was done at each visits checking on all treated digits:
- redness,
- soreness sensation,
- burning sensation,
- itching sensation,
- sign of skin atrophy,
- chapped fingers,
- miliaria.

The safety of the study was assessed by the adverse event reported and the laboratory parameters measured at each visit.

Study procedures:

<table>
<thead>
<tr>
<th>VISITS</th>
<th>Calcipotriol ointment under occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Weeks</td>
<td>0</td>
</tr>
<tr>
<td>Medical history</td>
<td>*</td>
</tr>
<tr>
<td>Recording of adverse events</td>
<td>*</td>
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<tr>
<td>Acceptability assessment</td>
<td>*</td>
</tr>
<tr>
<td>Laboratory examination:</td>
<td>*(1)</td>
</tr>
<tr>
<td>- S-total-calculator</td>
<td>*(1)</td>
</tr>
<tr>
<td>- S-albumin</td>
<td>*(1)</td>
</tr>
<tr>
<td>- S-albumin corrected calcium</td>
<td>*(1)</td>
</tr>
<tr>
<td>Investigator clinical assessment</td>
<td>*</td>
</tr>
<tr>
<td>Pregnancy test(3)</td>
<td>*</td>
</tr>
<tr>
<td>Supply of study medication</td>
<td>*</td>
</tr>
<tr>
<td>Collection of unused and used study medication</td>
<td>*</td>
</tr>
</tbody>
</table>

(1) In case of hypercalcemia (albumin corrected) or positive pregnancy test at visit 1, the investigator will contact the patient in order to stop the treatment.
(2) Or earlier in case of withdrawal. In case hypercalcemia (albumin corrected) occurs, the examination should be repeated until normalisation.
(3) In female patients of child-bearing potential
Efficacy results:

Two centres recruited 8 patients with 7 patients included in the treatment period. One patient was excluded from the analysis withdrew from the study 2 days after the first visit without taking any study medication. This patient was excluded in the intention-to-treat population. The analysis was conducted on the ITT population.

The study population included 5 males and 2 females with a mean age of 43 years (range 35-57). The mean duration of finger nail psoriasis was 2 years (range 5 months - 8 years). An antipsoriatic therapy for nail psoriasis (topical steroid without occlusion) was used by 1 patient prior the study. One patient used an antipsoriatic drug (desonide) on another location than finger nail.

All the included patients fulfilled the protocol criteria and entered in the ITT population.

The investigator's clinical assessment was done on the target nail chosen by the investigator. A scoring system (0=absent, 1=mild, 2=moderate, 3=severe) was used to assess the severity of the clinical signs (pitting, discoloration, subungual hyperkeratosis and onycholysis). All the clinical signs scores were summed up to give a total score of the severity of the target nail. The mean total score of severity decreased throughout the study.

\[
\begin{array}{c|c|c|c|c}
\text{Visit} & \text{Visit 1} & \text{Visit 2} & \text{Visit 3} & \text{Visit 4} \\
\hline
\text{Mean Total Score of Clinical Severity} & \text{4} & \text{4} & \text{4} & \text{3} \\
\end{array}
\]

In five patients out of 7, there was a decrease in the total score of clinical severity reaching 2 points. The best response to the study medication was obtained for the clinical sign: subungual hyperkeratosis.
This clinical sign was improved for 5 patients out of 7. The response for the other clinical signs was less pronounced. Two patients improved their onycholysis and the remaining patients have a stable severity of onycholysis for the study period. An improvement of the clinical signs pitting and discoloration was found in 1 patient. No clinical change was found in the remaining patients.

Score of severity:

<table>
<thead>
<tr>
<th>CRF</th>
<th>Visit</th>
<th>Severity of pitting</th>
<th>Severity of discoloration</th>
<th>Severity of onycholysis</th>
<th>Severity of subungual hyperkeratosis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>V1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>5</td>
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<tr>
<td></td>
<td>V2</td>
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<td>2</td>
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<td>1</td>
<td>5</td>
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<tr>
<td></td>
<td>V3</td>
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<td></td>
<td>V4</td>
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<td>V1</td>
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<td></td>
<td>V4</td>
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<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

0 = absent
1 = mild
2 = moderate
3 = severe
Safety results:
Seven patients used calcipotriol ointment under occlusion with a plastic glove overnight (at least 6 hours). The mean duration of treatment was 30 days (range 27-33). The presence of following effect was checked on all treated fingers by the investigators at each visit:
- redness,
- soreness sensation,
- burning sensation,
- itching sensation,
- sign of skin atrophy,
- chapped fingers,
- miliaria.

Five patients complained about redness and chapped fingers in all treated fingers. Temporally burning sensation was declared as adverse event by 1 patient.
Tolerability: adverse event reported

<table>
<thead>
<tr>
<th>Patients n°</th>
<th>V2</th>
<th>V3</th>
<th>V4</th>
</tr>
</thead>
<tbody>
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</tr>
</tbody>
</table>

*0=absent
1=mild
2=moderate
3=severe

No other adverse event was found throughout this study.

No clinically significant variation of biological parameters was found.

Conclusion:

This study has shown that the treatment with calcipotriol ointment under overnight occlusion every day for 4 weeks decreased the subungual hyperkeratosis. Onycholysis was improved lightly by the study treatment. No safety problem was appeared throughout the study. The tolerability of the treatment was acceptable, no important and/or unexpected side effect was found. The study was performed for one month with a good compliance by the patients. These data should be confirmed by a study with more patients and with a longer treatment period.
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Fax: [Redacted]

INVESTIGATOR

[Redacted], M.D.

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Fax: [Redacted]
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To: 31/01/97

[Name], Ph.D.  
From: 01/02/97  
To: 31/08/97

[Name], M.D.  
As per: 01/09/97

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France
6  **INDEPENDANT ETHICS COMMITTEE**

The protocol was reviewed and approved by the Ethics Committee (C.C.P.P.R.B) on September 21, 1995 (Appendix VII).

The protocol was notified to the Health Authorities (Appendix VII).

7  **COMPLIANCE WITH ETHICAL RESPONSIBILITIES**

7.1  **ETHICAL CONDUCT OF THE STUDY**

The study was conducted to conform with the principles of the Declaration of Helsinki as adopted by the 18th World Medical Assembly, 1964, and subsequent amendments Tokyo, 1975, Venice, 1983 and Hong Kong, 1989.

The protocol received favourable opinion from relevant Independent Ethics Committees (IEC) prior to inclusion of any patients.

The patient's informed consent (in writing) to participate in the study was obtained prior to enrolment in the study.

The study was notified by the appropriate Regulatory Authority.

The study was conducted in accordance with the principles of GCP.

7.2  **PATIENT INFORMATION AND CONSENT**

All patients received written and verbal information concerning the study (Appendix VI). This information emphasised that participation in the study was voluntary and that the patient could withdraw from the study at any time and for any reason.

Prior to consenting to participate in the study, they were asked if they had any questions regarding the study and the investigator explained all aspects of the study to the patient. Once the patient agreed to participate in the study, the
informed consent form (Appendix VI) was signed and dated by the patient and the investigator before or at visit 1.

The above was also included specifically in the individual Investigator Agreements signed by the investigators.

8 INSURANCE AND LIABILITY
The present study provided insurance of patients in the event of trial related injury or death in accordance with applicable French law and with the European Community Commission Guideline 3/3976/88 on Good Clinical Practice and Huriet's law.
INTRODUCTION AND RATIONALE

9.1 THE NAIL UNIT

The nail unit (1,2) is usually described as consisting of the following a) the nail plate, b) the proximal and lateral nail folds, c) the nail matrix, d) the nail bed and e) the hyponychium.

