Clinical Study Report

Efficacy and Safety of Calcipotriol plus Betamethasone Dipropionate Gel Compared with Tacalcitol Ointment and the Gel Vehicle Alone in Patients with Psoriasis Vulgaris

A phase III study comparing a gel containing Calcipotriol 50 mcg/g plus Betamethasone 0.5 mg/g (as dipropionate) with Tacalcitol ointment (4 mcg/g) and Gel Vehicle, used once daily in the treatment of Psoriasis Vulgaris

Multi-centre, prospective, Investigator-blind, randomised, 3-arm, active and vehicle controlled parallel group, 8 week study followed by an 8 week observation phase, in subjects with psoriasis vulgaris on the body

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.

LEO Pharmaceutical Products Ltd. A/S
(LEO Pharma A/S)
Medical Department

LEO 80185-G21
Final
16-JUN-2009
1 CLINICAL STUDY REPORT APPROVAL FORM

1.1 APPROVAL STATEMENT
The following persons have approved this Clinical Study Report using electronic signatures as presented on the last page of this document

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
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<tr>
<td></td>
<td>International Clinical Development, LEO</td>
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<td>Biostatistics Department, LEO</td>
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</table>

1.2 APPROVAL STATEMENT INVESTIGATORS
On behalf of all investigators, the International Co-ordinating Investigator approves the Clinical Study Report.

The International Co-ordinating Investigator

Dr. [Name], MD, [Country]

has approved this report as presented on the International Co-ordinating Investigator Clinical Study Report Approval Form adjoined as a separate page to this document.
2 REPORT STATEMENTS

2.1 COMPLIANCE WITH GOOD CLINICAL PRACTICE
This Clinical Study Report is designed to comply with the standards issued by the International Conference on Harmonisation (ICH) (E3 Structure and Content of Clinical Study Reports; E6 Good Clinical Practice; and E9 Statistical Principles for Clinical Trials).

2.2 TRADEMARKS
DAIVO BET /DOVO BET /TAC LONEX and DAIVONEX/DOVONEX are trademarks owned by LEO Pharma A/S (or its subsidiaries).

2.3 STUDY AUTHENTICATION
A form will be signed by the International Clinical trial Manager (ICTM) to confirm that this report provides a true and accurate record of results obtained and that the clinical trial 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
- national rules/regulations
- the approved (Consolidated) Clinical Study Protocol
- LEO Pharma Standard Operating Procedures

The signed form is included as an appendix to the main Clinical Study Report.
3 SYNOPSIS

Name of Sponsor/Manufacturer:
LEO Pharma A/S

Name of Investigational Product/Finished Product, if available:
DAIVOBET/DOVOBET gel (LEO 80185)

Name of Active Substance:
Calcipotriol + Betamethasone Dipropionate

Title of study/Protocol Code Number:
Efficacy and Safety of Calcipotriol plus Betamethasone Dipropionate Gel Compared with Tacalcitol Ointment and the Gel Vehicle Alone in Patients with Psoriasis Vulgaris

LEO 80185-G21

International Co-ordinating Investigator:
Dr. [Redacted], MD, [Redacted], Canada

Centre details:
Multicentre study conducted at 18 centres in Canada

Publication references:
To be decided

Study period details:
First subject first visit: 09 April 2008
Last subject last visit: 25 February 2009

Phase of development:
III

Objectives/hypothesis, if applicable:
The primary objective was to compare the efficacy of once daily treatment for up to 8 weeks of DAIVOBET/DOVOBET gel with tacalcitol 4 mcg/g ointment and the gel vehicle alone in subjects with psoriasis vulgaris on the body. Secondary objectives were to compare the safety of DAIVOBET/DOVOBET gel versus tacalcitol ointment and the gel vehicle alone, to investigate the occurrence and the time to relapse and occurrence of rebound after end of treatment in subjects with ‘controlled disease’ and to obtain quality of life data on subjects treated with DAIVOBET/DOVOBET gel, tacalcitol ointment and the gel vehicle alone.

Study methodology:
Multi-centre, prospective, randomised, Investigator-blind, active and vehicle controlled, 3-arm, parallel group 8 week study followed by an observation phase of up to 8 weeks in subjects with psoriasis vulgaris on the body. Subjects were randomised in a 2:2:1 ratio to receive once daily treatment for up to 8 weeks with either 1) DAIVOBET/DOVOBET gel or
2) Tacalcitol ointment OR 3) Gel vehicle. Prior to randomisation (Visit 1), a washout period (up to 4 weeks = 28 days) was completed if the subject was treated, or had recently been treated, with anti-psoriatic treatments or other relevant medication, as defined in the exclusion criteria. During the Treatment Phase, Visits were performed at baseline (Day 0) and at week 1, 2, 4, 6 and 8. If a subject cleared according to the Investigator’s global assessment of disease severity before week 8, the subject continued in the study and used study medication, as required, until the end of week 8. The initial study period was followed by a treatment-free observation period of 8 weeks for subjects who were graded to have ‘controlled disease’ (‘clear’ or ‘almost clear’) by the Investigator’s global assessment of disease severity at week 8. This was to investigate the occurrence and the time to relapse and occurrence of rebound. Visits took place at week 10, 12 and 16. An extra visit was scheduled for those subjects who experienced a worsening of body psoriasis and needed to reinitiate treatment between the two scheduled visits. Subjects who relapsed in the observation period, as verified by the Investigator, completed the trial at that visit and were given treatment according to the Investigator’s discretion. A follow-up visit took place 14 (± 2) days after the subject’s last on-treatment visit if a treatment related adverse event (possible, probable or not assessable relationship to study medication) was ongoing. Efficacy assessments including the investigator’s and the patient’s global assessment of disease severity and the investigator’s assessment of extent and clinical signs (redness, thickness and scaliness) were performed at all visits. Safety assessments were performed at all post randomisation visits.

Number of subjects enrolled:
A total of 450 subjects were planned: 180 subjects in the DAIVOBET/DOVOBET gel treatment group, 180 subjects in the tacalcitol ointment treatment group and 90 subjects in the gel vehicle treatment group. A total of 458 subjects were randomised: 183 subjects to DAIVOBET/DOVOBET gel, 184 subjects to tacalcitol ointment and 91 subjects in the gel vehicle.

Diagnosis and main criteria for subject selection:
Hospital out-patients or patients attending the private practice of a dermatologist, aged 18 years or above, with a diagnosis of psoriasis vulgaris on the trunk and/or limbs amenable to
### Investigational Product:

**DAIVOBET/DOVOBET gel (LEO 80185)**

- **Name of Active Substance:** Calcipotriol + Betamethasone Dipropionate

### Duration of Treatment:

The treatment period lasted for up to 8 weeks followed by a treatment free, observation period, of up to 8 weeks.

### Criteria for Evaluation:

#### Efficacy:

- **Primary response criterion:**
  - Subjects with ‘controlled disease’ (‘clear’ or ‘almost clear’ disease) according to Investigator’s global assessment of disease severity at week 8

- **Secondary response criteria:**
  - Subjects with ‘controlled disease’ according to the Investigator’s global assessment of disease severity at week 4
  - The percentage change in PASI from baseline to week 4 and 8
  - Subjects with relapse during the study and time to relapse
  - Subjects with rebound during the study

#### Quality of Life:

- Change in quality of life from baseline to week 4 and 8 using SF-36 (v2) and Skindex-16

#### Safety:

- Any reported adverse events or any reported adverse drug reactions. Reasons for withdrawal
The primary response criterion was analysed based on the full analysis set and per protocol analysis set. Two hypotheses were tested in sequential order: 1) DAVOBET/DOVOBET gel was superior to gel vehicle and 2) DAVOBET/DOVOBET gel was superior to tacalcitol ointment, for the proportion of subjects with ‘controlled disease’ at week 8 according to the Investigator’s global assessment of disease severity. The second hypothesis was only tested if the first test was significant (p<0.05). Testing was conducted at the 5% level of significance using the Cochran-Mantel-Haenszel (CMH) test adjusting for centre. For the secondary response criteria, the proportion of subjects with ‘controlled disease’ at week 4 according to the Investigator’s global assessment of disease severity was compared between the treatment groups using the CMH test. Analysis of variance (ANOVA) was used to compare the treatment groups for the percentage change in PASI at week 4 and 8 and quality of life measurements at week 4 and 8. Paired t-tests were used to analyse change in quality of life within treatment groups.

Safety analysis was based on the safety analysis set. The proportions of subjects who experienced adverse events and adverse drug reactions were compared between the treatment groups using chi-square tests.

Summary – Conclusions

Efficacy results:

A total of 458 subjects (mean age 51.6 years [range 18 to 82], 62.2% male, 93.9% white and 68.3% moderate, 29.5% severe and 2.2% very severe disease) were randomised and 398 completed the 8 week double blind treatment phase. The proportion of subjects who achieved ‘controlled disease’ at week 8 (LOCF) in the DAVOBET/DOVOBET gel group was 39.9% compared with 5.5% in the gel vehicle group and 17.9% in the tacalcitol group. DAVOBET/DOVOBET gel was statistically significantly more effective than the gel vehicle (OR 13.9; 95% CI 4.99 to 38.7; p<0.001) and the sequential test versus tacalcitol also showed that DAVOBET/DOVOBET gel was more effective (OR 3.42; 95% CI 2.05 to 5.70; p<0.001). There were no treatment by centre interactions (p>0.10). The analysis of the
per protocol analysis set supported the results for the full analysis set. The results for the secondary response criteria in the treatment phase of the study were as follows:

<table>
<thead>
<tr>
<th>Controlled Disease (IGA)N (%)</th>
<th>DAIVOBET Gel (N=183)</th>
<th>TACALCITOL (N=184)</th>
<th>GEL VEHICLE (N=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WEEK 4 (LOCF)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEAN % CHANGE IN PASI FROM BASELINE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WEEK 4</td>
<td>-53.1</td>
<td>-37.3*</td>
<td>-13.3*</td>
</tr>
<tr>
<td>WEEK 8</td>
<td>-57.0</td>
<td>-41.9*</td>
<td>-17.9*</td>
</tr>
<tr>
<td>* COMPARISON STATISTICALLY SIGNIFICANT IN FAVOUR OF DAIVOBET GEL</td>
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</table>

Among the subjects that entered the observation phase at the end of the 8-week treatment phase the occurrence of relapse and rebound was as follows:

<table>
<thead>
<tr>
<th>Relapse N(%)</th>
<th>DAIVOBET Gel (N=67)</th>
<th>TACALCITOL (N=31)</th>
<th>GEL VEHICLE (N=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RELAPSE</td>
<td>28 (41.8)</td>
<td>7 (22.6)</td>
<td>3 (60.0)</td>
</tr>
<tr>
<td>MEDIAN TIME TO RELAPSE</td>
<td>63 DAYS</td>
<td>61 DAYS</td>
<td>61 DAYS</td>
</tr>
<tr>
<td>REBOUND N(%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Quality of Life:

In the SF-36 (v2) general health questionnaire the scores for the Physical Component Summary and Mental Component Summary were similar among the groups. When comparing response within the DAIVOBET/DOVOBET gel group, there were no significant changes from baseline in the Physical Component Summary but the change from baseline in the Mental Component Summary score was statistically significant at Weeks 4 and 8 (p=0.002 and p=0.012 respectively). For the skin disease specific questionnaire (Skindex-16) the changes from baseline within each treatment group were statistically significant for total score in all treatment groups at Weeks 4 and 8 (p<0.001 for both timepoints). There were statistically significant differences in favour of DAIVOBET/DOVOBET gel at Weeks 4 and 8 compared with tacalcitol (p= 0.010 and p=0.007 respectively) and also compared with the gel vehicle (p<0.001 at both timepoints).
In the treatment phase of the study, the proportion of patients with at least one adverse event was similar and not statistically significant between the DAIVOBET/DOVOBET gel group (72 subjects, 39.6%) versus the tacalcitol group (83 subjects, 45.1%, p= 0.28) and versus the gel vehicle group (35 subjects, 38.5%, p=0.86). The proportion of subjects with at least one adverse drug reaction was significantly lower in the DAIVOBET/DOVOBET gel group than in the other two groups; 16 (8.8%) versus 29 (15.8%), p=0.042 for tacalcitol and 16 (8.8%) versus 16 (17.6%), p=0.033 for the gel vehicle. A similar pattern was observed for lesional/perilesional adverse events on the body. Pruritus and skin irritation were the most frequently reported adverse drug reactions and lesional/perilesional adverse events in the DAIVOBET/DOVOBET gel group; both reported by 6 (3.3) subjects. Pruritus was also the most common adverse drug reaction and lesional/perilesional adverse event in the other two groups and was reported with a higher frequency than in the DAIVOBET/DOVOBET gel group. In the tacalcitol group pruritus was reported as an adverse drug reaction by 11 (6.0%) subjects and as a lesional/perilesional adverse event by 12 (6.5%) subjects. In the gel vehicle group the same number 6 (6.6%) subjects reported pruritus as an adverse drug reaction and a lesional/perilesional adverse event. The other most common adverse drug reaction in the tacalcitol group was skin irritation reported by 4 (2.2%) subjects and in the gel vehicle group it was burning sensation reported by 4 (4.4%) subjects. Withdrawals due to adverse events in the treatment phase were lower in the DAIVOBET/DOVOBET gel group 3 (1.6%) subjects compared with 4 (2.2%) in the tacalcitol group and 4 (4.4%) in the gel vehicle group. In the observation phase no patients withdrew due to adverse events and the incidences of adverse events in the DAIVOBET/DOVOBET gel and the gel vehicle groups were not statistically significantly different (p=0.91) but there was a trend towards a higher incidence in the tacalcitol group (p=0.055). There were no deaths or treatment related serious adverse events.

Conclusion:

DAIVOBET/DOVOBET gel was statistically significantly more effective than the gel vehicle and tacalcitol ointment in the treatment of psoriasis vulgaris on the body. The incidence of adverse drug reactions and lesional/perilesional adverse events was also
<table>
<thead>
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<th>Name of Sponsor/Manufacturer:</th>
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<th>Name of Investigational Product/Finished Product, if available:</th>
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<td>DAIVOBET/DOVOBET gel (LEO 80185)</td>
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<th>Name of Active Substance:</th>
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<td>Calcipotriol + Betamethasone Dipropionate</td>
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Significantly lower resulting in a more favourable benefit/risk ratio for DAIVOBET/DOVOBET gel compared with the gel vehicle and tacalcitol ointment.

Report date: 16 June 2009
### 3.1 SCHEDULE/CHART OF STUDY PROCEDURES

#### 3.1.1 Schedule of Study Procedures

<table>
<thead>
<tr>
<th>Visit</th>
<th>Treatment</th>
<th>Observation</th>
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<tbody>
<tr>
<td></td>
<td>Wash-out</td>
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<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>7±2</td>
<td>14±2</td>
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<tr>
<td></td>
<td>28±2</td>
<td>42±2</td>
</tr>
<tr>
<td></td>
<td>56±2</td>
<td>+14±2</td>
</tr>
<tr>
<td></td>
<td>70±2</td>
<td>84±2</td>
</tr>
<tr>
<td>Day</td>
<td>70±2</td>
<td>84±2</td>
</tr>
<tr>
<td></td>
<td>112±2</td>
<td></td>
</tr>
<tr>
<td>Week</td>
<td>1</td>
<td>2</td>
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<tr>
<td></td>
<td>4</td>
<td>6</td>
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<td>8</td>
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<td>7</td>
<td>8</td>
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<td>9</td>
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</tr>
</tbody>
</table>

- **Informed consent**: x
- **Inclusion criteria**: x
- **Exclusion criteria**: x
- **Demographics**: x
- **Medical history**: x
- **Physical examination**: x
- **Concomitant medication**: x
- **Concurrent diagnoses**: x
- **Pregnancy test**: x
- **Randomisation**: x
- **Investigator’s global assessment of disease severity**: x
- **Investigator’s assessment of the extent of psoriasis vulgaris**: x
- **Investigator’s assessment of extent and severity of clinical signs**: x
- **Subject’s global assessment of disease severity**: x
- **Quality of Life**: x
- **Dispensing of Investigational Product**: x
- **Return of Investigational Product**: x
- **Compliance**: x
- **Adverse Event(s)**: x
- **Photography**: x
a) Informed consent was to be signed both by subject and (sub)investigator before any study related procedures, including washout
b) If female of childbearing potential
c) A washout period was to be completed if the subject received anti-psoriatic treatments or other relevant medication, as defined by the exclusion criteria. Duration of the washout phase could not exceed 4 weeks (28 days)
d) An extra visit was scheduled during observation phase if a subject needed to re-initiate treatment
e) If an adverse event (serious or non-serious) classified as possibly or probably related to the study treatment or not assessable in relation to the study treatment was ongoing at the last on-treatment visit
f) SF-36 (v2) and Skindex-16 was used
g) Photos of psoriatic lesions was taken at few designated centres
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5 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

5.1 LIST OF ABBREVIATIONS

ADR  Adverse Drug Reaction
AE   Adverse Event
ATC  Anatomical Therapeutic Chemical
CI   Confidence Interval
CMH  Cochran-Mantel-Haenszel
CPMP Committee for Proprietary Medicinal Products
CRF  Case Report Form
CRO  Contract Research Organisation
DK   Denmark
eCRF Electronic Case Report Form
EU   European Union
GCP  Good Clinical Practice
HPA  Hypothalamic-pituitary-adrenal
ICH  International Conference on Harmonisation
IEC  Independent Ethics Committee
IL-2 Interleukin-2
IRB  Institutional Review Board
LOCF Last Observation Carried Forward
MedDRA Medical Dictionary for Regulatory Activities
OR   Odds ratio
PASI Psoriasis Area and Severity Index
PUVA Psoralen plus Ultraviolet light A
QoL  Quality of Life
SAE  Serious Adverse Event
SD   Standard Deviation
SF-36 SF-36v2™ (the 36-item Short Form Health Survey (Version2)) - a survey that measures general health-related quality of life
Skindex-16 Skindex-16 (a 16-item survey that measures skin specific quality of life)
SOC  System Organ Class
SOP  Standard Operating Procedure
TPD  Therapeutic Product Directorate
UVA  Ultraviolet light A
5.2 DEFINITION OF TERMS

Terms defined by ICH Guidelines are not mentioned here.

**Assessment**
A (cluster of) characteristic(s) measured and/or recorded for a subject.

**Certified**
An acknowledgement verifying accuracy signed and dated by a person competent to sign off documents related to clinical trials.

**Concomitant Medication**
Any medication taken by a subject apart from the investigational product(s).

**Enrolled Subject**
A patient/subject for whom informed consent has been obtained and a CRF number assigned.

**Fraud**
Fabrication of data, selective and undisclosed rejection of undesired results, substitution with fictitious data, deliberately incorrect use of statistical methods for the purposes of reaching other conclusions than those warranted by the data, misinterpretation of results and conclusions, plagiarism of results or entire articles from other researchers, misrepresentation of other researchers’ results, unwarranted authorship, and misleading application for positions or funds.

**International Clinical Trial Manager**
The person appointed by LEO to be the main international representative responsible for all aspects of a clinical trial.

**Investigator Agreement**
A contract between LEO and an investigator specifying the conditions for the co-operation in the clinical trial and the investigators’ responsibilities.

**Investigator Staff Signature Form**
A form on which subinvestigators and other trial-related site staff sign and date and the Investigator authorises their trial-related tasks/duties.
**Investigator Trial File**
The collection of trial documents required by LEO GCP SOPs, ICH Guidelines and/or regulatory requirements to be on file at the investigator site.

**LEO**
LEO (no suffix): Refers to the corporate organisation of LEO Pharma.

**Monitor**
A person appointed by LEO to carry out monitoring of a clinical trial.

**National Clinical Trial Manager**
The person appointed by LEO to be the national representative responsible for all aspects of a clinical trial within a country.

**PASI50**
At least 50% reduction in PASI from baseline

**PASI75**
At least 75% reduction in PASI from baseline

**Patient Identification List**
A summary list kept by the investigator in the Investigator Trial File that records the names of all patients/subjects enrolled and the date of enrolment in the trial at that centre, with the patient’s/subject’s corresponding CRF Book Number, to allow the investigator/institution to reveal the identity of any patient/subject, if required.

**Patient Screening Log**
A document kept by the investigator which identifies patients/subjects who entered pre-trial screening. Patient Screening Log is synonymous with Subject Screening Log.

**Subject Study Card**
A card given to a patient/subject by the trial centre at the time trial medication is first dispensed to a patient/subject, to identify that the patient/subject is receiving treatment with an investigational product.

**Randomisation Code List**
A list of (sequential) numbers to each of which a treatment is allocated (assigned). Treatment may be revealed as a code letter (e.g., A, B, ...) or by directly revealing the specific treatment (investigational product, e.g., Calcipotriol ointment).
**Response Criterion**
An assessment or a transformation of the assessment(s) described on a patient/subject level, for which a statistical analysis is performed, i.e., a P-value or a confidence interval is stated, or for which tabulation serves as important supportive evidence of efficacy/safety.

**Treatment Code Envelope**
A sealed letter/envelope containing the identification of an individual subject’s treatment/investigational product(s).
6 ETHICS

6.1 INDEPENDENT ETHICS COMMITTEE (IEC) OR INSTITUTIONAL REVIEW BOARD (IRB)

The protocol and any relevant amendments were approved by/received favourable opinion from relevant Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs).

A list of IECs/IRBs consulted and a copy of all approvals/favourable opinions is given in Appendix VI.

The appropriate Regulatory Authority(ies) was notified of/approved the trial, as required.

6.2 ETHICAL CONDUCT OF THE STUDY

The trial was conducted to conform to the principles of the Declaration of Helsinki as adopted by the 18th World Medical Assembly, 1964, and subsequent amendments.

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

Signed Informed Consent was obtained from the subjects, to record, collect, process and transfer (to EU and non-EU countries) data. Such data will be handled in accordance with any national legislation implementing the EU Data Protection Directive (95/46/EC).

6.3 SUBJECT INFORMATION AND INFORMED CONSENT

All subjects received written and verbal information concerning the trial. This information emphasised that participation in the trial was voluntary and that the subject could withdraw from the trial at any time and for any reason. All subjects were given an opportunity to ask questions and were given sufficient time to consider all relevant issues before consenting.

The subject’s signed and dated informed consent to participate in the trial was obtained prior to any trial related procedure being carried out.

A representative subject information sheet and informed consent form is provided in Appendix V.

All investigators signed an Investigator Agreement before the study to confirm the above.
7 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

7.1 REPORT AUTHOR(S)

[Name], BSc (Hons) FICR, [Department], [Address]

[Name], MSc Stat, [Department], [Address]

[Name], MD, [Department], [Address]

[Name], Ph.D, [Department], [Address]

7.2 INVESTIGATORS, TRIAL CENTRES AND CROS

7.2.1 International Co-ordinating Investigator

The International Co-ordinating Investigator was responsible for approval of the protocol, CRF and study report, on behalf of all investigators, and as agreed to in an International Co-ordinating Investigator Agreement.

[Name], MD, [Address]

7.2.2 National Co-ordinating Investigators

The investigators listed below were responsible for national issues relating to the study as agreed to in the National Co-ordinating Investigator Agreements.
7.2.3 Investigators

Each participating investigator was responsible for all aspects of the trial conduct at his/her site, and as agreed to in an Investigator Agreement signed prior to trial initiation.

If subinvestigators were delegated trial related tasks/duties, this was documented on the Investigator Staff Signature Form. The complete list of all participating investigators and (sub)investigators is provided appendix VII.

7.2.4 Contract Research Organisation(s)

was responsible for the electronic data capture helpdesk and unblinding services as agreed to in a Service Agreement/Contract.

7.2.5 Data Monitoring Committees

Not applicable.

7.3 COMPANY PERSONNEL

On behalf of LEO, only the Director, International Clinical Development, LEO, and the Head of Biostatistics Department, LEO HQ, were authorised to approve the Clinical Study Protocol and Consolidated Clinical Study Protocol(s) comprising any subsequent amendment(s).

7.3.1 International Clinical Trial Manager

, Ph.D., LEO Pharma Inc, 123 Commerce Valley East, Suite 400, Thornhill, Ontario, L3T 7W8 Canada,

7.3.2 National Clinical Trial Manager

, MD, Pharm.D., LEO Pharma Inc, 123 Commerce Valley East, Suite 400, Thornhill, Ontario, L3T 7W8 Canada,
8 INSURANCE AND LIABILITY

The subjects in the present study were covered by the product and general liability insurance of LEO or LEO itself in the event of trial related injury or death, in accordance with applicable law and with the CPMP Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) of 17 July 1996.

9 INTRODUCTION AND RATIONALE

The study was performed as a phase III clinical study of DAIVOBET/DOVOBET gel (LEO80185), a two-compound product containing calcipotriol plus betamethasone dipropionate in a gel vehicle, in the treatment of psoriasis vulgaris on the body. The study was conducted in accordance with applicable national regulatory requirements.

DAIVOBET/DOVOBET gel is a further development of DAIVOBET/DOVOBET ointment. DAIVOBET/DOVOBET ointment has been approved in the EU through a mutual recognition procedure, by the Therapeutic Product Directorate (TPD) in Canada and by the Food and Drug Administration (FDA) in the US, as a topical, once daily treatment for psoriasis vulgaris. DAIVOBET/DOVOBET ointment was first launched in October 2001 in Denmark.

9.1 PSORIASIS VULGARIS

Psoriasis vulgaris is one of the most common chronic skin diseases, with a prevalence generally estimated at between 1–3% of the population (1, 2). It is characterised by sharply
marginated areas of affected skin which appear thickened, red and scaly. The scalp, elbows, knees, lower back, hands, feet and nails are commonly affected sites. About 80% of affected subjects complain about itching (3). Psoriasis is a significant problem in everyday life for the affected subjects, and has a significant impact on their health-related quality of life - an impact that increases with increasing skin involvement (4).

The psoriatic appearance of the skin is produced by an increased rate of epidermal proliferation with impaired differentiation of keratinocytes resulting in a thickened, undulating epidermis covered by a thickened, parakeratotic stratum corneum. Dermal capillaries become tortuous and dilated and there is infiltration of both epidermis and dermis with immunologically active cells (5, 6). Evidence from several sources has shown that the presence of activated T-cells in the skin plays an important role in the development of psoriasis (7). There is infiltration of CD4+ T-cells into the epidermis and CD8+ T-cells into the dermis, which are thought to be responsible for the development and maintenance of the psoriatic lesion. The signal inducing keratinocyte proliferation is probably mediated by Th1 cytokines such as interferon gamma and interleukin-2 (IL-2). Adhesion molecules on the endothelial cells and keratinocytes are also up-regulated in psoriasis, thereby causing migration of T-cells from the capillaries into the dermis where they are bound and may induce the psoriatic process (7).

Psoriasis vulgaris is a chronic disease for which there is currently no cure. Treatment is targeted at reducing the signs of erythema, scaling and infiltration and associated symptoms such as pruritus.

Topical corticosteroids and vitamin D analogues are effective and most commonly used therapies in treatment of psoriasis vulgaris. Adverse reactions associated with corticosteroids include skin atrophy, irreversible striae, telangiectasia, perioral dermatitis, glaucoma and acne. Additionally, continued corticosteroid therapy may result in tachyphylaxis, a condition with decreasing response to treatment. A rebound of disease may also occur if corticosteroid therapy is abruptly withdrawn. A common adverse reaction associated with Vitamin D therapy (calcipotriol, calcitriol, tacalcitol) is skin irritation.

Phototherapy (psoralen combined with ultraviolet radiation A (PUVA), broad-band or narrow-band ultraviolet radiation B (UVB)) and systemic treatments (methotrexate, oral retinoids and cyclosporine) are generally required in extensive, therapy-resistant and socially disabling disease and in the serious forms of erythrodermic and pustular psoriasis (8, 3). Among newest therapies are therapies with biological agents, which reduce the pathogenic effects of T-cells, either by a direct effect on the T-cells or by inhibition of their secreted
cytokines. Currently four such biological products (alefacept, etanercept, infliximab and ustekinumab) have been approved in EU, Canada and/or US for the treatment of moderate to severe chronic plaque psoriasis.

9.2 INVESTIGATIONAL PRODUCT DESCRIPTION

Calcipotriol
Calcipotriol is a Vitamin D analogue manufactured by LEO Pharma A/S. It is the active component of DAIVONEX/DOVONEX, which has been widely available world-wide for treatment of psoriasis since it was first approved in 1991.

Due to its main effects of inhibition of cell proliferation, stimulation of cell differentiation and regulation of inflammatory response, calcipotriol reverses the signs and symptoms associated with psoriasis vulgaris. Calcipotriol has been thoroughly investigated in preclinical safety studies and clinical trials, and there is an extensive post-marketing understanding available.

A number of short term studies have been conducted with calcipotriol ointment 50 mcg/g applied twice daily in psoriasis vulgaris of trunk and limbs. Calcipotriol ointment has been shown to be more effective than short contact dithranol (9) and coal tar treatment (10) and at least as effective as betamethasone 17-valerate 0.1% ointment (11, 12). It is well tolerated, adverse events being mainly application related; lesional/perilesional irritation that tended to be mild and subside despite continuation of treatment.

Long term efficacy and safety has been confirmed in four studies using calcipotriol ointment for up to 1 year (13, 14, 15, 16). In all trials, the most frequent characterisation of treatment related adverse events was burning/stinging/tingling occurring in up to 20% of the subjects. Laboratory test results showed no treatment related changes on blood parameters.

Overdosage with calcipotriol can cause systemic side effects in the form of hypercalcaemia, attributable to the effect of Vitamin D analogues on the calcium metabolism. However, extensive experience with topical use of calcipotriol in psoriasis has demonstrated no impact on calcium metabolism, when used in amounts of up to 100 g DAIVONEX/DOVONEX per week. Furthermore a broad safety margin has been demonstrated (17).
**Betamethasone dipropionate**

Betamethasone dipropionate is a synthetic fluorinated corticosteroid classified as a potent (WHO Group III) steroid. It has been available on prescription worldwide for many years for the treatment of various dermatological disorders including psoriasis vulgaris (18, 19, 20). It is widely used also in the treatment of scalp psoriasis. Like other corticosteroids it exerts its effect by suppressing various components of the inflammatory reaction of the disease.

Betamethasone dipropionate has been shown to have metabolic and toxicological effects typical for corticosteroids. The safety profile of betamethasone dipropionate is well established and an extensive clinical database demonstrates that it is a safe product for topical treatment of psoriasis. Adverse events with topical corticosteroids are generally local and include itching, skin atrophy and striae of the skin. Excessive and prolonged use may result in suppression of the Hypothalamic-Pituitary-Adrenal (HPA) axis which is generally reversible.

**DAIVOBET/DOVOBET gel (LEO 80185)**

DAIVOBET/DOVOBET gel is a combination product containing calcipotriol 50 mcg/g (as hydrate) and betamethasone 0.5 mg/g (as dipropionate) developed for topical treatment of psoriasis on the scalp and on the body.

Another combination product, Calcipotriol plus betamethasone dipropionate (DAIVOBET/DOVOBET/TACLONEX) ointment indicated for topical treatment of psoriasis vulgaris once daily, contains the same active substances (calcipotriol and betamethasone dipropionate) in the same concentration but in a different vehicle. As the strengths of calcipotriol and betamethasone dipropionate are identical in the two products the pharmacological and toxicological behaviour of the two well-established drug substances in DAIVOBET/DOVOBET gel is expected to be similar to the behaviour of DAIVOBET/DOVOBET/TACLONEX ointment.

A full Phase 1 programme consisting of seven studies on local tolerability and systemic safety of DAIVOBET/DOVOBET gel has been finalised. The studies are summarised in the Investigator’s Brochure: DAIVOBET/DOVOBET gel (LEO 80185) in Psoriasis Vulgaris, Edition No 7.

In summary, the studies showed that DAIVOBET/DOVOBET gel was not phototoxic or irritant. No sensitisation or photo allergic potential was identified. The atrophogenic potential of betamethasone dipropionate in DAIVOBET/DOVOBET gel was not statistically significantly different from a marketed WHO group III corticosteroid, Diprosone® ointment.
In general, ointments are thought to be more effective than gels due to the occlusive effect that enhances penetration through the skin (21). This also appears to be the case for the calcipotriol plus betamethasone dipropionate formulations. The vasoconstrictive effect of DAIVOBET/DOVOBET ointment was shown to be bioequivalent to that of a potent (WHO group III) corticosteroid, Diprosone® ointment (22), whereas LEO 80185 gel was less potent than Diprosone® ointment in the same experimental model (23). In addition, in two clinical psoriasis plaque test studies (24, 25), the antipsoriatic effect of calcipotriol plus betamethasone dipropionate gel was less than that of DAIVOBET/DOVOBET ointment. Nevertheless, it is expected that some subjects will find the gel formulation more cosmetically appealing than the ointment formulation, which might increase compliance and thereby the treatment response.

DAIVOBET/DOVOBET gel has been tested in five phase 3 studies (26, 27, 28, 29, 30) on scalp psoriasis and two clinical proof of concept studies (31, 32) on scalp and body psoriasis, respectively. The results from all clinical studies showed that DAIVOBET/DOVOBET gel is significantly more effective than monotherapy with betamethasone dipropionate in gel vehicle, calcipotriol (in the gel vehicle or as the marketed scalp solution) and the gel vehicle alone in the treatment of psoriasis vulgaris on the body and the scalp.

Overall, it can be concluded that based on existing preclinical data, extensive clinical experience with calcipotriol and betamethasone (individually and in combination), DAIVOBET/DOVOBET gel is considered to be well tolerated by humans. Combining calcipotriol and betamethasone dipropionate in the new vehicle is not expected to have new toxicological consequences and DAIVOBET/DOVOBET gel is considered to be a safe product for topical treatment of psoriasis.

DAIVOBET/DOVOBET gel was approved in 2008 for the treatment of scalp psoriasis in Europe the US and Canada and is marketed under the tradenames XAMIOL gel in Europe and Canada and TACLONEX SCALP suspension in the US.

**9.3 STUDY RATIONALE**

Although originally developed for use on the scalp, DAIVOBET/DOVOBET gel has physical properties suitable for the treatment of psoriasis on the trunk and limbs. The gel could be a more cosmetically acceptable alternative to DAIVOBET/DOVOBET/TACLONEX ointment, as it is less greasy than the ointment formulation.
DAIVOBET/DOVOBET/TACLONEX ointment has proven highly effective in the treatment of psoriasis vulgaris on trunk and limbs with an improved benefit/safety ratio compared to the one of each active component used as mono-therapy. The assumption is that calcipotriol plus betamethasone dipropionate combined in a gel vehicle would also be effective in the treatment of psoriasis vulgaris - a hypothesis supported by the results of the proof-of-concept study in psoriasis vulgaris on the body (32).

**Scientific rationale**
Calcipotriol is expected to exert its effect on psoriasis by inhibiting the cell proliferation, stimulating the cell differentiation and suppressing components of the inflammatory response, thereby reversing the signs and symptoms associated with the disease. Betamethasone dipropionate is expected to exert its effect on psoriasis by suppressing various components of the inflammatory response.

Using calcipotriol and betamethasone dipropionate in combination has been shown to result in an additive effect in the treatment of psoriasis vulgaris on the trunk and limbs (33, 34, 35, 36). By simultaneous use of the two active components it is expected that betamethasone dipropionate could counteract the local skin irritation that calcipotriol exhibits in some subjects, thereby allowing calcipotriol to exert its beneficial effects. On the other hand calcipotriol may reduce the amount of corticosteroid required due to a possible additive effect and thus reduce the risk of steroid-related adverse effects. Combining the two compounds in a gel vehicle with favourable cosmetic properties might improve subject compliance resulting in a better treatment response.

**Design**
The study was a multi-centre, prospective, randomised, Investigator-blind, active- and vehicle-controlled, 3-arm, parallel group, 8-week phase 3 clinical study investigating the efficacy and safety of DAIVOBET/DOVOBET gel in the treatment of psoriasis vulgaris on the body. Following the treatment phase, at week 8, subjects who had ‘controlled disease’ according to the Investigator’s global assessment of disease severity (IGA) entered a treatment-free observation period of up to 8 weeks in order to investigate the occurrence and the time to relapse and occurrence of rebound.

**Subjects**
Subjects with a clinical diagnosis of psoriasis vulgaris amenable to topical treatment graded as at least moderate severity by the IGA were eligible for enrolment in the study. This ensured
that subjects had a potential to achieve a change of at least two disease severity levels in order to meet the success criterion of ‘controlled disease’ (‘clear’ or ‘almost clear’ on the Investigator’s global assessment scale). From a clinical point of view, the improvement of at least two severity levels was considered a meaningful measure of success. However, it was expected that subjects with psoriasis vulgaris graded as “mild” would have a similar benefit from the treatment and thus, the trial population was expected to be representative of the population who would be considered for treatment with DAIVOBET/DOVOBET gel in future clinical practice.

**Treatment duration**

The treatment duration of 8 weeks was considered appropriate to obtain sufficient data on efficacy and safety of evaluated Investigational Products. This treatment duration was based on the results of a phase II, proof of concept study (32), which showed continuous improvement in the IGA up to week 8. A treatment duration of 8 weeks has been shown to be safe and effective in several studies of DAIVOBET/DOVOBET gel used on the scalp (26, 27, 28, 29, 30, 31) and in one study of DAIVOBET/DOVOBET/TACLONEX ointment on trunk and limbs (37).

Subjects whose psoriasis cleared at any of the on-treatment visits before the last visit at week 8, continued in the study and applied treatment as required in order to obtain an 8 weeks assessment for all subjects.

**Dosing**

A once daily treatment regimen was chosen as this was considered more convenient for the subject and was shown to be effective in previous studies. It decreases drug exposure and time spent on application and thus, probably enhances subject compliance.

**Assessments**

The Investigator’s global assessment of the disease severity was chosen as the primary parameter to measure efficacy.

Investigator’s global assessment is a static skin score system, consisting of a six point scale varying from ‘clear’ to ‘very severe’. The primary endpoint pertaining to the Investigator’s global assessment was subjects with ‘controlled disease’ (i.e. ‘clear’ or ‘almost clear’). The percentage of subjects who achieved the results of ‘clear’ and ‘almost clear’ was regarded as the best evidence of efficacy (38). Comparison of the proportion of subjects with ‘controlled disease’ between the treatment groups reflect the difference in the effect of the treatments.
In order to facilitate standardisation of assessments and to ensure less inter-rate variability, the Investigator’s global assessment scale contains detailed description of morphological characteristics of each severity category, thus assisting the Investigator in evaluation.

The Psoriasis Area and Severity Index (PASI), used as a secondary response criterion, is a well established index that has been used in all previous studies of psoriasis on trunk and/or limbs conducted by LEO.

**Concomitant treatments**

During the course of the study, subjects could not use any concomitant treatments with a possible effect on the psoriasis on trunk and/or limbs. This included various systemic treatments, but also topical treatments against e.g., eczema or psoriasis on the face, scalp and flexures which might have a systemic effect on the psoriasis lesions on trunk and/or limbs, i.e. potent WHO group III (face and flexures only) or very potent WHO group IV corticosteroids, or treatments which would limit the use of study drug due to safety reasons, i.e. vitamin D analogues. All other topical treatments were allowed on the face, scalp and flexures, thereby maintaining a treatment option during the study for subjects who also suffered from psoriasis elsewhere or from other dermatological disorders.

Subjects were not allowed to use any other vitamin D analogues such as calcipotriol or calcitriol in order to allow use of DAIVOBET/DOVOBET gel up to the maximum dose (100 g/week) without risking development of hypercalcaemia. Furthermore, considering the current product monograph for tacalcitol, subjects were not allowed to use high dose Vitamin D preparations (in excess of 500 IU Vitamin D).

A stable concomitant treatment regimen (no start or change of dosage during the study) with e.g., beta blockers, anti-malaria drugs, ACE inhibitors and lithium was allowed during the study. Even though these drugs have a potential effect on psoriasis, they are not known to cause fluctuations in the disease severity and therefore they were not considered to affect the subject’s response to study medication.

**Relapse and rebound**

As a secondary objective, relapse and rebound was investigated in those subjects who responded to the treatment. It has been shown that most relapses occur within the first months after discontinuation of treatment with topical corticosteroid (39). Therefore, an 8-week treatment-free observation period was expected to be sufficient to investigate the occurrence
and the time to relapse and occurrence of rebound after discontinuation of the Investigational Products. The evaluation of relapse and rebound was done in accordance with currently accepted definitions (39).

**Quality of Life**

To support the clinical decision-making when treating subjects, it is important to consider quality of life issues. Therefore, evaluation of quality of life (QoL) was included in this study. Both a general and skin specific questionnaires were included to assess the impact of a treatment of both general and skin-related QoL parameters. In this study, the current version of SF-36 (v2) was included to provide indication of the quality of life based on general health status of the subject and a Skindex-16 questionnaire was included in order to measure specific factors influencing the quality of life for subjects with skin disease.
10 STUDY OBJECTIVES

10.1 PRIMARY OBJECTIVE
The primary objective was to compare the efficacy of once daily treatment for up to 8 weeks of DAIVOBET/DOVOBET gel with tacalcitol ointment and the gel vehicle alone in subjects with psoriasis vulgaris on the body.