The nail plate is a keratinised cutaneous specialised structure. It is constituted of onychine and characterised by a lengthwise growth instead of desquamative evolution.

The proximal nail fold is a skin fold that lies over the proximal portion of the matrix and the proximal portion of the nail plate; the lateral nail folds encompass the nail plate on both sides.

The matrix lies beneath the proximal fold and is responsible for the manufacture and development of the nail plate. The nail plate represents the horny end-production of the matrix. Structurally, the matrix may be divided into 3 parts: a proximal portion producing the superficial portion of the plate, an intermediate producing the central part of the plate and a distal, the lunula, producing the under surface of the plate. The lunula is visible in certain digits.

The nail bed has two components: epidermis and dermis. Structurally, it is similar to skin, except that the epidermal layer of the nail is devoid of a stratum granulosum and lacks secretory and pilosebaceous annex.

The hyponychium is an epidermal extension which joins the distal extremity of the nail bed.
9.2 NAIL PSORIASIS

9.2.1 Clinical features

Psoriasis is one of the most common chronic skin disease, with a prevalence generally estimated at between 1.4% and 2.9% of the population (3,4).

It is characterized by sharply margined area of affected skin which appear thickened, red and scaly, and may sometime itch. This appearance is produced by a greatly increase rate of epidermal proliferation with impaired differentiation of keratinocytes. Dermal blood vessels are dilated and there is infiltration of the skin with immunologically active cells (5,6).

The pathogenesis is not yet well understood and controversy still exists as to whether the primary abnormality resides in the epidermal keratinocytes, dermal fibroblasts, cell of the immune system, blood vessels, or a combination of these (5,6).

Psoriatic involvement of finger nails and toenails has been reported in up to 80-90 percents of psoriatic patients (7).

The finger nails are more frequently affected than toenails and are more frequently documented (8).

The clinical features of psoriatic nail depend upon which parts of the nail are affected (1,2,9).

The characteristics of psoriasis nails are pitting, discoloration, onycholysis, subungual hyperkeratosis, as well as crumbling and grooving of nails and splinter haemorrhages.

The clinical manifestations of psoriasis nail unit may range from minimal (simple pitting) to extensive changes involving virtually the entire nail.
Pitting: The most common nail lesions are pits which are caused by small punctate psoriatic lesions initially located on the part of the matrix that forms the superficial layers of the nail plate. The pathogenesis involves abnormal keratinization with parakeratosis and production of retained nuclei on the surface of the nail plate. The pits generally tend to be large and deep.

Discoloration: Air under the separated nail plate imparts the spotty white color called leukonychia. Another common nail bed lesion is a translucent yellow-red discoloration on the nail plate that is caused by the trapping of neutrophils and exudate between the nail bed and the nail plate. The characteristic yellowish color is due to the accumulation of a blood glycoprotein that is seen when the hyponychium and the nail bed are involved in inflammatory reaction. These color changes have been described as the oil drop sign.

Onycholysis: Separation of the distal and lateral edges of the nail plate is the result of a psoriatic lesion occurring in the hyponychium and in the distal portion of the nail bed. The separation is usually partial. It most commonly starts at the free edge of the nail but may sometimes start in the nail plate centre.

Subungual hyperkeratosis: The uplifting of the nail plate depends upon the extent and activity of the psoriasis involving the underlying structures. The subungual thickening may have a silvery white color or a yellowish greasy, dark brown or green discoloration.

Splinter haemorrhages: Splinter haemorrhages are common and they occur in the distal nail bed.

9.2.2 Treatment of nail psoriasis

There is no consistently effective treatment for psoriatic nail involvement. Nails are difficult to treat and respond slowly to therapy.

Intralesional injections of corticosteroids (triamcinolone acetonide) are sometimes effective but are limited by pain due to the injection (10,11,12).
Another treatment is the application of high potency fluorinated steroids applied twice daily or under occlusion at night. However, it is not recommended for more than two weeks. Atrophy and telangiectasia of the skin may occur.

Fredriksson (13) reported improvement following the topical application of 1% fluorouracil (5FU) without occlusion for six months in patients with pitted and hypertrophic psoriatic nails. Its use should be limited to patients who have either matrix disease or marked subungual hyperkeratosis. This regimen is not indicated for distal onycholysis as it often aggravates the condition.

PUVA therapy (psoralens + UVA) has been shown to be beneficial in some patients (14) but is limited by the poor penetration of the UVA through the nail and a risk of photoonycholysis.

In some patients with severe psoriasis, improvement has been observed with oral retinoid (15,16), methotrexate and ciclosporin A (17,18). However, the side effects induced by these systemic treatments must be considered and these approaches for nail disease alone seem highly questionable.

### 9.3 CALCIPOTRIOL

#### 9.3.1 Pharmacology

Calcipotriol (MC 903) is a Vitamin D analogue manufactured by Leo Pharmaceutical Products.

![Structural formula of calcipotriol](image)
Pre-clinical studies have demonstrated calcipotriol to have a high binding affinity to the cellular receptor for calcitriol (1,25 dihydroxyvitamin D₃), the biologically active form of vitamin D₃ (19) and calcipotriol has been shown to be both a potent regulator of cell differentiation and an inhibitor of cell proliferation in human keratinocytes (19,20). Its systemic effect on calcium metabolism in rats is 100 to 200 times less than that of calcitriol (21).

9.3.2 Calcipotriol treatment in psoriasis of the trunk and limbs

A number of short term studies have been conducted with calcipotriol ointment 50μg/g applied twice daily. Calcipotriol ointment has been shown to be more effective than its short contact dithrocream (22) and coal tar treatment (23), and at least as effective as betamethasone 17-valerate 0.1% ointment (24,25). It was well tolerated; adverse events being mainly application related lesional/perilesional irritation which tended to be mild and subside despite continuation of treatment. Laboratory parameters showed no evidence of haemopoeitic abnormality or adverse effect on hepatic or renal function. Mean serum calcium did not change at the dosage levels of up to 100g/week used in these studies.

Long term efficacy and safety has been confirmed in four studies using calcipotriol ointment for up to 1 year (26,27,28,29). Calcipotriol ointment has been widely available worldwide for treatment of psoriasis since it was first approved in 1991.

The ointment formulation has also been successfully used in combination with UVB (30, 31, MC390 report), PUVA (32), cyclosporin A (33), and acitretin (MC9306 report). Use of calcipotriol ointment in children has likewise been investigated and it has been shown to be well tolerated and efficacious over a period of 8 weeks (34).

In all trials, the most frequently reported treatment related adverse event was burning/stinging/tingling occurring in about 20% of the patients. Laboratory test results showed no treatment related changes.
9.4 PRESENT STUDY: RATIONALE

Kokelj et al. (35) reported the activity of 3 months topical calcipotriol without occlusion in 7 patients affected by nail psoriasis. All patients had a prominent nail bed and hyponychial involvement with subungual hyperkeratosis and onycholysis; pitting was present in three cases.

After three months of therapy 5 patients showed an improvement of their nail psoriasis, especially with regard to subungual hyperkeratosis and onycholysis.

Of these 5 patients who have prolonged calcipotriol use for a further 3 months, complete clearing was observed in one.

Although the typical course of psoriasis, characterised by spontaneous improvement or worsening, makes it difficult to assess the real efficacy of treatment, this preliminary work indicate that topical calcipotriol may be a promising treatment, especially on account of its high tolerability that permits prolonged use without significant side effect. A randomised controlled trial is needed to compare the effectiveness of calcipotriol applied topically with placebo or other treatments for nail psoriasis.

Considering 1) the above results, 2) the difficult penetration of active components in nail, 3) the necessity for the patient to wash their hand after application in order to avoid inadvertent spread to the face; it is expected that calcipotriol could be used under occlusion at night in order to increase its efficacy.

However it appears important to assess the acceptability of such therapy in some nail psoriatic patients in order to evaluate the opportunity to perform a randomised, controlled trial including a large number of patients. This actually constitutes the main objective of this present study.
10  INVESTIGATIONAL PLAN
This section (section 10) presents a synopsis of the study protocol. This protocol itself is presented in Appendix IV.

10.1  STUDY OBJECTIVES
The study objectives were to assess the acceptability and safety of calcipotriol ointment used under occlusion for 4 weeks in the treatment of finger nail psoriasis.

10.2  STUDY DESIGN
This study was a multicentre, open, non controlled pilot study with calcipotriol ointment (50 µg/g) used under occlusion once daily at night (at least 6 hours) for 4 weeks.

10.3  PATIENTS NUMBER
For this pilot study, no formal sample size calculation was performed.

Ten evaluable patients were required. Evaluable patients were defined as patients who completed the treatment.

A patient withdrawn for adverse event related to study drug was also considered as an evaluable patient.

10.4  CRITERIA FOR PATIENTS SELECTION

10.4.1  Inclusion criteria

10.4.1.1  Clinical diagnosis of nail psoriasis on at least one finger and present or previous experience of skin psoriasis.
10.4.1.2 Out patients.

10.4.1.3 At least 18 years of age.

10.4.1.4 Either sex.

10.4.1.5 Women of child-bearing potential had to use an adequate method of contraception.

10.4.1.6 Signed consent following verbal and written information.

10.4.2 Exclusion criteria

10.4.2.1 Clinical evidence of nail infection.

10.4.2.2 Ongoing adverse event(s) due to previous therapy for nail psoriasis (e.g. redness, soreness, burning, itching, sign of skin atrophy, chapped fingers, miliaria).

10.4.2.3 Patients who needed systemic treatment, PUVA or UVB for their skin psoriasis during the study.

10.4.2.4 Systemic treatment for psoriasis or PUVA or UVB within the 2-weeks period prior to visit 1. Topical treatment for nail psoriasis had to be stopped at least 1 week before visit 1.

10.4.2.5 Pregnancy or women who wished to become pregnant during the study period or breast-feeding.

10.4.2.6 Current medication with > 400 IU vitamin D daily and/or 5000 IU vitamin A and/or calcium tablets.

10.4.2.7 Treatment with any other medication (topical or systemic) that could affect the course of the disease during the study period, i.e. lithium, β-adrenergic receptor blocking agents, systemic corticosteroids, antimalaric treatment.
10.4.2.8  Hypersensitivity to components of calcipotriol ointment or significant local or systemic adverse events during previous administration of calcipotriol.

10.4.2.9  Known or suspected of not being able to comply with a study protocol (eg-due to alcoholism, drug dependance or psychotic states).

10.4.2.10  Known severe immunodeficiency state.

10.4.2.11  Hypercalcemia at visit 1 defined as serum calcium (albumin corrected) above the upper limit of the reference range of the local laboratory. In case of hypercalcemia at visit 1, the investigator had to contact the patient immediately in order to stop the treatment.

10.4.2.12  Known significant renal disease.

10.4.2.13  Known significant hepatic disease.

10.4.2.14  Treatment with an investigational drug (i.e. agent which has not yet been approved for clinical use) within the 3 months prior to visit 1.

10.4.2.15  Current participation in any other clinical trial.

10.4.2.16  Previous participation in this study.

10.5  CRITERIA FOR EARLY WITHDRAWAL FROM THE STUDY

Patients could have been withdrawn for any of the following:

10.5.1  Voluntary withdrawal: patients were free to withdraw from the study at any time for any reason.

10.5.2  Unacceptable treatment response: the treatment was withdrawn if the investigator considered the treatment response to study medication unacceptable and if the patient needed alternative active treatment.

10.5.3  Medical deterioration: the investigator was free to withdraw the treatment at any time for medical reasons.
10.5.4 Compliance: discontinuous treatment for more than 3 consecutive days except if it was due to adverse event related to study drug.

10.5.5 Adverse events: any adverse event attributable to the study medication that the investigator considered unacceptable for the patient.

10.5.6 Hypercalcemia: any hypercalcemia, defined as serum calcium (albumin corrected) above the upper reference range. If hypercalcemia (albumin corrected) occurred at visit 1, the investigator contacted the patient immediately in order to stop the treatment.

10.5.7 Non inclusion criteria: non inclusion criteria becoming apparent during the trial.

10.6 TREATMENT ASSIGNMENT

Each patient entered in the study by order of presentation in the centre and an identification number was given at visit 1. This number was pre-printed on each page of the Case Record Form book.

Patients who were found to comply the eligibility criteria were assigned a treatment number (visit 1).

10.7 BLINDING OF STUDY

Not applicable in this open-study.

10.8 BREAKING OF THE BLINDING

Not applicable in this open-study.
10.9 INVESTIGATIONAL PRODUCT

10.9.1 Calcipotriol

Calcipotriol ointment (produced and certified by LEO Pharmaceutical Products, Ballerup, Denmark) containing 50 µg/g of calcipotriol in the following vehicle:
- Disodium hydrogen phosphate
- POE stearylether
- Propylen glycol
- Tetracemine disodium
- DL-alpha-tocopherol
- Petrolatum
- Paraffin liquid
- Purified water

A maximum of 1 tube of 30 g ointment was provided per week. Medication from batch number 9436831 expiry date November 1996 were used.

10.9.2 Occlusing dressing

Plastic gloves were provided at visits 1, 2 and 3 as occlusive system.

10.10 ADMINISTRATION OF STUDY MEDICATION

All affected finger nails were treated with the study medication.

Other topical medications were allowed for the other affected areas. In case of treatment with DAIVONEX® on other locations, the total amount (including study ointment) did not exceed 100 g/week.

The patients were instructed to apply a small quantity of study ointment on affected finger nails. No trial medication had been applied on other regions. The medication had been applied under occlusion with plastic gloves once daily in the evening and was kept the whole night (for at least 6 hours). Care was taken to avoid inadvertent spread of ointment to other regions.
10.11 DRUG ACCOUNTABILITY AND COMPLIANCE CHECKS

10.11.1 Compliance checks

The patient was asked if he/she had used the medication as prescribed. If not, the reason for non compliance was specified.

At all visits patients were asked to return all the dispensed tubes of trial medication, whether used or unused.

The returned tubes both used and unused were collected and stored by the investigator for later collection by the trial monitor.

All tubes had subsequently been weighed at LEO Pharmaceutical Products to determine the amount of ointment used.

10.11.2 Precautions/over dosage

Verified hypercalcemia (albumin corrected) caused cessation of administration of calcipotriol and withdrawal of the patient as specified in the Section 10.5.6.

Clinically important hypercalcemia was treated at the investigator's discretion with rehydration, bisphosphonate or according to local instructions.

10.11.3 Drug accountability

The investigators were fully responsible for maintaining adequate control of the test materials and for documenting all transactions with them. Study medications were stored in a safe and secure place and proper dispensing arrangements were made as follows:

10.11.3.1 Sponsor - Investigator inventory monitoring

All the trial medications supplied by and returned to Laboratories LEO S.A. were fully documented.
10.11.3.2 Investigator - Patient inventory monitoring

At each visit, all used or unused study medications were returned by the patient.