The primary response criterion was the proportion of subjects with ‘controlled disease’ (‘clear’ or ‘almost clear’) as measured by the IGA at week 8.

10.2 SECONDARY OBJECTIVES
The secondary objectives were:
- To compare safety of once daily treatment for up to 8 weeks of DAIVOBET/DOVOBET gel with tacalcitol ointment and the gel vehicle alone in subjects with psoriasis vulgaris on the body.
- To investigate the occurrence of and the time to relapse and occurrence of rebound after the end of treatment in subjects with ‘controlled disease’.
- To obtain data on the quality of life of subjects treated with DAIVOBET/DOVOBET gel, tacalcitol ointment and the gel vehicle alone, using quality of life questionnaires.

11 INVESTIGATIONAL PLAN
The Study Protocol is presented in Appendix I and the unique pages of the CRF Book are presented in Appendix II.

11.1 STUDY DESIGN
The study was a multi-centre, prospective, randomised, Investigator-blind, active- and vehicle-controlled, 3-arm, parallel group, 8-week phase III clinical study in subjects with psoriasis vulgaris on the trunk and/or limbs.

Subjects were randomised in a 2:2:1 ratio to one of the following three treatments applied once daily for up to 8 weeks:
1. DAIVOBET/DOVOBET gel
2. Tacalcitol ointment
3. Gel vehicle
11.1.1 Washout phase
Prior to randomisation, the subject entered a washout phase (if required) where anti-psoriatic treatments and other relevant medication were discontinued as defined by exclusion criteria. The duration of the washout period varied from 2 weeks up to 4 weeks (28 days) depending on which treatment the subject received. A subject was not eligible for washout if they had been treated with biologics recently and required more than 28 days washout period.

11.1.2 Treatment Phase
The treatment phase was initiated at Visit 1 (Day 0, baseline) when the subject was randomised to one of the three treatment groups. The treatment period continued for 56 days (8 weeks) and included 6 visits: Days 0, 7 (± 2), 14 (± 2), 28 (± 2), 42 (± 2) and 56 (± 2). The Investigators aimed to comply with the scheduled visit days. If the visit window of ± 2 days for any of Visit 2 to Visit 6 and Follow-up was not met, the Investigator had to list the reason in the subject’s medical record. Visit 2 to 6 which the subject attended while using the study medication were defined as on-treatment visits.

If a subject cleared according to the IGA before 8 weeks of treatment, the subject continued in the study and used study medication as required until the end of week 8.

11.1.3 Observation Phase
The treatment period was followed by an observation period of 8 weeks for subjects with ‘controlled disease’ according to the IGA at week 8. During this treatment-free observation period, the subject was evaluated at Weeks 10, 12 and 16 to investigate the occurrence and the time of disease relapse, and occurrence of disease rebound. An extra visit was scheduled during this period if a subject is experienced a worsening of psoriasis and needed to reinitiate treatment between two scheduled visits.

Subjects who experienced relapse/rebound of the disease during the observation period, as verified by the Investigator, completed the study, and were given treatment according to the Investigator’s discretion.

Subjects who continued in the observation period will also be followed-up for adverse events during that period.

11.1.4 Follow-up Phase
Subjects with an ongoing (serious or non-serious) adverse event at the last on-treatment visit classified as possibly or probably related to the Investigational Products or not assessable in
relation to the Investigational Products had a follow-up visit/contact. This follow-up visit/contact was made either as a telephone call or as a regular visit according to the Investigator’s discretion \((\pm 2)\) days after the last on-treatment visit, unless final outcome of the event had been determined in the meantime.

Serious adverse events were followed up until final outcome, and details for follow-up requirements for serious adverse events in general are given in Section 11.7.6.2.

### 11.1.5 Study Flow Chart

![Study Flow Chart]

Visits 1-6 are within the Treatment Phase.
Visits 7-9 are within the Observation Phase.

The dashed lines indicate that the washout and follow-up period (FU) are not mandatory phases, but only applicable in the cases described above.

### 11.2 TIME SCHEDULE

The planned time schedule was as follows:
Planned date of enrolment of first subject: February 2008
Planned date of enrolment of last subject: July 2008
Planned date of completion of last subject: November 2008

The actual date of enrolment of the first subject was 09-APR-2008 and the last subject was enrolled on 17-NOV-2008. The last subject completed the last visit on 25-FEB-2009.

11.3 NUMBER OF SUBJECTS/SAMPLE SIZE
A total of 450 subjects were planned to be enrolled in the study and randomised in a 2:2:1 ratio: 180 subjects in the DAIVOBET/DOVOBET gel treatment group, 180 subjects in the tacalcitol ointment treatment group and 90 subjects in the gel vehicle treatment group.

In previous studies with designs comparable to the design of this study the following estimates were obtained: in one phase II study with DAIVOBET/DOVOBET gel (MBL 0202 INT (32) the percentage of subjects having ‘controlled disease’ according to IGA was 28% in the DAIVOBET/DOVOBET gel treatment group and 0% in the gel vehicle treatment group. In one study with tacalcitol ointment (MCB 0001 INT (40), the average reduction in PASI was 40%. Based on studies where both PASI and Investigator’s global assessment were assessed (MCB 0003 INT (35), MBL 0202 INT (32), this is assumed to correspond to a ‘controlled disease’ proportion of 11-15%.

With 180 subjects in DAIVOBET/DOVOBET gel treatment group and 180 subjects in the tacalcitol ointment treatment group, a chi-square test would have 82% power to reject the null hypothesis of no difference between the two treatment groups regarding the primary response criterion, subjects with ‘controlled disease’ (‘clear’ or ‘almost clear’ disease) according to the IGA at week 8. Likewise, with 90 subjects in the gel vehicle treatment group, a chi-square test would have 99% power to reject the null hypothesis of no difference between the DAIVOBET/DOVOBET gel treatment group and the gel vehicle group. Thus, the overall power would be approximately 81%. The sample size calculation assumed that 28% of the subjects in DAIVOBET/DOVOBET gel treatment group, 15% of the subjects in the tacalcitol ointment treatment group and 5% of the subjects in the gel vehicle treatment group had ‘controlled disease’ and that a two-tailed significance level, \( \alpha \) of 0.05 was used. No adjustment of \( \alpha \)-level was needed since the multiple comparisons were performed by testing the two hypotheses in sequential order (see section 11.10.1.4.1 for details on the primary analysis).

Each centre aimed to recruit a minimum of 15 subjects and no centre was to recruit more than 45 subjects.
11.4 CRITERIA FOR SUBJECT SELECTION (IN- AND EXCLUSION)

11.4.1 Inclusion Criteria
1. Signed and dated informed consent obtained prior to any trial related procedure, including washout
2. Clinical diagnosis of psoriasis vulgaris involving trunk and/or arms and/or legs amenable to treatment with a maximum of 100 g of DAILOBET/DOVOBET gel per week or 10 g per day of tacalcitol ointment
3. Disease severity graded moderate, severe or very severe according to the Investigators’ global assessment of disease severity
4. A minimum PASI score for extent of 2 in at least one body region (i.e. psoriasis affecting at least 10% of arms, and/or 10% of trunk, and/or 10% of legs)
5. Subjects aged 18 years or above
6. Either sex
7. Any ethnic origin
8. Attending hospital out-patient clinic or the private practice of a dermatologist

11.4.2 Exclusion Criteria
1. Systemic treatment with biological therapies (marketed or not marketed), with a possible effect on psoriasis vulgaris (e.g. alefacept, efalizumab, etanercept, infliximab, adalimumab) within 3 months prior to randomisation
2. Systemic treatment with all other therapies than biologics, with a possible effect on psoriasis vulgaris (e.g., corticosteroids, retinoids, immunosuppressants) within 4 weeks prior to randomisation
3. Systemic treatment with Vitamin D preparations above 500 IU per day
4. PUVA or Grenz ray therapy within 4 weeks prior to randomisation
5. UVB therapy within 2 weeks prior to randomisation
6. Any topical treatment of the trunk/limbs (except for emollients) within 2 weeks prior to randomisation
7. Topical treatment for other relevant skin disorders on the face and flexures (e.g., facial psoriasis, flexural psoriasis, eczema) with potent or very potent (WHO group III-IV) corticosteroids or vitamin D analogues within 2 weeks prior to randomisation
8. Topical treatment for other relevant skin disorders on the scalp (e.g. scalp psoriasis) with very potent (WHO group IV) corticosteroids or vitamin D analogues within 2 weeks prior to randomisation
9. Planned initiation of, or changes to concomitant medication that could affect psoriasis vulgaris (e.g., beta blockers, ACE inhibitors, anti-malaria drugs, lithium) during the study
10. Current diagnosis of erythrodermic, exfoliative or pustular psoriasis
11. Subjects with any of the following conditions present on the treatment area: viral (e.g., herpes or varicella) lesions, fungal and bacterial skin infections, parasitic infections, skin manifestations in relation to syphilis or tuberculosis, rosacea, perioral dermatitis, acne vulgaris, atrophic skin, striae atrophicae, fragility of skin veins, ichthyosis, acne rosacea, ulcers and wounds
12. Known or suspected disorders of calcium metabolism associated with hypercalcaemia
13. Known or suspected severe renal insufficiency or severe hepatic disorders
14. Known or suspected hypersensitivity to component(s) of the Investigational Products
15. Current participation in any other interventional clinical study
16. Subjects who had received treatment with any non-marketed drug substance (i.e. an agent which was not available for clinical use following registration) within 4 weeks prior to randomisation, except for biologics (3 months)
17. Planned exposure to sun during the study that may affect psoriasis vulgaris
18. Previously randomised to this study
19. Subjects known or suspected of not being able to comply with a trial protocol (e.g. due to alcoholism, drug dependency or psychotic state)
20. Females of child-bearing potential wishing to become pregnant during the study, or are breast-feeding, or not using an adequate method of contraception during the study
21. Females of child-bearing potential with positive pregnancy test at Visit 1

11.4.3 Subject Screening Log
All investigative sites kept the subject screening log. Subjects listed on the log were all subjects visiting the Investigator in relation to participation in the trial. Date of screening, date of birth, sex and the reason for non-inclusion (or CRF number if the subject was randomised) were to be stated on the log.

11.4.4 Subject Registration
At Visit 1 each subject was assigned the next (ascending) CRF Number available at the trial site. The CRF Number together with subject’s date of birth was a unique subject identifier used throughout the trial, in lieu of the subject’s name. The CRF Number was completely distinct from the Randomisation Code Number.

For subjects entering the washout period, a Washout Fax Notification Form was completed and sent to LEO. If a subject was withdrawn from the washout, the site notified LEO by re-faxing the original Washout Fax Notification Form with edited information.
11.5 WITHDRAWAL CRITERIA

Subjects could have been withdrawn for any of the following reasons:

1. Unacceptable treatment efficacy: the investigator was free to withdraw the subject at any time for medical reasons.
2. Unacceptable adverse events: any adverse event that the investigator or the subject considered unacceptable.
3. Exclusion criteria: any exclusion criteria which emerged/became apparent during the subject’s participation in the study.
4. Voluntary withdrawal: subjects were free to withdraw from the study at any time and for any reason.
5. Other reasons: other reasons than stated above which required subjects to (be) withdraw(n) should be specified.

Subjects who were discovered, after enrolment/randomisation, not to have fulfilled all in/exclusion criteria at time of enrolment, were to be withdrawn from treatment unless the investigator, based on clinical and ethical evaluation, found withdrawal inappropriate. Such deviation(s) from the protocol were to be reported to LEO (and IEC/IRB, as appropriate).

Reason(s) for withdrawal were recorded in the CRF. Subjects withdrawn were not substituted.

11.6 INVESTIGATIONAL PRODUCTS

<table>
<thead>
<tr>
<th>Finished product (Brand) name (if available)/name investigational product</th>
<th>DAIJOBET/DOVOBET gel (LEO 80185)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation</td>
<td>Gel</td>
</tr>
</tbody>
</table>
| Active ingredient name/concentration | Calcipotriol 50 mcg/g (as hydrate)  
Betamethasone 0.5 mg/g (as dipropionate) |
| Excipients | Castor oil (hydrogenated)  
Polyoxypolyethylene (PPG)-15-Stearyl Ether (Arlamol E)  
Paraffin, liquid |
<p>| Pack size(s) | 50 g gel in 120 ml bottle |
| Manufacturer’s name | LEO Pharma, Denmark |
| Supplier’s name | LEO Pharma, Denmark |
| Certifier’s name | LEO Pharma, Denmark |
| Lot number(s)/expiry date(s) | 07 312 61 01/10 2009 |</p>
<table>
<thead>
<tr>
<th>Finished product (Brand) name (if available)/name investigational product</th>
<th>Curatoderm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation</td>
<td>Ointment</td>
</tr>
<tr>
<td>Active ingredient name/concentration</td>
<td>tcalcitol 4 mcg/g (as monohydrate)</td>
</tr>
<tr>
<td>Excipients</td>
<td>Paraffin, white soft</td>
</tr>
<tr>
<td></td>
<td>Paraffin, liquid</td>
</tr>
<tr>
<td></td>
<td>Diisopropyl adipate</td>
</tr>
<tr>
<td>Pack size(s)</td>
<td>100 g tubes</td>
</tr>
<tr>
<td>Manufacturer’s name</td>
<td>Germany (manufacturer) and (License)</td>
</tr>
<tr>
<td>Supplier’s name</td>
<td>LEO Pharma, Denmark</td>
</tr>
<tr>
<td>Certifier’s name</td>
<td>LEO Pharma, Denmark</td>
</tr>
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<td>Lot number(s)/expiry date(s)</td>
<td>739871/09 2010</td>
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<table>
<thead>
<tr>
<th>Finished product (brand) name (if available)/name investigational product</th>
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<tbody>
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<td>Gel</td>
</tr>
<tr>
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</tr>
<tr>
<td>Excipients</td>
<td>Castor oil (hydrogenated)</td>
</tr>
<tr>
<td></td>
<td>Polyoxypropylene (PPG)-15-Stearyl Ether (Arlamol E)</td>
</tr>
<tr>
<td></td>
<td>Paraffin, liquid</td>
</tr>
<tr>
<td>Pack size(s)</td>
<td>50 g gel in 120 ml bottle</td>
</tr>
<tr>
<td>Manufacturer’s name</td>
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</tr>
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</tr>
<tr>
<td>Lot number(s)/expiry date(s)</td>
<td>07 311 61 01/11 2009</td>
</tr>
</tbody>
</table>
11.6.1 Administration of Investigational Products

### DAIVOBET/DOVOBET gel

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Topical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing range</td>
<td>Up to 100 g gel per week</td>
</tr>
<tr>
<td>Dosing frequency</td>
<td>Once daily</td>
</tr>
<tr>
<td>Daily maximum</td>
<td>100 g</td>
</tr>
<tr>
<td>Time of day for dosing</td>
<td>No specific requirements</td>
</tr>
<tr>
<td>Relation of time of dosing to dietary intake</td>
<td>No specific requirements</td>
</tr>
</tbody>
</table>

### Tacalcitol Ointment

<table>
<thead>
<tr>
<th>Route of administration</th>
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</tr>
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<tbody>
<tr>
<td>Dosing range</td>
<td>Up to 10 g ointment per day</td>
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<td>Dosing frequency</td>
<td>Once daily</td>
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<tr>
<td>Daily maximum</td>
<td>10 g</td>
</tr>
<tr>
<td>Time of day for dosing</td>
<td>No specific requirement</td>
</tr>
<tr>
<td>Relation of time of dosing to dietary intake</td>
<td>No specific requirement</td>
</tr>
</tbody>
</table>

The study medication was dispensed to the subject by investigational staff, not the (sub)Investigator to ensure Investigator blinding throughout the study.

At Visit 1 (baseline), a treatment instruction sheet on how to apply study medication was given to the subject.

11.6.2 Precautions/Overdosage

Overdosage with tacalcitol may be associated with hypercalcaemia. In such cases, administration of the Investigational Product was to be stopped and the subject withdrawn from the study. Clinically important hypercalcaemia was to be managed at the Investigator’s discretion with rehydration, bisphosphonate administration or according to local instructions. Hypercalcaemia should rapidly subside when treatment is discontinued.

Overdosage with betamethasone dipropionate may result in suppression of pituitary adrenal function causing secondary adrenal insufficiency which is usually reversible. In such cases, symptomatic treatment was indicated. In case of chronic toxicity the corticosteroid treatment was to be discontinued gradually.
11.6.3 Treatment Assignment

Subjects who complied with all the protocol’s inclusion and exclusion criteria were randomised to receive treatment with either DAIVOBET/DOVOBET gel, tacalcitol ointment or gel vehicle. Treatment assignment was pre-planned according to a computer generated randomisation schedule in a 2:2:1 ratio. A subject was assigned the next (ascending) randomisation code number available at the site.

Each randomisation code number was exclusive to a subject treatment pack (STP) and determined the treatment group to which a subject was assigned (the randomisation code number and eCRF number were distinct from each other).

11.6.3.1 Randomisation Code List

No copy of the Randomisation Code List was kept during the study, as all copies were destroyed after packaging of the trial medication. Until the trial was unblinded, the randomisation files were archived in a secure area on a server at Clinical Data and Document Management, inaccessible to all persons involved with conduct/administration of the trial.

11.6.4 Blinding of Study

Due to difference in formulation and packaging, it was not possible to double blind the Investigational Products,

In order to keep the study investigator blinded, packing and labelling of the outer box was identical for all Investigational Products. However, the weight of the individual STP for DAIVOBET/DOVOBET gel and gel vehicle was slightly heavier than the STP for tacalcitol ointment.

Due to different formulation, Investigational Products were either packed in bottles (DAIVOBET/DOVOBET gel and gel vehicle) or in tubes (tacalcitol ointment). Handling of individual bottles/tubes of Investigational Products (e.g. dispensing, returning and drug accountability) was therefore handled by a designated third person. Individual bottles/tubes of Investigational Products were inaccessible for the (sub)Investigator(s) and other study staff involved in the evaluation of subjects and conduct of the trial.

Subjects were instructed not to reveal the formulation of the Investigational Products to the study investigator.
11.6.5 Breaking the Randomisation Code

11.6.5.1 Unblinding of Individual Subject Treatment

The unblinding was made by contacting the [ ] Helpdesk. [ ] then performed the unblinding using the Oracle Clinical system. The emergency unblinding requests were made only by (sub)Investigator and Drug Safety users (i.e. LEO Pharma Drug Safety department). The Investigator provided the Protocol Code Number, and either the subject CRF number or randomisation number. [ ] provided the date of birth and gender of the subject for confirmation. If it was the correct person, the unblinding was done and [ ] provided the treatment name to which the subject was allocated. [ ] sent an emergency unblinding confirmation to the person who had requested the unblinding.

The code was only to be broken in an emergency where Investigational Product identification was necessary. In such an event, the date and the reason for unblinding were recorded on the appropriate page in the CRF. The Investigator filed the unblinding confirmation in an appropriate way with the other confidential subject data. Only the Investigator had access to the unblinding confirmation.

If code break was considered necessary for other safety concerns, for example due to signals of important adverse drug reactions, code break was requested by the Drug Safety Department, LEO.

11.6.5.2 Unblinding of the Study

The trial was fully unblinded only when a final validated database was available, the Statistical Analysis Plan Update had been approved.

11.6.6 Drug Accountability and Compliance Checks

The Investigator was fully responsible for the investigational product at the site. Dispensing of medication could be delegated to a hospital pharmacy, for example, as locally applicable.

The person responsible for dispensing the medication was responsible for maintaining adequate control of the investigational products and for documenting all transactions with them. To ensure Investigator blinding, documentation pertaining to drug accountability was kept separately from other subject’s data and away from the Investigator.
11.6.6.1 Sponsor-Investigator Drug Accountability
All investigational products supplied by and returned to LEO were fully documented by the
monitor with the help of the person on site responsible for dispensing the medication by use
of drug accountability forms.

11.6.6.2 Investigator-Subject Drug Accountability
At each Visit 1-5, Investigational Products were dispensed to the subject. At Visits 2-6, the
Investigational Products, including empty bottles/ tubes, dispensed at the previous visit were
returned by the subject. An inventory (Individual Drug Accountability Form) was kept of all
trial medication given to and returned by each subject randomised in the trial. This inventory
was available for inspection at monitoring visits and was checked to ensure correct dispensing
of Investigational Products.

11.6.6.3 End of Trial Drug Accountability
All returned Investigational Product supplies were reconciled with the Individual Drug
Accountability Forms. All returned bottles/tubes were subsequently weighed to determine the
amount of Investigational Product used.

11.6.6.4 Treatment Compliance
At Visits 2-6 the subject was asked if s/he had used the medication as prescribed. If this was
not the case the degree and nature of non-compliance was specified.

11.6.7 Prior and Concomitant Treatment

Prior to the Study Treatment Phase

Treatments requiring washout:
- Systemic use of biological treatments, whether marketed or not marketed, directed
  against or with a possible effect on psoriasis vulgaris (e.g., alefacept, efalizumab,
  etanercept, infliximab adalimumab) (3 months*).
- Systemic treatment with all other therapies than biologicals, with a potential effect on
  psoriasis vulgaris (e.g., corticosteroids, retinoids, immunosuppressants) (4 weeks).
- PUVA or Grenz ray therapy (4 weeks).
- UVB therapy (2 weeks).
- Topical treatment of the arm, trunk and legs, except for emollients (2 weeks).
- Use of non-marketed or investigational products (4 weeks).

* Note: duration of the washout phase was not to exceed 4 weeks (28 days).
During the Study Treatment Phase
Concomitant treatment for conditions other than psoriasis vulgaris (with no potential effect on psoriasis vulgaris) was to be continued throughout the trial without any change in dosage whenever possible. Use of concomitant treatment was to be recorded in the subject's medical record and the CRF (treatment/drug name, dose, indication and dates of start and stop).

Use of non-marketed/other investigational products was not permitted during the trial.

Changes of doses (including starting) of drugs that, while not specifically indicated for treatment of the indication being studied, are known to have an effect (positive or negative) on the indication, were not permitted. This included but was not limited to beta-blockers, antimalaria drugs, lithium and ACE inhibitors.

In addition, systemic treatment with vitamin D preparations above 500 IU per day was not permitted.

Accordingly, only the following concomitant topical anti-psoriatic treatments were permitted during the study:
Scalp:
• All topical medications except very potent WHO group IV corticosteroids and vitamin D analogues.
• Unlimited use of emollients was allowed.

Face/Skin Folds (Flexures):
• All topical medications except potent and very potent WHO group III-IV corticosteroids and vitamin D analogues.
• Unlimited use of emollients was allowed.

During the Observational Phase
Active treatment used to treat the psoriasis lesions on the body were not permitted during the Observational Phase. Unlimited use of emollients was allowed. Other medications, as specified for the treatment phase were allowed.
### 11.7 STUDY PROCEDURES

#### 11.7.1 Schedule of Study Procedures

<table>
<thead>
<tr>
<th>Visit</th>
<th>Treatment</th>
<th>Observation</th>
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<td></td>
<td>Wash-out</td>
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<tr>
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<tr>
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<td>Randomisation</td>
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<td>Investigator’s global assessment of disease severity</td>
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</tr>
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<td>Investigator’s assessment of the extent of psoriasis vulgaris</td>
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<td></td>
</tr>
<tr>
<td>Investigator’s assessment of extent and severity of clinical signs</td>
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<td>Subject’s global assessment of disease severity</td>
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</tr>
<tr>
<td>Dispensing of Investigational Product</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Return of Investigational Product</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Compliance</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Adverse Event(s)</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Photography&lt;sup&gt;d)&lt;/sup&gt;</td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>
a) Informed consent was to be signed both by subject and (sub)investigator before any study related procedures, including washout
b) If female of childbearing potential
c) A washout period was to be completed if the subject received anti-psoriatic treatments or other relevant medication, as defined by the exclusion criteria. Duration of the washout phase could not exceed 4 weeks (28 days)
d) An extra visit was scheduled during observation phase if a subject needed to re-initiate of treatment
e) If an adverse event (serious or non-serious) classified as possibly or probably related to the study treatment or not assessable in relation to the study treatment was ongoing at the last on-treatment visit
f) SF-36 (v2) and Skindex-16 was used
g) Photos of psoriatic lesions were taken at few designated centres

11.7.2 Subject Eligibility
At Visit 1 (Day 0) the subject’s suitability for the study was to be checked according to the inclusion and exclusion criteria. Subject’s demographic details (date of birth, sex and ethnic origin) and duration of psoriasis vulgaris on the trunk and/or limbs, concomitant medication and concurrent diagnoses were to be recorded.

11.7.3 Clinical Assessment

11.7.3.1 Investigator Assessments
The (sub)Investigator made the following clinical assessments. Ideally, all assessments for a subject were made by the same (sub)Investigator.

Investigator’s global assessment of disease severity
At all visits the (sub)Investigator made a global assessment of the disease severity of the psoriasis on the trunk, arms and legs by use of the 6-point scale below. This assessment represents the average lesion severity on trunk, arm and legs. The assessment was based on the condition of the disease at the time of evaluation, and not in relation to the condition at a previous visit.
Clear
Plaque thickening = no elevation or thickening over normal skin
Scaling = no evidence of scaling
Erythema = none or hyperpigmentation or residual red coloration

Almost clear
Plaque thickening = none or possible thickening but difficult to ascertain whether there is a slight elevation above normal skin level
Scaling = none or residual surface dryness and scaling
Erythema = light pink coloration

Mild
Plaque thickening = slight but definite elevation
Scaling = fine scales partially or mostly covering lesions
Erythema = light red coloration

Moderate
Plaque thickening = moderate elevation with rounded or sloped edges
Scaling = most lesions at least partially covered
Erythema = definite red coloration

Severe
Plaque thickening = marked elevation typically with hard or sharp edges
Scaling = non-tenacious scale predominates, covering most or all of the lesions
Erythema = very bright red coloration

Very severe
Plaque thickening = very marked elevation typically with hard or sharp edges
Scaling = thick tenacious scale covers most or all of the lesions
Erythema = extreme red coloration; deep red coloration

Note: At Visit 1 the disease severity must have been graded as at least moderate in order to meet the inclusion criteria.

Subjects classified to be ‘clear’ at any of Visits 2-6 were able to stop treatment at the Investigator’s discretion. They were to remain in the study and attend all visits up to and including Visit 6. Although classified as ‘clear’, the subject still had study medication dispensed at each visit and restarted treatment if required, based on their own judgement. More than one discontinuation/restart cycle was allowed.

Investigator’s assessment of the extent and severity of clinical signs.
At all visits the (sub)Investigator assessed the extent and severity of clinical signs of the subject’s psoriasis on specific areas of the body in terms of three clinical signs: redness, thickness and scaliness.
The extent of psoriatic involvement was recorded for each of the three areas: arms (including hands), trunk (including neck) and legs (including buttocks and feet) using the following scale:

0 = no involvement
1 = <10%
2 = 10-29%
3 = 30-49%
4 = 50-69%
5 = 70-89%
6 = 90-100%

The severity of the psoriatic lesions in each of the three areas was recorded for each of the signs of redness, thickness and scaliness. For each clinical sign, a single score, reflecting the average severity of all psoriatic lesions on given body region, was determined according to the scale below:

Redness
0 = none (no erythema)
1 = mild (faint erythema, pink to very light red)
2 = moderate (definite light red erythema)
3 = severe (dark red erythema)
4 = very severe (very dark red erythema)

Thickness
0 = none (no plaque elevation)
1 = mild (slight, barely perceptible elevation)
2 = moderate (definite elevation but not thick)
3 = severe (definite elevation, thick plaque with sharp edge)
4 = very severe (very thick plaque with sharp edge)

Scaliness
0 = none (no scaling)
1 = mild (sparse, fine-scale lesions, only partially covered)
2 = moderate (coarser scales, most of lesions covered)
3 = severe (entire lesion covered with coarse scales)
4 = very severe (very thick coarse scales, possibly fissured)
Investigator’s assessment of the extent of psoriasis vulgaris

In order to obtain baseline data of psoriatic severity for all the subjects enrolled in the study, the (sub)Investigator also assessed the extent of the subject’s total psoriatic involvement at Visit 1.

The total psoriatic involvement (e.g., the arms, the legs, the trunk, the scalp, the face) was recorded as a percentage of the total body surface area (BSA), estimating that the surface of a full, flat palm (including the five fingers) correlates to approximately 1% of the total BSA.

11.7.3.2 Subject Assessments

Patient’s global assessment of disease severity

This assessment was made at all visits, based on the condition of the disease at the time of the evaluation and not in relation to the condition at a previous visit, using the scale below. The subject’s assessment was to be made prior to the Investigator assessments. The (sub)Investigator explained the categories of the scale to the subject and the subject told the (sub)Investigator which category to tick.

- Clear: No psoriasis symptoms at all
- Very mild: Very slight psoriasis symptoms, does not interfere with daily life
- Mild: Slight psoriasis symptoms, interferes with daily life only occasionally
- Moderate: Definite psoriasis symptoms, interferes with daily life frequently
- Severe: Intense psoriasis symptoms, interferes or restricts daily life very frequently

11.7.3.3 Quality of Life Assessments

The subjects assessments of quality of life was performed at Visit 1 (baseline), Visit 4 and at Visit 6 (end of treatment). The questionnaires was completed by the subject at the Investigator site before the subject had been assessed by the (sub)Investigator.

11.7.3.4 Imaging Assessments

Clinical photographs of the psoriasis vulgaris lesions on the body were taken by a few designated centres. Designated centres were provided with an instruction manual in order to standardise this part of the study. Only subjects consented to the photography procedure were used for clinical photos.

The photographs were taken strictly for scientific and marketing purposes; no efficacy or safety assessments were made using the photographs.
11.7.4 Laboratory Assessments
Not Applicable

11.7.4.1 Central Analysis
Not Applicable

11.7.4.2 Local Analysis
Prior to randomisation at Visit 1, a urine pregnancy test was performed in female subjects of child bearing potential. The test kits were provided by LEO.

11.7.5 Adverse Events

Adverse Event (AE): any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Adverse Drug Reaction (ADR): in the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or modification of physiological function (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

At all visits after treatment start, the subject was asked a non-leading question by the investigator: “Since I last saw you, have you had any problems?” No specific symptoms were asked for. If the answer was “NO”, no further questions were asked. If the answer was “YES”, the investigator recorded the event’s nature, intensity, duration, location for cutaneous AEs, suspected causal relationship to the investigational product and outcome.
It was important that the investigator also observed the subject for any changes not reported by the subject, and recorded these changes.

Only medically qualified (sub)investigators could assess the subject for (Serious) AEs.

11.7.5.1 Reporting of Adverse Events

Events, either reported by the subject or observed by the investigator, that fulfilled any of the above definitions were to be recorded on the AE page of the CRF book and described in the following manner:

The NATURE of the event was to be described in precise, standard medical terminology (i.e., not necessarily the exact words used by the subject). If known, a specific diagnosis should be stated (e.g., allergic contact dermatitis).

The INTENSITY of the event was described in terms of mild, moderate or severe according to the investigator’s clinical judgement.

Mild. The AE does not interfere in a significant manner with the subject’s normal functioning level. It may be an annoyance.

Moderate. The AE produces some impairment of functioning but is not hazardous to health. It is uncomfortable and/or an embarrassment.

Severe. The AE produces significant impairment of functioning or incapacitation and/or it is a hazard to the subject.

The DURATION of the event was described by the start date and end date.

The LOCATION for cutaneous AEs was described as either the face, scalp or trunk/limbs. Furthermore, the location was described in terms of lesional/perilesional (≤2 cm from the lesional border of the lesion(s) treated with investigational product) or distant (>2 cm from the lesional border)

The CAUSAL RELATIONSHIP of the event to the use of the investigational product was described in terms of probable, possible, not related or not assessable according to the investigator’s clinical judgement.
Probable
- Follows a reasonable temporal sequence from administration of the investigational product.
- Could not be reasonably explained by the subject’s clinical state, environmental or toxic factors or other therapies administered to the subject.
- Follows a known pattern of response to the investigational product.
- Disappears or decreases on cessation or reduction in dose of the investigational product.
- Reappears or worsens upon rechallenge.

Possible
- Follows a reasonable temporal sequence from administration of the investigational product.
- Could be reasonably explained by the subject’s clinical state, environmental or toxic factors or other therapies administered to the subject.
- Follows a known pattern of response to the investigational product.

Not related
- Does not follow a reasonable temporal sequence from administration of the investigational product.
- Could be reasonably explained by the subject’s clinical state, environmental or toxic factors or other therapies administered to the subject.
- Does not reappear or worsen upon rechallenge.
- Does not follow a known pattern of response to the investigational product.

Not assessable
- The AE cannot yet be judged otherwise because present information is insufficient or contradictory. A final judgement (i.e., probably, possibly, or not related) shall be made as more information becomes available at the latest when the subject has completed the trial.
The **OUTCOME** of the event was described in terms of:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovered/resolved</td>
<td>&quot;(S)AE stop date’ should be provided</td>
</tr>
<tr>
<td>Recovering/resolving</td>
<td>Can be used in cases where subject is known to be clearly recovering from an event. Event is, however, not resolved yet. Follow-up required</td>
</tr>
<tr>
<td>Not recovered/not resolved</td>
<td>Event is ongoing Follow-up required</td>
</tr>
<tr>
<td>Recovered with sequelae/</td>
<td>Used only with persistent incapacity/life long sequelae, e.g., blindness after diabetes mellitus, hemiparesis after stroke &quot;(S)AE stop date’ should be provided</td>
</tr>
<tr>
<td>resolved with sequelae</td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>&quot;(S)AE stop date’ (date of death) should be provided only for the events leading to death</td>
</tr>
<tr>
<td>Unknown</td>
<td>Unknown to Investigator, e.g., subject lost to follow-up</td>
</tr>
</tbody>
</table>

If the outcome was “not recovered/not resolved’ or “recovering/resolving’ or “unknown’ the AE stop date was to be left blank.

If the outcome was “recovered/resolved’ or “recovered with sequelae/resolved with sequelae’ or “fatal’ the AE stop date was to be entered.

During the trial all serious and non-Serious AEs were to be followed up to determine the final outcome.

Once a subject had completed the trial, the investigator was to follow-up for outcome on all non-Serious AEs classified as possibly/probably related to investigational product or not assessable for 14±2 days or until final outcome was determined, whichever came first.

**Pregnancy**

Pregnancy which occurred during a clinical trial with an investigational product was to be reported to LEO by use of the LEO Serious Adverse Event (SAE) Form – Clinical Trial and handled as an SAE with regard to reporting time frame. All pregnancies were to be followed-up until conclusion.
11.7.6 Serious Adverse Events

11.7.6.1 Definition of Serious Adverse Events

**Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR):** Any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires in-patient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity or
- is a congenital anomaly/birth defect

or other medically important conditions

~Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. (See the ICH Guideline E2A)~

11.7.6.2 Reporting of Serious Adverse Events

Any SAE related or unrelated to the investigational product occurring during the course of the trial were to be reported to LEO within **ONE** working day after first knowledge by the investigator.

Any SAE, related or unrelated to any trial procedures (e.g., wash-out, biopsies) occurring after informed consent had been obtained, and until the subject’s completion of the trial, were to be reported to LEO within ONE working day after first knowledge by the investigator.

**Note:** Hospitalisation or prolonged hospitalisation for logistic/convenience reasons or hospitalisation solely for study-related purposes do not fulfil the criteria for being an untoward medical occurrence and are therefore not an SAE.

Reports were made using the **LEO Serious Adverse Event FORM - CLINICAL TRIAL**, which was part of the electronic CRF. Sites had paper copies of this form which was to be used ONLY if the RDC system was not operational. In such cases the form was to be
completed and then sent/faxed to the local LEO company. The information provided on the form included a description of the clinical course of the serious adverse event and an assessment of the intensity, causal relationship to the investigational product(s) and/or trial procedures, the action taken and the outcome to date.

The initial report was followed by a detailed description later which might include copies of hospital records, autopsy reports and other documents when requested and applicable. If an investigator was in doubt whether to regard an adverse event as serious or not, the event was serious until the opposite had been established. The Independent Ethics Committee(s) and National Health Authorities were to be notified on such an event in writing according to local requirements.

For all SAEs (including those ongoing at the time the subject completed the trial and those serious adverse events occurring within the 14 days) the investigator was to follow-up for final outcome and until all queries had been resolved. Details of the follow-up were to be given (e.g., discontinuation of investigational treatment, if specific treatment was required, if hospitalisation was required etc.)

11.7.7 Changes to Planned Study Procedures

There was one amendment to the protocol (dated 15-FEB-2008) which added exclusion criterion 13 which excluded subjects who had known or suspected severe renal insufficiency or severe hepatic disorders (see section 11.4.2). The study was conducted in line with the protocol and its amendment.

11.8 EFFICACY EVALUATION

11.8.1 Primary Response Criterion

- Subjects with ‘controlled disease’ (‘clear’ or ‘almost clear’) according to IGA at week 8

11.8.2 Secondary Response Criteria

- Subjects with ‘controlled disease’ according to the IGA at week 4
- The percentage change in PASI from baseline to week 4 and 8
- Subjects with relapse during the study and time to relapse
- Subjects with rebound during the study
11.8.2.1 PASI

PASI is based on the investigator’s assessment of extent and severity of the disease locally (trunk, arms, legs) and calculated using the following formula:

- Arms: \(0.2 \times (R + T + S)E = X\)
- Trunk: \(0.3 \times (R + T + S)E = Y\)
- Legs: \(0.4 \times (R + T + S)E = Z\)

where: 
- \(R\) = score for redness;
- \(T\) = score for thickness;
- \(S\) = score for scaliness;
- \(E\) = score for extent

The sum of \(X + Y + Z\) gives the total PASI, which can range from 0 to 64.8. The PASI used in this study was modified to exclude assessment of the head, as study treatment was not used here.

11.8.2.2 Relapse

“Relapse” is defined as a reduction in the PASI improvement from baseline by at least 50% among subjects with ‘controlled disease’ according to IGA at week 8.

Time to relapse is defined as the time between the date of last on-treatment visit (could be before week 8 if a subject clears before week 8) and relapse of psoriasis. If a subject was graded as ‘clear’ according to the IGA before week 8, the subject had to confirm that no trial medication had been applied on the treatment area in the meantime.

11.8.2.3 Rebound

Rebound is defined as worsening of psoriasis to a PASI >125% of the baseline value among subjects with ‘controlled disease’ according to IGA at week 8.

11.8.3 Tertiary Response Criteria

- Subjects with ‘controlled disease’ according to the IGA at week 6
- Subjects with ‘controlled disease’ (‘clear’ or ‘very mild’) according to the patient’s global assessment of disease severity at week 8
- Subjects with PASI 75 (at least 75% reduction in PASI from baseline) at each visit
- Subjects with PASI 50 (at least 50% reduction in PASI from baseline) at each visit

11.8.4 Evaluation of Quality of Life (QoL)

- Change in quality of life from baseline to week 4 and week 8 according to by use of SF-36 (v2) and Skindex-16.
11.9 SAFETY EVALUATION

11.9.1 Evaluation of (Serious) Adverse Events
- Any adverse events reported.
- Any adverse drug reactions reported.
- The reasons for withdrawal from the study.

11.9.2 Evaluation of Laboratory Data
Not applicable.

11.10 STATISTICAL ANALYSIS

11.10.1 Planned Analysis
Details of the statistical analysis planned at the start of the study are given in the Study Protocol (Appendix I). In general, the analysis was as described in the protocol. A review of the proposed analysis was made and analysis sets derived before the treatment code was broken. Details are given in the Statistical Analysis Plan Update (Appendix III).

11.10.1.1 Subject Qualification for Analysis
All subjects recruited for the study (i.e. signed informed consent obtained and a CRF started) were to be accounted for in the study report.

All randomised subjects were included in the full analysis set (intention-to-treat analysis set) and were analysed for efficacy.

All subjects who receive any treatment with trial medication and for whom the presence or confirmed absence of adverse events was available were included in the safety analysis set and analysed for safety.

A per protocol analysis set was defined by excluding subjects from the full analysis set who received no treatment with trial medication, who provided no efficacy data following start of treatment, who were known to have taken the wrong trial medication throughout the treatment phase of the trial and/or who did not fulfil the disease defining inclusion criteria (i.e. inclusion criteria 2-4). Further exclusion of subjects or subject data was decided upon after the blind review of the data; remaining inclusion and exclusion criteria, concomitant medication that may have affected psoriasis and treatment compliance were reviewed.
The decisions regarding inclusion/exclusion of subjects and/or subject data from the trial analysis sets was documented in the Statistical Analysis Plan Update before the blind was broken, with the exception that inclusions/exclusions based on drug accountability data could not be confirmed before the study was unblinded.