An inventory was kept for all supplies issued and returned by each patient enrolled in the study. This inventory was available for inspection at monitoring visits and was checked to ensure correct dispensing of test medication.

10.12 CONCURRENT TREATMENT

Concurrent medications (except for agents mentioned in non inclusion criteria 10.4.2) for conditions other than psoriasis were continued throughout the study, without any change in dosage whenever possible. Any such treatment was recorded in the Case Record Form Book.

Topical treatments for finger nails psoriasis (except study ointment) were not allowed during study period and had to be stopped at least 1 week before visit 1.

Topical antipsoriatic medication was allowed during the study period for treatment of psoriatic lesions other than finger nails. Use of such medication was recorded in the Case Record Form Book. In case of treatment of other locations with DAIVONEX®, the total amount of ointment (including study ointment) did not exceed 100g/week.
## 10.13 STUDY PROCEDURES

The following diagram summarises the study procedures:

<table>
<thead>
<tr>
<th>VISITS</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weeks</strong></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>4</td>
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<tr>
<td>Medical history</td>
<td>*</td>
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<tr>
<td>Recording of adverse events</td>
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<tr>
<td>Acceptability assessment</td>
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<tr>
<td>Laboratory examination:</td>
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<tr>
<td>- S-total-calcium</td>
<td>*(1)</td>
<td></td>
<td>*(2)</td>
<td></td>
</tr>
<tr>
<td>- S-albumin</td>
<td>*(1)</td>
<td></td>
<td>*(2)</td>
<td></td>
</tr>
<tr>
<td>- S-albumin corrected calcium</td>
<td>*(1)</td>
<td></td>
<td>*(2)</td>
<td></td>
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<tr>
<td>Investigator clinical assessment</td>
<td></td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Pregnancy test *(3)</td>
<td></td>
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</tr>
<tr>
<td>Supply of study medication</td>
<td></td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Collection of unused and used study medication</td>
<td></td>
<td>*</td>
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</tr>
</tbody>
</table>

(1) In case of hypercalcemia (albumin corrected) or positive pregnancy test at visit 1, the investigator contacted the patient in order to stop the treatment.
(2) Or earlier in case of withdrawal. In case hypercalcemia (albumin corrected) occurred, the examination was repeated until normalisation.
(3) In female patients of child-bearing potential.

### 10.13.1 Medical history (visit 1 only)

At visit 1, the patient's suitability for the study was checked using the inclusion and non-inclusion criteria.

The patient's history was taken and any concurrent medication was recorded.

### 10.13.2 Clinical assessment

#### 10.13.2.1 Investigator's assessment

The same investigator examined the patient at all study visits.

The investigator chose a target nail that included typical and representative lesions.
The target nail was clearly identified on a diagram in the Case Record Form Book. Assessment of severity of clinical signs was based on that target nail.

10.13.2.2 Assessment of the affected nails

At visits 1, 2, 3 and 4, the investigator assessed the number of finger nails involved. The affected nails were recorded on a diagram included in the Case Record Form Book.

10.13.2.3 Assessment of severity of pitting

At visits 1, 2, 3 and 4, the investigator assessed the severity of pitting (target nail only) when evaluable using the scale below:

- 0 = absent
- 1 = mild
- 2 = moderate
- 3 = severe

10.13.2.4 Assessment of severity of discoloration

At visits 1, 2, 3 and 4, the investigator assessed the severity of discoloration (target nail only) when evaluable using the scale below:

- 0 = absent
- 1 = mild
- 2 = moderate
- 3 = severe

10.13.2.5 Assessment of severity of onycholysis

At visits 1, 2, 3, and 4, the investigator assessed the severity of onycholysis (target nail only) when evaluable using the scale below:

- 0 = absent
- 1 = mild
- 2 = moderate
- 3 = severe
10.13.2.6 Assessment of severity of subungual hyperkeratosis

At visits 1, 2, 3 and 4, the investigator assessed the severity of subungual hyperkeratosis (target nail only) when evaluable using the scale below:

- 0 = absent
- 1 = mild
- 2 = moderate
- 3 = severe

10.13.3 Acceptability assessment

At visits 2, 3 and 4, the presence of the following potential effects was checked on all treated digits:

- a) redness,
- b) soreness sensation,
- c) burning sensation,
- d) itching sensation,
- e) sign of skin atrophy,
- f) chapped fingers,
- g) miliaria,

If present, severity, relationship to the study drug was specified on the adverse event table of the Case Record Form.

10.13.4 Laboratory examinations

10.13.4.1 Biochemistry

Serum samples (S = Serum) for analysis of the parameters listed below were taken at visits 1 and 4, or upon withdrawn treatment:

- S - Total calcium
- S - Albumin
- S - Albumin corrected calcium

10.13.4.2 Pregnancy test

All female patients of child bearing age had a negative pregnancy test at visit 1.
10.14 CRITERIA FOR TOLERABILITY AND SAFETY

The criteria for tolerability and safety were:
- proportion of patients who achieved the treatment phase without significant adverse event,
- any adverse event reported during the study period,
- any significant change in S-calcium (albumin corrected) from visit 1 to end of treatment.

10.15 ADVERSE EVENT REPORTING

In addition to the specific points on acceptability (see section 10.13.3), the patient was asked a non-leading question by the investigator: "Since I last saw you, have you had any problem while using the treatment?"

If the answer was "NO", no further questions were asked. If the answer was "YES", the investigator recorded the event's nature, duration, location(s), severity, outcome and suspected relationship to the use of study medication.

In recording the patient's comments, the investigator observed the following definitions:

a) ADVERSE EVENT: any undesirable experience occurring to a subject during a clinical trial whether or not considered related to the investigational product.

b) SERIOUS ADVERSE EVENT: an adverse experience that is fatal, life threatening, disabling or which results in in-patient hospitalisation or prolongation of hospitalisation. In addition, congenital abnormality and occurrence of malignancy are always considered serious adverse events.

c) UNEXPECTED ADVERSE EVENT: an experience not previously reported (in nature, severity or incidence) in the current Product Monograph, in the general investigational plan, or elsewhere.
NOTE: Patient's remarks relating to the primary disease condition were not, as a general rule, included in the adverse event chart.

It was important that the investigator also observed the patient for any changes not reported by the patient, and record these changes.

Events either reported by the patient, or observed by the investigator, that fell into any of the above definitions were described in the following manner:

1) The nature of the event was described in precise, standard medical terminology (i.e. not necessarily the exact words used by the patient).

2) The duration of the event was described in terms of the number of days affected since the last visit.

3) The severity of the event was described according to the investigator opinion in terms of mild, moderate or severe.

4) The causal relationship of the event to use of the study medication was described in terms of:

   a) Unlikely: the adverse event:
      - did not follow a reasonable temporal sequence from administration of the drug,
      - could readily have been produced by the patient's clinical state, environmental or toxic factor or other therapies administered to the patient,
      - did not follow a known response pattern to the suspected drug,
      - did not reappear or worsen when the drug was readministered.

   b) Possible: the adverse event
      - followed a reasonable temporal sequence from administration of the drug,
      - could readily have been produced by the patient's clinical state, environmental or toxic factor or other therapies administered to the patient,
      - followed a known response pattern to the suspected drug.
c) **Probable**: the adverse event
- followed a temporal sequence from administration of the drug,
- could not be reasonably explained by the patient's clinical state, environmental or toxic factors or other therapies administered to the patient,
- disappeared or decreased on cessation or reduction in dose,
- followed a known pattern or response to the suspected drug.