11.10.1.2 Reasons for leaving the study
The reasons for leaving the study were presented for all randomised subjects and by treatment group. The reasons for leaving the study were also presented by last visit attended and by treatment group.

11.10.1.3 Baseline Characteristics
Descriptive statistics of demographics and other baseline characteristics were presented for all randomised subjects and by treatment group and centre.

Demographics included age, sex, race, ethnic origin and skin type. Physical examination included weight, height and blood pressure. Other baseline characteristics included duration of psoriasis on the trunk, arms and/or legs, other diagnoses, concomitant medication, IGA, Investigator’s assessment of extent and severity of disease locally (trunk, arms, legs), Investigator’s assessment of the extent of psoriasis vulgaris and subject’s global assessment of disease severity.

Categorical data was summarised using the number and percentage of subjects in each category and treatment group. Continuous data was summarised using the mean, median, standard deviation (SD), minimum and maximum values.

11.10.1.4 Analysis of Efficacy
The statistical analysis of efficacy was based on the defined response criteria (see Section 11.8).

11.10.1.4.1 Primary Efficacy Criterion
The primary response criterion was analysed for the full analysis set and the per protocol analysis set. The analysis for the full analysis set was regarded as primary while the analysis for the per protocol analysis set was regarded as supporting.
The analysis of the primary response criterion consisted of testing two hypotheses in sequential order both at a 5% level of significance, that is, the second hypothesis was only tested if the first test is statistically significant. In clinical terms the two hypotheses were as follows:

1. DAIVOBET/DOVOBET gel was superior to the gel vehicle with respect to the proportion of subjects with ‘controlled disease’ at week 8 according to the IGA.
2. DAIVOBET/DOVOBET gel was superior to tacalcitol ointment with respect to the proportion of subjects with ‘controlled disease’ at week 8 according to the IGA.

In statistical terms the hypotheses tested and their alternatives are as follows:

\[ H_01: \mu_{DAIVO/DOVO} = \mu_{vehicle} \quad \text{HA}_1: \mu_{DAIVO/DOVO} \neq \mu_{vehicle} \]
\[ H_02: \mu_{DAIVO/DOVO} = \mu_{Tacalcitol} \quad \text{HA}_2: \mu_{DAIVO/DOVO} \neq \mu_{Tacalcitol} \]

The proportion of subjects who achieved ‘controlled disease’ according to the IGA at week 8 was compared between DAIVOBET/DOVOBET gel and the gel vehicle using the Cochran-Mantel-Haenszel (CMH) test adjusting for the effect of centre. The CMH adjusted odds ratio (OR) (odds of ‘controlled disease’ for DAIVOBET/DOVOBET gel relative to that for the gel vehicle), its 95% confidence interval (CI) and p-value were calculated. The Breslow-Day test for homogeneity of the odds ratio across centres was performed.

The proportion of subjects who achieved ‘controlled disease’ according to the IGA at week 8 was compared between DAIVOBET/DOVOBET gel and tacalcitol ointment using the CMH test adjusting for the effect of centre. The CMH adjusted OR (odds of ‘controlled disease’ for DAIVOBET/DOVOBET gel relative to that for tacalcitol ointment), its 95% CI and P-value were calculated. The Breslow-Day test for homogeneity of the odds ratio across centres was performed.

The proportion of subjects who achieved ‘controlled disease’ at week 8 was tabulated by treatment group and by centre, by age group (≤ 35, 36-50, 51-64, ≥ 65 years), by sex, by ethnic origin, by race and by baseline disease severity according to the IGA. These tabulations were intended for descriptive purposes only and no statistical analyses of these data were undertaken.

11.10.1.4.2 Secondary Efficacy Criteria

A total of five secondary efficacy response criteria were defined. Three of these secondary response criteria were compared between the three treatment groups using statistical models,
whereas only descriptive statistics were presented for the response criteria relating to relapse and rebound. The analysis of these three secondary response criteria used a Bonferroni corrected level of significance of 0.0167 (0.05/3) to account for multiplicity. No further adjustment were done for the two statistical tests (two pair wise comparisons of DAIVOBET/DOVOBET gel vs. gel vehicle and DAIVOBET/DOVOBET gel vs. tacalcitol ointment) made within each response criterion since no claims were made unless both hypotheses were statistically significant.

The 98.33% CI for the secondary response criteria was only intended for descriptive purposes.

Unless specifically stated otherwise, the secondary efficacy criteria were analysed for the full analysis set only.

**Investigator’s global assessment of disease severity**

The proportion of subjects who achieved ‘controlled disease’ at week 4 according to the IGA were compared between the treatment groups using the CMH test adjusting for the effect of centre. For each of the comparisons, the OR (odds of ‘controlled disease’ for DAIVOBET/DOVOBET gel relative to that of each of the other treatments), its 98.33% CI and P-value were calculated.

The proportion of subjects who achieved ‘controlled disease’ were tabulated at week 1, 2, 4, 6 and 8 by treatment groups. The number and percentage of subjects in each of the 6 categories (‘clear’ to ‘very severe’) at each visit were tabulated for each of the treatments pooling all centres together.

**PASI**

The percentage change in PASI from baseline to week 4 and 8 (end of treatment phase) respectively were expected to be approximately normally distributed. Thus the treatment groups were compared using analysis of variance (ANOVA) including centre and treatment in the model as design variables. The presence of a treatment by centre interaction were tested but not included in the model. For each of the treatment comparisons, the difference (DAIVOBET/DOVOBET gel – gel vehicle, DAIVOBET/DOVOBET gel – tacalcitol ointment), its 98.33% CI and a P-value were calculated from the ANOVA.

The analyses for the percentage change in PASI from baseline to week 4 and 8 (end of treatment phase) was also performed for the per-protocol population.
The change in PASI (actual and percentage) from baseline to each visit was summarised as mean, median, standard deviation, minimum and maximum for each of the treatments pooling all centres together. The percentage change in PASI from baseline to week 4 and 8 was also presented for each centre by treatment group.

**Relapse**

Among subjects with ‘controlled disease’ at week 8, relapse occurred at the first of any visits in the observation phase where the PASI value exceeded the relapse level. The relapse level was equal to the baseline PASI value minus 50% of the reduction in PASI obtained from the baseline visit to the last on-treatment visit (could be before week 8 if a subject cleared before week 8). The time to relapse was defined as the number of days from the last on-treatment visit (could be before week 8 if a subject cleared before week 8) until relapse. Relapse was only observed among subjects defined as having ‘controlled disease’ at week 8, i.e. these subjects represent a selected population, and therefore only descriptive statistics was presented. Subjects with no PASI assessments in the observation phase were not included in the analyses of relapse.

The proportion of subjects who experienced relapse were tabulated by treatment group and by centre. The time until relapse was plotted for each treatment group as a Kaplan-Meier plot. If relapse had not occurred within the observation period, the subject was censored (at the date of last visit). The median time to relapse with lower and upper quartiles was calculated for each treatment group.

**Rebound**

Among subjects with ‘controlled disease’ at week 8, rebound occurred if the PASI value at any visit during the observation phase exceeded 125% of the baseline PASI value. Rebound was only observed among subjects defined as having ‘controlled disease’ at week 8, i.e. these subjects represented a selected population, and therefore only descriptive statistics were presented. Subjects with no PASI assessments in the observation phase were not included in the analyses of rebound.

The proportion of subjects who experienced rebound were tabulated by treatment group and by centre.
11.10.1.4.3 Tertiary Response Criteria

**Patient's global assessment of disease severity**

The proportion of subjects who achieved 'controlled disease' according to the patient's global assessment of disease severity were tabulated at Weeks 1, 2, 4, 6 and 8 by treatment group. The number and percentage of subjects in each of the 5 categories ('clear' to 'severe') at each visit were tabulated for each of the treatments pooling all centres together.

**PASI 75**

The proportion of subjects at each visit, who achieved at least 75% reduction in PASI from baseline, were tabulated for each of the treatments pooling all centres together.

**PASI 50**

The proportion of subjects at each visit, who achieved at least 50% reduction in PASI from baseline, were tabulated for each of the treatments pooling all centres together.

11.10.1.5 Evaluation of Quality of Life

**SF-36**

Quality of life assessed with the SF-36 (v2) health survey questionnaire was scored and analysed according to the SF-36 Clinical Reference Kit provided by [redacted] when SF-36 was licensed.

The change in quality of life from baseline to week 4 and 8 was analysed within treatment groups using paired t-tests.

Quality of life was furthermore compared at week 4 and 8 between treatment groups using ANOVA including treatment in the model as a design variable. For each of the treatment comparisons, the difference (DAIVOBET/DOVOBET gel – gel vehicle, DAIVOBET/DOVOBET gel – tacalcitol ointment), its 95% CI and a P-value were calculated.

**Skindex-16**

Three scale scores (Symptoms, Emotion and Functioning) and a total score were calculated based on the Skindex-16 questionnaire.

The change from baseline to week 4 and 8 in each of the scale scores and the total score were analysed within treatment groups using paired t-tests.
The scale scores and the total score were furthermore compared at week 4 and 8 between treatment groups using ANOVA including treatment in the model as a design variable. For each of the treatment comparisons, the difference (DAIVOBET/DOVOBET gel – gel vehicle, DAIVOBET/DOVOBET gel – tacalcitol ointment), its 95% CI and a P-value were calculated.

11.10.1.6 Analysis of Safety
The analysis of safety was presented for the safety analysis set.

11.10.1.6.1 Adverse events
Adverse events were coded during the course of the trial in accordance with the current version of the MedDRA dictionary. The adverse events were presented by Preferred Terms and Primary System Organ Class. The adverse events were presented separately for the treatment phase (week 1 to 8) and the observation phase.

The number of subjects who experienced each type of adverse events (according to MedDRA Preferred Terms within Primary System Organ Class) was tabulated by treatment group regardless of the number of times each adverse event was reported by each subject. The proportion of subjects with adverse events was compared between treatment groups by a chi-square test.

The causal relationship to trial medication for each type of adverse events (according to the coding system) was tabulated by treatment group. Where there were several recordings of causal relationship to trial medication for a given type of adverse event (according to the coding system), causal relationship was taken as the worst recording from the last report of that adverse event, since that was when the Investigator was in possession of most information and so best able to judge causal relationship. Where there were several recordings of intensity for a given type of adverse event, intensity was taken as the worst ever recording of that adverse event.

Adverse drug reactions were defined as adverse events for which the Investigator had not described the causal relationship to trial medication as “not related”. The number of subjects experiencing each type of adverse drug reaction was tabulated and compared by treatment group by the same principles as described for adverse events. The intensity for each type of adverse drug reaction was tabulated by treatment group.

Serious adverse events were evaluated separately, and a narrative for each given.
11.10.1.7 General Principles

All significance tests were two-sided. In the analyses where centre was adjusted for, the validity of the statistical tests depended on there being a sufficient number of subjects recruited in each treatment group at each centre. If this was not achieved in all centres, pooling of small centres was done for analyses purposes. If it was not possible to pool small centres to form a sufficient large pooled centre, this pooled centre was pooled with the smallest of the other centres.

All efficacy data were tabulated by visit using an observed cases approach (i.e. involving only those subjects who attended each specific visit). Last observation carried forward (LOCF) data at relevant visits was used for efficacy data that was statistically analysed (using the last non-missing value for subjects with missing data at a particular visit).

Drop-outs and missing values were accounted for by the analysis of last observation values and by the definition of trial analysis sets prior to unblinding.

All the analyses specified in the protocol were reviewed in relation to the blinded data actually obtained and the Statistical Analysis Plan Update was finalised before breaking the randomisation code.

11.10.2 Changes in the Conduct of the Study or Planned Analyses

There was one protocol amendment (dated 15-FEB-2008) as detailed in section 11.7.7. There were no changes to the planned analyses after blind review of the database. The study and statistical analysis were conducted in line with the protocol and its amendment and the Statistical Analysis Plan Update.

Between 05-JAN-2009 and 20-JAN-2009, some dmg accountability data entries were visible in the RDC system for some subjects. Therefore there was a possibility that some investigators who were performing the subject assessment could have been unblinded if they entered any subject data between these dates.

Following database lock and unblinding on 01-APR-2009, the database was unlocked to make corrections to the weights for three subjects because they had been recorded in pounds and therefore required conversion to kilograms. In addition for one subject the location of an adverse event was changed (face to scalp) and the withdrawal reason changed from ‘lack of efficacy’ to ‘unacceptable adverse event’. Moreover, drug accountability data were corrected
since it turned out that in some cases the weight of the packaging had been included in the weight of the returned medication.

11.11 DATA MONITORING COMMITTEES
Not applicable

11.12 QUALITY ASSURANCE/AUDIT
LEO has implemented a system of quality assurance, including all the elements described in this report. Within this system company Standard Operating Procedures (SOPs) are implemented to ensure that clinical studies are conducted in compliance with regulatory requirements and Good Clinical Practice. Quality control is applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly.

Investigational sites, facilities, laboratories and all data (including sources) and documentation were available for GCP audit by LEO or inspection by competent authorities.

For this trial, one site audit was conducted. The audit certificate is provided in Appendix X.

11.13 DATA HANDLING
LEO, as Sponsor of this study, is responsible to the Authorities for assuring the proper conduct of the trial with regard to protocol adherence and validity of the data recorded on the Case Report Forms. Monitors were assigned to serve as the principal link between (sub)investigators and LEO and to advise the investigators in the collection and maintenance of complete, legible, well organised, and easily retrievable data for the trial. In addition, they were to explain any aspect of the (conduct of the) trial, including interpretation of the protocol, and purpose of collection of the specified data and reporting responsibilities to the investigators.

Subject data were entered directly into the eCRFs by site staff at the visit or as soon as possible after the visit took place. Data was single entered by site staff and source verified by the monitor. Systematic data validation was performed by LEO data managers and the study statistician to obtain a clean database prior to the statistical analysis.

Data were and are handled in accordance with the general terms and conditions of the authorisation from the Danish Data Protection Agency to LEO Pharma A/S, as required, according to the Danish Personal Act and any national legislation implementing the Data
Protection Directive (95/46/EC). LEO DK is considered data responsible for all international clinical trials sponsored by LEO.

12 STUDY PERIOD

12.1 STUDY DATES

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>The first subject was enrolled on</td>
<td>09-APR-2008</td>
</tr>
<tr>
<td>The first subject was randomised on</td>
<td>09-APR-2008</td>
</tr>
<tr>
<td>The last subject was enrolled on</td>
<td>17-NOV-2008</td>
</tr>
<tr>
<td>The last subject was randomised on</td>
<td>17-NOV-2008</td>
</tr>
<tr>
<td>Last subject completed treatment on</td>
<td>15-JAN-2009</td>
</tr>
<tr>
<td>Last subject follow-up visit was on</td>
<td>25-FEB-2009</td>
</tr>
</tbody>
</table>

Thus, the study had a duration of 10 months and 16 days. The study period is shown by centre in section 18 in Table 51. Study enrolment over time is shown in Figure 1.

Figure 1: Study enrolment
12.2 UNBLINDING OF THE STUDY
The database was locked on 01-APR-2009 following validation of the blinded data and then the randomisation schedule was released from Data Management on 01-APR-2009.

13 STUDY POPULATION

13.1 DISPOSITION OF STUDY SUBJECTS

13.1.1 Subjects Enrolled and Randomised
A total of 458 subjects were enrolled (defined as informed consent signed and a CRF started) from 18 centres. All 458 subjects were randomised in the study (183 to DAIVOBET/DOVOBET gel; 184 to calcitriol ointment and 91 to the gel vehicle).

The numbers of subjects enrolled in the different centres ranged from five to 45. As shown in Table 1 the treatment groups followed the 2:2:1 randomisation pattern in all centres. All
centres attempted to recruit a minimum of 15 subjects and most centres (16 of the 18) reached this recruitment target.
### Table 1: Subject enrolment and randomisation by centre: enrolled and randomised subjects

<table>
<thead>
<tr>
<th>Centre</th>
<th>Total number of subjects enrolled (n=458)</th>
<th>Total number of subjects randomised (n=458)</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>24</td>
<td>24</td>
<td>9</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
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<td>15</td>
<td>6</td>
<td>6</td>
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<tr>
<td>8</td>
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<td>19</td>
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<td>7</td>
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</tr>
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<td>9</td>
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<td>38</td>
<td>15</td>
<td>15</td>
<td>8</td>
</tr>
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<td>10</td>
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<td>16</td>
<td>7</td>
<td>6</td>
<td>3</td>
</tr>
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<td>11</td>
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<td>16</td>
<td>6</td>
<td>7</td>
<td>3</td>
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<td>12</td>
<td>45</td>
<td>45</td>
<td>18</td>
<td>18</td>
<td>9</td>
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<tr>
<td>13</td>
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<td>25</td>
<td>10</td>
<td>9</td>
<td>6</td>
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<tr>
<td>14</td>
<td>37</td>
<td>37</td>
<td>15</td>
<td>15</td>
<td>7</td>
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<tr>
<td>15</td>
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<td>16</td>
<td>6</td>
<td>7</td>
<td>3</td>
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<td>1</td>
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<td>17</td>
<td>45</td>
<td>45</td>
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<td>18</td>
<td>9</td>
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<td>11</td>
<td>10</td>
<td>5</td>
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<tr>
<td>19</td>
<td>24</td>
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<td>10</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>20</td>
<td>36</td>
<td>36</td>
<td>14</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>21</td>
<td>9</td>
<td>9</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>458</strong></td>
<td><strong>458</strong></td>
<td><strong>183</strong></td>
<td><strong>184</strong></td>
<td><strong>91</strong></td>
</tr>
</tbody>
</table>

For individual subject data on enrolment and randomisation see Appendix XI, Listings 29 to 31. Further details of investigator centre codes are shown in Appendix VII.

#### 13.1.2 Subject Withdrawals

The reasons for withdrawal from the treatment phase of the study are given in Table 2. There were 60 subjects who withdrew from the study during the treatment phase (before or at week 8; Visit 6); 12 (6.6%) receiving DAIVOBET/DOVOBET gel, 21 (11.4%) receiving tacalcitol ointment and 27 (29.7%) receiving gel vehicle.

Withdrawals due to ‘unacceptable treatment efficacy’ occurred at a lower frequency in the DAIVOBET/DOVOBET gel group compared with the tacalcitol and gel vehicle groups: 2 (1.1%) subjects in the DAIVOBET/DOVOBET gel group, 12 (6.5%) subjects in the tacalcitol
ointment group and 20 (22.0%) subjects in the gel vehicle group. ‘Unacceptable adverse events’ accounted for withdrawal of 3 (1.6%) subjects in the DAILOBET/DOVOBET gel group, 4 (2.2%) subjects in the tacalcitol ointment group and 4 (4.4%) subjects in the gel vehicle group.

At the end of the treatment phase of the study a total of 398 (86.9%) subjects were categorised as completers; 171 (93.4%) receiving DAILOBET/DOVOBET gel, 163 (88.6%) receiving tacalcitol ointment and 64 (70.3%) receiving the gel vehicle.

Of the 389 completers, a total of 108 entered the 8 week observation phase (Table 3). Seven subjects who had ‘controlled disease’ at week 8 and were eligible to enter the observation phase withdrew at this point and did not enter the observation phase. The percentage of completers who entered the observation phase from the DAILOBET/DOVOBET gel group (68 of 183; 37.2%) was higher than in the tacalcitol group (35 of 184; 19.0%) and the gel vehicle group (5 of 91; 5.4%).
Table 2: Reasons for withdrawal from treatment phase: randomised subjects

<table>
<thead>
<tr>
<th>Reason for discontinuance</th>
<th>All randomised subjects (n=458)</th>
<th>DAVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
<td>%</td>
</tr>
<tr>
<td>Withdrawals</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria emerging</td>
<td>2</td>
<td>0.4</td>
<td>2</td>
<td>1.1</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>8</td>
<td>1.7</td>
<td>4</td>
<td>2.2</td>
</tr>
<tr>
<td>Other reason(s)</td>
<td>1</td>
<td>0.2</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Unacceptable adverse event(s)</td>
<td>11</td>
<td>2.4</td>
<td>3</td>
<td>1.6</td>
</tr>
<tr>
<td>Unacceptable treatment efficacy</td>
<td>34</td>
<td>7.4</td>
<td>2</td>
<td>1.1</td>
</tr>
<tr>
<td>Voluntary (and no other reason)</td>
<td>4</td>
<td>0.9</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total number withdrawn from treatment phase</td>
<td>60</td>
<td>13.1</td>
<td>12</td>
<td>6.6</td>
</tr>
</tbody>
</table>
Table 2: Reasons for withdrawal from treatment phase: randomised subjects (continued)

<table>
<thead>
<tr>
<th>Reason for discontinuance</th>
<th>All randomised subjects (n=458)</th>
<th>DAIWOET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
<td>%</td>
</tr>
<tr>
<td>Completers of treatment phase'</td>
<td>398</td>
<td>86.9</td>
<td>171</td>
<td>93.4</td>
</tr>
</tbody>
</table>

1) Patient unable to attend appointments due to transportation issues
2) A completer of the treatment phase is defined as a subject who attended visit 6.
The reasons for withdrawal from the observation phase of the study are given in Table 3.

Of the subjects included in the observation phase 59 (54.6%) subjects withdrew from the study during that phase; 45 (66.2%) in the DAIVOBET/DOVOBET gel group, 14 (40.0%) in the tacalcitol ointment group and 0 (0.0%) in the gel vehicle group. The most common reason for withdrawal during the observation phase in the DAIVOBET/DOVOBET gel group was 'relapse/rebound of the disease during follow up' reported for 36 (52.9%) subjects. In the tacalcitol group the most common reason was 'other' for 6 (17.1%) subjects. None of the five subjects in the gel vehicle group withdrew during the observation phase.
Table 3: Reasons for withdrawal from observation phase: randomised subjects

<table>
<thead>
<tr>
<th>Reason for discontinuance</th>
<th>All randomised subjects (n=108)</th>
<th>DAIVOBET Gel (n=68)</th>
<th>Tacalcitol (n=35)</th>
<th>Gel Vehicle (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
<td>%</td>
</tr>
<tr>
<td>Withdrawals</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experienced relapse/rebound</td>
<td>40</td>
<td>37.0</td>
<td>36</td>
<td>52.9</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>1</td>
<td>0.9</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Other reason(s)</td>
<td>11</td>
<td>10.2</td>
<td>5</td>
<td>7.4</td>
</tr>
<tr>
<td>Voluntary (and no other reason)</td>
<td>7</td>
<td>6.5</td>
<td>4</td>
<td>5.9</td>
</tr>
<tr>
<td>Total number withdrawn from observation phase</td>
<td>59</td>
<td>54.6</td>
<td>45</td>
<td>66.2</td>
</tr>
<tr>
<td>Completers of observation phase</td>
<td>49</td>
<td>45.4</td>
<td>23</td>
<td>33.8</td>
</tr>
</tbody>
</table>

1) One subject in the Tacalcitol group with relapse/rebound as withdrawal reason entered the observation phase in error (did not have controlled disease at week 8).

2) Other reasons include: Entered observation phase in error (1 subject in the DAIVOBET group, 3 subjects in the Tacalcitol group), Requested treatment (2 subjects in the DAIVOBET group, 1 subject in the Tacalcitol group), Unable to continue due to school commitments (1 subject in the DAIVOBET group), Protocol violation (injection of steroid in left knee, 1 subject in the Tacalcitol group), Psoriasis slightly worse and patient wishes to start active treatment (1 subject in the DAIVOBET group), Subject feels skin worse (1 subject in the Tacalcitol group).

3) Subjects who withdrew after visit 6 are assumed not to have entered the observation phase and are not included in this table.
Reasons for withdrawal are summarised by last visit attended in section 18, during the treatment phase in Table 52 and during the observation phase in Table 53. For individual subject data on withdrawal reasons see Appendix XI, Listing 5.

13.1.3 Visit Attendance

The number of subjects attending the scheduled trial visits with the primary reason for those subjects who withdrew is given for the treatment phase in Figure 2 and for the observation phase in Figure 3.
Figure 2: Visit attendance by treatment group in the treatment phase: randomised subjects

DAIVOBET Gel

<table>
<thead>
<tr>
<th>Visit</th>
<th>Number of patients</th>
<th>Primary reason for withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (day 0)</td>
<td>183</td>
<td>1. Lost to follow up</td>
</tr>
<tr>
<td>2 (week 1)</td>
<td>180</td>
<td>1. Not attending</td>
</tr>
<tr>
<td>3 (week 2)</td>
<td>177</td>
<td>1. Not attending</td>
</tr>
<tr>
<td>4 (week 4)</td>
<td>176</td>
<td>2. Lost to follow-up</td>
</tr>
<tr>
<td>5 (week 6)</td>
<td>170</td>
<td>1. Unacceptable adverse event(s)</td>
</tr>
<tr>
<td>6 (week 8)</td>
<td>171</td>
<td>4. Not attending</td>
</tr>
</tbody>
</table>

1. Exclusion criteria emerging
2. Other reason(s)
3. Unacceptable adverse event(s)
4. Unacceptable treatment efficacy
5. Lost to follow up
6. Unacceptable adverse event(s)
Figure 2: Visit attendance by treatment group in the treatment phase: randomised subjects (continued)

<table>
<thead>
<tr>
<th>Visit 1 (day 0)</th>
<th>Number of patients: 184</th>
<th>Primary reason for withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2 not attending</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Visit 2 (week 1)</th>
<th>Number of patients: 182</th>
<th>Primary reason for withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 Lost to follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 Unacceptable adverse event(s)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Visit 3 (week 2)</th>
<th>Number of patients: 179</th>
<th>Primary reason for withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 not attending</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Visit 4 (week 4)</th>
<th>Number of patients: 175</th>
<th>Primary reason for withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 Lost to follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 Unacceptable adverse event(s)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 Unacceptable treatment efficacy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 Voluntary (and no other reason)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Visit 5 (week 6)</th>
<th>Number of patients: 166</th>
<th>Primary reason for withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2 not attending</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Visit 6 (week 8)</th>
<th>Number of patients: 163</th>
<th>Primary reason for withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 Lost to follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 Unacceptable treatment efficacy</td>
</tr>
</tbody>
</table>
Figure 2: Visit attendance by treatment group in the treatment phase: randomised subjects (continued)

Gel Vehicle

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Primary reason for withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>91</td>
<td>1 not attending</td>
</tr>
<tr>
<td>90</td>
<td>Lost to follow-up, 1 Unacceptable adverse event(s), 1 Unacceptable treatment efficacy</td>
</tr>
<tr>
<td>86</td>
<td>1 not attending</td>
</tr>
<tr>
<td>81</td>
<td>1 Unacceptable adverse event(s), 3 Unacceptable treatment efficacy</td>
</tr>
<tr>
<td>69</td>
<td>1 not attending, 10 Unacceptable treatment efficacy, 2 Voluntary (and no other reason)</td>
</tr>
<tr>
<td>64</td>
<td>6 Unacceptable treatment efficacy</td>
</tr>
</tbody>
</table>
Figure 3: Visit attendance in the observation phase: randomised subjects

**DAIVO BET Gel**

<table>
<thead>
<tr>
<th>Visit 6 (week 8)</th>
<th>171</th>
<th>103</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 7 (week 10)</td>
<td>68</td>
<td>1 Exclusion criteria emerging</td>
</tr>
<tr>
<td>Visit 8 (week 12)</td>
<td>44</td>
<td>1 Other reason(s)</td>
</tr>
<tr>
<td>Extra visit</td>
<td>1</td>
<td>4 Other reason(s)</td>
</tr>
<tr>
<td>Visit 9 (week 16)</td>
<td>23</td>
<td>19 Experienced relapse/rebound</td>
</tr>
</tbody>
</table>

**Tacalcitol**

<table>
<thead>
<tr>
<th>Visit 6 (week 8)</th>
<th>163</th>
<th>124</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 7 (week 10)</td>
<td>35</td>
<td>3 Other reason(s)</td>
</tr>
<tr>
<td>Visit 8 (week 12)</td>
<td>27</td>
<td>1 Lost to follow-up</td>
</tr>
<tr>
<td>Visit 9 (week 16)</td>
<td>21</td>
<td>2 Experienced relapse/rebound</td>
</tr>
</tbody>
</table>

**Gel Vehicle**

<table>
<thead>
<tr>
<th>Visit 6 (week 8)</th>
<th>64</th>
<th>59</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 7 (week 10)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Visit 8 (week 12)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Visit 9 (week 16)</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>
13.2 PROTOCOL DEVIATIONS

Major protocol deviations are summarised in Table 4. Deviations are shown by centre in Table 54 in section 18.

Table 4: Major protocol deviations: randomised subjects

<table>
<thead>
<tr>
<th>Protocol deviation</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disallowed medication at baseline</td>
<td>0 (0.0%)</td>
<td>2 (1.1%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Disallowed medication started after baseline</td>
<td>8 (4.4%)</td>
<td>4 (2.2%)</td>
<td>4 (4.4%)</td>
</tr>
<tr>
<td>Lost to follow-up after baseline</td>
<td>1 (0.5%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Non-compliance</td>
<td>2 (1.1%)</td>
<td>2 (1.1%)</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>UVB therapy prior to randomisation</td>
<td>0 (0.0%)</td>
<td>1 (0.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Violation of visit windows</td>
<td>4 (2.2%)</td>
<td>4 (2.2%)</td>
<td>4 (4.4%)</td>
</tr>
<tr>
<td>Total number of deviations¹</td>
<td>15 (8.2%)</td>
<td>13 (7.1%)</td>
<td>9 (9.9%)</td>
</tr>
<tr>
<td>Total number of subjects</td>
<td>14 (7.7%)</td>
<td>11 (6.0%)</td>
<td>9 (9.9%)</td>
</tr>
</tbody>
</table>

¹ Only deviations that led to exclusion of data from the per protocol analysis are included in this table. A single patient could have more than one deviation.

The percentages of patients with protocol deviations were generally similar among the three treatment groups. The most common protocol deviation was ‘disallowed medication started after baseline’ and ‘violation of visit windows’ reported in the DAIVOBET/DOVOBET gel group for 8 (4.4%) and 4 (2.2%) subjects respectively, in the tacalcitol group for 4 (2.2%) and 4 (2.2%) respectively and in the gel vehicle group for 4 (4.4%) subjects for both deviations. No subjects violated the disease specific eligibility criteria.

Further details on the protocol deviations leading to exclusion of subjects and subject data from the per protocol analysis set are detailed in section 14.1.3.

Individual subject data on protocol deviations are given in Appendix XI, Listing 6.
14 EFFICACY EVALUATION

14.1 DATA SETS ANALYSED

For individual subject data on reasons for exclusions from analysis sets and study analysis sets see Appendix XI, Listing 7 and 32. The different analysis sets are illustrated in Figure 4.

14.1.1 Full Analysis Set

All randomised subjects were included in the full analysis set. The full analysis set therefore consists of 458 subjects (183 in the DAIVOBET/DOVOBET gel group, 184 in the tacalcitol ointment group and 91 in the gel vehicle group).

14.1.2 Safety Analysis Set

The safety analysis set comprised all subjects who received any treatment with trial medication and for whom the presence or confirmed absence of adverse events was available. One subject (CRF [redacted]) was lost to follow up after Visit 1. This subject provided no information on the presence or confirmed absence of adverse events and was excluded from the safety analysis set.

In the Statistical Analysis Plan Update, two subjects (CRF [redacted] and [redacted]) were to be excluded from the safety analysis set if it could be confirmed that no medication was taken (by return of unopened/not used trial medication). However, this could not be confirmed from the drug accountability data and hence these two subjects were included in the safety analysis set.

The safety analysis set therefore consists of 457 subjects (182 in the DAIVOBET/DOVOBET gel group, 184 in the tacalcitol ointment group and 91 in the gel vehicle group).

14.1.3 Per-Protocol Analysis Set

The per protocol analysis set consists of those subjects in the full analysis set who have applied study medication, who provided efficacy data following the start of treatment and who met all inclusion/disease definition criteria described in the protocol. Other reasons for excluding subjects or subject data from the per protocol analysis set are: the use of therapies and medications which are not allowed (exclusion criteria 1-8 and 16, see section 11.4.2), disallowed diagnoses at baseline (exclusion criteria 10-14, see section 11.4.2) and non-compliance, including violation of visit windows. The grounds for excluding subjects or subject data are detailed below.
No subjects were excluded due to disallowed diagnoses at baseline. The following subjects were excluded from the per protocol analysis set for the following reasons:

- One subject (CRF [redacted]) was lost to follow up after Visit 1. This subject provided no efficacy data after the start of treatment.
- Three subjects (CRF [redacted] and [redacted] met exclusion criterion 3 at baseline (Systemic treatment with Vitamin D preparations above 500 IU per day, see section 11.4.2).
- One subject (CRF [redacted]) met exclusion criterion 5 at baseline (UVB therapy within 2 weeks prior to randomisation, see section 11.4.2).
- Five subjects (CRF [redacted] and [redacted] failed to apply the trial medication (for other reasons than clearance) more than half of the days up until their last on-treatment visit.
- Four subjects (CRF [redacted] and [redacted]) started using disallowed medication between Visit 1 and Visit 2.

Since the purpose of the analysis for the per protocol analysis set is to provide a sensitivity analysis for the primary and most important secondary analyses, the main focus is on week 4 and week 8 with LOCF at both times. Therefore for subjects whose assessment at Visit 4 was more than 37 days after baseline (i.e. 9 days after Day 28) the last visit before Visit 4 was regarded as the week 4 (LOCF) assessment and for subjects whose last assessment was more than 65 days after baseline (i.e. 9 days after Day 56) the last visit before Visit 6 was regarded as the week 8 (LOCF) assessment.

Two subjects (CRF [redacted] and [redacted]) came later than 37 days after baseline for the week 4 visit, and hence this visit was excluded for the per protocol analysis. Eleven subjects (CRF [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] and [redacted]) came later than 65 days after baseline for the week 8 visit, and hence this visit was excluded for the per protocol analysis.

Seven subjects used disallowed medication between their next-to-last visit (if after Visit 1) and their last visit, and hence had their last visit excluded from the per protocol analysis (CRF [redacted], CRF [redacted] (visit 5), CRF [redacted] (visit 6), CRF [redacted] (visit 6), CRF [redacted] (visit 6), CRF [redacted] (visit 5) and CRF [redacted] (visit 6)). Three subjects had more than one visit excluded from the per protocol analysis due to the use of disallowed medication (CRF [redacted] and CRF [redacted] had visit 4, 5 and 6 excluded; CRF [redacted] had visit 5 and 6 excluded). CRF [redacted] also used disallowed medication, but this subject was already excluded from the per protocol population because of non-compliance.
Therefore a total of 14 subjects were excluded and hence the per protocol analysis set consists of 444 subjects (177 in the DAIVOBET/DOVOBET gel group, 178 in the tacalcitol group and 89 in the gel vehicle group) of which 20 have an earlier last visit date than the last visit actually attended.
Figure 4: Schematic presentation of the trial analysis sets

**DAIVOBET Gel**
- Enrolled patients: 183
- Randomised patients = Full analysis set: 183 → 1 Lost to follow-up after Visit 1
- Safety analysis set: 182 → 5
  - 3 Disallowed medication before visit 2
  - 2 Non-compliance
- Per protocol analysis set: 177

**Tacalcitol**
- Enrolled patients: 184
- Randomised patients = Full analysis set: 184
- Safety analysis set: 184 → 6
  - 2 Disallowed medication at baseline
  - 1 UVB therapy prior to randomisation
  - 1 Disallowed medication before visit 2
  - 1 Non-compliance
  - 1 Non-compliance and disallowed medication
- Per protocol analysis set: 178

**Gel Vehicle**
- Enrolled patients: 91
- Randomised patients = Full analysis set: 91
- Safety analysis set: 91 → 2
  - 1 Disallowed medication before visit 2
  - 1 Non-compliance
- Per protocol analysis set: 89
14.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and baseline characteristics are presented for all randomised subjects. The demographics (age, sex and race) are presented in Tables 5 to 7. The baseline disease characteristics: skin type, duration of psoriasis vulgaris, the IGA, extent of psoriasis vulgaris, and the patient’s global assessment of disease severity are presented in Tables 8 to 12. Concurrent diagnoses and concomitant drug treatment at baseline are presented in Tables 13 and 14.

Mean age is shown in Table 5. The overall mean age was similar in all treatment groups and was 50.9 years in the DAIVOBET/DOVOBET gel group, 51.7 years in the tacalcitol group and 52.8 years in the gel vehicle group. The distribution of age by centre is given in Table 59 in section 18.

Table 5: Age: randomised subjects

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>All randomised subjects (n=458)</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>51.6</td>
<td>50.9</td>
<td>51.7</td>
<td>52.8</td>
</tr>
<tr>
<td>SD</td>
<td>14.0</td>
<td>14.3</td>
<td>13.4</td>
<td>14.9</td>
</tr>
<tr>
<td>Median</td>
<td>52.0</td>
<td>51.0</td>
<td>53.0</td>
<td>54.0</td>
</tr>
<tr>
<td>Minimum</td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Maximum</td>
<td>82</td>
<td>79</td>
<td>82</td>
<td>82</td>
</tr>
<tr>
<td>Number</td>
<td>458</td>
<td>183</td>
<td>184</td>
<td>91</td>
</tr>
</tbody>
</table>

For individual subject data on age see Appendix XI, Listing 8.
The distribution of sex is shown in Table 6. The overall distribution of sex was similar in all treatment groups and was consistent with the overall distribution of 62.2% males and 37.8% females. The distribution of sex by centre is given in Table 60 in section 18.

Table 6: Sex: randomised subjects

<table>
<thead>
<tr>
<th>Sex</th>
<th>All randomised subjects (n=458)</th>
<th>DAIWOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects %</td>
<td>Number of Subjects %</td>
<td>Number of Subjects %</td>
<td>Number of Subjects %</td>
</tr>
<tr>
<td>Male</td>
<td>285 62.2</td>
<td>117 63.9</td>
<td>115 62.5</td>
<td>53 58.2</td>
</tr>
<tr>
<td>Female</td>
<td>173 37.8</td>
<td>66 36.1</td>
<td>69 37.5</td>
<td>38 41.8</td>
</tr>
<tr>
<td>Total</td>
<td>458 100.0</td>
<td>183 100.0</td>
<td>184 100.0</td>
<td>91 100.0</td>
</tr>
</tbody>
</table>

For individual subject data on sex see Appendix XI, Listing 8.

The distribution of race is shown in Table 7. Nearly all the subjects (93.9%) were White. The distribution of race by centre is given in Table 61 in section 18. Ethnicity is summarised in section 18, Table 62. Few subjects self reported Hispanic or Latino ethnicity; three (1.6%) subjects in the DAIWOBET/DOVOBET group, two (1.1%) in the tacalcitol group and one (1.1%) in the gel vehicle group.
Table 7: Race: randomised subjects

<table>
<thead>
<tr>
<th>Race</th>
<th>All randomised subjects (n=458)</th>
<th>DAIUBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
<td>%</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>2</td>
<td>0.4</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Asian</td>
<td>5</td>
<td>1.1</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Black or African American</td>
<td>4</td>
<td>0.9</td>
<td>2</td>
<td>1.1</td>
</tr>
<tr>
<td>Native Hawaiian or Other Pacific Islander</td>
<td>1</td>
<td>0.2</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>White</td>
<td>430</td>
<td>93.9</td>
<td>173</td>
<td>94.5</td>
</tr>
<tr>
<td>Other</td>
<td>16</td>
<td>3.5</td>
<td>5</td>
<td>2.7</td>
</tr>
<tr>
<td>Total</td>
<td>458</td>
<td>100.0</td>
<td>183</td>
<td>100.0</td>
</tr>
</tbody>
</table>

For individual subject data on race and ethnicity see Appendix XI, Listing 8.
Skin type is shown in Table 8. Most subjects were skin types II (white; always burns easily), III (white; burns moderately) and IV (white; burns minimally). The distribution of skin type was similar among the groups. The distribution of skin type by centre is presented in Table 63 in section 18.

Table 8: Skin type: randomised subjects

<table>
<thead>
<tr>
<th>Skin type</th>
<th>All randomised subjects (n=458)</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
<td>%</td>
</tr>
<tr>
<td>I</td>
<td>12</td>
<td>2.6</td>
<td>5</td>
<td>2.7</td>
</tr>
<tr>
<td>II</td>
<td>146</td>
<td>31.9</td>
<td>56</td>
<td>30.6</td>
</tr>
<tr>
<td>III</td>
<td>167</td>
<td>36.5</td>
<td>66</td>
<td>36.1</td>
</tr>
<tr>
<td>IV</td>
<td>106</td>
<td>23.1</td>
<td>47</td>
<td>25.7</td>
</tr>
<tr>
<td>V</td>
<td>22</td>
<td>4.8</td>
<td>7</td>
<td>3.8</td>
</tr>
<tr>
<td>VI</td>
<td>5</td>
<td>1.1</td>
<td>2</td>
<td>1.1</td>
</tr>
<tr>
<td>Total</td>
<td>458</td>
<td>100.0</td>
<td>183</td>
<td>100.0</td>
</tr>
</tbody>
</table>

For individual subject data on skin type see Appendix XI, Listing 8.

The mean duration of psoriasis vulgaris is shown in Table 9. The mean duration of psoriasis vulgaris was similar among treatment groups and was 21.2 years in the DAIVOBET/DOVOBET group, 19.1 years in the tacalcitol group and 18.5 years in the gel vehicle group. The distribution of duration of disease by centre is presented in Table 64 in section 18.
Table 9: Duration of psoriasis vulgaris: randomised subjects

<table>
<thead>
<tr>
<th>Duration (years)</th>
<th>All randomised subjects (n=458)</th>
<th>DAIYOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>19.8</td>
<td>21.2</td>
<td>19.1</td>
<td>18.5</td>
</tr>
<tr>
<td>SD</td>
<td>13.3</td>
<td>13.2</td>
<td>12.9</td>
<td>14.3</td>
</tr>
<tr>
<td>Median</td>
<td>18.0</td>
<td>20.0</td>
<td>17.0</td>
<td>16.0</td>
</tr>
<tr>
<td>Minimum</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Maximum</td>
<td>70</td>
<td>58</td>
<td>60</td>
<td>70</td>
</tr>
<tr>
<td>Number</td>
<td>458</td>
<td>183</td>
<td>184</td>
<td>91</td>
</tr>
</tbody>
</table>

For individual subject data on duration of disease see Appendix XI, Listing 33.

The distribution of the IGA is shown in Table 10. The distribution of the IGA was similar among the three treatment groups. Most subjects had moderate disease: 130 (71.0%) in the DAIYOBET/DOVOBET group, 119 (64.7%) in the tacalcitol group and 64 (70.3%) in the gel vehicle group. Few subjects had very severe disease. The distribution of the IGA at baseline by centre is given in Table 65 in section 18.

Table 10: Investigator’s global assessment of disease severity: randomised subjects

<table>
<thead>
<tr>
<th>Investigator Assessment</th>
<th>All randomised subjects (n=458)</th>
<th>DAIYOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
<td>%</td>
</tr>
<tr>
<td>Moderate</td>
<td>313</td>
<td>68.3</td>
<td>130</td>
<td>71.0</td>
</tr>
<tr>
<td>Severe</td>
<td>135</td>
<td>29.5</td>
<td>50</td>
<td>27.3</td>
</tr>
<tr>
<td>Very severe</td>
<td>10</td>
<td>2.2</td>
<td>3</td>
<td>1.6</td>
</tr>
<tr>
<td>Total</td>
<td>458</td>
<td>100.0</td>
<td>183</td>
<td>100.0</td>
</tr>
</tbody>
</table>

For individual subject data on the IGA see Appendix XI, Listing 11.

The mean extent of psoriasis vulgaris at baseline is shown in Table 11. The mean extent was similar among the three treatment groups; 9.0% in the DAIYOBET/DOVOBET group, 9.5%
in the tacalcitol group and 9.4% in the gel vehicle group. The investigator’s assessment of extent of psoriasis vulgaris at baseline by centre is given in Table 67 in section 18.

Table 11: Investigator’s assessment of extent of psoriasis vulgaris: randomised subjects

<table>
<thead>
<tr>
<th>Total area involved (%)</th>
<th>All randomised subjects (n=658)</th>
<th>DAIVOBBT Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>9.3</td>
<td>9.0</td>
<td>9.5</td>
<td>9.4</td>
</tr>
<tr>
<td>SD</td>
<td>8.2</td>
<td>7.7</td>
<td>9.6</td>
<td>6.2</td>
</tr>
<tr>
<td>Median</td>
<td>7.0</td>
<td>7.0</td>
<td>7.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Minimum</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Maximum</td>
<td>84</td>
<td>72</td>
<td>84</td>
<td>41</td>
</tr>
<tr>
<td>Number</td>
<td>458</td>
<td>183</td>
<td>184</td>
<td>91</td>
</tr>
</tbody>
</table>

The investigators assessments of the extent and severity of the clinical signs (redness, thickness, scaliness) on the arms, trunk and legs (from which the PASI was calculated) are shown in section 18 Table 68 and Table 69, Table 70 and Table 71 (trunk) and Table 72 and Table 73 (legs).

For individual subject data on extent of psoriasis vulgaris, extent and severity of the clinical signs and the PASI see Appendix XI, Listings 12 and 13.

The distribution of the patient’s global assessment of disease severity is shown in Table 12. The overall distribution was similar among the three treatment groups. Most subjects had moderate disease; 111 (60.7%) in the DAVOBET/DOVOBET group, 92 (50.3%) in the tacalcitol group and 61 (67.8%) in the gel vehicle group. Few subjects reported very mild disease. The distribution of the patient’s assessment of disease severity at baseline by centre is given in Table 66 in section 18.
Table 12: Patient’s global assessment of disease severity: randomised subjects

<table>
<thead>
<tr>
<th>Subject Assessment</th>
<th>All randomised subjects (n=458)</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td>Very Mild</td>
<td>16</td>
<td>3.5</td>
<td>8</td>
<td>4.4</td>
</tr>
<tr>
<td>Mild</td>
<td>68</td>
<td>14.9</td>
<td>24</td>
<td>13.1</td>
</tr>
<tr>
<td>Moderate</td>
<td>264</td>
<td>57.9</td>
<td>111</td>
<td>60.7</td>
</tr>
<tr>
<td>Severe</td>
<td>108</td>
<td>23.7</td>
<td>40</td>
<td>21.9</td>
</tr>
<tr>
<td>Total</td>
<td>456</td>
<td>100.0</td>
<td>183</td>
<td>100.0</td>
</tr>
</tbody>
</table>

For individual subject data on the patient’s global assessment of disease severity see Appendix XI, Listing 14.

Concurrent diagnoses were categorised according to the MedDRA (Medical Dictionary for Regulatory Activities) coding system. All categorisation was done prior to unblinding the study using MedDRA version 6.1.

Table 13 shows the number of subjects with concurrent diagnoses at baseline categorised to each primary System Organ Class (SOC). The percentage of subjects with at least one concurrent diagnosis at baseline was similar at baseline in all three treatment groups with 167 (91.3%) in the DAIVOBET/DOVOBET gel group, 162 (88.0%) in the tacalcitol group and 84 (92.3%) in the gel vehicle group. The most common diagnoses were in the SOC ‘Musculoskeletal and connective tissues disorders’ 176 (38.4%) subjects and ‘Surgical and medical procedures’ 162 (35.4%) subjects.
Table 13: Concurrent diagnoses at baseline by MedDRA primary system organ class: randomised subjects

<table>
<thead>
<tr>
<th>System Organ Classification</th>
<th>All randomised subjects (n=458)</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>8</td>
<td>8</td>
<td>1.7</td>
<td>2</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>74</td>
<td>61</td>
<td>13.3</td>
<td>26</td>
</tr>
<tr>
<td>Congenital, familial and genetic disorders</td>
<td>4</td>
<td>4</td>
<td>0.9</td>
<td>0</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>15</td>
<td>15</td>
<td>3.3</td>
<td>6</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>38</td>
<td>34</td>
<td>7.4</td>
<td>19</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>30</td>
<td>29</td>
<td>6.3</td>
<td>16</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>111</td>
<td>97</td>
<td>21.2</td>
<td>36</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>16</td>
<td>16</td>
<td>3.5</td>
<td>5</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>10</td>
<td>9</td>
<td>2.0</td>
<td>1</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>139</td>
<td>112</td>
<td>24.5</td>
<td>60</td>
</tr>
</tbody>
</table>
Table 13: Concurrent diagnoses at baseline by MedDRA Primary System Organ Class: randomised subjects (continued)

<table>
<thead>
<tr>
<th>System Organ Classification</th>
<th>All randomised subjects (n=458)</th>
<th>DAIWO BET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>40</td>
<td>7.6</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>19</td>
<td>3.9</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Investigations</td>
<td>25</td>
<td>4.8</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>188</td>
<td>31.4</td>
<td>75</td>
<td>57</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>209</td>
<td>38.4</td>
<td>96</td>
<td>79</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>38</td>
<td>7.2</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>99</td>
<td>20.7</td>
<td>39</td>
<td>39</td>
</tr>
</tbody>
</table>
Table 13: Concurrent diagnoses at baseline by MedDRA Primary System Organ Class: randomised subjects (continued)

<table>
<thead>
<tr>
<th>System Organ Classification¹</th>
<th>All randomised subjects (n=458)</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Diag.²</td>
<td>No. Subj.²</td>
<td>%</td>
<td>No. Diag.³</td>
</tr>
<tr>
<td>Pregnancy, puerperium and perinatal conditions</td>
<td>1</td>
<td>1</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>97</td>
<td>84</td>
<td>18.3</td>
<td>37</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>9</td>
<td>9</td>
<td>2.0</td>
<td>4</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>30</td>
<td>30</td>
<td>6.6</td>
<td>16</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>64</td>
<td>61</td>
<td>13.3</td>
<td>21</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>125</td>
<td>110</td>
<td>24.0</td>
<td>48</td>
</tr>
<tr>
<td>Social circumstances</td>
<td>21</td>
<td>21</td>
<td>4.6</td>
<td>7</td>
</tr>
<tr>
<td>Surgical and medical procedures</td>
<td>224</td>
<td>162</td>
<td>35.4</td>
<td>91</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>157</td>
<td>149</td>
<td>32.5</td>
<td>62</td>
</tr>
</tbody>
</table>
**Table 13: Concurrent diagnoses at baseline by MedDRA Primary System Organ Class: randomised subjects (continued)**

<table>
<thead>
<tr>
<th>System Organ Classification'</th>
<th>All randomised subjects (n=458)</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Diag.'</td>
<td>No. Subj.'</td>
<td>%</td>
<td>No. Diag.'</td>
</tr>
<tr>
<td>Total number of diagnoses'</td>
<td>1791</td>
<td>712</td>
<td>90.2</td>
<td>740</td>
</tr>
<tr>
<td>Total number of subjects</td>
<td>413</td>
<td></td>
<td>90.2</td>
<td>167</td>
</tr>
</tbody>
</table>

1) Classification according to MedDRA version 6.1
2) Different diagnoses within the same preferred term and involving the same subject have been counted as one. A single patient could appear in multiple classes.
3) Number of diagnoses
4) Number of subjects

For individual subject data on medical history and concurrent diagnoses see Appendix XI, Listings 33 and 34.
At Visit 1, the use of concomitant medications was recorded. These medications were coded according to the WHO Anatomical Therapeutic Chemical (ATC) Classification System. The numbers of subjects taking concomitant medication at baseline are shown in Table 14. The percentage of subjects taking at least one medication at baseline was similar in all three treatment groups with 139 (76.0%) in the DAIVOBE T/DOVOBET gel group, 140 (76.1%) in the tacalcitol group and 73 (80.2%) in the gel vehicle group. The most common medications were those coded in the classes (ATC) as ‘Cardiovascular system’ (176 subjects; 38.4%), ‘Alimentary tract and metabolism’ (150 subjects; 32.8%) and ‘Nervous system’ (147 subjects; 32.1%). ‘Dermatologicals’ were taken by 75 (16.4%) subjects.
Table 14: Concomitant drug treatment at baseline: randomised subjects

<table>
<thead>
<tr>
<th>ATC classification index level 1</th>
<th>All randomised subjects (n=458)</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Drugs</td>
<td>No. Subj.</td>
<td>%</td>
<td>No. Drugs</td>
</tr>
<tr>
<td><strong>ALIMENTARY TRACT AND METABOLISM</strong></td>
<td>254</td>
<td>150</td>
<td>32.8</td>
<td>96</td>
</tr>
<tr>
<td><strong>ANTIINFECTIVES FOR SYSTEMIC USE</strong></td>
<td>7</td>
<td>6</td>
<td>1.3</td>
<td>1</td>
</tr>
<tr>
<td><strong>ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS</strong></td>
<td>3</td>
<td>3</td>
<td>0.7</td>
<td>1</td>
</tr>
<tr>
<td><strong>BLOOD AND BLOOD FORMING ORGANS</strong></td>
<td>101</td>
<td>94</td>
<td>20.5</td>
<td>37</td>
</tr>
<tr>
<td><strong>CARDIOVASCULAR SYSTEM</strong></td>
<td>395</td>
<td>176</td>
<td>38.4</td>
<td>164</td>
</tr>
<tr>
<td><strong>DERMATOLOGICALS</strong></td>
<td>99</td>
<td>75</td>
<td>16.4</td>
<td>37</td>
</tr>
<tr>
<td><strong>GENITO URINARY SYSTEM AND SEX HORMONES</strong></td>
<td>48</td>
<td>44</td>
<td>9.6</td>
<td>18</td>
</tr>
<tr>
<td><strong>MUSCULO- SKELETAL SYSTEM</strong></td>
<td>109</td>
<td>96</td>
<td>21.0</td>
<td>46</td>
</tr>
<tr>
<td><strong>NERVOUS SYSTEM</strong></td>
<td>206</td>
<td>147</td>
<td>32.1</td>
<td>88</td>
</tr>
<tr>
<td><strong>RESPIRATORY SYSTEM</strong></td>
<td>97</td>
<td>62</td>
<td>13.5</td>
<td>28</td>
</tr>
<tr>
<td><strong>SENSORY ORGANS</strong></td>
<td>13</td>
<td>10</td>
<td>2.2</td>
<td>6</td>
</tr>
</tbody>
</table>
Table 14: Concomitant drug treatment at baseline: randomised subjects (continued)

<table>
<thead>
<tr>
<th>ATC classification index level 1</th>
<th>All randomised subjects (n=458)</th>
<th>DAIROBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Drugs</td>
<td>No. Subj.</td>
<td>%</td>
<td>No. Drugs</td>
</tr>
<tr>
<td>SYSTEMIC HORMONAL PREP</td>
<td>32</td>
<td>32</td>
<td>7.0</td>
<td>15</td>
</tr>
<tr>
<td>VARIOUS</td>
<td>18</td>
<td>18</td>
<td>3.9</td>
<td>4</td>
</tr>
<tr>
<td><strong>Total number of drugs</strong></td>
<td>1382</td>
<td></td>
<td></td>
<td>541</td>
</tr>
<tr>
<td><strong>Total number of subjects</strong></td>
<td>352</td>
<td>76.9</td>
<td></td>
<td>139</td>
</tr>
</tbody>
</table>

1) Anatomical Therapeutic Chemical (ATC) classification index
2) Drugs with the same ATC classification level 4 code and generic name/preferred term name which have been taken by the same subject have been counted as one
3) Number of subjects

For individual subject data on concomitant medication see Appendix XI, Listing 35.
Other baseline characteristics, height, weight and vital signs (systolic and diastolic blood pressure), are summarised in section 18 in Table 55 (height), Table 56 (weight), Table 57 (systolic blood pressure) and Table 58 (diastolic blood pressure). Mean height was similar among the groups; 169.7cm for the DAIVO BET/DOVO BET group, 169.4cm in the tacalcitol group and 168.5cm in the gel vehicle group. Mean weight was similar among the groups and was 89.5 Kg for the DAIVO BET/DOVO BET group, 90.5 Kg for the tacalcitol group and 86.5 Kg for the gel vehicle group. Mean systolic and diastolic blood pressures were similar among the groups. Mean systolic blood pressure was 127.3mmHg and mean diastolic blood pressure was 78.1mmHg.

For individual subject data on height, weight and blood pressure see Appendix XI, Listing 36.

14.3 TREATMENT

14.3.1 Use of and Compliance with Prescribed Trial Medication

Compliance with prescribed study medication is summarised in Table 15. Compliance data was available for the total treatment period for all subjects except two: one subject in the DAIVO BET/DOVO BET gel group was lost to follow up and did not provide any data and one subject in the gel vehicle group who did not provide any compliance data at Visit 4.

Among the subjects who had compliance data recorded 119 subjects (65.0%) in the DAIVO BET/DOVO BET gel group, 126 (68.5%) in the tacalcitol group and 58 (63.7%) in the gel vehicle group applied the treatment as instructed. A further 53 (29.0%) subjects in the DAIVO BET/DOVO BET gel group, 45 (24.5%) in the tacalcitol group and 22 (24.2%) in the gel vehicle group missed 10% applications or less.
Table 15: Compliance with treatment instructions: randomised subjects

<table>
<thead>
<tr>
<th>Medication used as prescribed</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td>Yes</td>
<td>119</td>
<td>65.0</td>
<td>126</td>
</tr>
<tr>
<td>No: &lt;= 10% applications missed</td>
<td>53</td>
<td>29.0</td>
<td>45</td>
</tr>
<tr>
<td>&gt;10% and &lt;=20% applications missed</td>
<td>6</td>
<td>3.3</td>
<td>5</td>
</tr>
<tr>
<td>&gt;20% and &lt;=30% applications missed</td>
<td>1</td>
<td>0.5</td>
<td>3</td>
</tr>
<tr>
<td>&gt;30% and &lt;=40% applications missed</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
</tr>
<tr>
<td>&gt;40% and &lt;=50% applications missed</td>
<td>2</td>
<td>1.1</td>
<td>1</td>
</tr>
<tr>
<td>&gt;50% applications missed</td>
<td>1</td>
<td>0.5</td>
<td>2</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
</tr>
</tbody>
</table>

Total: 183 100.0 184 100.0 91 100.0

1) Applications missed due to clearance are not counted as missed applications
2) CRF 1111 was lost to follow-up after visit 1 and did not provide compliance data. CRF 1111 did not provide compliance data at visit 4.

For individual subject data on compliance see Appendix XI, Listing 9.

14.4 Efficacy Results

14.4.1 Primary Response Criterion

14.4.1.1 Controlled Disease according to the IGA at Weeks 8

The percentage of subjects with ‘controlled disease’ at week 8 (LOCF) and the statistical analysis is shown in Table 16 for the full analysis set, in Table 17 for the per protocol analysis set and by centre in section 18, Table 74.

The proportion of subjects who achieved ‘controlled disease’ at week 8 (LOCF) in the DAIVOBET/DOVOBET gel group was 39.9% compared with 5.5% in the gel vehicle group and 17.9% in the tacalcitol group. DAIVOBET/DOVOBET gel was statistically significantly more effective than the gel vehicle (OR 13.9; 95% CI 4.99 to 38.7; p<0.001) and the sequential test versus tacalcitol also showed the superior efficacy of DAIVOBET/DOVOBET gel.
(OR 3.42; 95% CI 2.05 to 5.70; p<0.001). The analysis of the per protocol analysis set supported the results for the full analysis set. For both these analyses, the Breslow-Day test to investigate the consistency of the response across centres was not statistically significant which means that no treatment by centre interactions were found (p>0.10).

Table 16: Subjects with ‘Controlled disease’ according to the investigator’s global assessment of disease severity at week 8 and results of statistical analysis: full analysis set

<table>
<thead>
<tr>
<th>Controlled disease</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled</td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Controlled</td>
<td>73</td>
<td>33</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>39.9</td>
<td>17.9</td>
<td>5.5</td>
</tr>
<tr>
<td>Non-controlled</td>
<td>110</td>
<td>151</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>60.1</td>
<td>82.1</td>
<td>94.5</td>
</tr>
<tr>
<td>Total</td>
<td>183</td>
<td>184</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Odds ratio(^1)</td>
<td>3.42</td>
<td>13.9</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>2.05 to 5.70</td>
<td>4.99 to 38.7</td>
<td></td>
</tr>
<tr>
<td>CMH test(^2)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Breslow-Day test(^3)</td>
<td>0.99</td>
<td>0.88</td>
<td></td>
</tr>
</tbody>
</table>

1) Cochran-Mantel-Haenszel Odds for Controlled disease (Daivobet Gel relative to Tacalcitol/Gel vehicle) adjusted for centre
2) Cochran-Mantel-Haenszel test for the hypothesis of odds ratio equal to 1
3) Test for homogeneity of odds ratios across centres
Table 17: Subjects with ‘Controlled disease’ according to the investigator’s global assessment of disease severity at week 8 and results of statistical analysis: per protocol analysis set

<table>
<thead>
<tr>
<th>Controlled disease</th>
<th>DAVOBET Gel (n=177)</th>
<th>Tacalcitol (n=178)</th>
<th>Gel Vehicle (n=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
<td>%</td>
</tr>
<tr>
<td>Controlled</td>
<td>73</td>
<td>31</td>
<td>5</td>
</tr>
<tr>
<td>Non-controlled</td>
<td>104</td>
<td>147</td>
<td>84</td>
</tr>
<tr>
<td>Total</td>
<td>177</td>
<td>178</td>
<td>89</td>
</tr>
</tbody>
</table>

| Odds ratio¹       | 3.83                | 14.4               |
| 95% CI            | 2.27 to 6.46        | 5.17 to 40.1       |
| CMH test²         | < 0.001             | < 0.001            |
| Breslow-Day test³ | 0.97                | 0.88               |

¹) Cochran-Mantel-Haenszel Odds for Controlled disease (Davobet Gel relative to Tacalcitol/Gel vehicle) adjusted for centre
²) Cochran-Mantel-Haenszel test for the hypothesis of odds ratio equal to 1
³) Test for homogeneity of odds ratios across centres

For individual subject data on the IGA see Appendix XI, Listing 11.

14.4.1.2 Controlled Disease according to the IGA in Subgroups

The proportion of subjects who achieved ‘controlled disease’ at week 8 is presented by age group (≤ 35, 36-50, 51-64, ≥ 65), by sex, by ethnic origin, by race, by skin type and by baseline disease severity.

The proportion of subjects who achieved ‘controlled disease’ at week 8 by age group is presented in Table 18. ‘Controlled disease’ occurred in all age groups in the DAVOBET/DOVOBET gel and tacalcitol groups. Few subjects in the gel vehicle group achieved ‘controlled disease’ and in the 36-50 years age group no subjects achieved ‘controlled disease’. The percentage of subjects who achieved ‘controlled disease’ was greater in all age groups in the DAVOBET/DOVOBET gel group compared with the other two treatment groups.
Table 18: Subjects with ‘Controlled disease’ according to the investigator’s global assessment of disease severity at week 8 by age group: full analysis set

<table>
<thead>
<tr>
<th>Age group</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td>&lt;=35</td>
<td>Controlled</td>
<td>12</td>
<td>41.4</td>
</tr>
<tr>
<td></td>
<td>Non-controlled</td>
<td>17</td>
<td>58.6</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>29</td>
<td>100.0</td>
</tr>
<tr>
<td>36-50</td>
<td>Controlled</td>
<td>29</td>
<td>48.3</td>
</tr>
<tr>
<td></td>
<td>Non-controlled</td>
<td>31</td>
<td>51.7</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>60</td>
<td>100.0</td>
</tr>
<tr>
<td>51-64</td>
<td>Controlled</td>
<td>15</td>
<td>25.4</td>
</tr>
<tr>
<td></td>
<td>Non-controlled</td>
<td>44</td>
<td>74.6</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>59</td>
<td>100.0</td>
</tr>
<tr>
<td>&gt;=65</td>
<td>Controlled</td>
<td>17</td>
<td>48.6</td>
</tr>
<tr>
<td></td>
<td>Non-controlled</td>
<td>18</td>
<td>51.4</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>35</td>
<td>100.0</td>
</tr>
<tr>
<td>Total</td>
<td>Controlled</td>
<td>73</td>
<td>39.9</td>
</tr>
<tr>
<td></td>
<td>Non-controlled</td>
<td>110</td>
<td>60.1</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>183</td>
<td>100.0</td>
</tr>
</tbody>
</table>

The proportion of subjects who achieved ‘controlled disease’ at week 8 by sex is presented in Table 19. ‘Controlled disease’ occurred in both males and females in all treatment groups. Both males and females showed a greater response rate with DAIVOBET/DOVOBET gel compared with the other two treatment groups.
Table 19: Subjects with ‘Controlled disease’ according to the investigator’s global assessment of disease severity at week 8 by sex: full analysis set

<table>
<thead>
<tr>
<th>Sex</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled</td>
<td>49 (41.9)</td>
<td>21 (18.3)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Non-controlled</td>
<td>68 (58.1)</td>
<td>94 (81.7)</td>
<td>52 (98.1)</td>
</tr>
<tr>
<td>Total</td>
<td>117 (100.0)</td>
<td>115 (100.0)</td>
<td>53 (100.0)</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled</td>
<td>24 (36.4)</td>
<td>12 (17.4)</td>
<td>4 (10.5)</td>
</tr>
<tr>
<td>Non-controlled</td>
<td>42 (63.6)</td>
<td>57 (82.6)</td>
<td>34 (89.5)</td>
</tr>
<tr>
<td>Total</td>
<td>66 (100.0)</td>
<td>69 (100.0)</td>
<td>38 (100.0)</td>
</tr>
<tr>
<td>Total</td>
<td>73 (39.9)</td>
<td>33 (17.9)</td>
<td>5 (5.5)</td>
</tr>
<tr>
<td>Non-controlled</td>
<td>110 (60.1)</td>
<td>151 (82.1)</td>
<td>86 (94.5)</td>
</tr>
<tr>
<td>Total</td>
<td>183 (100.0)</td>
<td>184 (100.0)</td>
<td>91 (100.0)</td>
</tr>
</tbody>
</table>

The proportion of subjects who achieved ‘controlled disease’ at week 8 by race is presented in Table 75 in section 18 and by ethnic origin in Table 76 in section 18. It is difficult to make any comments regarding the response rates in the different racial and ethnicity subgroups due to the predominance of Whites and Non Hispanic/Non Latino subjects in all three treatment groups.

The proportion of subjects who achieved ‘controlled disease’ at week 8 by skin type is presented in Table 77 in section 18. There were few subjects with skin types I, V and VI so it is difficult to make any comments regarding the response rates in these subgroups. However in the skin types II and III higher percentages of subjects in the DAIVOBET/DOVOBET gel group achieved ‘controlled disease’ compared with the other two treatment groups. For skin type II 19 (33.9%) subjects in the DAIVOBET/DOVOBET gel group achieved ‘controlled disease’ versus 10 (15.4%) for tacalcitol and one (4.0%) for the gel vehicle. The corresponding figures for skin type III were 33 (50.0%) for DAIVOBET/DOVOBET gel versus 11 (17.2%) for tacalcitol and 1 (2.7%) for the gel vehicle. The response rates for skin type IV
were similar for DAIVOBET/DOVOBET gel (29.8%) and tacalcitol (25.6%) and both were higher than the gel vehicle (15.0%).

The proportion of subjects who achieved ‘controlled disease’ at week 8 by baseline disease severity is presented in Table 20. A higher percentage of subjects in the DAIVOBET/DOVOBET gel group achieved ‘controlled disease’ in all disease severities compared with tacalcitol and the gel vehicle.

Table 20: Subjects with ‘Controlled disease’ according to the investigator’s global assessment of disease severity at week 8 by baseline disease severity: full analysis set

<table>
<thead>
<tr>
<th>Baseline IGA Controlled disease</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled</td>
<td>54</td>
<td>41.5</td>
<td>25</td>
</tr>
<tr>
<td>Non-controlled</td>
<td>76</td>
<td>58.5</td>
<td>94</td>
</tr>
<tr>
<td>Total</td>
<td>130</td>
<td>100.0</td>
<td>119</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled</td>
<td>17</td>
<td>34.0</td>
<td>7</td>
</tr>
<tr>
<td>Non-controlled</td>
<td>33</td>
<td>66.0</td>
<td>51</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>100.0</td>
<td>58</td>
</tr>
<tr>
<td>Very severe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled</td>
<td>2</td>
<td>66.7</td>
<td>1</td>
</tr>
<tr>
<td>Non-controlled</td>
<td>1</td>
<td>33.3</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>100.0</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>73</td>
<td>39.9</td>
<td>33</td>
</tr>
<tr>
<td>Non-controlled</td>
<td>110</td>
<td>60.1</td>
<td>151</td>
</tr>
<tr>
<td>Total</td>
<td>183</td>
<td>100.0</td>
<td>184</td>
</tr>
</tbody>
</table>

For individual subject data on the IGA see Appendix XI, Listing 11.

14.4.2 Secondary and Tertiary Response Criteria

14.4.2.1 Investigator’s global assessment of disease severity

For individual subject data on the IGA see Appendix XI, Listing 11.
14.4.2.1.1 Controlled Disease according to the IGA at Week 4
The percentage of subjects with ‘controlled disease’ at week 4 (LOCF) and the statistical analysis is shown in Table 21.

At week 4 the proportion of subjects who achieved ‘controlled disease’ at week 4 (LOCF) in the DAIVOBET/DOVOBET gel group was 18.6% compared with 6.5% in the tacalcitol group and 1.1% in the gel vehicle group. DAIVOBET/DOVOBET gel was statistically significantly more effective than tacalcitol (OR; 3.51; 98.33% CI; 1.46 to 8.40; p<0.001) and the gel vehicle (OR; 32.9; 98.33% CI; 2.07 to 522; p<0.001). There were no treatment by centre interactions (p<0.10).

Table 21: Subjects with ‘Controlled disease’ according to the investigator’s global assessment of disease severity at week 4 and results of statistical analysis: full analysis set

<table>
<thead>
<tr>
<th>Disease Status</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td>Controlled</td>
<td>34</td>
<td>18.6</td>
<td>12</td>
</tr>
<tr>
<td>Non-controlled</td>
<td>149</td>
<td>81.4</td>
<td>172</td>
</tr>
<tr>
<td>Total</td>
<td>183</td>
<td>100.0</td>
<td>184</td>
</tr>
<tr>
<td>Odds ratio¹</td>
<td>3.51</td>
<td></td>
<td>32.9</td>
</tr>
<tr>
<td>98.33% CI</td>
<td>1.46 to 8.40</td>
<td></td>
<td>2.07 to 522</td>
</tr>
<tr>
<td>CMH test²</td>
<td>&lt; 0.001</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Breslow-Day test³</td>
<td>0.21</td>
<td></td>
<td>0.99</td>
</tr>
</tbody>
</table>

1) Cochran-Mantel-Haenszel Odds for Controlled disease (Daivobet Gel relative to Tacalcitol/Gel vehicle) adjusted for centre
2) Cochran-Mantel-Haenszel test for the hypothesis of odds ratio equal to 1
3) Test for homogeneity of odds ratios across centres

14.4.2.1.2 Development of Controlled Disease according to the IGA
The percentage of subjects with ‘controlled disease’ according to the IGA at weeks 1, 2, 4, 6 and 8 is presented for the full analysis set in Table 22 and Figure 5 (LOCF). At every visit a higher percentage of subjects in the DAIVOBET/DOVOBET gel group had ‘controlled disease’ compared to the other two treatment groups. At week 1 ‘controlled disease’ was
observed in the DAIVOBET/DOVOBET gel group only and not in the other two groups which may indicate a faster response to DAIVOBET/DOVOBET gel.
Table 22: Subjects with ‘Controlled disease’ according to the investigator’s global assessment of disease severity at weeks 1, 2, 4, 6 and 8: full analysis set

<table>
<thead>
<tr>
<th>Visit</th>
<th>Controlled disease</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
<td>%</td>
</tr>
<tr>
<td>VISIT 1/ DAY 0</td>
<td>Controlled</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Non-controlled</td>
<td>183</td>
<td>100.0</td>
<td>184</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>183</td>
<td>100.0</td>
<td>184</td>
</tr>
<tr>
<td>VISIT 2/ WEEK 1</td>
<td>Controlled</td>
<td>7</td>
<td>3.9</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Non-controlled</td>
<td>173</td>
<td>96.1</td>
<td>182</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>180</td>
<td>100.0</td>
<td>182</td>
</tr>
<tr>
<td>VISIT 3/ WEEK 2</td>
<td>Controlled</td>
<td>17</td>
<td>9.6</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Non-controlled</td>
<td>160</td>
<td>90.4</td>
<td>170</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>177</td>
<td>100.0</td>
<td>179</td>
</tr>
<tr>
<td>VISIT 4/ WEEK 4</td>
<td>Controlled</td>
<td>33</td>
<td>18.8</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Non-controlled</td>
<td>143</td>
<td>81.3</td>
<td>163</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>176</td>
<td>100.0</td>
<td>175</td>
</tr>
<tr>
<td>VISIT 5/ WEEK 6</td>
<td>Controlled</td>
<td>44</td>
<td>25.9</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Non-controlled</td>
<td>126</td>
<td>74.1</td>
<td>143</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>170</td>
<td>100.0</td>
<td>166</td>
</tr>
<tr>
<td>VISIT 6/ WEEK 8</td>
<td>Controlled</td>
<td>72</td>
<td>42.1</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>Non-controlled</td>
<td>99</td>
<td>57.9</td>
<td>130</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>171</td>
<td>100.0</td>
<td>163</td>
</tr>
</tbody>
</table>
Figure 5: Percentage of subjects with ‘Controlled disease’ according to the investigator’s global assessment of disease severity at weeks 1, 2, 4, 6 and 8 (LOCF): full analysis set

The distribution of the IGA by visit is presented for the full analysis set in Table 23. At all visits except Visit 6 (week 8) the only treatment group in which any subjects achieved the disease category ‘clear’ was the DAIVOBET/DOVOBET group.
Table 23: Investigator’s global assessment of disease severity by visit: full analysis set

<table>
<thead>
<tr>
<th>Visit</th>
<th>Controlled disease</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
<td></td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>VISIT 1/ DAY 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Almost clear</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>130</td>
<td>71.0</td>
<td>119</td>
<td>64.7</td>
</tr>
<tr>
<td>Severe</td>
<td>50</td>
<td>27.3</td>
<td>58</td>
<td>31.5</td>
</tr>
<tr>
<td>Very severe</td>
<td>3</td>
<td>1.6</td>
<td>7</td>
<td>3.8</td>
</tr>
<tr>
<td>Total</td>
<td>183</td>
<td>100.0</td>
<td>184</td>
<td>100.0</td>
</tr>
<tr>
<td>VISIT 2/ WEEK 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Almost clear</td>
<td>7</td>
<td>3.9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mild</td>
<td>57</td>
<td>31.7</td>
<td>30</td>
<td>16.5</td>
</tr>
<tr>
<td>Moderate</td>
<td>103</td>
<td>57.2</td>
<td>133</td>
<td>73.1</td>
</tr>
<tr>
<td>Severe</td>
<td>13</td>
<td>7.2</td>
<td>19</td>
<td>10.4</td>
</tr>
<tr>
<td>Very severe</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>180</td>
<td>100.0</td>
<td>182</td>
<td>100.0</td>
</tr>
<tr>
<td>VISIT 3/ WEEK 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear</td>
<td>3</td>
<td>1.7</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Almost clear</td>
<td>14</td>
<td>7.9</td>
<td>9</td>
<td>5.0</td>
</tr>
<tr>
<td>Mild</td>
<td>83</td>
<td>46.9</td>
<td>45</td>
<td>25.1</td>
</tr>
<tr>
<td>Moderate</td>
<td>73</td>
<td>41.2</td>
<td>108</td>
<td>60.3</td>
</tr>
<tr>
<td>Severe</td>
<td>4</td>
<td>2.3</td>
<td>17</td>
<td>9.5</td>
</tr>
<tr>
<td>Very severe</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total</td>
<td>177</td>
<td>100.0</td>
<td>179</td>
<td>100.0</td>
</tr>
<tr>
<td>VISIT 4/ WEEK 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear</td>
<td>5</td>
<td>2.8</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Almost clear</td>
<td>28</td>
<td>15.9</td>
<td>12</td>
<td>6.9</td>
</tr>
<tr>
<td>Mild</td>
<td>89</td>
<td>50.6</td>
<td>63</td>
<td>36.0</td>
</tr>
<tr>
<td>Moderate</td>
<td>51</td>
<td>29.0</td>
<td>84</td>
<td>48.0</td>
</tr>
<tr>
<td>Severe</td>
<td>2</td>
<td>1.1</td>
<td>16</td>
<td>9.1</td>
</tr>
</tbody>
</table>
Table 23: Investigator’s global assessment of disease severity by visit: full analysis set (continued)

<table>
<thead>
<tr>
<th>Visit</th>
<th>Controlled disease</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
<td>%</td>
</tr>
<tr>
<td>VISIT 4/ WEEK 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very severe</td>
<td>1</td>
<td>0.6</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total</td>
<td>176</td>
<td>100.0</td>
<td>175</td>
<td>100.0</td>
</tr>
<tr>
<td>VISIT 5/ WEEK 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear</td>
<td>3</td>
<td>1.8</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Almost clear</td>
<td>41</td>
<td>24.1</td>
<td>23</td>
<td>13.9</td>
</tr>
<tr>
<td>Mild</td>
<td>81</td>
<td>47.6</td>
<td>70</td>
<td>42.2</td>
</tr>
<tr>
<td>Moderate</td>
<td>43</td>
<td>25.3</td>
<td>59</td>
<td>35.5</td>
</tr>
<tr>
<td>Severe</td>
<td>1</td>
<td>0.6</td>
<td>14</td>
<td>8.4</td>
</tr>
<tr>
<td>Very severe</td>
<td>1</td>
<td>0.6</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total</td>
<td>170</td>
<td>100.0</td>
<td>166</td>
<td>100.0</td>
</tr>
<tr>
<td>VISIT 6/ WEEK 8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear</td>
<td>6</td>
<td>3.5</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>Almost clear</td>
<td>66</td>
<td>38.6</td>
<td>32</td>
<td>19.6</td>
</tr>
<tr>
<td>Mild</td>
<td>53</td>
<td>31.0</td>
<td>63</td>
<td>38.7</td>
</tr>
<tr>
<td>Moderate</td>
<td>44</td>
<td>25.7</td>
<td>56</td>
<td>34.4</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0.0</td>
<td>10</td>
<td>6.1</td>
</tr>
<tr>
<td>Very severe</td>
<td>2</td>
<td>1.2</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>Total</td>
<td>171</td>
<td>100.0</td>
<td>163</td>
<td>100.0</td>
</tr>
</tbody>
</table>

14.4.2.2 PASI

For individual subject data on PASI and the investigator’s assessment of the elements of the PASI (extent and the clinical signs; redness, thickness and scaliness) see Appendix XI, Listings 12 and 13.

14.4.2.2.1 Percentage Change in PASI

The percentage change in PASI from baseline to Weeks 4 and 8 and the results of the statistical analysis are presented for the full analysis set in Table 24. The results for the per protocol analysis set are given in Table 78 Section 18. The percentage change in PASI from baseline to weeks 4 and 8 by centre are shown in Table 79 Section 18. The investigators assessment of the extent and the individual clinical signs (redness, thickness and scaliness)
that are included in the PASI are summarised at weeks 4 and 8 in Section 18 in Table 82 and Table 83 (arms), Table 84 and Table 85 (trunk) and Table 86 and Table 87 (legs).

At week 4 the mean percentage change in PASI from baseline was $-53.1$ for the DAIVOBET/DOVOBET gel group, $-37.3$ for the tacalcitol group and $-13.3$ for the gel vehicle group. DAIVOBET/DOVOBET gel was statistically significantly more effective than tacalcitol (difference $-15.5; 98.33\% \text{ CI} -22.1$ to $-8.95; p<0.001$) and the gel vehicle (difference $-39.8; 98.33\% \text{ CI} -47.8$ to $-31.7; p<0.001$). The test for treatment by centre interaction was not statistically significant ($p=0.33$).