**NOTE**: All adverse events were followed-up to determine outcome of the reaction. Details of follow-up care were given (i.e. if treatment was required, if hospitalisation was required, etc.).

Serious and unexpected adverse events had to be reported immediately (always within 24 hours) to the company.

Within 5 working days an Adverse Event Form had to be submitted to the Company accounting for the adverse event(s). The information provided on the Form had to include a full description of the clinical course, account for any concurrent drug therapy given during the study period and, where possible, contained relevant documentation (e.g. in case of death a copy of the post-mortem report). The report had also to include a statement from the investigator as to the possible causal relationship between the adverse event and the study medication.

If an investigator was in doubt whether to regard an adverse event as serious or unexpected, the event was serious/unexpected until the opposite was proved.

**In addition**, the National Regulatory Authorities had to be informed in accordance with the article L209-12 ("Code de la Santé Publique").
11 QUALITY ASSURANCE
The trial protocol and the conduct of the trial as a whole were designed to comply
with the European Community Guidelines and Good Clinical Practice (no. 3/3976/88, July 1991), including archiving of study documents.

Any activity in relation to the trial may be subject to independent Internal Audit.

During the study no audit was carried out.

12 STATISTICAL ANALYSIS PLAN
According to the protocol, no statistical analysis (including statistical inference)
was performed.
To account for acceptability and safety of the study drug, descriptive statistics
were calculated for all variables, and summarised by the tables included in the
report.

13 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED
ANALYSIS
Not applicable.
14 RESULTS

14.1 STUDY PERIOD

Two centres participated in the study. One in [redacted] with Dr [redacted] as investigator, one in [redacted] with Dr [redacted] as investigator.

The first patient was included in this study on October 20, 1995 (CRF [redacted] centre [redacted]).

The last patient was included on February 2, 1996 and completed the study on March 1, 1996 (CRF [redacted] centre [redacted]). That was the end of the study.

The duration of the enrolment in the study was 4.5 months (from October 20, 1995 to March 1, 1996).

Table 1: Dates of the first visit and the last visit by study centre

<table>
<thead>
<tr>
<th>Study centre</th>
<th>Date of first patient visit</th>
<th>Date of last control visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr [redacted]</td>
<td>20/10/95</td>
<td>26/12/95</td>
</tr>
<tr>
<td>Dr [redacted]</td>
<td>21/11/95</td>
<td>01/03/96</td>
</tr>
</tbody>
</table>

Figure 1: Cumulative number of included patients with time
Table 2: Interval between control visits and visit 1

<table>
<thead>
<tr>
<th>Visit 1 to visit 2</th>
<th>Interval between visit</th>
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<tbody>
<tr>
<td></td>
<td>Mean (days)</td>
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<tr>
<td></td>
<td>Number</td>
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<td>Visit 1 to visit 3</td>
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<tr>
<td></td>
<td>1.85</td>
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<td>2</td>
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<td>Visit 1 to visit 4</td>
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<td>2.12</td>
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<td>14</td>
</tr>
<tr>
<td></td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>7</td>
</tr>
</tbody>
</table>

14.2 STUDY POPULATION

Patients were recruited from 2 French centres. Eight patients were included in this study following all the inclusion/exclusion criteria. Seven patients attended the final study visit (visit 4 according to the protocol).

One patient (CRF[redacted]) was withdrawn from this study 2 days after visit 1 without taking any study drug because the corrected calcium was upper than the limit (corrected calcium: 2.68 mmol/l for reference range 2.25 - 2.60 mmol/l).

Table 3: Number of patients included at visit 1 and number of patients on study drug

<table>
<thead>
<tr>
<th>Study centre</th>
<th>Number of patients included at visit 1</th>
<th>Number of patients on study drug</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>
All the patients, who took the study mediation, attended all the control visits (visit 2, visit 3 and visit 4). There was no withdrawal from the study medication.

14.3 INTENTION-TO-TREAT (ITT) POPULATION

One patient (CRF was excluded from the ITT population because did not take any study medication and withdrew from the study 2 days after visit 1.

The remaining 7 patients followed the 4 weeks of treatment according to the protocol. They were included in the ITT population.

14.4 SAFETY POPULATION

One patient (CRF (see 14.2 and 14.3) was excluded from the safety population.

The remaining 7 patients were included in the safety population.

14.5 PER PROTOCOL (PP) POPULATION

All patients in the ITT population was considered as available in the PP population.

14.6 PROTOCOL DEVIATION

There was no protocol deviation.

14.7 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The data were analysed from the ITT population. Patient was excluded from the analysis (see section 14.2 and 14.3).
14.7.1 Demographic variable

Two females (29%) and 5 males (71%) included in this study.

The mean age of the patients included in the ITT population was 43 years (range 35 to 57).

Table 4: Demographic data

<table>
<thead>
<tr>
<th>Study centre</th>
<th>Number of patients</th>
<th>Mean age (years) (Min. - Max.)</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr [redacted]</td>
<td>4</td>
<td>46 (36-57)</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Dr [redacted]</td>
<td>3</td>
<td>39 (35-46)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>43 (35-57)</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

14.7.2 Time of diagnosis

The mean duration of finger nail psoriasis for the patients was 2 years (range 5 months to 8 years).

Table 5: Duration of finger psoriasis

<table>
<thead>
<tr>
<th>Study centre</th>
<th>Number of patients</th>
<th>Mean duration of finger nail psoriasis (min./max.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr [redacted]</td>
<td>4</td>
<td>2 y + 10 m (6 m/8 y)</td>
</tr>
<tr>
<td>Dr [redacted]</td>
<td>3</td>
<td>11 m (5 m/1 y + 3 m)</td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>2 y (5 m/8 y)</td>
</tr>
</tbody>
</table>

14.7.3 Previous treatment (nail psoriasis only)

One patient (CRF [redacted] had used a topical steroid without occlusion to treat finger nail psoriasis before entering this study.

The remaining 6 patients had never used any medication for their finger nail psoriasis before this study.
14.7.4 Concurrent treatment for psoriasis

A medication, desonide (Locapred®) was used for psoriasis on the buttocks once per day during the study period by one patient (CRF...)
The remaining 6 patients did not use any medication for psoriasis lesions.

14.7.5 Concomitant diagnosis

One patient (CRF... suffered from constipation in addition to psoriasis. This complaint continued throughout the study.
The remaining 6 patients did not suffer from any disease.

14.7.6 Concurrent treatment

One patient (CRF... used during the study clidinium bromure, chlordiazepoxide (Librax®) with a posology of 5 mg/day and 10 mg/day respectively for each medications.
Another patient (CRF... used a contraceptive medication with norethisterone, ethinylestradiol (Triella®) at visit 1 and throughout the study.

14.7.7 Investigator's clinical assessment

- 3 patients (CRFs... had 10 finger nails affected with psoriasis,
- 1 patient (CRF... had 6 finger nails affected with psoriasis,
- 2 patients (CRFs... had 3 finger nails affected with psoriasis,
- 1 patient (CRF... had 2 finger nails affected with psoriasis.