Similarly at week 8 DAIVOBET/DOVOBET gel was also statistically significantly more effective than tacalcitol (difference $-14.7; 98.33\% \text{ CI} -22.6$ to $-6.90; p<0.001$) and the gel vehicle (difference $-39.1; 98.33\% \text{ CI} -48.7$ to $-29.5; p<0.001$). The mean percentage changes in PASI from baseline were $-57.0$ for the DAIVOBET/DOVOBET gel group, $-41.9$ for the tacalcitol group and $-17.9$ for the gel vehicle group. The test for treatment by centre interaction was not statistically significant ($p=0.67$).
Table 24: Percentage change in PASI from baseline to weeks 4 and 8 and statistical analysis: full analysis set

<table>
<thead>
<tr>
<th>Percentage change in PASI</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VISIT 4 / WEEK 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Least squares mean¹</td>
<td>-53.6</td>
<td>-38.1</td>
<td>-13.8</td>
</tr>
<tr>
<td>Mean</td>
<td>-53.1</td>
<td>-37.3</td>
<td>-13.3</td>
</tr>
<tr>
<td>SD</td>
<td>27.4</td>
<td>26.4</td>
<td>27.7</td>
</tr>
<tr>
<td>Median</td>
<td>-56.3</td>
<td>-40.0</td>
<td>-11.2</td>
</tr>
<tr>
<td>Minimum</td>
<td>-100</td>
<td>-96</td>
<td>-77</td>
</tr>
<tr>
<td>Maximum</td>
<td>102</td>
<td>29</td>
<td>58</td>
</tr>
<tr>
<td>Number</td>
<td>183</td>
<td>184</td>
<td>91</td>
</tr>
<tr>
<td>Difference²</td>
<td>-15.5</td>
<td>-39.8</td>
<td></td>
</tr>
<tr>
<td>98.33% CI</td>
<td>-22.1 to -8.95</td>
<td>-47.8 to -31.7</td>
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</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>VISIT 6 / WEEK 8</td>
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<tr>
<td>Least squares mean¹</td>
<td>-57.0</td>
<td>-42.3</td>
<td>-17.9</td>
</tr>
<tr>
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<td>-57.0</td>
<td>-41.9</td>
<td>-17.9</td>
</tr>
<tr>
<td>SD</td>
<td>29.6</td>
<td>33.4</td>
<td>35.3</td>
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<tr>
<td>Median</td>
<td>-63.6</td>
<td>-43.0</td>
<td>-20.0</td>
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<tr>
<td>Minimum</td>
<td>-100</td>
<td>-100</td>
<td>-100</td>
</tr>
<tr>
<td>Maximum</td>
<td>87</td>
<td>47</td>
<td>69</td>
</tr>
<tr>
<td>Number</td>
<td>183</td>
<td>184</td>
<td>91</td>
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<td>-39.1</td>
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</tr>
<tr>
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<td>-22.6 to -6.90</td>
<td>-48.7 to -29.5</td>
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</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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</tr>
</tbody>
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1) Adjusted for the effect of centre
2) Daivobet gel minus Tacalcitol/Gel vehicle, adjusted for the effect of centre

The PASI at Visit 1 (Day 0) and the percentage change in PASI from baseline to weeks 1, 2, 4, 6 and 8 is summarised for the full analysis set in Table 25 and the percentage change in PASI over time by treatment group is shown in Figure 6. The percentage change in PASI increased over time in all three treatment groups but was always higher in the DAIVOBET/DOVOBET group compared with the other two groups.
Table 25: Percentage change in PASI from baseline to week 1, 2, 4, 6, and 8 and baseline
PASI: full analysis set

<table>
<thead>
<tr>
<th>Visit</th>
<th>Percentage change</th>
<th>DAIVOGEL Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASI at VISIT 1/ DAY 0</td>
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</tr>
<tr>
<td>Mean</td>
<td>8.93</td>
<td>9.86</td>
<td>9.38</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>3.99</td>
<td>5.31</td>
<td>3.34</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>8.40</td>
<td>9.00</td>
<td>8.70</td>
<td></td>
</tr>
<tr>
<td>Minimum</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
<td>37</td>
<td>59</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>183</td>
<td>184</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>VISIT 2/ WEEK 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>-30.23</td>
<td>-23.11</td>
<td>-13.61</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>21.90</td>
<td>20.04</td>
<td>17.96</td>
<td></td>
</tr>
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<td>Median</td>
<td>-30.41</td>
<td>-23.30</td>
<td>-10.75</td>
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</tr>
<tr>
<td>Minimum</td>
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<td>-77</td>
<td></td>
</tr>
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<td></td>
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<tr>
<td>Number</td>
<td>180</td>
<td>182</td>
<td>90</td>
<td></td>
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<tr>
<td>VISIT 3/ WEEK 2</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>-44.18</td>
<td>-32.40</td>
<td>-15.19</td>
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<td>26.18</td>
<td>22.63</td>
<td>21.74</td>
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<td>Median</td>
<td>-44.44</td>
<td>-32.50</td>
<td>-13.51</td>
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<td>Minimum</td>
<td>-100</td>
<td>-89</td>
<td>-77</td>
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<td>Maximum</td>
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<td></td>
</tr>
<tr>
<td>Number</td>
<td>177</td>
<td>179</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>VISIT 4/ WEEK 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>-54.22</td>
<td>-38.75</td>
<td>-14.47</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>26.66</td>
<td>25.88</td>
<td>28.75</td>
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<tr>
<td>Median</td>
<td>-56.31</td>
<td>-42.11</td>
<td>-12.12</td>
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<tr>
<td>Minimum</td>
<td>-100</td>
<td>-96</td>
<td>-77</td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
<td>102</td>
<td>29</td>
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<td></td>
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<tr>
<td>Number</td>
<td>176</td>
<td>175</td>
<td>81</td>
<td></td>
</tr>
</tbody>
</table>
Table 25: Percentage change in PASI from baseline to week 1, 2, 4, 6 and 8 and baseline
PASI: full analysis set (continued)

<table>
<thead>
<tr>
<th>Visit Percentage change</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VISIT 5/ WEEK 6</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Mean</td>
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<td>-46.80</td>
<td>-22.89</td>
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<tr>
<td>SD</td>
<td>27.56</td>
<td>27.51</td>
<td>32.36</td>
</tr>
<tr>
<td>Median</td>
<td>-61.78</td>
<td>-49.76</td>
<td>-21.70</td>
</tr>
<tr>
<td>Minimum</td>
<td>-100</td>
<td>-94</td>
<td>-100</td>
</tr>
<tr>
<td>Maximum</td>
<td>102</td>
<td>43</td>
<td>69</td>
</tr>
<tr>
<td>Number</td>
<td>170</td>
<td>166</td>
<td>69</td>
</tr>
<tr>
<td><strong>VISIT 6/ WEEK 8</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>-59.54</td>
<td>-46.30</td>
<td>-27.95</td>
</tr>
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<td>-48.31</td>
<td>-31.70</td>
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<td>Minimum</td>
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<td>-100</td>
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<tr>
<td>Number</td>
<td>171</td>
<td>163</td>
<td>64</td>
</tr>
</tbody>
</table>
Figure 6: Percentage change in PASI over time (LOCF) by treatment group: full analysis set

14.4.2.2 Actual Change in PASI

The PASI at baseline and the actual change in PASI from baseline to weeks 1, 2, 4, 6 and 8 is summarised for the full analysis set in Table 26. PASI decreased gradually in all treatment groups over time but the decrease in actual PASI in the DAIVOBET/DOVOBET group was always greater than in the other two groups.
Table 26: Actual change in PASI from baseline to week 1, 2, 4, 6 and 8 and baseline PASI: full analysis set

<table>
<thead>
<tr>
<th>Visit Percentage change</th>
<th>DAVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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</thead>
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<td><strong>PASI at VISIT 1/ DAY 0</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
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<td>9.38</td>
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<tr>
<td>SD</td>
<td>3.99</td>
<td>5.31</td>
<td>3.34</td>
</tr>
<tr>
<td>Median</td>
<td>8.40</td>
<td>9.00</td>
<td>8.70</td>
</tr>
<tr>
<td>Minimum</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Maximum</td>
<td>37</td>
<td>59</td>
<td>23</td>
</tr>
<tr>
<td>Number</td>
<td>183</td>
<td>184</td>
<td>91</td>
</tr>
<tr>
<td><strong>VISIT 2/ WEEK 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
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<td>-1.17</td>
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<tr>
<td>SD</td>
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<td>1.48</td>
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<td>Median</td>
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<td>-1.80</td>
<td>-0.85</td>
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<tr>
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<td>90</td>
</tr>
<tr>
<td><strong>VISIT 3/ WEEK 2</strong></td>
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<td></td>
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<td>-3.92</td>
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<td>-2.90</td>
<td>-1.20</td>
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<td>3</td>
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<tr>
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<td>86</td>
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<td><strong>VISIT 4/ WEEK 4</strong></td>
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<td>-3.85</td>
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<td>SD</td>
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<td>-3.30</td>
<td>-1.00</td>
</tr>
<tr>
<td>Minimum</td>
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<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Number</td>
<td>176</td>
<td>175</td>
<td>81</td>
</tr>
</tbody>
</table>
Table 26: Actual change in PASI from baseline to week 1, 2, 4, 6 and 8 and baseline PASI: full analysis set (continued)

<table>
<thead>
<tr>
<th>Visit</th>
<th>Percentage change</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VISIT 5/ WEEK 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>-5.22</td>
<td>-4.57</td>
<td>-1.94</td>
<td></td>
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<tr>
<td>SD</td>
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<td>2.87</td>
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</tr>
<tr>
<td>Median</td>
<td>-4.80</td>
<td>-4.00</td>
<td>-2.00</td>
<td></td>
</tr>
<tr>
<td>Minimum</td>
<td>-29</td>
<td>-31</td>
<td>-9</td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
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<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>170</td>
<td>166</td>
<td>69</td>
<td></td>
</tr>
</tbody>
</table>

| VISIT 6/ WEEK 8 |                   |                       |                    |                    |
| Mean   | -5.40             | -4.57                 | -2.40              |
| SD     | 4.09              | 4.11                  | 2.76               |
| Median | -4.90             | -4.20                 | -2.65              |
| Minimum| -34               | -25                   | -9                 |
| Maximum| 11                | 7                     | 4                  |
| Number | 171               | 163                   | 64                 |

14.4.2.2.3 PASI at baseline and each subsequent visit

PASI by visit is summarised in Table 80 section 18. Mean PASI over time is presented in Figure 7. Mean PASI decreased over time in all three groups and was greater in the DAIVOBET/DOVOBET gel group compared with the other two groups.
14.4.2.2.4 PASI 75
The proportion of subjects achieving at least 75% reduction in PASI from baseline at each visit is shown in Table 27. The highest percentages of subjects achieving PASI 75 occurred in the DAIVOBET/DOVOBET gel group compared with the other two treatment groups. No subjects in the tacalcitol group achieved PASI 75 at Visit 2 (week 1).
Table 27: Proportion of subjects achieving at least 75% reduction in PASI from baseline at each visit: full analysis set

<table>
<thead>
<tr>
<th>Visit</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td>VISIT 2/ WEEK 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;= 75% PASI reduction</td>
<td>5</td>
<td>2.8</td>
<td>0</td>
</tr>
<tr>
<td>&lt; 75% PASI reduction</td>
<td>175</td>
<td>97.2</td>
<td>182</td>
</tr>
<tr>
<td>Total</td>
<td>180</td>
<td>100.0</td>
<td>182</td>
</tr>
<tr>
<td>VISIT 3/ WEEK 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;= 75% PASI reduction</td>
<td>23</td>
<td>13.0</td>
<td>8</td>
</tr>
<tr>
<td>&lt; 75% PASI reduction</td>
<td>154</td>
<td>87.0</td>
<td>171</td>
</tr>
<tr>
<td>Total</td>
<td>177</td>
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<td>179</td>
</tr>
<tr>
<td>VISIT 4/ WEEK 4</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&gt;= 75% PASI reduction</td>
<td>36</td>
<td>20.5</td>
<td>19</td>
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<td>&lt; 75% PASI reduction</td>
<td>140</td>
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<td>156</td>
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<tr>
<td>Total</td>
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<td>&gt;= 75% PASI reduction</td>
<td>54</td>
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<td>28</td>
</tr>
<tr>
<td>&lt; 75% PASI reduction</td>
<td>116</td>
<td>68.2</td>
<td>138</td>
</tr>
<tr>
<td>Total</td>
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<td>100.0</td>
<td>166</td>
</tr>
<tr>
<td>VISIT 6/ WEEK 8</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&gt;= 75% PASI reduction</td>
<td>59</td>
<td>34.5</td>
<td>42</td>
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<tr>
<td>&lt; 75% PASI reduction</td>
<td>112</td>
<td>65.5</td>
<td>121</td>
</tr>
<tr>
<td>Total</td>
<td>171</td>
<td>100.0</td>
<td>163</td>
</tr>
</tbody>
</table>

14.4.2.2.5 PASI 50
The proportion of subjects achieving at least 50% reduction in PASI from baseline at each visit is shown in Table 28. The highest percentages of subjects achieving PASI 50 occurred in
the DAIVOBET/DOVOBET gel group followed by the tacalcitol group then the vehicle gel group.
### Table 28: Proportion of subjects achieving at least 50% reduction in PASI from baseline at each visit: full analysis set

<table>
<thead>
<tr>
<th>Visit</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td><strong>VISIT 2/ WEEK 1</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&gt; = 50% PASI reduction</td>
<td>38</td>
<td>21.1</td>
<td>17</td>
</tr>
<tr>
<td>&lt; 50% PASI reduction</td>
<td>142</td>
<td>78.9</td>
<td>165</td>
</tr>
<tr>
<td>Total</td>
<td>180</td>
<td>100.0</td>
<td>182</td>
</tr>
<tr>
<td><strong>VISIT 3/ WEEK 2</strong></td>
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</tr>
<tr>
<td>&gt; = 50% PASI reduction</td>
<td>74</td>
<td>41.8</td>
<td>40</td>
</tr>
<tr>
<td>&lt; 50% PASI reduction</td>
<td>103</td>
<td>58.2</td>
<td>139</td>
</tr>
<tr>
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<td>&lt; 50% PASI reduction</td>
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<td>121</td>
</tr>
<tr>
<td>Total</td>
<td>176</td>
<td>100.0</td>
<td>175</td>
</tr>
<tr>
<td><strong>VISIT 5/ WEEK 6</strong></td>
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<td></td>
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<tr>
<td>&gt; = 50% PASI reduction</td>
<td>120</td>
<td>70.6</td>
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<tr>
<td>&lt; 50% PASI reduction</td>
<td>50</td>
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<td>83</td>
</tr>
<tr>
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<td>166</td>
</tr>
<tr>
<td><strong>VISIT 6/ WEEK 8</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&gt; = 50% PASI reduction</td>
<td>119</td>
<td>69.6</td>
<td>80</td>
</tr>
<tr>
<td>&lt; 50% PASI reduction</td>
<td>52</td>
<td>30.4</td>
<td>83</td>
</tr>
<tr>
<td>Total</td>
<td>171</td>
<td>100.0</td>
<td>163</td>
</tr>
</tbody>
</table>

### 14.4.2.3 Patient’s global assessment of disease severity

For individual subject data on the patient’s global assessment of disease severity and subjects achieving ‘controlled disease’ see Appendix XI, Listing 14.
14.4.2.3.1 ‘Controlled disease’ according to the patient’s global assessment of disease severity at weeks 1, 2, 4, 6 and 8.

The percentage of subjects with ‘controlled disease’ by visit is summarised in Table 29. At every visit a higher percentage of subjects in the DAIVOBET/DOVOBET gel group had ‘controlled disease’ compared to the other two treatment groups.
Table 29: Subjects with ‘Controlled disease’ according to the Patient’s global assessment of disease severity at week 1, 2, 4, 6 and 8: full analysis set

<table>
<thead>
<tr>
<th>Visit</th>
<th>Controlled disease</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>VISIT 1/ DAY 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled</td>
<td>8</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Non-controlled</td>
<td>175</td>
<td>177</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>183</td>
<td>183</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>VISIT 2/ WEEK 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled</td>
<td>17</td>
<td>8</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Non-controlled</td>
<td>163</td>
<td>174</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>180</td>
<td>182</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>VISIT 3/ WEEK 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled</td>
<td>31</td>
<td>15</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Non-controlled</td>
<td>146</td>
<td>164</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>177</td>
<td>179</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>VISIT 4/ WEEK 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled</td>
<td>52</td>
<td>21</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Non-controlled</td>
<td>123</td>
<td>154</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>175</td>
<td>175</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>VISIT 5/ WEEK 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled</td>
<td>57</td>
<td>27</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Non-controlled</td>
<td>113</td>
<td>139</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>170</td>
<td>166</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>VISIT 6/ WEEK 8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled</td>
<td>69</td>
<td>35</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Non-controlled</td>
<td>102</td>
<td>128</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>171</td>
<td>163</td>
<td>64</td>
<td></td>
</tr>
</tbody>
</table>

14.4.2.3.2 Patient’s global assessment of disease severity at weeks 1, 2, 4, 6 and 8

The distribution of the patient’s global assessment of disease severity by visit is summarised in Table 30.
Table 30: Patient’s global assessment of disease severity by visit: full analysis set

<table>
<thead>
<tr>
<th>Visit Patients assessment</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td>VISIT 1/ DAY 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Very Mild</td>
<td>24</td>
<td>13.1</td>
<td>32</td>
</tr>
<tr>
<td>Mild</td>
<td>111</td>
<td>60.7</td>
<td>92</td>
</tr>
<tr>
<td>Severe</td>
<td>40</td>
<td>21.9</td>
<td>53</td>
</tr>
<tr>
<td>Total</td>
<td>183</td>
<td>100.0</td>
<td>183</td>
</tr>
<tr>
<td>VISIT 2/ WEEK 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Very Mild</td>
<td>17</td>
<td>9.4</td>
<td>7</td>
</tr>
<tr>
<td>Mild</td>
<td>49</td>
<td>27.2</td>
<td>56</td>
</tr>
<tr>
<td>Moderate</td>
<td>94</td>
<td>52.2</td>
<td>89</td>
</tr>
<tr>
<td>Severe</td>
<td>20</td>
<td>11.1</td>
<td>29</td>
</tr>
<tr>
<td>Total</td>
<td>180</td>
<td>100.0</td>
<td>182</td>
</tr>
<tr>
<td>VISIT 3/ WEEK 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear</td>
<td>3</td>
<td>1.7</td>
<td>0</td>
</tr>
<tr>
<td>Very Mild</td>
<td>28</td>
<td>15.8</td>
<td>15</td>
</tr>
<tr>
<td>Mild</td>
<td>67</td>
<td>37.9</td>
<td>49</td>
</tr>
<tr>
<td>Moderate</td>
<td>68</td>
<td>38.4</td>
<td>92</td>
</tr>
<tr>
<td>Severe</td>
<td>11</td>
<td>6.2</td>
<td>23</td>
</tr>
<tr>
<td>Total</td>
<td>177</td>
<td>100.0</td>
<td>179</td>
</tr>
<tr>
<td>VISIT 4/ WEEK 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear</td>
<td>5</td>
<td>2.9</td>
<td>0</td>
</tr>
<tr>
<td>Very Mild</td>
<td>47</td>
<td>26.9</td>
<td>21</td>
</tr>
<tr>
<td>Mild</td>
<td>70</td>
<td>40.0</td>
<td>53</td>
</tr>
<tr>
<td>Moderate</td>
<td>45</td>
<td>25.7</td>
<td>84</td>
</tr>
<tr>
<td>Severe</td>
<td>8</td>
<td>4.6</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>175</td>
<td>100.0</td>
<td>175</td>
</tr>
</tbody>
</table>
Table 30: Patient's global assessment of disease severity by visit: full analysis set (continued)

<table>
<thead>
<tr>
<th>Visit</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td>VISIT 5/ WEEK 6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear</td>
<td>8</td>
<td>4.7</td>
<td>1</td>
</tr>
<tr>
<td>Very Mild</td>
<td>49</td>
<td>28.8</td>
<td>26</td>
</tr>
<tr>
<td>Mild</td>
<td>71</td>
<td>41.8</td>
<td>57</td>
</tr>
<tr>
<td>Moderate</td>
<td>35</td>
<td>20.6</td>
<td>70</td>
</tr>
<tr>
<td>Severe</td>
<td>7</td>
<td>4.1</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>170</td>
<td>100.0</td>
<td>166</td>
</tr>
<tr>
<td>VISIT 6/ WEEK 8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear</td>
<td>10</td>
<td>5.8</td>
<td>4</td>
</tr>
<tr>
<td>Very Mild</td>
<td>59</td>
<td>34.5</td>
<td>31</td>
</tr>
<tr>
<td>Mild</td>
<td>57</td>
<td>33.3</td>
<td>59</td>
</tr>
<tr>
<td>Moderate</td>
<td>41</td>
<td>24.0</td>
<td>58</td>
</tr>
<tr>
<td>Severe</td>
<td>4</td>
<td>2.3</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>171</td>
<td>100.0</td>
<td>163</td>
</tr>
</tbody>
</table>

14.4.2.4 Subjects with relapse and time to relapse in the observation period

At the end of the treatment phase of the study 67 subjects in the DAIVOBET/DOVOBET gel group, 31 subjects in the tacalcitol group and 5 subjects in the gel vehicle group had 'controlled disease' and entered the observation phase.

The proportion of subjects who experienced relapse is summarised in Table 31 for the subset of the full analysis set that entered the observation phase. The data are presented by centre in Table 81 in section 18. A summary of the Kaplan-Meier estimates for time to relapse is given in Table 32.

In the observation period relapse (defined as a reduction in the PASI improvement from baseline of at least 50%) was observed in 28 of 67 (41.8%) subjects in the DAIVOBET/DOVOBET gel group. In the tacalcitol group 7 of 31 (22.6%) experienced relapse and 3 of 5 (60.0%) experienced relapse in the gel vehicle group. The median time to relapse was 63 days in the DAIVOBET/DOVOBET gel group. In the other two treatment groups median time to relapse was 61 days.
Table 31: Subjects with relapse during the observation period: those subjects in the full analysis set who achieved ‘Controlled disease’ according to the investigator’s global assessment of disease severity at week 8

<table>
<thead>
<tr>
<th>Relapse</th>
<th>DAIVOBET Gel (n=67)</th>
<th>Tacalcitol (n=31)</th>
<th>Gel Vehicle (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td>Relapse</td>
<td>28</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>41.8%</td>
<td>22.6%</td>
<td>60.0%</td>
</tr>
<tr>
<td>No Relapse</td>
<td>39</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>58.2%</td>
<td>77.4%</td>
<td>40.0%</td>
</tr>
<tr>
<td>Total</td>
<td>67</td>
<td>31</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

1) 7 patients had controlled disease but withdrew after week 8, these patients were not included in this table.

Table 32: Summary of Kaplan-Meier estimates for time to relapse: those subjects in the full analysis set who achieved ‘Controlled disease’ according to the investigator’s global assessment of disease severity at week 8

<table>
<thead>
<tr>
<th>Kaplan-Meier estimates</th>
<th>DAIVOBET Gel (n=67)</th>
<th>Tacalcitol (n=31)</th>
<th>Gel Vehicle (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to relapse (days)</td>
<td>63</td>
<td>61</td>
<td>61</td>
</tr>
<tr>
<td>Lower quartile (days)</td>
<td>28</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>Upper quartile (days)</td>
<td>63</td>
<td>61</td>
<td>61</td>
</tr>
</tbody>
</table>

1) 7 patients had controlled disease but withdrew after week 8, these patients were not included in this table.
2) Upper quartile in the DAIVOBET group cannot be estimated due to the large number of censored patients (i.e. patients who had not relapsed when leaving the study).

The probability of not experiencing a relapse plotted against the number of days elapsed since the subject’s last on-treatment visit is presented in Figure 8.
At the start of the observation phase, for about the first 10 days, few subjects experienced relapse. In the DAILOBET/DOVOBET group the majority of subjects relapsed between 10 and 30 days and the median time to relapse was 63 days. It must be noted that the number of subjects in the DAILOBET/DOVOBET gel group differed considerably from the other two groups in this non-randomised subset of the full analysis set.

For individual subject data on relapse see Appendix XI, Listing 13.

14.4.2.5 Subjects with rebound during the observation period
No subjects experienced rebound during the observation period. For individual subject data on rebound see Appendix XI, Listing 13.

14.4.2.6 Investigator’s assessments in the observation period
The PASI in the observation period by visit and IGA in the observation period by visit are presented in Section 18 Table 88 and Table 89 respectively. As the observation phase
continued the mean PASI increased in all three groups and the percentages of subjects with ‘clear/almost clear’ according to the IGA deceased in all three groups.

For individual subject data on the PASI see Appendix XI, Listing 13 and for the IGA see Appendix XI Listing 11.

14.4.2.7 Patient’s assessments in the observation period
The patient’s global assessment of disease severity in the observation period by visit is presented in Section 18 Table 90. As the observation phase continued the percentages of subjects with ‘clear/very mild’ deceased in all three groups.

For individual subject data on the Patient’s global assessment of disease severity see Appendix XI Listing 14.

14.4.3 Statistical/Analytical Issues
The analyses were conducted according to the protocol as summarised in section 11.10 and the Statistical Analysis Plan Update in Appendix III.

14.4.4 Concomitant Treatment
Concomitant medication taken during the study is listed for individual subjects in Appendix XI, Listing 35.

14.5 EFFICACY CONCLUSIONS
The analysis of the proportion of subjects who achieved ‘controlled disease’ according to the IGA at week 8 (LOCF) showed that DAIVO BET/DOVO BET gel was statistically significantly more effective than the gel vehicle and also tacalcitol ointment. The proportion of subjects who achieved ‘controlled disease’ was 39.9% in the DAIVO BET/DOVO BET gel group compared with 5.5% in the gel vehicle group and 17.9% in the tacalcitol group. The analysis of the per protocol analysis set supported the results for the full analysis set.

DAIVO BET/DOVO BET gel was also found to be statistically significantly more effective than both the gel vehicle and tacalcitol ointment in terms of the proportion of subjects who achieved ‘controlled disease’ according to the IGA at week 4 (LOCF) and the percentage change in PASI from baseline to weeks 4 and 8. In addition the percentages of subjects who achieved PASI 75, PASI 50 and ‘controlled disease’ according to the patient’s global assessment of disease severity were greater at every visit in the DAIVO BET/DOVO BET gel group compared to the other two treatment groups.
Of the 389 subjects who completed the treatment phase of the study, a total of 103 had controlled disease and entered the 8 week observation phase. The percentage of completers who had controlled disease and entered the observation phase from the DAIVOBET/DOVOBET gel group (67 of 183; 36.6%) was higher than in the tacalcitol group (31 of 184; 16.8%) and the gel vehicle group (5 of 91; 5.5%). No subjects experienced a rebound of their psoriasis. Relapse (defined as a reduction in the PASI improvement from baseline of at least 50%) was observed in 28 of 67 (41.8%) subjects in the DAIVOBET/DOVOBET gel group. In the tacalcitol group 7 of 31 (22.6%) experienced relapse and 3 of 5 (60.0%) experienced relapse in the gel vehicle group. The median time to relapse was 63 days in the DAIVOBET/DOVOBET gel group. In the other two treatment groups the median time to relapse was 61 days. The purpose of gathering data on relapse data in this study was to describe relapse in the DAVOBET/DOVOBET gel group. To ensure the blind was maintained data was also collected for the comparator groups, however these data are difficult to interpret because they are based on selected subgroups which are not randomised. Therefore direct comparisons between the groups are not valid.

14.6 EVALUATION OF QUALITY OF LIFE
The quality of life questionnaires are available in Appendix III of the Study Protocol (see Appendix I) and further details about the evaluation and analysis of each scale are given in section 11.10.1.5.

14.6.1 SF-36(v2)
The scales and changes in the individual scales measured in the SF-36 (v2) general health questionnaire are presented in section 18 Table 91 and Table 92 (Physical Functioning), Table 93 and Table 94 (Role Physical), Table 95 and Table 96 (Bodily Pain), Table 97 and Table 98 (General Health), Table 99 and Table 100 (Vitality), Table 101 and Table 102 (Social Functioning), Table 103 and Table 104 (Role Emotional), Table 105 and Table 106 (Mental Health) and Table 107 (Reported Health Transition).

For individual subject data collected by the SF-36 (v2) see Appendix XI, Listings 16 (Physical Functioning), 17 (Role Physical), 18 (Bodily Pain), 19 (General Health), 20 (Vitality), 21 (Social Functioning), 22 (Role Emotional), 23 (Mental Health) and 24 (Reported Health Transition).

The Physical Component and Mental Component Summary Measures which summarise the data in the all the individual scales (except the Reported Health Transition scale) are pre-
sented below. Scores for the summary measures range from 0 to 100 and the higher the score the better the quality of life.

The Reported Health Transition scale which compares health status compared with one week ago, is presented in section 18 in Table 107 In the DAIVOBET/DOVOBET gel group the percentages of subjects who reported ‘much better’ or ‘somewhat better’ than one week ago increased as the subjects progressed through the study. This pattern was not observed in the tacalcit o or the gel vehicle groups in which the percentages at all visits were similar.

14.6.1.1 Physical Component Summary

The Physical Component Summary (which includes the data from the individual scales Physical Functioning, Role Physical, Bodily Pain and General Health) is presented by visit for the full analysis set in Table 33 and the change from baseline to weeks 4 and 8 is given in Table 34.

At all visits the Physical Component Summary scores across the treatment groups were similar. When comparing response within each treatment group, the change from baseline in the Physical Component Summary score was not statistically significant at any timepoint in any of the three treatment groups.
Table 33: ‘Physical Component Summary’ measure based on the SF-36 (v2) health survey questionnaire by visit and the results of statistical analysis: full analysis set

<table>
<thead>
<tr>
<th>VISIT</th>
<th>PCS</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/ DAY</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>51.1</td>
<td>50.1</td>
<td>50.1</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>8.4</td>
<td>9.0</td>
<td>9.6</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>53.8</td>
<td>52.8</td>
<td>52.6</td>
<td></td>
</tr>
<tr>
<td>Minimum</td>
<td>23.2</td>
<td>19.2</td>
<td>18.2</td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
<td>64.5</td>
<td>66.3</td>
<td>62.7</td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>180</td>
<td>183</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td>1.67</td>
<td>1.77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>-0.20 to 3.54</td>
<td>-0.61 to 4.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>0.079</td>
<td></td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>4/ WEEK 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>51.6</td>
<td>49.9</td>
<td>49.8</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>8.3</td>
<td>9.4</td>
<td>8.5</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>54.8</td>
<td>52.6</td>
<td>51.7</td>
<td></td>
</tr>
<tr>
<td>Minimum</td>
<td>27.2</td>
<td>19.7</td>
<td>24.7</td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
<td>62.4</td>
<td>66.2</td>
<td>66.6</td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>171</td>
<td>173</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td>1.67</td>
<td>1.77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>-0.20 to 3.54</td>
<td>-0.61 to 4.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>0.079</td>
<td></td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>6/ WEEK 8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>51.8</td>
<td>49.8</td>
<td>50.4</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>8.2</td>
<td>9.8</td>
<td>9.5</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>55.0</td>
<td>52.9</td>
<td>53.6</td>
<td></td>
</tr>
<tr>
<td>Minimum</td>
<td>23.0</td>
<td>20.2</td>
<td>12.0</td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
<td>62.2</td>
<td>65.4</td>
<td>62.5</td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>167</td>
<td>160</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td>2.06</td>
<td>1.36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.08 to 4.04</td>
<td>-1.32 to 4.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>0.041</td>
<td></td>
<td>0.32</td>
<td></td>
</tr>
</tbody>
</table>

1) ANOVA difference, Daivobet Gel minus Tacalcitol/Gel vehicle
Table 34: Change in ‘Physical Component Summary’ measure based on the SF-36 (v2) health survey questionnaire from baseline to weeks 4 and 8 and the results of statistical analysis: full analysis set

<table>
<thead>
<tr>
<th>VISIT PCS change</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VISIT 4/ WEEK 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.4</td>
<td>-0.1</td>
<td>-0.3</td>
</tr>
<tr>
<td>SD</td>
<td>5.1</td>
<td>4.7</td>
<td>5.3</td>
</tr>
<tr>
<td>Median</td>
<td>0.4</td>
<td>0.0</td>
<td>-0.4</td>
</tr>
<tr>
<td>Minimum</td>
<td>-21.0</td>
<td>-14.0</td>
<td>-13.1</td>
</tr>
<tr>
<td>Maximum</td>
<td>17.7</td>
<td>16.2</td>
<td>25.4</td>
</tr>
<tr>
<td>Number</td>
<td>169</td>
<td>172</td>
<td>75</td>
</tr>
<tr>
<td>P-value¹</td>
<td>0.32</td>
<td>0.87</td>
<td>0.68</td>
</tr>
<tr>
<td>VISIT 6/ WEEK 8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.4</td>
<td>-0.1</td>
<td>0.7</td>
</tr>
<tr>
<td>SD</td>
<td>5.0</td>
<td>6.1</td>
<td>5.8</td>
</tr>
<tr>
<td>Median</td>
<td>0.2</td>
<td>0.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Minimum</td>
<td>-15.5</td>
<td>-20.5</td>
<td>-14.9</td>
</tr>
<tr>
<td>Maximum</td>
<td>17.1</td>
<td>17.3</td>
<td>20.6</td>
</tr>
<tr>
<td>Number</td>
<td>164</td>
<td>159</td>
<td>59</td>
</tr>
<tr>
<td>P-value¹</td>
<td>0.35</td>
<td>0.90</td>
<td>0.39</td>
</tr>
</tbody>
</table>

¹) Paired T-test, within treatment group comparison

The scales and changes in the individual scales that contribute to the Physical Component Summary are presented in section 18 Table 93 and Table 94 (Physical Functioning), Table 95 and Table 96 (Role Physical), Table 97 and Table 98 (Bodily Pain) and Table 99 and Table 100 (General Health).

An increase in the scores over time for Bodily Pain was observed for all three groups indicating an increased quality of life as the study progressed. In the DAIVOBET/DOVOBET gel the scores for Role Physical and General Health also tended to increase over time. For Physical Functioning the scores remained similar over time in all three groups.

14.6.1.2 Mental Component Summary

The Mental Component Summary (which includes the data from the individual scales Vitality, Social Functioning, Role Emotional and Mental Health) is presented by visit for the
full analysis set in Table 35 and the change from baseline to weeks 4 and 8 is given in Table 36.

At all visits the Mental Component Summary scores across the treatment groups were similar. When comparing response within each treatment group, the change from baseline in the Mental Component Summary score was statistically significant at Weeks 4 and 8 in the DAIVOBET/DOVOBET gel group (p=0.002 and p=0.012 respectively) and at week 8 in the tacalcitol group (p=0.003). No statistically significant changes were observed within the gel vehicle group.
Table 35: ‘Mental Component Summary’ measure based on the SF-36 (v2) health survey questionnaire by visit and the results of statistical analysis: full analysis set

<table>
<thead>
<tr>
<th>VISIT</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Median</td>
</tr>
<tr>
<td>VISIT 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/ DAY 0</td>
<td>Mean</td>
<td>50.9</td>
<td>10.8</td>
</tr>
<tr>
<td>VISIT 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4/ WEEK 4</td>
<td>Mean</td>
<td>52.8</td>
<td>9.5</td>
</tr>
<tr>
<td>VISIT 6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6/ WEEK 8</td>
<td>Mean</td>
<td>52.9</td>
<td>9.9</td>
</tr>
</tbody>
</table>

1) ANOVA difference, Daivobet Gel minus Tacalcitol/Gel vehicle
Table 36: Change in ‘Mental Component Summary’ measure based on the SF-36 (v2) health survey questionnaire from baseline to weeks 4 and 8 and the results of statistical analysis: full analysis set

<table>
<thead>
<tr>
<th>VISIT 4/ WEEK 4</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>1.6</td>
<td>0.8</td>
<td>-1.1</td>
</tr>
<tr>
<td>SD</td>
<td>6.8</td>
<td>6.9</td>
<td>9.6</td>
</tr>
<tr>
<td>Median</td>
<td>0.4</td>
<td>0.9</td>
<td>-0.7</td>
</tr>
<tr>
<td>Minimum</td>
<td>-14.9</td>
<td>-21.7</td>
<td>-28.3</td>
</tr>
<tr>
<td>Maximum</td>
<td>33.4</td>
<td>30.0</td>
<td>28.9</td>
</tr>
<tr>
<td>Number</td>
<td>169</td>
<td>172</td>
<td>75</td>
</tr>
<tr>
<td>P-value¹</td>
<td>0.002</td>
<td>0.11</td>
<td>0.34</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VISIT 6/ WEEK 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>SD</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Minimum</td>
</tr>
<tr>
<td>Maximum</td>
</tr>
<tr>
<td>Number</td>
</tr>
<tr>
<td>P-value¹</td>
</tr>
</tbody>
</table>

¹) Paired T-test, within treatment group comparison

The scales and changes in the individual scales that contribute to the Mental Component Summary are presented in section 18 Table 99 and Table 100 (Vitality), Table 101 and Table 102 (Social Functioning), Table 103 and Table 104 (Role Emotional) and Table 105 and Table 106 (Mental Health).

An increase in the scores over time for Vitality was observed for all three groups indicating an increased quality of life as the study progressed. In the DAIVOBET/DOVOBET gel and tacalcitol groups the scores for Social Functioning, Role Emotional and Mental Health also tended to increase over time.
14.6.2 Skindex-16

For individual subject data collected by the Skindex-16 see Appendix XI, Listings 25 (Symptoms), 26 (Emotions) and 27 (Functioning).

The total score is presented by visit in Table 37 and the change in total score from baseline to weeks 4 and 8 is given in Table 38. Scores for the summary measures range from 0 to 100 and the lower the score the better the quality of life.

The total score was similar at baseline among the three treatment groups. There were statistically significant differences in favour of DAIVOBET/DOVOBET gel at Weeks 4 and 8 compared with tacalcitol (p= 0.010 and p=0.007 respectively) and also compared with the gel vehicle (p<0.001 at both timepoints).

Within each treatment group the changes from baseline were statistically significant for all three treatment groups at Weeks 4 and 8 (p<0.001 for all timepoints).
Table 37: Total score based on the Skindex-16 questionnaire by visit and results of statistical analysis: full analysis set

<table>
<thead>
<tr>
<th>VISIT</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/ DAY 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>56.3</td>
<td>56.4</td>
<td>58.8</td>
</tr>
<tr>
<td>SD</td>
<td>24.4</td>
<td>22.7</td>
<td>23.8</td>
</tr>
<tr>
<td>Median</td>
<td>57.3</td>
<td>57.3</td>
<td>60.4</td>
</tr>
<tr>
<td>Minimum</td>
<td>0.0</td>
<td>0.0</td>
<td>7.3</td>
</tr>
<tr>
<td>Maximum</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Number</td>
<td>182</td>
<td>183</td>
<td>91</td>
</tr>
<tr>
<td>4/ WEEK 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>32.2</td>
<td>39.2</td>
<td>50.0</td>
</tr>
<tr>
<td>SD</td>
<td>26.2</td>
<td>23.7</td>
<td>26.7</td>
</tr>
<tr>
<td>Median</td>
<td>27.1</td>
<td>40.6</td>
<td>47.9</td>
</tr>
<tr>
<td>Minimum</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Maximum</td>
<td>100.0</td>
<td>100.0</td>
<td>93.8</td>
</tr>
<tr>
<td>Number</td>
<td>175</td>
<td>173</td>
<td>78</td>
</tr>
<tr>
<td>Difference¹</td>
<td>-7.06</td>
<td>-17.8</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>-12.4 to -1.73</td>
<td>-24.6 to -11.0</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>0.010</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>6/ WEEK 8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>28.2</td>
<td>35.6</td>
<td>43.7</td>
</tr>
<tr>
<td>SD</td>
<td>25.4</td>
<td>23.6</td>
<td>26.1</td>
</tr>
<tr>
<td>Median</td>
<td>20.3</td>
<td>33.9</td>
<td>43.8</td>
</tr>
<tr>
<td>Minimum</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Maximum</td>
<td>100.0</td>
<td>91.7</td>
<td>100.0</td>
</tr>
<tr>
<td>Number</td>
<td>170</td>
<td>162</td>
<td>63</td>
</tr>
<tr>
<td>Difference¹</td>
<td>-7.36</td>
<td>-15.4</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>-12.7 to -2.00</td>
<td>-22.6 to -8.25</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>0.007</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

1) ANOVA difference, Daivobet Gel minus Tacalcitol/Gel vehicle
Table 38: Change in total score based on the Skindex-16 questionnaire from baseline to weeks 4 and 8 and results of statistical analysis: full analysis set

<table>
<thead>
<tr>
<th>VISIT Total Score Change</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VISIT 4/ WEEK 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>-24.0</td>
<td>-17.1</td>
<td>-7.0</td>
</tr>
<tr>
<td>SD</td>
<td>21.6</td>
<td>19.6</td>
<td>16.0</td>
</tr>
<tr>
<td>Median</td>
<td>-22.4</td>
<td>-15.6</td>
<td>-6.8</td>
</tr>
<tr>
<td>Minimum</td>
<td>-82.3</td>
<td>-88.5</td>
<td>-63.5</td>
</tr>
<tr>
<td>Maximum</td>
<td>22.9</td>
<td>34.4</td>
<td>39.6</td>
</tr>
<tr>
<td>Number</td>
<td>174</td>
<td>172</td>
<td>78</td>
</tr>
<tr>
<td>P-value&lt;sup&gt;1&lt;/sup&gt;</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>VISIT 6/ WEEK 8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>-27.1</td>
<td>-19.4</td>
<td>-10.3</td>
</tr>
<tr>
<td>SD</td>
<td>24.2</td>
<td>18.7</td>
<td>19.7</td>
</tr>
<tr>
<td>Median</td>
<td>-28.1</td>
<td>-17.7</td>
<td>-9.4</td>
</tr>
<tr>
<td>Minimum</td>
<td>-86.5</td>
<td>-77.1</td>
<td>-66.7</td>
</tr>
<tr>
<td>Maximum</td>
<td>50.0</td>
<td>25.0</td>
<td>36.5</td>
</tr>
<tr>
<td>Number</td>
<td>169</td>
<td>161</td>
<td>63</td>
</tr>
<tr>
<td>P-value&lt;sup&gt;1&lt;/sup&gt;</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

1) Paired T-test, within treatment group comparison

The scores and changes in scores for the individual components (Symptoms, Emotions and Functioning) are presented in section 18 Table 108 and Table 109 (Symptoms), Table 110 and Table 111 (Emotions) and Table 112 and Table 113 (Functioning).

The Symptoms scores tended to decrease over time in all three treatment groups indicating an increase in quality of life. The changes in the Symptoms scores were highest in the DAIVOBET/DOVOBET group followed by the tacalcitol group and the lowest changes were seen in the gel vehicle group. A similar pattern was observed in the Emotions scores. For Functioning the scores also tended to decrease over time but the changes were not as marked.

14.7 QUALITY OF LIFE CONCLUSIONS

In the SF-36 (v2) general health questionnaire the scores for the Physical Component Summary and Mental Component Summary were similar among the groups. When comparing
response within the DAIVOBET/DOVOBET gel group, there were no significant changes from baseline in the Physical Component Summary but the change from baseline in the Mental Component Summary score was statistically significant at Weeks 4 and 8 (p=0.002 and p=0.012 respectively).

For the skin disease specific questionnaire (Skindex-16) the changes from baseline within each treatment group were statistically significant for total score in all treatment groups at Weeks 4 and 8 (p<0.001 for both timepoints). There were statistically significant differences in favour of DAIVOBET/DOVOBET gel at Weeks 4 and 8 compared with tacalcitol (p=0.010 and p=0.007 respectively) and also compared with the gel vehicle (p<0.001 at both timepoints).

15 SAFETY EVALUATION

15.1 DURATION AND EXTENT OF EXPOSURE TO TREATMENT WITH TRIAL MEDICATION

For individual subject data on study medication used see Appendix XI, Listing 10.

The duration of exposure to treatment summarised in Table 39 was calculated for the safety analysis set and the average amount of study medication used per week during the study is shown in Table 40.

The mean duration of treatment was similar for all treatment groups (7.65 weeks for DAIVOBET/DOVOBET gel, 7.44 weeks for tacalcitol and 6.77 weeks for the gel vehicle). The mean amount of study medication used per week over the total treatment period was lower in the DAIVOBET/DOVOBET gel group and gel vehicle group compared with the tacalcitol group (27.5 g/week and 26.2 g/week for DAIVOBET/DOVOBET gel and gel vehicle groups versus 33.2 g/week in the tacalcitol group). It must be noted that the amounts reflect actual use and include data from subjects who achieved ‘clear’ who were allowed to use the treatment ‘as needed’.
Table 39: Duration and extent of exposure to treatment: safety analysis set

<table>
<thead>
<tr>
<th>Duration and extent of treatment exposure (weeks)</th>
<th>Dayvobet Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>7.65</td>
<td>7.44</td>
<td>6.77</td>
</tr>
<tr>
<td>SD</td>
<td>1.43</td>
<td>1.70</td>
<td>2.46</td>
</tr>
<tr>
<td>Minimum</td>
<td>0.3</td>
<td>0.1</td>
<td>0.7</td>
</tr>
<tr>
<td>Maximum</td>
<td>12.1</td>
<td>12.1</td>
<td>13.1</td>
</tr>
<tr>
<td>Number</td>
<td>182</td>
<td>184</td>
<td>91</td>
</tr>
<tr>
<td>Extent of exposure to treatment (subject-treatment-weeks)</td>
<td>1393</td>
<td>1369</td>
<td>616</td>
</tr>
</tbody>
</table>
Table 40: Average amount of study medication used per week between visits and over the total study period: randomised subjects

<table>
<thead>
<tr>
<th>Visit interval</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1 to Visit 2 (1 week)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>22.9</td>
<td>30.3</td>
<td>21.8</td>
</tr>
<tr>
<td>SD</td>
<td>20.1</td>
<td>23.0</td>
<td>16.1</td>
</tr>
<tr>
<td>Minimum</td>
<td>0.6</td>
<td>0.0</td>
<td>2.8</td>
</tr>
<tr>
<td>Maximum</td>
<td>89.7</td>
<td>108.4</td>
<td>72.7</td>
</tr>
<tr>
<td>Number</td>
<td>178</td>
<td>179</td>
<td>89</td>
</tr>
<tr>
<td>Visit 2 to Visit 3 (1 week)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>26.1</td>
<td>32.2</td>
<td>24.0</td>
</tr>
<tr>
<td>SD</td>
<td>24.4</td>
<td>23.7</td>
<td>17.5</td>
</tr>
<tr>
<td>Minimum</td>
<td>0.0</td>
<td>0.0</td>
<td>2.8</td>
</tr>
<tr>
<td>Maximum</td>
<td>117.9</td>
<td>130.8</td>
<td>71.3</td>
</tr>
<tr>
<td>Number</td>
<td>175</td>
<td>174</td>
<td>85</td>
</tr>
<tr>
<td>Visit 3 to Visit 4 (2 weeks)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>27.2</td>
<td>33.1</td>
<td>25.9</td>
</tr>
<tr>
<td>SD</td>
<td>22.6</td>
<td>23.8</td>
<td>19.2</td>
</tr>
<tr>
<td>Minimum</td>
<td>0.0</td>
<td>0.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Maximum</td>
<td>90.5</td>
<td>95.0</td>
<td>87.2</td>
</tr>
<tr>
<td>Number</td>
<td>171</td>
<td>169</td>
<td>78</td>
</tr>
<tr>
<td>Visit 4 to Visit 5 (2 weeks)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>28.3</td>
<td>33.6</td>
<td>26.5</td>
</tr>
<tr>
<td>SD</td>
<td>25.3</td>
<td>28.0</td>
<td>22.6</td>
</tr>
<tr>
<td>Minimum</td>
<td>0.3</td>
<td>0.0</td>
<td>1.7</td>
</tr>
<tr>
<td>Maximum</td>
<td>160.4</td>
<td>218.9</td>
<td>112.4</td>
</tr>
<tr>
<td>Number</td>
<td>169</td>
<td>164</td>
<td>68</td>
</tr>
<tr>
<td>Visit 5 to Visit 6 (2 weeks)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>29.3</td>
<td>32.2</td>
<td>26.0</td>
</tr>
<tr>
<td>SD</td>
<td>25.2</td>
<td>25.1</td>
<td>22.6</td>
</tr>
<tr>
<td>Minimum</td>
<td>0.0</td>
<td>0.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Maximum</td>
<td>108.5</td>
<td>96.5</td>
<td>94.3</td>
</tr>
<tr>
<td>Number</td>
<td>163</td>
<td>154</td>
<td>63</td>
</tr>
</tbody>
</table>
Table 40: Amount of study medication used per week between visits and over the total study period: randomised subjects

<table>
<thead>
<tr>
<th>Visit interval</th>
<th>DAIVO BET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial medication used (g per week)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit 1 to End of Treatment (total treatment period)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>27.5</td>
<td>33.2</td>
<td>26.2</td>
</tr>
<tr>
<td>SD</td>
<td>21.4</td>
<td>23.2</td>
<td>18.6</td>
</tr>
<tr>
<td>Minimum</td>
<td>0.7</td>
<td>0.2</td>
<td>2.3</td>
</tr>
<tr>
<td>Maximum</td>
<td>92.0</td>
<td>95.0</td>
<td>72.1</td>
</tr>
<tr>
<td>Number(^1)</td>
<td>159</td>
<td>150</td>
<td>58</td>
</tr>
</tbody>
</table>

1) Calculated by subtracting the weight of the used bottles from the mean normal weight of full bottles, dividing by the number of days exposed to treatment and multiplying by 7. Negative weights have been set to zero.

2) Some subjects returned all unused medication at End of Treatment, and thus provided data for visit 1 to End of Treatment, only. Only subjects who returned all dispensed bottles/tubes provide data.

15.2 ADVERSE EVENTS REPORTED

For individual subject data on adverse events see Appendix XI, Listing 28.

15.2.1 Adverse Events in the Treatment Phase

The number of subjects with adverse events reported in the treatment phase within each MedDRA primary SOC and the statistical analysis is given in Table 41.
Table 41: Adverse events reported in the treatment phase by MedDRA primary system organ class and results of statistical analysis: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>DAIVOBET Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>7</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>6</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>31</td>
<td>32</td>
<td>11</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>4</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Investigations</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>6</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>6</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 41: Adverse events reported in the treatment phase by MedDRA primary system organ class and results of statistical analysis: safety analysis set (continued)

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>DAIVOBET Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>1</td>
<td>0.5</td>
<td>2</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>14</td>
<td>7.7</td>
<td>28</td>
</tr>
<tr>
<td>Surgical and medical procedures</td>
<td>1</td>
<td>0.5</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>3</td>
<td>1.6</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total number of adverse events</strong></td>
<td><strong>98</strong></td>
<td><strong>124</strong></td>
<td><strong>48</strong></td>
</tr>
<tr>
<td><strong>Total number of subjects</strong></td>
<td><strong>72</strong></td>
<td><strong>83</strong></td>
<td><strong>35</strong></td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td><strong>0.28</strong></td>
<td><strong>0.28</strong></td>
<td><strong>0.28</strong></td>
</tr>
</tbody>
</table>

1) Classification according to MedDRA version 6.1
2) Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes
3) Chi-squared test

The proportion of patients with at least one adverse event was similar and not statistically significant between the DAIVOBET/DOVOBET Gel group (72 subjects, 39.6%) versus the tacalcitol group (83 subjects, 45.1%, p=0.28) and versus the gel vehicle group (35 subjects, 38.5%, p=0.86). The most common adverse events in all three groups were in the SOC ‘Infections and infestations’ reported by 31 (17.0%) subjects in the DAIVOBET/DOVOBET gel group, 32 (17.4%) in the tacalcitol group and 11 (12.1%) in the gel vehicle group. ‘Skin and subcutaneous tissue disorders’ were reported with lower incidence in the DAIVOBET/DOVOBET gel group (7.7%) compared with the tacalcitol group (15.2%) and the gel vehicle group (11.0%).

The adverse events reported in the treatment phase by at least 1% of subjects in any treatment group are summarised by SOC and preferred term in Table 42.
Table 42: Adverse events reported in the treatment phase occurring in ≥1% of subjects in any treatment group by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class¹</th>
<th>Preferred Term²</th>
<th>DAIVOBET Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
<td>%</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Anaemia</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Leukocytosis</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Myocardial infarction</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Ear pain</td>
<td>2</td>
<td>1.1</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Diarrhoea</td>
<td>1</td>
<td>0.5</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Gastrooesophageal reflux disease</td>
<td>2</td>
<td>1.1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Toothache</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
</tr>
</tbody>
</table>
Table 42: Adverse events reported in the treatment phase occurring in >=1% of subjects in any treatment group by MedDRA primary system organ class and preferred term: safety analysis set (continued)

<table>
<thead>
<tr>
<th>System Organ Class¹ Preferred Term¹</th>
<th>DAIVOBET Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Application site burning</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
</tr>
<tr>
<td>Pitting oedema</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>2</td>
<td>1.1</td>
<td>1</td>
</tr>
<tr>
<td>Folliculitis</td>
<td>2</td>
<td>1.1</td>
<td>0</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>2</td>
<td>1.1</td>
<td>6</td>
</tr>
<tr>
<td>Gastroenteritis viral</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
</tr>
<tr>
<td>Influenza</td>
<td>3</td>
<td>1.6</td>
<td>2</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>11</td>
<td>6.0</td>
<td>6</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Pharyngitis streptococcal</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 42: Adverse events reported in the treatment phase occurring in >=1% of subjects in any treatment group by MedDRA primary system organ class and preferred term: safety analysis set (continued)

<table>
<thead>
<tr>
<th>System Organ Class¹ Preferred Term¹</th>
<th>DAIVOBET Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinusitis</td>
<td>1</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>8</td>
<td>4.4</td>
<td>10</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>2</td>
<td>1.1</td>
<td>1</td>
</tr>
<tr>
<td>Back injury</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
</tr>
<tr>
<td>Excoriation</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Fall</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
</tr>
<tr>
<td>Joint sprain</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Limb injury</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>1</td>
<td>0.5</td>
<td>2</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1</td>
<td>0.5</td>
<td>2</td>
</tr>
<tr>
<td>Back pain</td>
<td>1</td>
<td>0.5</td>
<td>2</td>
</tr>
</tbody>
</table>
Table 42: Adverse events reported in the treatment phase occurring in >=1% of subjects in any treatment group by MedDRA primary system organ class and preferred term: safety analysis set (continued)

<table>
<thead>
<tr>
<th>System Organ Class &amp; Preferred Term</th>
<th>DAIVOBET Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monoarthritis</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Muscle cramp</td>
<td>2</td>
<td>1.1</td>
<td>0</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>1</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burning sensation</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
</tr>
<tr>
<td>Headache</td>
<td>5</td>
<td>2.7</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Pharyngolaryngeal pain</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Productive cough</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatitis contact</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>6</td>
<td>3.3</td>
<td>13</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>1</td>
<td>0.5</td>
<td>3</td>
</tr>
</tbody>
</table>
Table 42: Adverse events reported in the treatment phase occurring in $\geq$1% of subjects in any treatment group by MedDRA primary system organ class and preferred term: safety analysis set (continued)

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>DAVOBST Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
<td>%</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash scaly</td>
<td>1</td>
<td>0.5</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Skin burning sensation</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Skin desquamation</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Skin inflammation</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Skin irritation</td>
<td>6</td>
<td>3.3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Urticaria</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension</td>
<td>3</td>
<td>1.6</td>
<td>1</td>
</tr>
</tbody>
</table>

Total number of adverse events: 98  124  48

Total number of subjects: 72  83  35

1) Classification according to MedDRA version 6.1
2) Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes
The most common adverse events in the DAIVOBE/DOVOBET gel group were nasopharyngitis in 11 (6.0%) subjects and upper respiratory tract infection in 8 (4.4%) subjects. The most common adverse event in the tacalcitol and the gel vehicle groups was pruritus reported by 13 (7.1%) and 7 (7.7%) subjects respectively. Pruritus was reported at lower frequency in the DAIVOBE/DOVOBET gel group with 6 (3.3%) subjects reporting this event.

A summary of all adverse events in the treatment phase by SOC and preferred term is given in section 18 in Table 114 and relationship of adverse events to study medication is given in section 18 in Table 115.

The majority of adverse events were considered ‘Not related’. In the DAIVOBE/DOVOBET gel group, 78 events were categorised as ‘Not related’, 8 as ‘Possible’, 11 as ‘Probable’ and 1 as ‘Not assessable’. In the tacalcitol group, 90 events were categorised as ‘Not related’, 10 as ‘Possible’ and 24 as ‘Probable’ and the corresponding number in the gel vehicle group were 29 ‘Not related’, 9 ‘Possible’ and 10 ‘Probable’. Most adverse events not categorised as ‘Not related’ were in the ‘Skin and subcutaneous tissue disorders’ system organ class with 14 adverse drug reactions in the DAIVOBE/DOVOBET gel group, 23 in the tacalcitol group and 12 in the gel vehicle group.

Adverse drug reactions reported in the treatment phase are summarised by SOC and preferred term in Table 43.
Table 43: Adverse drug reactions reported in the treatment phase by MedDRA primary system organ class and preferred term and results of statistical analysis: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>DAIVOBE Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td>General disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>and administration</td>
<td>Application site burning</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
</tr>
<tr>
<td>site conditions</td>
<td>Application site pruritus</td>
<td>1</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Infections and</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>infestations</td>
<td>Body tinea</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Folliculitis</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Nail tinea</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Otitis externa</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Sinusitis</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Tinea pedis</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 43: Adverse drug reactions reported in the treatment phase by MedDRA primary system organ class and preferred term and results of statistical analysis: safety analysis set (continued)

<table>
<thead>
<tr>
<th>System Organ Class†</th>
<th>Preferred Term†</th>
<th>DAIVOBI Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
<td>%</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Muscle cramp</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Burning sensation</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>2</td>
<td>1.1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Migraine</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Dry skin</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Brythema</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 43: Adverse drug reactions reported in the treatment phase by MedDRA primary system organ class and preferred term and results of statistical analysis: safety analysis set (continued)

<table>
<thead>
<tr>
<th>System Organ Class\Preferred Term</th>
<th>DAIVOBET Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>6 3.3%</td>
<td>11 6.0%</td>
<td>6 6.6%</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>0 0.0%</td>
<td>1 0.5%</td>
<td>0 0.0%</td>
</tr>
<tr>
<td>Rash scaly</td>
<td>1 0.5%</td>
<td>3 1.6%</td>
<td>1 1.1%</td>
</tr>
<tr>
<td>Skin burning sensation</td>
<td>0 0.0%</td>
<td>1 0.5%</td>
<td>2 2.2%</td>
</tr>
<tr>
<td>Skin desquamation</td>
<td>0 0.0%</td>
<td>2 1.1%</td>
<td>0 0.0%</td>
</tr>
<tr>
<td>Skin inflammation</td>
<td>0 0.0%</td>
<td>0 0.0%</td>
<td>1 1.1%</td>
</tr>
<tr>
<td>Skin irritation</td>
<td>6 3.3%</td>
<td>4 2.2%</td>
<td>1 1.1%</td>
</tr>
<tr>
<td>Urticaria</td>
<td>0 0.0%</td>
<td>0 0.0%</td>
<td>1 1.1%</td>
</tr>
<tr>
<td>Total number of drug reactions\Total number of subjects</td>
<td>20 16 8.8%</td>
<td>34 29 15.8%</td>
<td>19 16 17.6%</td>
</tr>
</tbody>
</table>

P-value: 0.042 0.033

1) Classification according to MedDRA version 6.1
2) Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes
3) Chi-squared test
The proportion of subjects with at least one adverse drug reaction was significantly lower in the DAIVOET/DOVOET gel group than in the other two groups; 16 (8.8%) versus 29 (15.8%), p=0.042 for tacalcitol and 16 (8.8%) versus 16 (17.6%), p=0.033 for the gel vehicle. The most frequently reported adverse drug reactions in the DAIVOET/DOVOET gel group were pruritus and skin irritation both reported by 6 (3.3) subjects. Pruritus was also the most common adverse drug reaction reported in the other two groups but at a higher frequency than in the DAIVOET/DOVOET group. Pruritus was reported by 11 (6.0%) subjects in the tacalcitol group and 6 (6.6%) in the gel vehicle group. The other most common adverse drug reaction in the tacalcitol group was skin irritation reported by 4 (2.2%) subjects. In the gel vehicle group burning sensation was the other most common adverse drug reaction reported by 4 (4.4%) subjects.

The intensity of adverse drug reactions reported in the treatment phase by SOC and preferred term are summarised in Table 44.
Table 44: Intensity of adverse drug reactions reported in the treatment phase by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class' Preferred Term</th>
<th>DAIVOBET Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Application site burning</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Application site pruritus</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body tinea</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Folliculitis</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nail tinea</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Otitis externa</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tinea pedis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle cramp</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

continued...
Table 44: Intensity of adverse drug reactions reported in the treatment phase by MedDRA primary system organ class and preferred term: safety analysis set (continued)

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>DAIVOBET Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Burning sensation</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Migraine</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Dry skin</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Erythema</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Pruritus</td>
<td>2</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Psoriasis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Rash scaly</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Skin burning sensation</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Skin desquamation</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Skin inflammation</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Skin irritation</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Urticaria</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 44: Intensity of adverse drug reactions reported in the treatment phase by MedDRA primary system organ class and preferred term: safety analysis set (continued)

<table>
<thead>
<tr>
<th>System Organ Class\Preferred Term</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAIVOBET Gel (n=182)</td>
<td>12</td>
<td>7</td>
<td>1</td>
<td>20</td>
<td>11</td>
<td>3</td>
<td>7</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Tacalcitul Gel (n=184)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gel Vehicle (n=91)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1) Classification according to MedDRA version 6.1
2) Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
Most adverse drug reactions in the DAIVOBET/DOVOBET gel and tacalcitol groups were of mild intensity but in the gel vehicle group most were of moderate intensity. Few adverse drug reactions were of severe intensity; one (skin irritation) in the DAIVOBET/DOVOBET gel group, three (one burning sensation and two pruritus) in the tacalcitol group and two (both pruritus) in the gel vehicle group.

15.2.1.1 Lesional/perilesional Adverse Events on the Body in the Treatment Phase
The number of subjects with lesional/perilesional adverse events on the body reported in the treatment phase within each MedDRA Primary SOC and preferred term is given in Table 45.
Table 45: Lesional/perilesional adverse events on the body reported in the treatment phase by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class1 Preferred Term1</th>
<th>DAIVOBET Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Application site burning</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
</tr>
<tr>
<td>Application site dryness</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Application site pruritus</td>
<td>1</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Folliculitis</td>
<td>2</td>
<td>1.1</td>
<td>0</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contusion</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Excoriation</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
</tr>
<tr>
<td>Limb injury</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
</tbody>
</table>

*continued...*
Table 45: Lesional/perilesional adverse events on the body reported in the treatment phase by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class¹ Preferred Term¹</th>
<th>DAIVOBET Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoplasm skin</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burning sensation</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Skิน and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry skin</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Erythema</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>6</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Rash scaly</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Skin burning sensation</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Skin desquamation</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Skin inflammation</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Skin irritation</td>
<td>6</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

¹MedDRA preferred term
Table 45: Lesional/perilesional adverse events on the body reported in the treatment phase by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class¹</th>
<th>Preferred Term</th>
<th>Number of Subjects</th>
<th>%</th>
<th>Number of Subjects</th>
<th>%</th>
<th>Number of Subjects</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Urticaria</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>Total number of adverse events²</td>
<td>18</td>
<td>8.8</td>
<td>35</td>
<td>17.4</td>
<td>14</td>
<td>15.4</td>
</tr>
<tr>
<td></td>
<td>Total number of subjects</td>
<td>16</td>
<td>8.8</td>
<td>32</td>
<td>17.4</td>
<td>14</td>
<td>15.4</td>
</tr>
</tbody>
</table>

¹ Classification according to MedDRA version 6.1
² Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes
The proportion of subjects with at least one lesional/perilesional adverse event on the body was lower in the DAIVOBET/DOVOBET gel group (16 subjects; 8.8%) than in the other two treatment groups; 32 subjects (17.4%) in the tacalcitol group and 14 subjects (15.4%) in the gel vehicle group. The most frequently reported lesional/perilesional adverse event on the body in the DAIVOBET/DOVOBET gel group were pruritus and skin irritation both reported by 6 (3.3) subjects. Pruritus was also the most common lesional/perilesional adverse event reported in the other two groups but at a higher frequency than in the DAIVOBET/DOVOBET group. Lesional/perilesional pruritus was reported by 12 (6.5%) subjects in the tacalcitol group and 6 (6.6%) in the gel vehicle group. The other most common lesional/perilesional adverse event in the tacalcitol group was skin irritation reported by 4 (2.2%) subjects. In the gel vehicle group burning sensation was the other most common lesional/perilesional adverse event reported by 3 (3.3%) subjects.
15.2.2 Adverse Events in the Observation Phase

The number of subjects with adverse events reported in the observation phase within each MedDRA Primary SOC and the statistical analysis is given in section 18 Table 116.

The proportion of subjects with at least one adverse event in the observation phase was similar and not statistically significant in the DAIVOBET/DOVOBET gel and the gel vehicle groups; 15 (22.1%) subjects and 1 (20.0%) subject respectively; p=0.91. There was a trend towards a higher incidence in the tacalcitol group; 14 (40.0%) subjects (p=0.055). The most common adverse events in the DAIVOBET/DOVOBET gel and tacalcitol groups were in the SOC ‘Infections and infestations’ and upper respiratory tract infection was the most common adverse event. There was only one subject in the gel vehicle group with two adverse events (arthralgia and localised osteoarthritis).

A summary of all adverse events in the observation phase by SOC and preferred term is given in section 18 in Table 117 and relationship of adverse events to study medication is given in section 18 in Table 118.

In the observation phase all the adverse events, except four in the DAIVOBET/DOVOBET gel group (pharyngitis, eye swelling, drug hypersensitivity and hordeolum) and two in the tacalcitol group (cellulites and tendonitis) were considered ‘Not related’. There were no adverse drug reactions reported to the gel vehicle in the observation phase.

Adverse drug reactions reported in the observation phase are summarised by SOC and preferred term in Table 46.
Table 46: Adverse drug reactions reported in the observational phase by MedDRA primary system organ class and preferred term and results of statistical analysis: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class\Preferred Term</th>
<th>DAIVOBET Gel (n=68)</th>
<th>Tacalcitol (n=35)</th>
<th>Gel Vehicle (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye swelling</td>
<td>1</td>
<td>1.5</td>
<td>0</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug hypersensitivity</td>
<td>1</td>
<td>1.5</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellulitis</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Hordeolium</td>
<td>1</td>
<td>1.5</td>
<td>0</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>1</td>
<td>1.5</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tendonitis</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Total number of drug reactions¹</td>
<td>4</td>
<td>4.4</td>
<td>2</td>
</tr>
<tr>
<td>Total number of subjects</td>
<td>3</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>P-value¹</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1) Classification according to MedDRA version 6.1
2) Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes
3) Chi-squared test
There were few adverse drug reactions in the observation phase and proportion of subjects with at least one adverse drug reaction was similar and not statistically different among the three treatment groups.

The intensity of adverse drug reactions reported in the observation phase by SOC and preferred term are summarised in Table 47.
Table 47: Intensity of adverse drug reactions reported in the observation phase by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class’ Preferred Term</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye swelling</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Drug hypersensitivity</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellulitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hordeolum</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tendonitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>Total number of adverse drug reactions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

1) Classification according to MedDRA version 6.1
2) Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
Most adverse drug reactions in the observation phase were of mild intensity and none were reported as of severe intensity.

15.2.2.1 Lesional/perilesional Adverse Events on the Body in the Observation Phase

The number of subjects with lesional/perilesional adverse events on the body reported in the observational phase within each MedDRA Primary SOC and preferred term is given in Table 48.

One subject in the DAIVOBET/DOVOBET gel group reported one lesional/perilesional adverse event (pruritus) on the body and this was considered ‘Not related’ to study medication. There were no other lesional/perilesional adverse events on the body reported in the observation phase.
Table 48: Lesional/perilesional adverse events on the body reported in the observation phase by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class¹</th>
<th>Preferred Term</th>
<th>DAIVOBET Gel (n=68)</th>
<th>Tacalcitol (n=35)</th>
<th>Gel Vehicle (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Pruritus</td>
<td>1</td>
<td>1.5</td>
<td>0</td>
</tr>
</tbody>
</table>

1) Classification according to MedDRA version 6.1
2) Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
15.3 DEATHS, OTHER SERIOUS ADVERSE EVENTS AND OTHER SIGNIFICANT ADVERSE EVENTS

There were no deaths reported during the study.

15.3.1 Other Serious Adverse Events

15.3.1.1 Other Serious Adverse Events in the Treatment Phase

In the treatment phase four subjects (CRF=■■■■ CRF=■■■■ CRF=■■■■ and CRF=■■■■ in the tacalcitol group and one subject (CRF=■■■■ in the gel vehicle group reported serious adverse events. No subjects in the DAIVOBET/DOVOBET gel group reported such events. All were considered not related to study medication. These serious adverse events are summarised within each MedDRA Primary SOC by Preferred Term in Table 49 and narratives are provided in section 15.3.1.3.
Table 49: Serious adverse events reported in the treatment phase by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>DAIVOBET Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arrhythmia</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Myocardial infarction</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gastroenteritis</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Squamous cell carcinoma</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cervical dysplasia</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total number of adverse events</td>
<td></td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total number of subjects</td>
<td></td>
<td>0</td>
<td>4</td>
<td>2.2</td>
</tr>
</tbody>
</table>

1) Classification according to MedDRA version 6.1
2) Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
15.3.1.2 Other Serious Adverse Events in the Observation Phase
In the observation phase no further serious adverse events were reported.

15.3.1.3 Narratives for Other Serious Adverse Events

CRF Number: 
Event: Myocardial infarction

The investigator considered the event to be not related to the study medication.

CRF Number: 
Event: Arrhythmia

The investigator considered the event to be not related to the study medication.
CRF Number: [Redacted]
Event: Bronchitis acute

The investigator considered the event to be not related to the study medication.

CRF Number: [Redacted]
Event: Squamous cell carcinoma

The investigator considered the event to be not related to the study medication.

CRF Number: [Redacted]
Event: Gastroenteritis
The investigator considered the event to be not related to the study medication.

CRF Number: 
Event: Cervical dysplasia

The investigator considered the event to be not related to the study medication.

15.3.2 Other Significant Adverse Events

15.3.2.1 Adverse Events Leading to Withdrawal in the Treatment Phase
Adverse events were recorded as the reason for withdrawal in the treatment phase for 3 (1.6%) subjects in the DAIWOET/DOVOET gel group, 4 (2.2%) in the tacalcitol group and 4 (4.4%) in the gel vehicle group. The adverse events within each MedDRA primary SOC by preferred term that led to withdrawal in the treatment phase are summarised in Table 50. Narratives are provided for subjects who discontinued due to adverse events in the DAIWOET/DOVOET gel group in 15.3.2.3.
Table 50: Adverse events leading to withdrawal from the treatment phase by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class\Preferred Term\</th>
<th>Number of Subjects</th>
<th>Number of Subjects</th>
<th>Number of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DAIVOBET Gel (n=182)</td>
<td>Tacalcitol (n=184)</td>
<td>Gel Vehicle (n=91)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burning sensation</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry skin</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin burning sensation</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Skin irritation</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Urticaria</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total number of adverse events\</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Total number of subjects</td>
<td>3</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

1) Classification according to MedDRA version 6.1
2) Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
15.3.2.2 Adverse Events Leading to Withdrawal in the Observation Phase
In the observation phase no subjects withdrew due to adverse events.

15.3.2.3 Narratives for Adverse Events Leading to Withdrawal

15.3.2.3.1 DAIVOBET/DOVOBET
CRF Number: [Redacted]
Event: Dry skin, pruritus

The investigator considered both of the events to be probably related to the study medication.

CRF Number: [Redacted]
Event: Psoriasis

The investigator considered the event to be not related to the study medication.
CRF Number: [redacted]
Event: Skin irritation

The investigator considered the event to be not assessable with regard to relationship to the study medication.

15.3.2.3.2 Tacalcitol
CRF Number: [redacted]
Event: Pruritus

The investigator considered the event to be probably related to the study medication.
The investigator considered the event to be probably related to the study medication.

CRF Number: 
Event: Pruritus, burning sensation

The investigator considered both of the events to be probably related to the study medication.

CRF Number: 
Event: Skin Irritation

The investigator considered the event to be probably related to the study medication.

15.3.2.3.3 Gel vehicle
CRF Number: 
Event: Burning
The investigator considered the event to be probably related to the study medication.

CRF Number: [Blank]
Event: Pruritus

The investigator considered the event to be possibly related to the study medication.

CRF Number: [Blank]
Event: Pruritus

The investigator considered the event to be probably related to the study medication.

CRF Number: [Blank]
Event: Urticaria, skin burning sensation, pruritus

The
investigator considered each of the three events to be probably related to the study medication.

15.4 LABORATORY DATA
Not applicable

15.5 VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY
Not applicable

15.6 SAFETY CONCLUSIONS
In the treatment phase of the study, the proportion of patients with at least one adverse event was similar and not statistically significant between the DAIVOBET/DOVOBET gel group (72 subjects, 39.6%) versus the tacalcitol group (83 subjects, 45.1%, p=0.28) and versus the gel vehicle group (35 subjects, 38.5%, p=0.86).

The proportion of subjects with at least one adverse drug reaction was significantly lower in the DAIVOBET/DOVOBET gel group than in the other two groups; 16 (8.8%) versus 29 (15.8%), p=0.042 for tacalcitol and 16 (8.8%) versus 16 (17.6%), p=0.033 for the gel vehicle. A similar pattern was observed for lesional/perilesional adverse events on the body. Pruritus and skin irritation were the most frequently reported adverse drug reactions and lesional/perilesional adverse events in the DAIVOBET/DOVOBET gel group; both reported by 6 (3.3) subjects. Pruritus was also the most common adverse drug reaction and lesionl/perilesional adverse event in the other two groups and was reported with a higher frequency than in the DAIVOBET/DOVOBET gel group. In the tacalcitol group pruritus was reported as an adverse drug reaction by 11 (6.0%) subjects and as a lesional/perilesional adverse event by 12 (6.5%) subjects. In the gel vehicle group the same number 6 (6.6%) subjects reported pruritus as an adverse drug reaction and a lesional/perilesional adverse event. The other most common adverse drug reaction in the tacalcitol group was skin irritation reported by 4 (2.2%) subjects and in the gel vehicle group it was burning sensation reported by 4 (4.4%) subjects.

Withdrawals due to adverse events in the treatment phase were lower in the DAIVOBET/DOVOBET gel group 3 (1.6%) subjects compared with 4 (2.2%) in the tacalcitol group and 4 (4.4%) in the gel vehicle group.
In the observation phase no patients withdrew due to adverse events and the incidences of adverse events in the DAIVOBET/DOVOBET gel and the gel vehicle groups were not statistically significantly different (p=0.91) but there was a trend towards a higher incidence in the tacalcitol group (p=0.055). There were no treatment related deaths or serious adverse events.

16 DISCUSSION

16.1 SUMMARY OF RESULTS

The primary objective was to compare the efficacy of once daily treatment for up to 8 weeks of DAIVOBET/DOVOBET gel with tacalcitol ointment and the gel vehicle alone in subjects with psoriasis vulgaris on the body. The primary response criterion was the proportion of subjects with ‘controlled disease’, defined as ‘clear’ or ‘almost clear’ as measured by the IGA at week 8.

The proportion of subjects who achieved ‘controlled disease’ at week 8 (LOCF) in the DAIVOBET/DOVOBET gel group was 39.9% compared with 5.5% in the gel vehicle group and 17.9% in the tacalcitol group. DAIVOBET/DOVOBET gel was statistically significantly more effective than the gel vehicle (OR 13.9; 95% CI 4.99 to 38.7; p<0.001) and the sequential test also showed that DAIVOBET/DOVOBET gel was more effective than tacalcitol (OR 3.42; 95% CI 2.05 to 5.70; p<0.001). The analysis of the per protocol analysis set supported the results for the full analysis set.

DAIVOBET/DOVOBET gel was also found to be statistically significantly more effective than both the gel vehicle and tacalcitol ointment in terms of the proportion of subjects who achieved ‘controlled disease’ according to the IGA at week 4 (LOCF) and the percentage change in PASI from baseline to weeks 4 and 8. The percentage changes in PASI from baseline to Weeks 4 and 8 were −53.1 and −57.0 respectively for DAIVOBET/DOVOBET gel, −37.3 and −41.9 respectively for tacalcitol and −13.3 and −17.9 respectively for the gel vehicle.

In the observation phase relapse (defined as a reduction in the PASI improvement from baseline of at least 50%) was observed in 28 of 67 (41.8%) subjects in the DAIVOBET/DOVOBET gel group. In the tacalcitol group 7 of 31 (22.6%) experienced relapse and 3 of 5 (60.0%) experienced relapse in the gel vehicle group. The median time to relapse was 63 days in the DAIVOBET/DOVOBET gel group. In the other two treatment groups median time to relapse was 61 days.
For the quality of life evaluation using the SF-36 (v2) general health questionnaire the scores for the Physical Component Summary and Mental Component Summary were similar among the groups. When comparing response within the DAIVOBET/DOVOBET gel group, there were no significant changes from baseline in the Physical Component Summary but the change from baseline in the Mental Component Summary score was statistically significant at Weeks 4 and 8 (p=0.002 and p=0.012 respectively). For the skin disease specific questionnaire (Skindex-16) the changes from baseline within each treatment group were statistically significant for total score in all treatment groups at Weeks 4 and 8 (p<0.001 for both timepoints). There were statistically significant differences in favour of DAIVOBET/DOVOBET gel at Weeks 4 and 8 compared with tacalcitol (p=0.010 and p=0.007 respectively) and also compared with the gel vehicle (p<0.001 at both timepoints).

In the treatment phase of the study, the proportion of patients with at least one adverse event was similar and not statistically significant between the DAIVOBET/DOVOBET gel group (72 subjects, 39.6%) versus the tacalcitol group (83 subjects, 45.1%, p=0.28) and versus the gel vehicle group (35 subjects, 38.5%, p=0.86).

The proportion of subjects with at least one adverse drug reaction was significantly lower in the DAIVOBET/DOVOBET gel group than in the other two groups; 16 (8.8%) versus 29 (15.8%), p=0.042 for tacalcitol and 16 (8.8%) versus 16 (17.6%), p=0.033 for the gel vehicle. A similar pattern was observed for lesional/perilesional adverse events on the body. Pruritus and skin irritation were the most frequently reported adverse drug reactions and lesional/perilesional adverse events in the DAIVOBET/DOVOBET gel group; both reported by 6 (3.3) subjects. Pruritus was also the most common adverse drug reaction and lesional/perilesional adverse event in the other two groups and was reported with a higher frequency than in the DAIVOBET/DOVOBET gel group. In the tacalcitol group pruritus was reported as an adverse drug reaction by 11 (6.0%) subjects and as a lesional/perilesional adverse event by 12 (6.5%) subjects. In the gel vehicle group the same number 6 (6.6%) subjects reported pruritus as an adverse drug reaction and a lesional/perilesional adverse event. The other most common adverse drug reaction in the tacalcitol group was skin irritation reported by 4 (2.2%) subjects and in the gel vehicle group it was burning sensation reported by 4 (4.4%) subjects.

Withdrawals due to adverse events in the treatment phase were lower in the DAIVOBET/DOVOBET gel group 3 (1.6%) subjects compared with 4 (2.2%) in the tacalcitol group and 4 (4.4%) in the gel vehicle group.
In the observation phase no patients withdrew due to adverse events and the incidences of adverse events in the DAIVOBET/DOVOBET gel and the gel vehicle groups were not statistically significantly different (p=0.91) but there was a trend towards a higher incidence in the tacalcitol group (p=0.055). There were no deaths or treatment related serious adverse events.

16.2 DESIGN AND CONDUCT OF THE STUDY

A total of 450 patients were planned to be included in the study and randomised in a 2:2:1 ratio to DAIVOBET/DOVOBET gel (180 subjects), tacalcitol (180 subjects) and the gel vehicle (90 subjects). The target enrolment was reached and 458 subjects were enrolled and randomised (183 to DAIVOBET/DOVOBET gel, 184 to tacalcitol and 91 to the gel vehicle).

The sample size was based on the results obtained in previous studies with designs comparable to the current study and the following estimates were obtained: in one phase II study with DAIVOBET/DOVOBET gel (32) the percentage of subjects having 'controlled disease' according to the investigator's assessment of disease severity was 28% in the DAIVOBET/DOVOBET gel group and 0% in the gel vehicle group. In one study with tacalcitol ointment (40) the average reduction in PASI was 40%. Based on studies where both IGA and PASI were assessed (35, 32) it was assumed that 40% reduction in PASI corresponded to a 'controlled disease' proportion of 11-15%.

With 180 subjects in both the DAIVOBET/DOVOBET gel and tacalcitol treatment groups, a chi-square test had 82% power to reject the null hypothesis of no difference between the two groups with regard to the primary response criterion; patients with 'controlled disease' ('clear' or 'almost clear' disease) according to the investigator's global assessment of disease severity at week 8. Likewise with 90 subjects in the gel vehicle group, a chi-square test had 99% power to reject the null hypothesis of no difference between the DAIVOBET/DOVOBET gel group and the gel vehicle group. The overall power was thus approximately 81%. The sample size calculations assumed that 28% of the subjects in the DAIVOBET/DOVOBET gel group, 15% in the tacalcitol group and 5% in the gel vehicle group would have 'controlled disease'. A two-tailed significance level, α of 0.05 was used and no adjustment for multiple comparisons was deemed necessary because the two hypotheses were tested sequentially (DAIVOBET/DOVOBET gel versus the gel vehicle followed by DAIVOBET/DOVOBET gel versus tacalcitol). Each centre attempted to recruit a minimum of 15 subjects and this target was met in 16 of the 18 centres ( and recruited 5 and 9 subjects respectively).
At week 8 the percentages of patients with ‘controlled disease’ were 39.9% for DAIVOBET/DOVOBET gel, 17.9% for tacalcitol and 5.5% for the gel vehicle. The response rate for DAIVOBET/DOVOBET gel was higher than the estimated 28% which was based on one previous phase 2 study (32) and also slightly higher than the estimates from previous studies for the tacalcitol and gel vehicle groups.

The study could not be double-blinded due to the different physical properties (gel and ointment) of the marketed product (tacalcitol). However all efforts were made to ensure that the investigator who was performing the clinical assessments remained blind to the treatment administered. This was achieved by ensuring that a person other than the investigator dispensed the study treatment and also by including in the subject’s treatment instructions a request that they did not reveal the formulation to the investigator.

There was one amendment to the protocol which excluded subjects with known or suspected severe renal impairment or severe hepatic disorders.

The subject population included in the study were adults of either sex, 18 years or above with a diagnosis of psoriasis vulgaris on the trunk and/or limbs amenable to treatment with a maximum of 100 g of gel or 70 g of tacalcitol ointment per week. Subjects had to have a disease severity of at least moderate according to the investigator’s global assessment of disease severity and a minimum PASI for extent of 2 in at least one body region.