The target nail was chosen by the investigators. For 3 patients, right index finger was the target nail. Two patients had, as target nail, the right thumb. The left thumb was target nail for 1 patient and the remaining patient had the right middle finger as target nail.
The investigators assessed the severity of the clinical signs in target nail only:

- **Severity of pitting:**
  * for 1 patient (CRF   4 patients (CRFs ) had a mild pitting at baseline,
  * 1 patient (CRF  1 patient (CRF  had a severe pitting at baseline,

- **Severity of discoloration:**
  * for 1 patient (CRF  1 patient (CRF  discoloration was absent at baseline,
  * 4 patients (CRFs  1 patient (CRF  had a moderate discoloration at baseline.

- **Severity of onycholysis:**
  * for 1 patient (CRF  4 patients (CRFs  2 patients (CRFs  had a moderate onycholysis at baseline.

- **Severity of subungual hyperkeratosis:**
  * for 1 patient (CRF  2 patients (CRFs  4 patients (CRFs  had a moderate subungual hyperkeratosis.

A scoring system was used to assess the severity of the clinical signs (in target nail only):

- 0: absent
- 1: mild
- 2: moderate
- 3: severe
All the clinical signs score (pitting, discoloration, onycholysis, subungual hyperkeratosis) were added to give a total score. Each sign had the same weight. The mean total score was 5 (range 3 to 6) at baseline.

**Table 6:** Severity of the clinical signs

<table>
<thead>
<tr>
<th>Patient CRF number</th>
<th>Pitting</th>
<th>Discoloration</th>
<th>Onycholysis</th>
<th>Subungual hyperkeratosis</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>NE</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>NE</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>NE</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>NE</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>NE</td>
<td>3</td>
<td>NE</td>
<td>1</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>NE</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

NE: Not Evaluable

Finger nail psoriasis was found, in the right hand only, for 1 patient (CRF NE). The remaining 6 patients had finger nail psoriasis on both hands.

### 14.8 EFFICACY RESULTS

Because of the long duration required by all treatment for nail psoriasis (3 to 6 months), this pilot study was not expected to give any information on the efficacy of calcipotriol ointment in this indication.

Nevertheless the data of the investigator's assessment are described below.

#### 14.8.1 Number of nails affected with psoriasis

During the 4 weeks of treatment under occlusion no nails affected with psoriasis were cured.
14.8.2 Severity of pitting

The assessment of the severity of pitting was done by the investigator in the target nail at each control visit (V2, V3, V4).

One patient (CRF improved pitting after 4 weeks of treatment with calcipotriol ointment under occlusion. The severity of pitting was judged by the investigator as moderate at the baseline visit and as mild at the end of treatment (visit 4).

For the remaining 6 patients the severity of pitting did not change during the study period.

Figure 2: Score of severity of pitting at subsequent visits
14.8.3 Severity of discoloration

The assessment of the severity of discoloration was done by the investigator in the target nail at each control visit (V2, V3, V4).

One patient (CRF changed discoloration from mild to absent after 1 week of treatment.

Figure 3: Score of severity of discoloration at subsequent visits
14.8.4 Severity of onycholysis

The assessment of the severity of onycholysis was done by the investigator in the target nail at each control visit (V2, V3, V4).

Two patients improved their onycholysis during the study treatment. One patient (CRF • changed • onycholysis from moderate to mild after 2 weeks of treatment. Another one (CRF ■ moved from moderate to mild for the severity of onycholysis after 1 week of treatment.

The remaining 5 patients did not change their onycholysis during the study.

Figure 4: Score of severity of onycholysis at subsequent visits
14.8.5 **Severity of subungual hyperkeratosis**

The assessment of the severity of subungual hyperkeratosis was done by the investigator in the target nail at each control visit (V2, V3, V4).

Five patients improved their subungual hyperkeratosis during the study. One patient (CRF moved from mild to absent after 1 week of treatment. Two patients (CRFs changed their severity of subungual hyperkeratosis from moderate to mild after 2 weeks of treatment and from mild to absent after 4 weeks of treatment with calcipotriol ointment under occlusion. One patient (CRF improved subungual hyperkeratosis after 1 week of treatment from moderate to mild and this severity remained stable until the end of treatment. The last patient (CRF moved score from moderate to mild after 4 weeks of treatment.

*Figure 5: Score of severity of subungual hyperkeratosis*
14.8.6 Total score of clinical signs

The mean of the total score was 5 at baseline. This total score improved throughout the study period, since it decreased to 4 at visit 2, 4 at visit 3 and 3 at visit 4 after 4 weeks of treatment with calcipotriol ointment under occlusion.

Table 7: Score of the severity of clinical signs at each visits

<table>
<thead>
<tr>
<th>Patient CRF N°</th>
<th>Visit N°</th>
<th>Pitting</th>
<th>Discoloration</th>
<th>Onycholysis</th>
<th>Subungual hyperkeratosis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>V1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>V2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>V3</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>V4</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>V1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>V2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>V3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>V4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>V1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>V2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>V3</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>V4</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>V1</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>V2</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>V3</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>V4</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>V1</td>
<td>3</td>
<td>-</td>
<td>1</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>V2</td>
<td>3</td>
<td>-</td>
<td>1</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>V3</td>
<td>3</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>V4</td>
<td>3</td>
<td>-</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>V1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>V2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>V3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>V4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>V1</td>
<td>-</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>V2</td>
<td>-</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>V3</td>
<td>-</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>V4</td>
<td>-</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

0 = absent
1 = mild
2 = moderate
3 = severe
14.8.7 Acceptability assessment

At each control visit 2, 3 and 4 the presence of following potential effects was checked on all treated digits:
- redness
- soreness sensation
- burning sensation
- itching sensation
- sign of skin atrophy
- chapped fingers
- miliaria

by the investigators.

Three patients (CRFs and) complained about redness in the digits treated. For patients and this redness was found at the end of the study (visit 4). For patient this effect had appeared after 1 week of treatment in all digits affected with psoriasis and continued during the study.
Three patients (CRFs) complained about chapped fingers in the digits treated:
- patient suffered from visit 3 to visit 4,
- patient between visit 3 and visit 4,
- patient from 1 week of treatment to the end of the study.

One patient (CRF) complained about a burning sensation, between visit 2 and visit 3. This burning sensation concerned only 2 treated digits of 10 affected with psoriasis. The duration of this adverse effect was 2 days.

14.9 USE OF AND COMPLIANCE WITH PRESCRIBED STUDY MEDICATION

One patient (CRF) did not use calcipotriol ointment under occlusion every night, stopped treatment for 2 days during the second week of treatment because suffered from a burning sensation.

Except this patient, all the remaining patients used the study medication according to the protocol.

14.10 DURATION AND EXTENT OF EXPOSURE TO TREATMENT WITH STUDY MEDICATION

All the 7 patients included in this study continued until the end according to the protocol.

The mean duration of treatment with calcipotriol ointment under occlusion was 30 days (range 27 to 33).
Table 8: Duration of treatment

<table>
<thead>
<tr>
<th>Study centre</th>
<th>Patient CRF number</th>
<th>Duration of treatment (day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

14.11 CONCURRENT TREATMENT

Two patients (CRFs use_1_) used a concurrent treatment during the study period:
- patient_1_ used Librax® for chronic constipation,
- patient_2_ used Triella® for contraception.

Table 9: Non psoriatic concurrent treatment

<table>
<thead>
<tr>
<th>Therapeutic category (ATC system)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Alimentary tract and metabolism</td>
<td>1</td>
</tr>
<tr>
<td>Genito-urinary system and sex hormone</td>
<td>1</td>
</tr>
</tbody>
</table>

| Total number of patient (n=7)                         | 2 |

14.12 SAFETY EVALUATION

The safety and the tolerability criteria were the main criteria for the study.

The specific tolerability points were reported in section 14.8.7, and the safety points are reported below.

The safety criteria were:
- any reported adverse event,
- any significant change in S-calcium (albumin corrected) from visit 1 to end of treatment.
14.12.1 Adverse events reported

In addition to the specific points on acceptability (see 14.8.7), the patient was asked a non-leading question by the investigator: "Since I last saw you, have you had any problems while using the treatment?". If the answer was "No", no further question was asked. If the answer was "Yes" the investigator recorded the event's nature, duration, location(s), severity, outcome and suspected relationship to the use of study medication.

For each adverse event, the following related details were recorded in the CRF:

1- the nature of the adverse event in the investigator's terminology,
2- for skin related adverse events, the location as to whether it appeared on the left side, the right side or on both sides of the body,
3- whether the adverse event was application related,
4- the number of days since the preceding visit that the patient was affected by the adverse event,
5- the investigators opinion on the severity of the adverse event to "mild", "moderate" or "severe",
6- whether the investigator considered the relationship of the adverse event to the study drug to be "unlikely", "possible" or "probable".

All adverse events were classified following "WHO System Organ Class" in the group "Skin and appendage disorders".

All the potential effects found in the acceptability assessment (see Section 14.8.7) were reported as an adverse event described as following:

- patient [ ] suffered from scaling (slight peeling) on the distal phalanxes from day 16 to the end of the treatment. This AE was classified as mild severity and probable relationship to study drug by the investigator. No specific treatment was used,
- patient [redacted] suffered from scaling of terminal phalanxes of 2 digits out of 10 affected with psoriasis and treated. This AE was from day 27 to the end of the study and classified as mild severity and probable relationship to study drug by the investigator. No specific treatment was used,

- patient [redacted] suffered from scaling of terminal phalanxes of all digits from day 5 to the end of the study. This AE was classified as mild severity and probable relationship to study drug by the investigator. The same patient suffered from burning, with mild severity and probable relationship to study drug, 2 days during the second week of treatment [redacted] presented a redness of the distal digits, with mild severity and probable relationship to study drug from day 19 to the end of the study. No specific treatment was used by this patient for these AEs,

- patient [redacted] suffered from redness of peri ungueal area and pulpe. This AE was from the first day of treatment to the end of the study and it was classified as moderate severity and probable relationship to study drug. No specific treatment was used,

- patient [redacted] presented a redness of pulp and hyponichium from day 16 to the end of the study, with a mild severity and probable relationship to study drug.

No systemic AE and no other side effect were found throughout this study.
Table 10: Adverse events

<table>
<thead>
<tr>
<th>Patient CRF N°</th>
<th>AE Description</th>
<th>From (day)</th>
<th>To (day)</th>
<th>Severity</th>
<th>Relationship to study drug</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Scaling (slight peeling) of distal phalanxes</td>
<td>16</td>
<td>end of study</td>
<td>mild</td>
<td>probable</td>
</tr>
<tr>
<td></td>
<td>Scaling of terminal phalanxes</td>
<td>27</td>
<td>end of study</td>
<td>mild</td>
<td>probable</td>
</tr>
<tr>
<td></td>
<td>Scaling of terminal phalanxes</td>
<td>5</td>
<td>end of study</td>
<td>mild</td>
<td>probable</td>
</tr>
<tr>
<td></td>
<td>Redness of distal digits</td>
<td>19</td>
<td>end of study</td>
<td>mild</td>
<td>probable</td>
</tr>
<tr>
<td></td>
<td>Burning around nails</td>
<td>2 days</td>
<td></td>
<td>mild</td>
<td>probable</td>
</tr>
<tr>
<td></td>
<td>Redness (periungueal + pulpe)</td>
<td>1</td>
<td>end of study</td>
<td>moderate</td>
<td>probable</td>
</tr>
<tr>
<td></td>
<td>Redness (pulp + hyponichium)</td>
<td>16</td>
<td>end of study</td>
<td>mild</td>
<td>probable</td>
</tr>
</tbody>
</table>

14.12.2 Deaths, other serious adverse events and other significant adverse events

No serious AE was observed in this study.
No patient withdrawn from this study due to AE.

14.13 LABORATORY EXAMINATIONS

A slight hypercalcemia (S-calcium = 2.63 mmol/l) was discovered at visit 4 for one patient. This hypercalcemia continued 49 days after the end of treatment. This variation of the calcemia was judged not clinically significant by the investigator.

No variation of the biological parameters was found for the remaining 6 patients.
Table 11:  S-calcium, S-albumin, corrected calcium

| Patient CRF N° | Visit 1 | | | Visit 4 | | | |
|----------------|--------|--------|--------|--------|--------|--------|
|                | S-calcium | S-albumin | Corrected calcium | S-calcium | S-albumin | Corrected calcium |
|                | (mmol/l) | (mg/l) | (mmol/l) | (mmol/l) | (mg/l) | (mmol/l) |
| •              | 2.43    | 40     | 2.43    | nd      | nd      | nd      |
| •              | 2.53    | 41     | 2.56    | 2.63    | 43      | 2.71    |
| •              | 2.50    | 43     | 2.58    | 2.45    | 45      | 2.58    |
| •              | 2.38    | 45     | 2.50    | 2.35    | 49      | 2.58    |
| •              | 2.35    | 42     | 2.30    | 2.22    | 38      | 2.25    |
| •              | 2.45    | 46     | 2.32    | 2.30    | 50      | 2.12    |
| •              | 2.52    | 42     | 2.47    | 2.37    | 39      | 2.35    |

Normal range:

- S-calcium: 2.37-2.62 mmol/l
- S-albumin: 37-53 mg/l
- Corrected calcium: 2.25-2.60 mmol/l

nd = not done
15 DISCUSSION

This study was conducted with the objective to evaluate the safety of treatment under occlusion with calcipotriol. The efficacy was analysed to know if this treatment could be valuable.

Calcipotriol is an effective drug for treating psoriasis. Studies showed that calcipotriol is as effective or superior to betamethasone-17-valerate (24,25).

To treat psoriatic nail is difficult and the penetration of active compound through the hyperkeratosis is very poor. Most often the treatment of psoriatic nail is mechanical by a manicure to get rid of debris (36).

In previous studies, a clinical improvement was showed in psoriatic nail after 12 weeks of treatment with topical calcipotriol without any occlusion (37). Three months of treatment of calcipotriol without occlusion showed both a subjective and objective improvement in 5 patients out of 7 treated (35). To avoid unintentional spread of calcipotriol on the face the patients are usually asked to wash their hands after application.

Considering all these points above, calcipotriol used under occlusion at night should increase the efficacy without decreasing the tolerability and safety. In this pilot study, calcipotriol ointment (50 μg/g) have been used under occlusion once daily at night (at least 6 hours). A maximum of 30 g of calcipotriol ointment was allowed per week. Plastic gloves have been used as occlusive system.

That was a two centres, open and non controlled study. The treatment period was 4 weeks, it was a bit short to prove a real efficacy, but a trend toward efficacy and safety of this occlusive treatment is strongly suggested.

The study was conducted over a period of 4.5 months with 2 investigators. Eight patients were recruited but one patient never took any medication was excluded from the analysis.
Due to the fact that few patients were included in this clinical study, a descriptive analysis was performed.

At baseline the patients were 43 years old with an history of nail psoriasis of 2 years. For the 7 patients included that was the first time of occlusive treatment. Six patients out of 7 had no previous experience about treatment for their nail psoriasis.

Calcipotriol was never used before by all patients included. Six patients out of 7 presented nail psoriasis is both hands.