At baseline, the treatment groups were well balanced with regards to demographic details (age, sex and race) and baseline characteristics (skin type, duration of psoriasis, investigators global assessment of disease severity, extent of psoriasis and the patient’s global assessment of disease severity). The subject population included in this study would be expected to be representative of the adult population suffering from psoriasis vulgaris.

All disease specific inclusion/exclusion criteria were met for all patients and no patients were excluded from the per protocol analysis set due to disallowed diagnoses at baseline. One subject was excluded from the per protocol analysis set because they were lost to follow up after Visit 1 and did not provide any post randomisation efficacy, eight subjects were excluded because they took disallowed medication either at baseline or during the study and five subjects were excluded due to poor compliance. So the per protocol analysis set consisted of 444 subjects (177 in the DAIVOBET/DOVOBET gel group, 178 in the tacalcitol group and 89 in the gel vehicle group). For some subjects data from an earlier visit was used.
in the per protocol analysis because they attended their last visit after week 8 (13 subjects) or they had subsequently used a disallowed medication (7 subjects).

The mean duration of exposure was approximately 7 weeks in all three treatment groups. However, the mean amount of study medication used per week over the total treatment period was lower in the DAIVOBET/DOVOBET gel group and gel vehicle group compared with the tacalcitol group (27.5 g/week and 26.2 g/week for DAIVOBET/DOVOBET gel and gel vehicle groups versus 33.2 g/week in the tacalcitol group). Compliance with study medication was good in all three treatment groups with over 60% of subjects who were fully complaint and applied the treatment as instructed and over 24% of subjects missed 10% applications or less. The study results therefore can be considered reliable as compliance in the study is likely to be in agreement with what can be expected when the treatment is used in daily life.

The efficacy and safety of the treatment was assessed in terms of clinical assessments (disease severity, extent and severity of clinical signs of psoriasis, adverse events) made by the investigator. All assessments for a subject were to be made by the same investigator whenever possible. In addition, the subjects were to assess disease severity using a scale different from that used by the investigator. Both scales were based on the condition of the disease at time of the evaluation but the investigator’s global assessment of disease severity was a six-point scale ranging from ‘clear’ to ‘very severe’ disease and the patient’s global assessment of disease severity was a five-point scale ranging from ‘clear’ to ‘severe’. The investigator’s assessment was based on the morphological characteristics of the lesions, while the patient’s assessment focussed on subjective symptoms and impact on daily life. The extent and severity of the clinical signs was assessed by the investigator for each of the signs of redness, thickness and scaliness and the PASI was calculated.

In the observation phase assessments of relapse and rebound were based on the PASI. The definitions were in accordance with the EMEA Guidelines on Clinical Investigation of Medicinal Products Indicated for the Treatment of Psoriasis (38). The guideline states that relapse may be defined as ‘relapse of psoriasis necessitating re-initiation of treatment’ so for this study relapse was defined as ‘a reduction in the PASI improvement from baseline by at least 50%’. Rebound is defined by the guideline as ‘worsening of psoriasis over the baseline value’ so for this study rebound was defined as ‘worsening of psoriasis to a PASI >125% of the baseline value’. Most relapses have been reported to occur within the first month after discontinuation of a topical steroid (39) so the observation period of 8 weeks should have been long enough to detect any relapse.
Quality of life (both general and skin related) was assessed by the subject during the treatment phase. The SF-36 (v2) is an internationally validated questionnaire consisting of 36 questions relating to the general health of the subject and the Skindex-16 is a validated questionnaire consisting of 16 questions concerning the skin condition. Both questionnaires were administered before the subject was seen by the investigator so that the subject’s answers could not be influenced by any interaction with the investigator.

Prior to study initiation in order to standardise evaluations, investigators were trained in the study procedures and clinical assessments. Compliance with GCP was ensured through monitoring by LEO Pharma.

In conclusion, the study was well designed and conducted and the results are considered reliable and may be extrapolated to other adult patients with psoriasis vulgaris.

16.3 INTERPRETATION OF STUDY RESULTS

DAIVOBET/DOVOBET gel was shown to be statistically significantly more effective than the gel vehicle and tacalcitol ointment. At week 8 the percentages of patients with ‘controlled disease’ were 39.9% for DAIVOBET/DOVOBET gel, 5.5% for the gel vehicle and 17.9% for tacalcitol ointment. The analysis of the secondary response criteria supported the conclusions of the primary analysis. DAIVOBET/DOVOBET gel was also found to be statistically significantly more effective than both the gel vehicle and tacalcitol ointment in terms of the proportion of subjects who achieved ‘controlled disease’ according to the IGA at week 4 (LOCF) and the percentage change in PASI from baseline to weeks 4 and 8. For DAIVOBET/DOVOBET gel the percentage changes in PASI from baseline to Weeks 4 and 8 were −53.1 and −57.0 respectively, for tacalcitol −37.3 and −41.9 respectively and for the gel vehicle −13.3 and −17.9 respectively.

For the primary response criterion, the response rate to DAIVOBET/DOVOBET gel in the current study was some 10% higher than that observed in the previous phase 2 study (32) in which 27.2% achieved ‘controlled disease’ at week 8. Similarly the response rate for the gel vehicle in the current study was also higher than observed in the phase 2 study (32) where no patients in the gel vehicle group achieved ‘controlled disease’. The estimates of response of 11-15% for tacalcitol were based on a number of studies (32, 35, 40) and the response observed in the current study for tacalcitol ointment was also slightly higher than anticipated. The superior efficacy of DAIVOBET/DOVOBET gel versus tacalcitol was achieved even though the subjects in the tacalcitol group applied more study treatment per week (a mean of 33.2 g/week versus 27.5 g/week).
In terms of the percentage changes in PASI from baseline to Weeks 4 and 8 the response to DAIVO BET/DOVO BET gel in the current study was similar to that observed in the phase 2 study (32) but slightly higher for the gel vehicle. In the phase 2 study the percentage changes on PASI were -48.1 and -55.3 respectively for DAIVO BET/DOVO BET gel and -16.9 and -11.9 respectively for the gel vehicle.

The assessment of relapse and rebound after treatment was included in this study in accordance with the EMEA guideline on Clinical Investigation of Medicinal Products Indicated for the Treatment of Psoriasis (38). Data on relapse and rebound in the comparator groups in the present study are difficult to interpret because they are based on selected subgroups which are not randomised and therefore direct comparisons between groups are not valid.

In the current study a higher percentage of subjects in the DAIVO BET/DOVO BET gel group (67 of 183; 36.6%) entered the observation period than in the tacalcitol ointment group (31 of 184; 16.8%) and vehicle group (5 of 91; 5.5%). In the DAIVO BET/DOVO BET gel group relapse was observed in 41.8% of subjects and the median time to relapse was 63 days.

These results for relapse are similar to those observed in a previous study of similar design comparing DAIVO BET/DOVO BET gel with DAIVONEX/DOVONEX scalp solution in scalp psoriasis (30). In this study, as in the current study, a higher number of patients in the DAIVO BET/DOVO BET gel group entered the observation period and relapse occurred in 54.1% of subjects. However in the current study the median time to relapse following successful treatment with DAIVO BET/DOVO BET gel was longer in psoriasis vulgaris on the body (63 days) compared to that observed in scalp psoriasis (35 days). Rebound of the psoriasis vulgaris on the body was not reported in the current study. Rebound of scalp psoriasis was however reported in two patients (1.5%) in the DAIVO BET/DOVO BET gel group in the previous study (30).

Relapse and rebound of psoriasis vulgaris on the body has been assessed in a previous study (30) using the ointment formulation of DAIVO BET/DOVO BET. In contrast to the current study, both were assessed during treatment rather than following successful treatment. They were, however, defined in the same way as in the current study using the PASI. Subjects were randomised to receive treatment with DAIVO BET/DOVO BET ointment for 4 weeks followed for 8 weeks by either 1) DAIVONEX/DOVONEX cream, 2) DAIVONEX/DOVONEX cream on weekdays and DAIVO BET/DOVO BET ointment on weekends or 3) vehicle. The frequency of relapse was between 18.6% and 46.6% which is
similar to that observed in the current study. The frequency of rebound was between 2.4% and 10.2% which is higher than observed in the current study but this may be due to the differences in methodology.

The quality of life assessments in the present study found similar results among the groups when evaluated using the SF-36 (v2) general health questionnaire. Within the DAIVO BET/DOVO BET group the only significant changes from baseline were in the Mental Component Summary at Weeks 4 and 8 so treatment with DAIVO BET/DOVO BET does not appear to have an effect on Physical Components. The skin disease specific questionnaire (Skindex-16) however detected statistically significant changes from baseline within all three treatment groups and DAIVO BET/DOVO BET gel appeared to have statistically significantly better effect on the quality of life at all timepoints compared with both tacalcitol and the gel vehicle. These results are similar to those found in a previous study in which DAIVO BET/DOVO BET gel was used to treat scalp psoriasis (30). In this study no statistically significant differences were observed between DAIVO BET/DOVO BET gel and DAIVONEX/DOVONEX scalp solution in the SF-36(v2) general health questionnaire but the Skindex-16 questionnaire was able to differentiate between the two treatments and DAIVO BET/DOVO BET gel appeared to be more effective than DAIVO BET/DOVO BET scalp solution in terms of skin related quality of life. It is interesting to note that in this study as in the current study the differences between DAIVO BET/DOVO BET gel and the other treatment were more apparent in the symptoms and emotions components than in the functioning component. These results may indicate that effective treatment of psoriasis has more effect on emotions and symptoms than functioning.

The incidence of adverse events, adverse drug reactions and lesional/perilesional adverse events reported to DAIVO BET/DOVO BET gel in the present study is similar to that observed in the phase 2 study (32). The profile of adverse events was also similar. The most common adverse drug reactions in this study were pruritus and skin irritation both of which are well known adverse events of DAIVO BET/DOVO BET gel.

In conclusion, since the study results derived from the different clinical assessments used in the study consistently show that DAIVO BET/DOVO BET gel is superior to the gel vehicle and tacalcitol ointment and the safety profile of DAIVO BET/DOVO BET gel is similar to that observed in previous studies, the study results are considered to be valid.
17 CONCLUSIONS

DAIVOBET/DOVOBET gel was statistically significantly more effective than the gel vehicle and tacalcitol ointment in the treatment of psoriasis vulgaris on the body. The incidence of adverse drug reactions and lesional/perilesional adverse events was also significantly lower resulting in a more favourable benefit/risk ratio for DAIVOBET/DOVOBET gel compared with the gel vehicle and tacalcitol ointment.
18 TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

Baseline

Table 51: Study period by centre: enrolled subjects

<table>
<thead>
<tr>
<th>Centre</th>
<th>Date of first Subject visit</th>
<th>Date of last Subject visit</th>
<th>Duration of study (weeks)</th>
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<tr>
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<td>17-apr-2008</td>
<td>09-dec-2008</td>
<td>33.7</td>
</tr>
<tr>
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<td>10-feb-2009</td>
<td>41.7</td>
</tr>
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<td>09-sep-2008</td>
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<td>28-jan-2009</td>
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<tr>
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<td>05-jun-2008</td>
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<td>24-feb-2009</td>
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<tr>
<td></td>
<td>24-apr-2008</td>
<td>03-dec-2008</td>
<td>31.9</td>
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</table>

All enrolled subjects | 09-apr-2008 | 25-feb-2009 | 46.0 |
Table 52: Reasons for withdrawal from treatment phase and last visit attended: randomised subjects

<table>
<thead>
<tr>
<th>Reason for withdrawal</th>
<th>DAIVOBET Gel (n=183) Last visit attended</th>
<th>Tacalcitol (n=184) Last visit attended</th>
<th>Gel Vehicle (n=91) Last visit attended</th>
</tr>
</thead>
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<tr>
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<td>3</td>
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<td>2</td>
</tr>
<tr>
<td>OTHER REASON(S)</td>
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<td>0</td>
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<td>UNACCEPTABLE ADVERSE EVENT(S)</td>
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<td>0</td>
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<td>UNACCEPTABLE TREATMENT EFFICACY</td>
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<td>0</td>
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<td>VOLUNTARY (AND NO OTHER REASON)</td>
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<td>0</td>
</tr>
<tr>
<td>Total number of withdrawn subjects</td>
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<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

1) Patient unable to attend appointments due to transportation issues
Table 53: Reasons for withdrawal from observation phase and last visit attended: randomised subjects

<table>
<thead>
<tr>
<th>Reason for withdrawal</th>
<th>DAIVOBET Gel (n=60)</th>
<th>Tacalcitol (n=35)</th>
<th>Gel Vehicle (n=5)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Last visit attended</td>
<td>Last visit attended</td>
<td>Last visit attended</td>
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<tr>
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<td>7</td>
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<td>9</td>
</tr>
<tr>
<td>LOST TO FOLLOW-UP</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>OTHER REASON(S)¹</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>SUBJECT EXPERIENCED RELAPSE/REBOUND DURING THE OBSERVATION PHASE²</td>
<td>19</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>VOLUNTARY (AND NO OTHER REASON)</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total number of withdrawn subjects</strong></td>
<td><strong>24</strong></td>
<td><strong>21</strong></td>
<td><strong>0</strong></td>
</tr>
</tbody>
</table>

1) Other reasons include: Entered observation phase in error (1 subject in the DAIVOBET group, 3 subjects in the Tacalcitol group), Requested treatment (2 subjects in the DAIVOBET group, 1 subject in the Tacalcitol group), Unable to continue due to school commitments (1 subject in the DAIVOBET group), Protocol violation (injection of steroid in left knee, 1 subject in the Tacalcitol group), Psoriasis slightly worse and patient wishes to start active treatment (1 subject in the DAIVOBET group), Subject feels skin worse (1 subject in the Tacalcitol group)

2) One subject with relapse/rebound as withdrawal reason entered the observation phase in error (did not have controlled disease at week 8)
Table 54: Protocol deviations by centre: randomised subjects

<table>
<thead>
<tr>
<th>Centre Protocol deviation</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
<td>%</td>
</tr>
<tr>
<td>Disallowed medication at baseline</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Disallowed medication started after baseline</td>
<td>1 0.5</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Lost to follow-up after baseline</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Non-compliance</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>UVB therapy prior to randomisation</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Violation of visit windows</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Total number of deviations (^1)</td>
<td>1 0.5</td>
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<td>0 0.0</td>
</tr>
<tr>
<td>Total number of subjects</td>
<td>1 0.5</td>
<td>0 0.0</td>
<td>0 0.0</td>
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</tbody>
</table>
Table 54: Protocol deviations by centre: randomised subjects

<table>
<thead>
<tr>
<th>Centre Protocol deviation</th>
<th>DAIOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td>Disallowed medication at baseline</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Disallowed medication started after baseline</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Lost to follow-up after baseline</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Non-compliance</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>UVB therapy prior to randomisation</td>
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<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Violation of visit windows</td>
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<tr>
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<tr>
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<tr>
<td>Disallowed medication started after baseline</td>
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</tbody>
</table>

¹ Including: Disallowed medication at baseline, Disallowed medication started after baseline, Lost to follow-up after baseline, Non-compliance, UVB therapy prior to randomisation, Violation of visit windows, Total number of deviations.
Table 54: Protocol deviations by centre: randomised subjects

<table>
<thead>
<tr>
<th>Centre Protocol deviation</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Lost to follow-up after baseline</td>
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<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Non-compliance</td>
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<td>0 0.0</td>
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<tr>
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<tr>
<td>Disallowed medication started after baseline</td>
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<td>1 0.5</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Lost to follow-up after baseline</td>
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<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Non-compliance</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
</tbody>
</table>
Table 54: Protocol deviations by centre: randomised subjects

<table>
<thead>
<tr>
<th>Centre Protocol deviation</th>
<th>DAIVOBE Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td>UVB therapy prior to randomisation</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
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<tr>
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<tr>
<td>Disallowed medication started after baseline</td>
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<tr>
<td>Lost to follow-up after baseline</td>
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<td>UVB therapy prior to randomisation</td>
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<tr>
<td>Violation of visit windows</td>
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Table 54: Protocol deviations by centre: randomised subjects

<table>
<thead>
<tr>
<th>Centre Protocol deviation</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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<tr>
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Table 54: Protocol deviations by centre: randomised subjects

<table>
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<tr>
<th>Centre Protocol deviation</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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MEDDK 13MAY09:08:30:08 protocol dev by centre.doc
Table 54: Protocol deviations by centre: randomised subjects

<table>
<thead>
<tr>
<th>Centre Protocol deviation</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td>Lost to follow-up after baseline</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Non-compliance</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>UVB therapy prior to randomisation</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Violation of visit windows</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Total number of deviations¹</td>
<td>1</td>
<td>0.5</td>
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<tr>
<td>Total number of subjects</td>
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</tr>
<tr>
<td>Disallowed medication at baseline</td>
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<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Disallowed medication started after baseline</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
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<tr>
<td>Lost to follow-up after baseline</td>
<td>1</td>
<td>0.5</td>
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<tr>
<td>Non-compliance</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 54: Protocol deviations by centre: randomised subjects

<table>
<thead>
<tr>
<th>Centre Protocol deviation</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol Gel (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td>UVB therapy prior to randomisation</td>
<td>0 0.0</td>
<td>1 0.5</td>
<td>0 0.0</td>
</tr>
<tr>
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<td>0 0.0</td>
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<td>1 0.5</td>
<td>1 1.1</td>
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<td>1 0.5</td>
<td>1 1.1</td>
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<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
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<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
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<td>0 0.0</td>
<td>0 0.0</td>
<td>0 0.0</td>
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<tr>
<td>Non-compliance</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>0 0.0</td>
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<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Violation of visit windows</td>
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<td>0 0.0</td>
<td>1 1.1</td>
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Table 54: Protocol deviations by centre: randomised subjects

<table>
<thead>
<tr>
<th>Centre Protocol deviation</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td>Total number of deviations¹</td>
<td>1</td>
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<td>0</td>
</tr>
<tr>
<td>Total number of subjects</td>
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<tr>
<td>Lost to follow-up after baseline</td>
<td>0</td>
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<tr>
<td>Non-compliance</td>
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<td>0.0</td>
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<tr>
<td>UVB therapy prior to randomisation</td>
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<td>0.0</td>
<td>0</td>
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<tr>
<td>Violation of visit windows</td>
<td>0</td>
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</tr>
<tr>
<td>Total number of deviations¹</td>
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Table 54: Protocol deviations by centre: randomised subjects

<table>
<thead>
<tr>
<th>Centre Protocol deviation</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
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<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
</tr>
<tr>
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<td>0.0</td>
<td>0</td>
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<tr>
<td>Lost to follow-up after baseline</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
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<tr>
<td>Non-compliance</td>
<td>0</td>
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<tr>
<td>UVB therapy prior to randomisation</td>
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<td>0.0</td>
<td>0</td>
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<tr>
<td>Violation of visit windows</td>
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<td>0.5</td>
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</tr>
<tr>
<td>Total number of deviations¹</td>
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</tr>
<tr>
<td>Total number of subjects</td>
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<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Disallowed medication at baseline</td>
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<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Disallowed medication started after baseline</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 54: Protocol deviations by centre: randomised subjects

<table>
<thead>
<tr>
<th>Centre Protocol deviation</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td>-----------------------------------</td>
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<td>--------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Lost to follow-up after baseline</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Non-compliance</td>
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<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>UVB therapy prior to randomisation</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Violation of visit windows</td>
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<tr>
<td>Total number of deviations (^1)</td>
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<tr>
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<td>0.5</td>
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<tr>
<td>Disallowed medication started after baseline</td>
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<td>1.1</td>
<td>0</td>
</tr>
<tr>
<td>Lost to follow-up after baseline</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Non-compliance</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
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</tbody>
</table>
Table 54: Protocol deviations by centre: randomised subjects

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<thead>
<tr>
<th>Centre Protocol deviation</th>
<th>DAIVO BET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects %</td>
<td>Number of Subjects %</td>
<td>Number of Subjects %</td>
</tr>
<tr>
<td>UVB therapy prior to randomisation</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Violation of visit windows</td>
<td>1 0.5</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
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<td>1 1.1</td>
</tr>
<tr>
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<td>1 1.1</td>
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<td>0 0.0</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Disallowed medication started after baseline</td>
<td>1 0.5</td>
<td>0 0.0</td>
<td>1 1.1</td>
</tr>
<tr>
<td>Lost to follow-up after baseline</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Non-compliance</td>
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<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>UVB therapy prior to randomisation</td>
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<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Violation of visit windows</td>
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<td>0 0.0</td>
<td>1 1.1</td>
</tr>
</tbody>
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Table 54: Protocol deviations by centre: randomised subjects

<table>
<thead>
<tr>
<th>Centre Protocol deviation</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td>Total number of deviations(^1)</td>
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<tr>
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<td>0 0.0</td>
</tr>
<tr>
<td>Disallowed medication started after baseline</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Lost to follow-up after baseline</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Non-compliance</td>
<td>0 0.0</td>
<td>1 0.5</td>
<td>0 0.0</td>
</tr>
<tr>
<td>UVB therapy prior to randomisation</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Violation of visit windows</td>
<td>1 0.5</td>
<td>1 0.5</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Total number of deviations(^1)</td>
<td>1 0.5</td>
<td>2 1.1</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Total number of subjects</td>
<td>1 0.5</td>
<td>2 1.1</td>
<td>0 0.0</td>
</tr>
</tbody>
</table>
Table 54: Protocol deviations by centre: randomised subjects

<table>
<thead>
<tr>
<th>Centre Protocol deviation</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
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<td>2</td>
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<td>0</td>
</tr>
<tr>
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<td>1</td>
</tr>
<tr>
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<tr>
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</tr>
<tr>
<td>Total number of deviations¹</td>
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<td>14</td>
<td>11</td>
<td>9</td>
</tr>
</tbody>
</table>

¹ Only deviations that led to exclusion of data from the per protocol analysis are included in this table. A single patient could have more than one deviation.
Table 55: Height: randomised subjects

<table>
<thead>
<tr>
<th>Height (cm)</th>
<th>All randomised subjects (n=458)</th>
<th>DAIVOBRT Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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</thead>
<tbody>
<tr>
<td>Mean</td>
<td>169.4</td>
<td>169.7</td>
<td>169.4</td>
<td>168.5</td>
</tr>
<tr>
<td>SD</td>
<td>9.5</td>
<td>9.6</td>
<td>9.4</td>
<td>9.6</td>
</tr>
<tr>
<td>Median</td>
<td>170.0</td>
<td>170.0</td>
<td>170.0</td>
<td>169.0</td>
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<tr>
<td>Minimum</td>
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<td>148</td>
<td>145</td>
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<tr>
<td>Maximum</td>
<td>196</td>
<td>195</td>
<td>196</td>
<td>195</td>
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<tr>
<td>Number</td>
<td>454</td>
<td>180</td>
<td>183</td>
<td>91</td>
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</table>

Table 56: Weight: randomised subjects

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>All randomised subjects (n=458)</th>
<th>DAIVOBRT Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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</thead>
<tbody>
<tr>
<td>Mean</td>
<td>89.3</td>
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<td>90.5</td>
<td>86.5</td>
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<tr>
<td>SD</td>
<td>22.2</td>
<td>22.5</td>
<td>22.5</td>
<td>20.9</td>
</tr>
<tr>
<td>Median</td>
<td>86.0</td>
<td>87.0</td>
<td>88.0</td>
<td>84.0</td>
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<tr>
<td>Minimum</td>
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<td>43</td>
<td>47</td>
<td>51</td>
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<tr>
<td>Maximum</td>
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<td>455</td>
<td>181</td>
<td>183</td>
<td>91</td>
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### Table 57: Systolic blood pressure: randomised subjects

<table>
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<th>Systolic blood pressure (mmHg)</th>
<th>All randomised subjects (n=458)</th>
<th>DAI Vapor Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
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<td>126.0</td>
<td>125.5</td>
</tr>
<tr>
<td>SD</td>
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<td>17.0</td>
<td>16.1</td>
<td>15.4</td>
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<tr>
<td>Median</td>
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</tr>
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<td>183</td>
<td>184</td>
<td>91</td>
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</table>
Table 59: Age by centre: randomised subjects

<table>
<thead>
<tr>
<th>Centre Age (years)</th>
<th>All randomised subjects (n=458)</th>
<th>DAIVOBRT Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean 50.0 ± 13.6</td>
<td>Mean 48.0 ± 17.6</td>
<td>Mean 47.9 ± 11.2</td>
<td>Mean 58.0 ± 8.0</td>
</tr>
<tr>
<td></td>
<td>SD 14.4</td>
<td>SD 17.6</td>
<td>SD 11.2</td>
<td>SD 8.0</td>
</tr>
<tr>
<td></td>
<td>Median 52.0 ± 28</td>
<td>Median 43.0 ± 28</td>
<td>Median 50.0 ± 28</td>
<td>Median 58.0 ± 47</td>
</tr>
<tr>
<td></td>
<td>Minimum 68 ± 9</td>
<td>Minimum 68 ± 9</td>
<td>Minimum 68 ± 65</td>
<td>Minimum 67 ± 47</td>
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<tr>
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<td>Maximum 68 ± 9</td>
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<td>Maximum 65 ± 10</td>
<td>Maximum 67 ± 10</td>
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<td>Number 24 ± 9</td>
<td>Number 24 ± 10</td>
<td>Number 24 ± 10</td>
<td>Number 5 ± 2</td>
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<tr>
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<td>Mean 54.3 ± 16.0</td>
<td>Mean 59.3 ± 9.7</td>
<td>Mean 50.8 ± 17.1</td>
<td>Mean 51.3 ± 26.4</td>
</tr>
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<td>SD 9.7</td>
<td>SD 17.1</td>
<td>SD 26.4</td>
</tr>
<tr>
<td></td>
<td>Median 59.0 ± 22</td>
<td>Median 61.0 ± 42</td>
<td>Median 47.5 ± 31</td>
<td>Median 59.0 ± 22</td>
</tr>
<tr>
<td></td>
<td>Minimum 73 ± 6</td>
<td>Minimum 69 ± 31</td>
<td>Minimum 73 ± 22</td>
<td>Minimum 73 ± 22</td>
</tr>
<tr>
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Table 59: Age by centre: randomised subjects

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Table 59: Age by centre: randomised subjects

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Table 59: Age by centre: randomised subjects

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Table 59: Age by centre: randomised subjects

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Table 60: Sex by centre: randomised subjects

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Table 60: Sex by centre: randomised subjects

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MEDDK 29APR09:08:17:13 sex by centre.doc
Table 61: Race by centre: randomised subjects

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American Indian or Alaska Native
Table 61: Race by centre: randomised subjects

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<th>Gel Vehicle (n=91)</th>
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Table 61: Race by centre: randomised subjects

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<th>Gel Vehicle (n=91)</th>
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Table 61: Race by centre: randomised subjects

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<th>Centre Race</th>
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<th>Gel Vehicle (n=91)</th>
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| American Indian or Alaska Native| 0                    | 0.0                | 0                  | 0.0 | 0                  | 0.0 |
| Asian                            | 0                    | 0.0                | 0                  | 0.0 | 0                  | 0.0 |
| Black or African American        | 0                    | 0.0                | 0                  | 0.0 | 0                  | 0.0 |
| Native Hawaiian or Other         | 1                    | 6.7                | 0                  | 0.0 | 0                  | 0.0 |
Table 61: Race by centre: randomised subjects

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<thead>
<tr>
<th>Centre Race</th>
<th>DAIVOBET Gel (n=183)</th>
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### Table 61: Race by centre: randomised subjects

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**Note:** Numbers may not sum to 100 due to rounding.
Table 61: Race by centre: randomised subjects

<table>
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<tr>
<th>Centre Race</th>
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Table 61: Race by centre: randomised subjects

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Table 62: Ethnicity by centre: randomised subjects

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Table 62: Ethnicity by centre: randomised subjects

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Table 62: Ethnicity by centre: randomised subjects

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Table 62: Ethnicity by centre: randomised subjects

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Table 63: Skin type by centre: randomised subjects

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Table 63: Skin type by centre: randomised subjects

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Table 63: Skin type by centre: randomised subjects

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Table 63: Skin type by centre: randomised subjects

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Note: The table shows the number and percentage of subjects with different skin types in three different treatments: DAIVOBE Gel, Tacalcitol, and Gel Vehicle. The data is presented for each centre.
Table 63: Skin type by centre: randomised subjects

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Table 63: Skin type by centre: randomised subjects

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MEDDK 29APR09:08:18:07 skin type by centre.doc
### Table 64: Duration of psoriasis vulgaris by centre: randomised subjects

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Table 64: Duration of psoriasis vulgaris by centre: randomised subjects

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Table footnote: 29APR09:08:18:15 duration by centre.doc
Table 64: Duration of psoriasis vulgaris by centre: randomised subjects

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|        | Mean             | 15.0                            | 17.7                 | 15.9               | 7.8               |
|        | SD               | 11.0                            | 10.6                 | 11.8               | 7.2               |
|        | Median           | 13.0                            | 16.5                 | 12.5               | 5.0               |
|        | Minimum          | 0                               | 3                    | 0                  | 0                 |
|        | Maximum          | 40                              | 40                   | 40                 | 20                |
|        | Number           | 45                              | 18                   | 18                 | 9                 |

|        | Mean             | 19.8                            | 21.4                 | 15.9               | 23.2              |
|        | SD               | 14.8                            | 16.4                 | 11.4               | 17.6              |
|        | Median           | 13.0                            | 14.0                 | 11.0               | 24.5              |
|        | Minimum          | 1                               | 1                    | 1                  | 3                 |
|        | Maximum          | 48                              | 48                   | 30                 | 40                |
|        | Number           | 25                              | 10                   | 9                  | 6                 |

|        | Mean             | 17.7                            | 24.8                 | 13.1               | 12.4              |
|        | SD               | 13.8                            | 15.7                 | 11.7               | 6.7               |
|        | Median           | 14.0                            | 27.0                 | 10.0               | 13.0              |
|        | Minimum          | 1                               | 3                    | 1                  | 2                 |
|        | Maximum          | 55                              | 55                   | 45                 | 20                |
|        | Number           | 37                              | 15                   | 15                 | 7                 |
Table 64: Duration of psoriasis vulgaris by centre: randomised subjects

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Table 64: Duration of psoriasis vulgaris by centre: randomised subjects

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Table 65: Investigator's global assessment of disease severity by centre: randomised subjects

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Table 65: Investigator’s global assessment of disease severity by centre: randomised subjects

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Table 65: Investigator's global assessment of disease severity by centre: randomised subjects

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Table 65: Investigator's global assessment of disease severity by centre: randomised subjects

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Table 65: Investigator's global assessment of disease severity by centre: randomised subjects

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Table 66: Patient's global assessment of disease severity by centre: randomised subjects

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Table 66: Patient's global assessment of disease severity by centre: randomised subjects

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| Mild | 24 | 13.1 | 32 | 17.5 | 12 | 13.3 |
| Moderate | 111 | 60.7 | 92 | 50.3 | 61 | 67.8 |
| Severe | 40 | 21.9 | 53 | 29.0 | 15 | 16.7 |
| Total | 183 | 100.0 | 183 | 100.0 | 90 | 100.0 |
Table 67: Investigator’s assessment of the extent of psoriasis vulgaris by centre: randomised subjects

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Table 67: Investigator's assessment of the extent of psoriasis vulgaris by centre: randomised subjects

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Table 67: Investigator’s assessment of the extent of psoriasis vulgaris by centre: randomised subjects

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Table 67: Investigator's assessment of the extent of psoriasis vulgaris by centre: randomised subjects

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Table 68: Investigator's assessment of extent of psoriasis vulgaris on arms: randomised subjects

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<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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<td>Number of Subjects</td>
<td>Number of Subjects</td>
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<tr>
<td>Total</td>
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<td>183</td>
<td>184</td>
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MEDDK 29APR09:09:05:25 extent arms.doc
Table 69: Investigator's assessment of severity of clinical signs of psoriasis vulgaris on arms: randomised subjects

<table>
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<tr>
<th>Clinical sign</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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<td>%</td>
<td>%</td>
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<tr>
<td>Total</td>
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<td>184</td>
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Table 70: Investigator's assessment of extent of psoriasis vulgaris on trunk: randomised subjects

<table>
<thead>
<tr>
<th>Extent</th>
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<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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<td>Number of Subjects</td>
<td>%</td>
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Table 71: Investigator's assessment of severity of clinical signs of psoriasis vulgaris on trunk: randomised subjects

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<th>Clinical sign</th>
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<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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<tr>
<td></td>
<td>%</td>
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<td>%</td>
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<td>184</td>
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Table 72: Investigator's assessment of extent of psoriasis vulgaris on legs: randomised subjects

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<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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<td>Number of Subjects %</td>
<td>Number of Subjects %</td>
<td>Number of Subjects %</td>
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<td>59 (32.2)</td>
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<td>102 (55.7)</td>
<td>104 (56.5)</td>
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<td>14 (7.7)</td>
<td>12 (6.5)</td>
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<tr>
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<td>2 (0.4)</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>70 - 89%</td>
<td>2 (0.4)</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>90 - 100%</td>
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<td>1 (0.5)</td>
<td>0 (0.0)</td>
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<tr>
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<td>183 (100.0)</td>
<td>184 (100.0)</td>
<td>91 (100.0)</td>
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Table 73: Investigator's assessment of severity of clinical signs of psoriasis vulgaris on legs: randomised subjects

<table>
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<th>Clinical sign</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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<td>Number of Subjects</td>
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<td>3 1.6</td>
<td>1 1.1</td>
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<td>3 1.6</td>
<td>2 2.2</td>
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<td>96 52.5</td>
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<td>85 46.2</td>
<td>43 47.3</td>
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<td>11 6.0</td>
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<td>184 100.0</td>
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<td>2 1.1</td>
<td>1 1.1</td>
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<tr>
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<td>4 2.2</td>
<td>8 4.3</td>
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<tr>
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<td>184 100.0</td>
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<td>3 1.6</td>
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<td>64 34.8</td>
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<td>3 3.3</td>
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<td>184 100.0</td>
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Efficacy

Table 74: Subjects with 'Controlled disease' according to investigator's global assessment of disease severity at week 8 by centre: full analysis set

<table>
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<th>Centre</th>
<th>Controlled disease (LOCF)</th>
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<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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<td>Number of Subjects</td>
<td>%</td>
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<td>77.8</td>
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<td>2</td>
<td>33.3</td>
<td>1</td>
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<tr>
<td></td>
<td>Non-controlled</td>
<td>4</td>
<td>66.7</td>
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<tr>
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</table>
Table 74: Subjects with 'Controlled disease' according to investigator's global assessment of disease severity at week 8 by centre: full analysis set

<table>
<thead>
<tr>
<th>Centre</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
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<td>4 (57.1%)</td>
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</tr>
<tr>
<td>Total</td>
<td>6 (100.0%)</td>
<td>7 (100.0%)</td>
<td>3 (100.0%)</td>
</tr>
<tr>
<td>Controlled</td>
<td>9 (50.0%)</td>
<td>3 (16.7%)</td>
<td>1 (11.1%)</td>
</tr>
<tr>
<td>Non-controlled</td>
<td>9 (50.0%)</td>
<td>15 (83.3%)</td>
<td>8 (88.9%)</td>
</tr>
<tr>
<td>Total</td>
<td>18 (100.0%)</td>
<td>18 (100.0%)</td>
<td>9 (100.0%)</td>
</tr>
<tr>
<td>Controlled</td>
<td>7 (70.0%)</td>
<td>4 (44.4%)</td>
<td>2 (33.3%)</td>
</tr>
<tr>
<td>Non-controlled</td>
<td>3 (30.0%)</td>
<td>5 (55.6%)</td>
<td>4 (66.7%)</td>
</tr>
<tr>
<td>Total</td>
<td>10 (100.0%)</td>
<td>9 (100.0%)</td>
<td>6 (100.0%)</td>
</tr>
<tr>
<td>Controlled</td>
<td>9 (60.0%)</td>
<td>5 (33.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Non-controlled</td>
<td>6 (40.0%)</td>
<td>10 (66.7%)</td>
<td>7 (100.0%)</td>
</tr>
<tr>
<td>Total</td>
<td>15 (100.0%)</td>
<td>15 (100.0%)</td>
<td>7 (100.0%)</td>
</tr>
<tr>
<td>Controlled</td>
<td>3 (50.0%)</td>
<td>1 (14.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Non-controlled</td>
<td>3 (50.0%)</td>
<td>6 (85.7%)</td>
<td>3 (100.0%)</td>
</tr>
<tr>
<td>Total</td>
<td>6 (100.0%)</td>
<td>7 (100.0%)</td>
<td>3 (100.0%)</td>
</tr>
<tr>
<td>Controlled</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Non-controlled</td>
<td>2 (100.0%)</td>
<td>2 (100.0%)</td>
<td>1 (100.0%)</td>
</tr>
</tbody>
</table>
Table 74: Subjects with 'Controlled disease' according to investigator's global assessment of disease severity at week 8 by centre: full analysis set

<table>
<thead>
<tr>
<th>Centre Controlled disease (LOCF)</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Controlled</strong></td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><strong>Non-controlled</strong></td>
<td>14</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>18</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td>54.5</td>
<td>80.0</td>
<td>50.0</td>
</tr>
<tr>
<td><strong>Non-controlled</strong></td>
<td>11</td>
<td>8</td>
<td>5</td>
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<td><strong>Total</strong></td>
<td>11</td>
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<td>5</td>
</tr>
<tr>
<td></td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td>100.0</td>
<td>88.9</td>
<td>100.0</td>
</tr>
<tr>
<td><strong>Non-controlled</strong></td>
<td>10</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>10</td>
<td>100.0</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>100.0</td>
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<td>100.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>73</td>
<td>33</td>
<td>5</td>
</tr>
<tr>
<td><strong>Controlled</strong></td>
<td>110</td>
<td>151</td>
<td>86</td>
</tr>
<tr>
<td><strong>Non-controlled</strong></td>
<td>183</td>
<td>184</td>
<td>91</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>183</td>
<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Table 75: Subjects with 'Controlled disease' according to investigator's global assessment of disease severity at week 8 by race: full analysis set

<table>
<thead>
<tr>
<th>Race</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>American Indian or Alaska</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Native</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Non-controlled</td>
<td>1</td>
<td>100.0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>100.0</td>
<td>1</td>
</tr>
<tr>
<td>Asian</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Non-controlled</td>
<td>1</td>
<td>100.0</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>100.0</td>
<td>2</td>
</tr>
<tr>
<td>Black or African American</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Controlled</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Non-controlled</td>
<td>2</td>
<td>100.0</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>100.0</td>
<td>2</td>
</tr>
<tr>
<td>Native Hawaiian or Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pacific Islander</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Non-controlled</td>
<td>1</td>
<td>100.0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>100.0</td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled</td>
<td>72</td>
<td>41.6</td>
<td>81.9</td>
</tr>
<tr>
<td>Non-controlled</td>
<td>101</td>
<td>58.4</td>
<td>81.9</td>
</tr>
<tr>
<td>Total</td>
<td>173</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled</td>
<td>1</td>
<td>20.0</td>
<td>2</td>
</tr>
<tr>
<td>Non-controlled</td>
<td>4</td>
<td>80.0</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>100.0</td>
<td>9</td>
</tr>
</tbody>
</table>
Table 75: Subjects with 'Controlled disease' according to investigator's global assessment of disease severity at week 8 by race: full analysis set

<table>
<thead>
<tr>
<th>Race Controlled disease (LOCF)</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td>Total</td>
<td>183</td>
<td>100.0</td>
<td>184</td>
</tr>
<tr>
<td>Controlled</td>
<td>73</td>
<td>39.9</td>
<td>33</td>
</tr>
<tr>
<td>Non-controlled</td>
<td>110</td>
<td>60.1</td>
<td>151</td>
</tr>
</tbody>
</table>
Table 76: Subjects with 'Controlled disease' according to investigator's global assessment of disease severity at week 8 by ethnic origin: full analysis set

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>DAIVOGET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td><strong>Hispanic or Latino</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Non-controlled</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Not Hispanic or Latino</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled</td>
<td>71</td>
<td>33</td>
<td>5</td>
</tr>
<tr>
<td>Non-controlled</td>
<td>109</td>
<td>149</td>
<td>85</td>
</tr>
<tr>
<td>Total</td>
<td>180</td>
<td>182</td>
<td>90</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>183</td>
<td>184</td>
<td>91</td>
</tr>
</tbody>
</table>
Table 77: Subjects with 'Controlled disease' according to investigator's global assessment of disease severity at week 8 by skin type: full analysis set

<table>
<thead>
<tr>
<th>Skin type</th>
<th>Control</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled</td>
<td>3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Non-controlled</td>
<td>2</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

II

<table>
<thead>
<tr>
<th>Skin type</th>
<th>Control</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled</td>
<td>19</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Non-controlled</td>
<td>37</td>
<td>55</td>
<td>24</td>
</tr>
<tr>
<td>Total</td>
<td>56</td>
<td>65</td>
<td>25</td>
</tr>
</tbody>
</table>