The investigators judged, at baseline, the severity of clinical sign of psoriatic nail as mild or moderate for the majority of patients.

The study medication, calcipotriol ointment under occlusion, was used for 4 weeks according the protocol by 6 patients out of 7. One patient stopped the treatment for 2 days by own decision due to an adverse event.

All the clinical signs (pitting, discoloration, onycholysis, subungual hyperkeratosis) were scored by the investigators to assess the severity at each control visit. These scores were added to have an overall clinical assess. At baseline, the mean clinical severity was scored 5. Throughout the study, an improvement was found and the score of the clinical severity decreased regularly.

The best efficacy of treatment with calcipotriol ointment under occlusion once daily at night, was found in subungual hyperkeratosis. This clinical sign was improved by 5 patients out of 7 during the treatment period of 4 weeks. The efficacy of calcipotriol under occlusion in the remaining clinical signs (onycholysis, discoloration and pitting) was less clear.
Abesamis-Cubillan (37) showed that 12 weeks of treatment with topical calcipotriol were effective in reducing pitting, ridging, subungual hyperkeratosis and associated onycholysis.

In this clinical study, the patients with nail psoriasis were treated for a short period (4 weeks) with calcipotriol ointment under occlusion. Farber and col. (9) think that the treatment against nail psoriasis with topic products should be long, around 4 to 6 months.

Nevertheless, after 4 weeks of treatment with calcipotriol ointment under occlusion, a light efficacy in hyperkeratosis and a tendency of improvement in onycholysis were found. If the treatment period would have been longer the efficacy could be proved in all clinical signs. A Clinical study should be performed to confirm this data.

No patients withdrew of the study due to side effect, but one patient did not use calcipotriol ointment under occlusion for 2 days due to burning sensation. He restarted the treatment after this break without any burning. The treatment induced a scaling (chapped fingers) and/or erythema (redness) in almost all patients (5/7) with a severity judged by the investigator as mild for 4 patients. At each control visit the presence of these specific effects (redness, soreness sensation, burning sensation, itching sensation, sign of skin atrophy, chapped fingers and miliaria) were inquired by the investigators.

No side effect was judged as severe by the investigators.

No clinical significant change was found throughout treatment with calcipotriol ointment under occlusion once daily at night.
CONCLUSION
This study has shown that the treatment with calcipotriol ointment under overnight occlusion every day for 4 weeks decreased the subungual hyperkeratosis. Onycholysis was improved lightly by the study treatment. No safety problem was appeared throughout the study. The tolerability of the treatment was acceptable, no important and/or unexpected side effect was found. The study was performed for one month with a good compliance by the patients. These data should be confirmed by a study with more patients and with a longer treatment period.
17 REFERENCES

1 Baran R., Dawber R.P.R. (eds)
Disease of the nails and their management.

2 Scher R.K.
The nails.

Series II No.212

4 Brandrup F., Green A.
The prevalence of psoriasis in Denmark.
Acta Derm Venereol 1981; 61: 344-6

5 Christophers E, Schubert C.
Psoriasis.
In: Thody AJ, Friedmann PS, eds: Scientific basis of dermatology, a physiological

6 Bos J.D.
The pathomechanisms of psoriasis; the skin immune system and cyclosporin.

7 Samman P.
The nail in disease.

8 Zaias N.
Psoriasis of the nail: a clinical-pathologic study.

9 Farber E.M., Nall L.,
Nail psoriasis.

10 Bleecker J.J.
Intradermal triamcinolone acetonide treatment of psoriatic nail dystrophy with
Port-O-jet.

11 Bedi T.R.
Intradermal triamcinolone treatment of psoriatic onycho-dystrophy.
12 Peachey R.D.G., Pye R.J., Harman R.R.M.
The treatment of psoriatic nail dystrophy with intradermal steroid injections.

13 Fredriksson T.
Topically applied fluorouracil in the treatment of psoriatic nails.
Arch Dermatol 1974; 110; 735-6.

14 Marx J.L., Scher R.K., Shupck J.L.
Response of psoriatic nails to oral photochemotherapy.

15 Rahinovitz H.S., Scher R.K., Shupack J.L.
Response of psoriatic nail to the aromatic retinoid etretinate.

16 Baran R.
Etretinate and the nails (study of 130 cases) possible mechanisms of some side
effects.

17 Totsi A., Guerra L., Bardazzi F., Lanzanini M.
Topical cyclosporin for psoriasis.
Dermatologica 1990; 180: 110.

18 Arnold W.P., Gerritsen M.J.P., Van de Kerkhoff P.C.
Response of nail psoriasis to cyclosporin.

19 Binderup L. and Bramm E.
Effects of a novel vitamin D analogue MC 903 on cell proliferation and
differentiation in vitro and on calcium metabolism in vivo.

20 Kragballe K.
MC 903, a non-calciotropic vitamin D₃ analogue stimulates differentiation and
inhibits proliferation of cultured human keratinocytes.

21 Binderup L & E Bramm
Effects of a novel vitamin D analogue MC 903 on cell proliferation and
differentiation in vitro and on calcium metabolism in vivo.

22 Berth-Jones J. et al.
A multicentre, parallel-group comparison of calcipotriol ointment and short­
contact dithranol therapy in chronic plaque psoriasis.
23 Tham SN, Lim KC and Cheong WK
A comparative study of calcipotriol ointment and tar in chronic plaque psoriasis.

24 Cunliffe W.J., Berth-Jones J., Claudia A. et al.
Comparative study of calcipotriol (MC 903) ointment and betamethasone 17-valerate ointment in patients with psoriasis vulgaris.

25 Kragballe K. et al.
Double blind right/left comparison of calcipotriol and betamethasone valerate in treatment of psoriasis vulgaris.

26 Kragballe K., Fogh K., Sogaard H.
Long-term efficacy and tolerability of topical calcipotriol in psoriasis.

Long-term use of topical calcipotriol in chronic plaque psoriasis.

28 Poyner T., Hugues I.W., Dass B.K., Adnitt P.I.
Long-term treatment of chronic plaque psoriasis with calcipotriol.

29 Ellis J P, Griffiths W A D, Klaber MR
Long-term treatment of chronic plaque psoriasis with calcipotriol ointment in patients unresponsive to short contact dithranol.

30 Kokelj F, Lavaroni G, Guadagnini A
U.V.B. versus U.V.B. plus calcipotriol (MC 903) therapy for psoriasis vulgaris.
Acta Derm Venereol (Stockh) 1995; 75: 386-87.

31 Kraballe K
Combination of topical calcipotriol (MC 903) and UVB radiation for psoriasis vulgaris.

32 Frappaz A., Thivolet J.
Calcipotriol in combination with PUVA: a randomized double blind placebo study in severe psoriasis.
33 Grossman R. et al.
A novel therapeutic approach to psoriasis-combination calcipotriol ointment and very low-dose cyclosporine: results of a multicenter placebo controlled study.

34 Darley CR, Cunliffe WJ, Ferguson J, Hutchinson PE, Klaber R
Safety and efficacy of calcipotriol ointment (Dovonex) in treating children with psoriasis vulgaris.

35 Kokelj F., Lavaroni G., Piraccini B.M., Totsi A.
Nail psoriasis treated with calcipotriol (MC903): an open study.

36 Larko O.
Problem sites; scalp, palm and sole, and nail.

37 Abenasis-Cubillan E., Camara C., Garcia AG., Frez L.
Efficacy of topical calcipotriol in the treatment of nail psoriasis: a randomized double-blind placebo controlled trial.