III

<table>
<thead>
<tr>
<th>Skin type</th>
<th>Control</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled</td>
<td>33</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Non-controlled</td>
<td>33</td>
<td>53</td>
<td>36</td>
</tr>
<tr>
<td>Total</td>
<td>66</td>
<td>64</td>
<td>37</td>
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</tbody>
</table>

IV

<table>
<thead>
<tr>
<th>Skin type</th>
<th>Control</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled</td>
<td>14</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Non-controlled</td>
<td>33</td>
<td>29</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>47</td>
<td>39</td>
<td>20</td>
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</tbody>
</table>

V

<table>
<thead>
<tr>
<th>Skin type</th>
<th>Control</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Non-controlled</td>
<td>3</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>8</td>
<td>7</td>
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</tbody>
</table>

VI

<table>
<thead>
<tr>
<th>Skin type</th>
<th>Control</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Non-controlled</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 77: Subjects with 'Controlled disease' according to investigator's global assessment of disease severity at week 8 by skin type: full analysis set

<table>
<thead>
<tr>
<th>Skin type Controlled disease (LOCF)</th>
<th>DAIVOSET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled</td>
<td>73</td>
<td>39.9</td>
<td>33</td>
</tr>
<tr>
<td>Non-controlled</td>
<td>110</td>
<td>60.1</td>
<td>151</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>183</td>
<td>100.0</td>
<td>184</td>
</tr>
</tbody>
</table>
Table 78: Percentage change in PASI from baseline to weeks 4 and 8 and results of statistical analysis: per protocol analysis set

<table>
<thead>
<tr>
<th>Percentage change in PASI</th>
<th>DAIIVOBET Gel (n=177)</th>
<th>Tacalcitol (n=178)</th>
<th>Gel Vehicle (n=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VISIT 4/ WEEK 4</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Least squares mean¹</td>
<td>-54.6</td>
<td>-38.4</td>
<td>-14.6</td>
</tr>
<tr>
<td>Mean</td>
<td>-54.3</td>
<td>-38.0</td>
<td>-14.1</td>
</tr>
<tr>
<td>SD</td>
<td>26.8</td>
<td>26.2</td>
<td>26.8</td>
</tr>
<tr>
<td>Median</td>
<td>-56.4</td>
<td>-40.4</td>
<td>-11.3</td>
</tr>
<tr>
<td>Minimum</td>
<td>-100</td>
<td>-96</td>
<td>-77</td>
</tr>
<tr>
<td>Maximum</td>
<td>102</td>
<td>29</td>
<td>41</td>
</tr>
<tr>
<td>Number</td>
<td>177</td>
<td>178</td>
<td>89</td>
</tr>
<tr>
<td>Difference²</td>
<td>-15.2</td>
<td>-40.0</td>
<td></td>
</tr>
<tr>
<td>98.33% CI</td>
<td>-22.8 to -9.61</td>
<td>-48.1 to -32.0</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>VISIT 6/ WEEK 8</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Least squares mean¹</td>
<td>-58.1</td>
<td>-42.7</td>
<td>-18.7</td>
</tr>
<tr>
<td>Mean</td>
<td>-58.2</td>
<td>-42.6</td>
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</tr>
<tr>
<td>SD</td>
<td>28.7</td>
<td>32.9</td>
<td>34.4</td>
</tr>
<tr>
<td>Median</td>
<td>-64.0</td>
<td>-43.6</td>
<td>-20.0</td>
</tr>
<tr>
<td>Minimum</td>
<td>-100</td>
<td>-100</td>
<td>-100</td>
</tr>
<tr>
<td>Maximum</td>
<td>87</td>
<td>47</td>
<td>69</td>
</tr>
<tr>
<td>Number</td>
<td>177</td>
<td>178</td>
<td>89</td>
</tr>
<tr>
<td>Difference²</td>
<td>-15.4</td>
<td>-39.4</td>
<td></td>
</tr>
<tr>
<td>98.33% CI</td>
<td>-23.2 to -7.61</td>
<td>-49.0 to -29.9</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>
Table 79: Percentage change in PASI from baseline to weeks 4 and 8 by centre: full analysis set

<table>
<thead>
<tr>
<th>Centre Percentage change</th>
<th>All randomised subjects (n=458)</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (n=458)</td>
<td>Mean (n=183)</td>
<td>Mean (n=184)</td>
<td>Mean (n=91)</td>
</tr>
<tr>
<td>PASI at VISIT 1</td>
<td>10.5 10.2 10.7 10.5</td>
<td>10.2 10.7 10.5</td>
<td>9.4 9.4 8.9</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td>SD (n=458)</td>
<td>SD (n=183)</td>
<td>SD (n=184)</td>
<td>SD (n=91)</td>
</tr>
<tr>
<td></td>
<td>4.2 4.3 4.9 2.9</td>
<td>4.3 4.9 2.9</td>
<td>6 6 8</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Median (n=458)</td>
<td>Median (n=183)</td>
<td>Median (n=184)</td>
<td>Median (n=91)</td>
</tr>
<tr>
<td></td>
<td>9.1 9.3 9.4 8.9</td>
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Table 79: Percentage change in PASI from baseline to weeks 4 and 8 by centre: full analysis set

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| PASI at VISIT 1          |                               |                      |                   |                   |
| Mean                     | 9.1                           | 8.9                  | 9.6               | 8.5               |
| SD                       | 2.9                           | 3.5                  | 2.6               | 2.4               |
| Median                   | 8.9                           | 8.0                  | 9.8               | 8.1               |
| Minimum                  | 3                             | 3                    | 6                 | 5                 |
| Maximum                  | 17                            | 17                   | 16                | 12                |
| Number                   | 38                            | 15                   | 15                | 8                 |
| VISIT 4/ WEEK 4          |                               |                      |                   |                   |
| Mean                     | -37.0                         | -48.8                | -34.0             | -20.3             |
| SD                       | 25.4                          | 25.1                 | 19.0              | 27.9              |
| Median                   | -40.1                         | -50.0                | -42.1             | -15.7             |
| Minimum                  | -83                           | -83                  | -60               | -72               |
| Maximum                  | 23                            | 15                   | 1                 | 23                |
| Number                   | 38                            | 15                   | 15                | 8                 |
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PASI at VISIT 1

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**MMDB**: 28APR91:09:3162 percentage change PASI centre.doc
Table 79: Percentage change in PASI from baseline to weeks 4 and 8 by centre: full analysis set

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PASI at VISIT 1
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- SD 9.9
- Median 10.8
- Minimum 2
- Maximum 59
- Number 45

VISIT 4/ WEEK 4
- Mean -37.1
- SD 42.8
- Median -46.9
Table 79: Percentage change in PASI from baseline to weeks 4 and 8 by centre: full analysis set

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Table 79: Percentage change in PASI from baseline to weeks 4 and 8 by centre: full analysis set

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PASI at VISIT 1

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SD 3.7  4.6  3.6  1.0
Median 7.5  5.4  9.6  8.4
Minimum 2  2  5  7
Maximum 16  16  14  8
Number 16  6  7  3

VISIT 4/ WEEK 4

Mean -34.9  -69.5  -23.3  7.5
SD 37.2  19.5  25.8  26.4
Table 79: Percentage change in PASI from baseline to weeks 4 and 8 by centre: full analysis set

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MMADK 20APR09:09:33:02 percentage change PASI_centre.doc
Table 79: Percentage change in PASI from baseline to weeks 4 and 8 by centre: full analysis set

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Table 79: Percentage change in PASI from baseline to weeks 4 and 8 by centre: full analysis set

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Table 79: Percentage change in PASI from baseline to weeks 4 and 8 by centre: full analysis set

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| PASI at VISIT 1          |                                  |                      |                    |                   |
| Mean                     | 8.3                              | 8.2                  | 8.2                | 8.6               |
| SD                       | 1.9                              | 2.1                  | 2.1                | 1.4               |
| Median                   | 8.2                              | 8.5                  | 8.0                | 8.3               |
| Minimum                  | 4                                | 4                    | 5                  | 7                 |
| Maximum                  | 13                               | 13                   | 12                 | 11                |
| Number                   | 36                               | 14                   | 15                 | 7                 |

| VISIT 4/ WEEK 4          |                                  |                      |                    |                   |
| Mean                     | -53.1                            | -71.1                | -45.4              | -33.8             |
| SD                       | 26.3                             | 14.0                 | 23.5               | 31.2              |
| Median                   | -55.0                            | -71.5                | -44.0              | -31.5             |
| Minimum                  | -97                              | -97                  | -89                | -71               |
| Maximum                  | 19                               | -50                  | -17                | 19                |
| Number                   | 36                               | 14                   | 15                 | 7                 |

| VISIT 6/ WEEK 8          |                                  |                      |                    |                   |
| Mean                     | -57.7                            | -74.4                | -56.1              | -27.6             |
| SD                       | 33.0                             | 13.4                 | 27.3               | 50.2              |
| Median                   | -67.0                            | -79.2                | -68.4              | -44.6             |
| Minimum                  | -92                              | -92                  | -86                | -85               |
| Maximum                  | 69                               | -54                  | -17                | 69                |
| Number                   | 36                               | 14                   | 15                 | 7                 |

| PASI at VISIT 1          |                                  |                      |                    |                   |
| Mean                     | 11.0                             | 7.7                  | 17.6               | 7.6               |
| SD                       | 7.5                              | 2.6                  | 10.8               | 1.4               |
| Median                   | 8.5                              | 8.2                  | 16.8               | 7.6               |
Table 79: Percentage change in PASI from baseline to weeks 4 and 8 by centre: full analysis set

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Table 80: PASI by visit: full analysis set

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Table 80: PASI by visit: full analysis set

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Table 81: Subjects with relapse during the observation period by centre: those subjects in the full analysis set who achieved 'Controlled disease' according to investigator's global assessment of disease severity at week 8

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<td>%</td>
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<tr>
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<tr>
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<tr>
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<td>1 100.0</td>
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<td>1 33.3</td>
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<tr>
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<tr>
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<td>0 0.0</td>
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<tr>
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<tr>
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Table 81: Subjects with relapse during the observation period by centre: those subjects in the full analysis set who achieved 'Controlled disease' according to investigator's global assessment of disease severity at week 8

<table>
<thead>
<tr>
<th>Centre Relapse</th>
<th>DAI(O)BET Gel (n=67)</th>
<th>Tacalcitol (n=31)</th>
<th>Gel Vehicle (n=5)</th>
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<td>Number of Subjects</td>
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<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
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<td>2</td>
</tr>
<tr>
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<td>1</td>
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<td>2</td>
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</tr>
<tr>
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<td>0</td>
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<tr>
<td>Total</td>
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<td>0</td>
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<td>1</td>
<td>0</td>
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<tr>
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<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
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<td>3</td>
<td>1</td>
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<tr>
<td>Relapse</td>
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<td>0</td>
</tr>
<tr>
<td>No Relapse</td>
<td>3</td>
<td>1</td>
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<tr>
<td>Total</td>
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<td>2</td>
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<tr>
<td>Relapse</td>
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<td>0</td>
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</tr>
<tr>
<td>No Relapse</td>
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<td>1</td>
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Table 81: Subjects with relapse during the observation period by centre: those subjects in the full analysis set who achieved 'Controlled disease' according to investigator's global assessment of disease severity at week 8

<table>
<thead>
<tr>
<th>Centre Relapse</th>
<th>DAIVOBET Gel (n=67)</th>
<th>Tacalcitol (n=31)</th>
<th>Gel Vehicle (n=5)</th>
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<td>Relapse</td>
<td>3 42.9</td>
<td>0 0.0</td>
<td>0 0.0</td>
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<tr>
<td>No Relapse</td>
<td>4 57.1</td>
<td>5 100.0</td>
<td>0 0.0</td>
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<tr>
<td>Total</td>
<td>7 100.0</td>
<td>5 100.0</td>
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<tr>
<td>Relapse</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>0 0.0</td>
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<tr>
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<tr>
<td>Total</td>
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<td>0 0.0</td>
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Total
Relapse 28 41.8 7 22.6 3 60.0
No Relapse 39 58.2 24 77.4 2 40.0
Total 67 100.0 31 100.0 5 100.0

1) 7 patients had controlled disease but withdrew after week 8, these patients were not included in this table.
Table 82: Investigator's assessment of extent of psoriasis vulgaris on arms at week 4 and 8: full analysis set

<table>
<thead>
<tr>
<th>Extent (LOCF)</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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<td>Number of Subjects</td>
</tr>
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<tr>
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<td>17</td>
<td>9.3</td>
<td>7</td>
</tr>
<tr>
<td>&lt; 10%</td>
<td>99</td>
<td>54.1</td>
<td>80</td>
</tr>
<tr>
<td>10 - 29%</td>
<td>62</td>
<td>33.9</td>
<td>88</td>
</tr>
<tr>
<td>30 - 49%</td>
<td>5</td>
<td>2.7</td>
<td>8</td>
</tr>
<tr>
<td>50 - 69%</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>90 - 100%</td>
<td>0</td>
<td>0.0</td>
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</tr>
<tr>
<td>Total</td>
<td>183</td>
<td>100.0</td>
<td>184</td>
</tr>
</tbody>
</table>

| VISIT 6/ WEEK 8 |                     |                   |                  |                     |
| No involvement | 22                   | 12.0             | 9                | 4.9             | 4                | 4.4             |
| < 10%         | 109                  | 59.6            | 91               | 49.5            | 36               | 39.6            |
| 10 - 29%      | 49                   | 26.8            | 76               | 41.3            | 48               | 52.7            |
| 30 - 49%      | 3                    | 1.6             | 7                | 3.8             | 2                | 2.2             |
| 50 - 69%      | 0                    | 0.0             | 0                | 0.0             | 1                | 1.1             |
| 90 - 100%     | 0                    | 0.0             | 1                | 0.5             | 0                | 0.0             |
| Total         | 183                  | 100.0           | 184              | 100.0           | 91               | 100.0           |
Table 83: Investigator’s assessment of severity of clinical signs of psoriasis vulgaris on arms at week 4 and 8: full analysis set

<table>
<thead>
<tr>
<th>Clinical sign (LOCF)</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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</thead>
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<td>Number of Subjects</td>
<td>% Number of</td>
<td>% Number of</td>
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<td>Subjects</td>
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<tr>
<td>Mild</td>
<td>84</td>
<td>45.9</td>
<td>51</td>
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<tr>
<td>Moderate</td>
<td>71</td>
<td>38.8</td>
<td>96</td>
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<tr>
<td>Severe</td>
<td>8</td>
<td>4.4</td>
<td>26</td>
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<tr>
<td>Very severe</td>
<td>0</td>
<td>0.0</td>
<td>4</td>
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<tr>
<td>Total</td>
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<td>100.0</td>
<td>184</td>
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<tr>
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<td>45.4</td>
<td>69</td>
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<td>37.2</td>
<td>78</td>
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Table 83: Investigator's assessment of severity of clinical signs of psoriasis vulgaris on arms at week 4 and 8: full analysis set

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<tr>
<th>Clinical sign (LOCF)</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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<td>93</td>
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<tr>
<td>Very severe</td>
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<td>2</td>
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<td>81</td>
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Table 84: Investigator's assessment of extent of psoriasis vulgaris on trunk at week 4 and 8: full analysis set

<table>
<thead>
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<th>Extent (LOCF)</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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<td>%</td>
<td>%</td>
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</tr>
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<td>85 (46.4)</td>
<td>64 (34.8)</td>
<td>22 (24.2)</td>
</tr>
<tr>
<td>&lt; 10%</td>
<td>80 (43.7)</td>
<td>75 (40.8)</td>
<td>49 (53.8)</td>
</tr>
<tr>
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<td>16 (8.7)</td>
<td>34 (18.5)</td>
<td>18 (19.8)</td>
</tr>
<tr>
<td>30 - 49%</td>
<td>1 (0.5)</td>
<td>8 (4.3)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>50 - 69%</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>70 - 89%</td>
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<td>2 (1.1)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Total</td>
<td>183 (100.0)</td>
<td>184 (100.0)</td>
<td>91 (100.0)</td>
</tr>
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<td>VISIT 6/ WEEK 8</td>
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<td></td>
</tr>
<tr>
<td>No involvement</td>
<td>95 (51.9)</td>
<td>72 (39.1)</td>
<td>27 (29.7)</td>
</tr>
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<td>&lt; 10%</td>
<td>72 (39.3)</td>
<td>74 (40.2)</td>
<td>43 (47.3)</td>
</tr>
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<td>32 (17.4)</td>
<td>19 (20.9)</td>
</tr>
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<td>2 (1.1)</td>
<td>4 (2.2)</td>
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<td>2 (1.1)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Total</td>
<td>183 (100.0)</td>
<td>184 (100.0)</td>
<td>91 (100.0)</td>
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</table>
Table 85: Investigator's assessment of severity of clinical signs of psoriasis vulgaris on trunk at week 4 and 8: full analysis set

<table>
<thead>
<tr>
<th>Clinical sign</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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</thead>
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</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
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</tr>
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<td>85</td>
<td>64</td>
<td>22</td>
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<tr>
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<td>13</td>
</tr>
<tr>
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<td>33</td>
</tr>
<tr>
<td>Severe</td>
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<td>23</td>
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<tr>
<td>Very severe</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
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<td>184</td>
<td>91</td>
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<td>52</td>
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<td>13</td>
</tr>
<tr>
<td>Moderate</td>
<td>28</td>
<td>60</td>
<td>32</td>
</tr>
<tr>
<td>Severe</td>
<td>8</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>Very severe</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>183</td>
<td>184</td>
<td>91</td>
</tr>
<tr>
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<td></td>
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</tr>
<tr>
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<td>105</td>
<td>69</td>
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<tr>
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<td>56</td>
<td>55</td>
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</tr>
<tr>
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<td>54</td>
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</tr>
<tr>
<td>Severe</td>
<td>2</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Very severe</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>183</td>
<td>184</td>
<td>91</td>
</tr>
<tr>
<td><strong>THICKNESS, WEEK 8</strong></td>
<td></td>
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</tr>
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<td>None</td>
<td>113</td>
<td>80</td>
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<td>48</td>
<td>49</td>
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<td>47</td>
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<td>Severe</td>
<td>3</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Very severe</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>183</td>
<td>184</td>
<td>91</td>
</tr>
</tbody>
</table>
Table 85: Investigator’s assessment of severity of clinical signs of psoriasis vulgaris on trunk at week 4 and 8: full analysis set

<table>
<thead>
<tr>
<th>Clinical sign</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td><strong>SCALINESS, WEEK 4</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>112 (61.2)</td>
<td>79 (42.9)</td>
<td>25 (27.5)</td>
</tr>
<tr>
<td>Mild</td>
<td>54 (29.5)</td>
<td>71 (38.6)</td>
<td>27 (29.7)</td>
</tr>
<tr>
<td>Moderate</td>
<td>15 (8.2)</td>
<td>30 (16.3)</td>
<td>34 (37.4)</td>
</tr>
<tr>
<td>Severe</td>
<td>2 (1.1)</td>
<td>4 (2.2)</td>
<td>4 (4.4)</td>
</tr>
<tr>
<td>Very severe</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Total</td>
<td>183 (100.0)</td>
<td>184 (100.0)</td>
<td>91 (100.0)</td>
</tr>
<tr>
<td><strong>SCALINESS, WEEK 8</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>111 (60.7)</td>
<td>84 (45.7)</td>
<td>30 (33.0)</td>
</tr>
<tr>
<td>Mild</td>
<td>54 (29.5)</td>
<td>63 (34.2)</td>
<td>24 (26.4)</td>
</tr>
<tr>
<td>Moderate</td>
<td>15 (8.2)</td>
<td>33 (17.9)</td>
<td>28 (30.8)</td>
</tr>
<tr>
<td>Severe</td>
<td>3 (1.6)</td>
<td>4 (2.2)</td>
<td>8 (8.8)</td>
</tr>
<tr>
<td>Very severe</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Total</td>
<td>183 (100.0)</td>
<td>184 (100.0)</td>
<td>91 (100.0)</td>
</tr>
</tbody>
</table>
Table 86: Investigator's assessment of extent of psoriasis vulgaris on legs at week 4 and 8: full analysis set

<table>
<thead>
<tr>
<th>Extent (LGCP)</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td><strong>VISIT 4/ WEEK 4</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No involvement</td>
<td>13 (7.1)</td>
<td>6 (3.3)</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>&lt; 10%</td>
<td>97 (53.0)</td>
<td>88 (47.8)</td>
<td>30 (33.0)</td>
</tr>
<tr>
<td>10 - 29%</td>
<td>65 (35.5)</td>
<td>80 (43.5)</td>
<td>47 (51.6)</td>
</tr>
<tr>
<td>30 - 49%</td>
<td>8 (4.4)</td>
<td>8 (4.3)</td>
<td>11 (12.1)</td>
</tr>
<tr>
<td>70 - 89%</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>90 - 100%</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Total</td>
<td>183 (100.0)</td>
<td>184 (100.0)</td>
<td>91 (100.0)</td>
</tr>
<tr>
<td><strong>VISIT 6/ WEEK 8</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No involvement</td>
<td>16 (8.7)</td>
<td>9 (4.9)</td>
<td>3 (3.3)</td>
</tr>
<tr>
<td>&lt; 10%</td>
<td>111 (60.7)</td>
<td>94 (51.1)</td>
<td>33 (36.3)</td>
</tr>
<tr>
<td>10 - 29%</td>
<td>50 (27.3)</td>
<td>71 (38.6)</td>
<td>42 (46.2)</td>
</tr>
<tr>
<td>30 - 49%</td>
<td>6 (3.3)</td>
<td>9 (4.9)</td>
<td>12 (13.2)</td>
</tr>
<tr>
<td>70 - 89%</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>90 - 100%</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Total</td>
<td>183 (100.0)</td>
<td>184 (100.0)</td>
<td>91 (100.0)</td>
</tr>
</tbody>
</table>
Table 87: Investigator's assessment of severity of clinical signs of psoriasis vulgaris on legs at week 4 and 8: full analysis set

<table>
<thead>
<tr>
<th>Clinical sign (LOCF)</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td><strong>REDNESS, WEEK 4</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>13 (7.1%)</td>
<td>7 (3.8%)</td>
<td>2 (2.2%)</td>
</tr>
<tr>
<td>Mild</td>
<td>69 (37.7%)</td>
<td>41 (22.3%)</td>
<td>9 (9.9%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>88 (48.1%)</td>
<td>95 (51.6%)</td>
<td>45 (49.5%)</td>
</tr>
<tr>
<td>Severe</td>
<td>13 (7.1%)</td>
<td>33 (17.9%)</td>
<td>33 (36.3%)</td>
</tr>
<tr>
<td>Very severe</td>
<td>0 (0.0%)</td>
<td>8 (4.3%)</td>
<td>2 (2.2%)</td>
</tr>
<tr>
<td>Total</td>
<td>183 (100.0%)</td>
<td>184 (100.0%)</td>
<td>91 (100.0%)</td>
</tr>
<tr>
<td><strong>REDNESS, WEEK 8</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>19 (10.4%)</td>
<td>10 (5.4%)</td>
<td>3 (3.3%)</td>
</tr>
<tr>
<td>Mild</td>
<td>86 (47.0%)</td>
<td>55 (29.9%)</td>
<td>9 (9.9%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>63 (34.4%)</td>
<td>82 (44.6%)</td>
<td>49 (53.8%)</td>
</tr>
<tr>
<td>Severe</td>
<td>15 (8.2%)</td>
<td>28 (15.2%)</td>
<td>28 (30.8%)</td>
</tr>
<tr>
<td>Very severe</td>
<td>0 (0.0%)</td>
<td>9 (4.9%)</td>
<td>2 (2.2%)</td>
</tr>
<tr>
<td>Total</td>
<td>183 (100.0%)</td>
<td>184 (100.0%)</td>
<td>91 (100.0%)</td>
</tr>
<tr>
<td><strong>THICKNESS, WEEK 4</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>28 (15.3%)</td>
<td>17 (9.2%)</td>
<td>5 (5.5%)</td>
</tr>
<tr>
<td>Mild</td>
<td>91 (49.7%)</td>
<td>66 (35.9%)</td>
<td>12 (13.2%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>56 (30.6%)</td>
<td>79 (42.9%)</td>
<td>57 (62.6%)</td>
</tr>
<tr>
<td>Severe</td>
<td>8 (4.4%)</td>
<td>22 (12.0%)</td>
<td>16 (17.6%)</td>
</tr>
<tr>
<td>Very severe</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>Total</td>
<td>183 (100.0%)</td>
<td>184 (100.0%)</td>
<td>91 (100.0%)</td>
</tr>
<tr>
<td><strong>THICKNESS, WEEK 8</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>37 (20.2%)</td>
<td>28 (15.2%)</td>
<td>8 (8.8%)</td>
</tr>
<tr>
<td>Mild</td>
<td>90 (49.2%)</td>
<td>63 (34.2%)</td>
<td>13 (14.3%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>48 (26.2%)</td>
<td>76 (41.3%)</td>
<td>58 (63.7%)</td>
</tr>
<tr>
<td>Severe</td>
<td>8 (4.4%)</td>
<td>16 (8.7%)</td>
<td>11 (12.1%)</td>
</tr>
<tr>
<td>Very severe</td>
<td>0 (0.0%)</td>
<td>1 (0.5%)</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>Total</td>
<td>183 (100.0%)</td>
<td>184 (100.0%)</td>
<td>91 (100.0%)</td>
</tr>
</tbody>
</table>
Table 87: Investigator's assessment of severity of clinical signs of psoriasis vulgaris on legs at week 4 and 8: full analysis set

<table>
<thead>
<tr>
<th>Clinical sign (LOCF)</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td>SCALINESS, WEEK 4</td>
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</tr>
<tr>
<td>None</td>
<td>38</td>
<td>20.8</td>
<td>26</td>
</tr>
<tr>
<td>Mild</td>
<td>101</td>
<td>55.2</td>
<td>91</td>
</tr>
<tr>
<td>Moderate</td>
<td>40</td>
<td>21.9</td>
<td>55</td>
</tr>
<tr>
<td>Severe</td>
<td>4</td>
<td>2.2</td>
<td>12</td>
</tr>
<tr>
<td>Very severe</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>183</td>
<td>100.0</td>
<td>184</td>
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<td>SCALINESS, WEEK 8</td>
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<td></td>
</tr>
<tr>
<td>None</td>
<td>43</td>
<td>23.5</td>
<td>34</td>
</tr>
<tr>
<td>Mild</td>
<td>95</td>
<td>51.9</td>
<td>79</td>
</tr>
<tr>
<td>Moderate</td>
<td>42</td>
<td>23.0</td>
<td>62</td>
</tr>
<tr>
<td>Severe</td>
<td>2</td>
<td>1.1</td>
<td>8</td>
</tr>
<tr>
<td>Very severe</td>
<td>1</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>183</td>
<td>100.0</td>
<td>184</td>
</tr>
</tbody>
</table>
Table 88: PASI in the observation phase by visit: those subjects in the full analysis set who achieved 'Controlled disease' according to investigator's global assessment of disease severity at week 8

<table>
<thead>
<tr>
<th>Visit</th>
<th>DAIVOBET Gel (n=67)</th>
<th>Tacalcitol (n=31)</th>
<th>Gel Vehicle (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VISIT 7/ WEEK 10</td>
<td>Mean: 3.51</td>
<td>Mean: 2.09</td>
<td>Mean: 1.46</td>
</tr>
<tr>
<td></td>
<td>SD: 2.26</td>
<td>SD: 1.23</td>
<td>SD: 1.40</td>
</tr>
<tr>
<td></td>
<td>Median: 3.10</td>
<td>Median: 2.00</td>
<td>Median: 0.80</td>
</tr>
<tr>
<td></td>
<td>Minimum: 0</td>
<td>Minimum: 0</td>
<td>Minimum: 0</td>
</tr>
<tr>
<td></td>
<td>Maximum: 9</td>
<td>Maximum: 5</td>
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</tr>
<tr>
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<td>Number: 67</td>
<td>Number: 31</td>
<td>Number: 5</td>
</tr>
<tr>
<td>VISIT 8/ WEEK 12</td>
<td>Mean: 3.75</td>
<td>Mean: 2.14</td>
<td>Mean: 1.60</td>
</tr>
<tr>
<td></td>
<td>SD: 2.45</td>
<td>SD: 1.25</td>
<td>SD: 1.07</td>
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<td>Median: 3.60</td>
<td>Median: 2.00</td>
<td>Median: 1.60</td>
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</tr>
<tr>
<td></td>
<td>Maximum: 11</td>
<td>Maximum: 5</td>
<td>Maximum: 3</td>
</tr>
<tr>
<td></td>
<td>Number: 44</td>
<td>Number: 27</td>
<td>Number: 5</td>
</tr>
<tr>
<td>VISIT 9/ WEEK 16</td>
<td>Mean: 4.05</td>
<td>Mean: 2.70</td>
<td>Mean: 3.74</td>
</tr>
<tr>
<td></td>
<td>SD: 2.97</td>
<td>SD: 1.88</td>
<td>SD: 1.89</td>
</tr>
<tr>
<td></td>
<td>Median: 3.30</td>
<td>Median: 2.80</td>
<td>Median: 3.30</td>
</tr>
<tr>
<td></td>
<td>Minimum: 0</td>
<td>Minimum: 0</td>
<td>Minimum: 2</td>
</tr>
<tr>
<td></td>
<td>Maximum: 13</td>
<td>Maximum: 7</td>
<td>Maximum: 7</td>
</tr>
<tr>
<td></td>
<td>Number: 23</td>
<td>Number: 21</td>
<td>Number: 5</td>
</tr>
</tbody>
</table>

1) 7 patients had controlled disease but withdrew after week 8, these patients were not included in this table.
Table 89: Investigator's global assessment of disease severity in the observation phase by visit: those subjects in the full analysis set who achieved 'Controlled disease' according to investigator's global assessment of disease severity at week 8

<table>
<thead>
<tr>
<th>Visit Controlled disease</th>
<th>DAIVOBET Gel (n=67)</th>
<th>Tacalcitol Gel (n=31)</th>
<th>Gel Vehicle (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>VISIT 7/ WEEK 10</td>
<td>Clear</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Almost clear</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>26</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>67</td>
<td>31</td>
</tr>
<tr>
<td>VISIT 8/ WEEK 12</td>
<td>Clear</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Almost clear</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>18</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>44</td>
<td>27</td>
</tr>
<tr>
<td>VISIT 9/ WEEK 16</td>
<td>Clear</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Almost clear</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>23</td>
<td>21</td>
</tr>
</tbody>
</table>

1) 7 patients had controlled disease but withdrew after week 8, these patients were not included in this table.
Table 90: Patient's global assessment of disease severity in the observation phase by visit: those subjects in the full analysis set who achieved 'Controlled disease' according to investigator's global assessment of disease severity at week 8

<table>
<thead>
<tr>
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<th>DAIVOBET Gel (n=67)</th>
<th>Tacalcitol (n=31)</th>
<th>Gel Vehicle (n=5)</th>
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<td></td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
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<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
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<td><strong>VISIT 7/ WEEK 10</strong></td>
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<td>1</td>
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<tr>
<td>Very Mild</td>
<td>19</td>
<td>16</td>
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<td>10</td>
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</tr>
<tr>
<td>Moderate</td>
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<td>0</td>
</tr>
<tr>
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<td>1</td>
<td>0</td>
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<td>1</td>
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<tr>
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<td>14</td>
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<td>8</td>
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<tr>
<td>Moderate</td>
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<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
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<tr>
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<td>8</td>
<td>2</td>
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<tr>
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<td>7</td>
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<td>0</td>
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<tr>
<td>Total</td>
<td>23</td>
<td>21</td>
<td>5</td>
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1) 7 patients had controlled disease but withdrew after week 8, these patients were not included in this table.
Quality of Life

Table 91: Physical Functioning scale based on the SF-36 (v2) health survey questionnaire by visit: full analysis set

<table>
<thead>
<tr>
<th>VISIT</th>
<th>Physical Functioning Scale</th>
<th>DAIWOET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>VISIT 1/ DAY 0</td>
<td></td>
<td>84.1</td>
<td>21.7</td>
<td>81.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>95.0</td>
<td>0</td>
<td>90.0</td>
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<tr>
<td></td>
<td></td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>VISIT 4/ WEEK 4</td>
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<td>21.2</td>
<td>81.7</td>
</tr>
<tr>
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<td></td>
<td>95.0</td>
<td>10</td>
<td>90.0</td>
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<tr>
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<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>VISIT 6/ WEEK 8</td>
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<td>10</td>
<td>90.0</td>
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<td></td>
<td>100</td>
<td>100</td>
<td>100</td>
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<td></td>
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<td>63</td>
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</table>
Table 92: Change in Physical Functioning scale based on the SF-36 (v2) health survey questionnaire from baseline to week 4 and 8: full analysis set

<table>
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<tr>
<th>VISIT</th>
<th>Physical Functioning Change</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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<td>14.8</td>
<td>14.4</td>
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<td>Median</td>
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<td>0.0</td>
<td>0.0</td>
</tr>
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<td>65</td>
</tr>
<tr>
<td></td>
<td>Number</td>
<td>172</td>
<td>173</td>
<td>77</td>
</tr>
<tr>
<td>VISIT 6/ WEEK 8</td>
<td>Mean</td>
<td>-0.4</td>
<td>0.5</td>
<td>-0.1</td>
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<tr>
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<td>SD</td>
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<td>16.0</td>
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</tr>
<tr>
<td></td>
<td>Median</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
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<td></td>
<td>Minimum</td>
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<td></td>
<td>Maximum</td>
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<td>85</td>
<td>35</td>
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<td></td>
<td>Number</td>
<td>169</td>
<td>162</td>
<td>62</td>
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</table>
Table 93: Role Physical scale based on the SF-36 (v2) health survey questionnaire by visit: full analysis set

<table>
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<tr>
<th>VISIT</th>
<th>Role Physical Scale</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Median</td>
</tr>
<tr>
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<td>22.7</td>
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</table>
Table 94: Change in Role Physical scale based on the SF-36 (v2) health survey questionnaire from baseline to week 4 and 8: full analysis set

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<thead>
<tr>
<th>VISIT</th>
<th>Role Physical Change</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>-0.6</td>
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<tr>
<td></td>
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<td>16.8</td>
<td>17.0</td>
<td>19.2</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
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<td></td>
<td>Minimum</td>
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<td>-63</td>
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<td></td>
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</tr>
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<td></td>
<td>Number</td>
<td>175</td>
<td>173</td>
<td>78</td>
</tr>
</tbody>
</table>

<table>
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<tr>
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<th>Role Physical Change</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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<td>1.4</td>
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<td>18.0</td>
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<td></td>
<td>Median</td>
<td>0.0</td>
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<td>81</td>
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<td>Number</td>
<td>171</td>
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Table 95: Bodily Pain scale based on the SF-36 (v2) health survey questionnaire by visit: full analysis set

<table>
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<tr>
<th>VISIT 1/ DAY 0</th>
<th>DAIYOGET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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<tr>
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<td>70.5</td>
<td>73.6</td>
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<td>SD</td>
<td>25.7</td>
<td>24.6</td>
<td>23.4</td>
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<td>Median</td>
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<td>100</td>
</tr>
<tr>
<td>Number</td>
<td>183</td>
<td>184</td>
<td>91</td>
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<table>
<thead>
<tr>
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<tr>
<td>Minimum</td>
</tr>
<tr>
<td>Maximum</td>
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<td>Number</td>
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<table>
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<th>VISIT 6/ WEEK 8</th>
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<td>SD</td>
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<tr>
<td>Maximum</td>
</tr>
<tr>
<td>Number</td>
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Table 96: Change in Bodily Pain scale based on the SF-36 (v2) health survey questionnaire from baseline to week 4 and 8: full analysis set

<table>
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<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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<tr>
<td>Bodily Pain Change</td>
<td>Mean: 5.2</td>
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<td>0.4</td>
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<tr>
<td></td>
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<td>18.1</td>
<td>19.2</td>
</tr>
<tr>
<td></td>
<td>Median: 0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Minimum: -48</td>
<td>-58</td>
<td>-70</td>
</tr>
<tr>
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<td>Maximum: 78</td>
<td>59</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Number: 175</td>
<td>173</td>
<td>78</td>
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<table>
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<tr>
<th>VISIT 6/ WEEK 8</th>
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<th>3.9</th>
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<td>19.4</td>
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<td>Median: 0.0</td>
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<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Minimum: -49</td>
<td>-64</td>
<td>-70</td>
</tr>
<tr>
<td></td>
<td>Maximum: 78</td>
<td>59</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>Number: 168</td>
<td>162</td>
<td>63</td>
</tr>
</tbody>
</table>
Table 97: General Health scale based on the SF-36 (v2) health survey questionnaire by visit: full analysis set

<table>
<thead>
<tr>
<th>VISIT</th>
<th>General Health Scale</th>
<th>DAIVOGET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VISIT 1/ DAY 0</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>74.9</td>
<td>72.1</td>
<td>72.3</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>18.7</td>
<td>18.6</td>
<td>20.0</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>77.0</td>
<td>72.0</td>
<td>72.0</td>
<td></td>
</tr>
<tr>
<td>Minimum</td>
<td>15</td>
<td>20</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
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<td></td>
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<td>Number</td>
<td>182</td>
<td>184</td>
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</tr>
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<td>20.3</td>
<td>19.8</td>
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<td>Median</td>
<td>77.0</td>
<td>72.0</td>
<td>72.0</td>
<td></td>
</tr>
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<tr>
<td>Number</td>
<td>173</td>
<td>173</td>
<td>77</td>
<td></td>
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<td></td>
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<td>70.5</td>
<td>70.8</td>
<td></td>
</tr>
<tr>
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<td>20.2</td>
<td>21.1</td>
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<tr>
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<td>72.0</td>
<td>72.0</td>
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<tr>
<td>Number</td>
<td>171</td>
<td>162</td>
<td>63</td>
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</tr>
</tbody>
</table>
Table 98: Change in General Health scale based on the SF-36 (v2) health survey questionnaire from baseline to week 4 and 8: full analysis set

<table>
<thead>
<tr>
<th>VISIT</th>
<th>General Health Change</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
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<td>-3.5</td>
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<td>9.6</td>
<td>11.0</td>
<td>14.1</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>0.0</td>
<td>0.0</td>
<td>-3.0</td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
<td>-27</td>
<td>-30</td>
<td>-42</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>33</td>
<td>42</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Number</td>
<td>172</td>
<td>173</td>
<td>76</td>
</tr>
<tr>
<td>VISIT 6/ WEEK 8</td>
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<td>-1.0</td>
<td>-1.7</td>
</tr>
<tr>
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<td>SD</td>
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<td>14.8</td>
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<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
<td>-30</td>
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<td>-45</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
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<td>Number</td>
<td>170</td>
<td>162</td>
<td>62</td>
</tr>
</tbody>
</table>
Table 99: Vitality scale based on the SF-36 (v2) health survey questionnaire by visit: full analysis set

<table>
<thead>
<tr>
<th>VISIT 1/ DAY 0</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
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<td>66.1</td>
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<tr>
<td>SD</td>
<td>19.5</td>
<td>19.1</td>
<td>17.1</td>
</tr>
<tr>
<td>Median</td>
<td>68.8</td>
<td>68.8</td>
<td>62.5</td>
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<td>94</td>
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<td>62.5</td>
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<td>100</td>
<td>100</td>
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Table 100: Change in Vitality scale based on the SF-36 (v2) health survey questionnaire from baseline to week 4 and 8: full analysis set

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<tr>
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<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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<td>44</td>
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<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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<td>16.7</td>
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<td>44</td>
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Table 101: Social Functioning scale based on the SF-36 (v2) health survey questionnaire by visit: full analysis set

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<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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<td>SD 23.3</td>
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<td>Median 100.0</td>
<td>Median 100.0</td>
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<td>Maximum 100</td>
<td>Maximum 100</td>
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<td>Number 173</td>
<td>Number 78</td>
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<td>Number 62</td>
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Table 102: Change in Social Functioning scale based on the SF-36 (v2) health survey questionnaire from baseline to week 4 and 8: full analysis set

<table>
<thead>
<tr>
<th>VISIT Social Functioning Change</th>
<th>DAIVOCR Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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<td>62</td>
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Table 103: Role Emotional scale based on the SF-36 (v2) health survey questionnaire by visit: full analysis set

<table>
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<th>VISIT</th>
<th>Role Emotional Scale</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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<td>100.0</td>
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<td>Minimum</td>
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<td>173</td>
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<td>Number</td>
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Table 104: Change in Role Emotional scale based on the SF-36 (v2) health survey questionnaire from baseline to week 4 and 8: full analysis set

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<th>VISIT</th>
<th>Role Emotional Change</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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<td>16.7</td>
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<td>-50</td>
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<td>50</td>
</tr>
<tr>
<td></td>
<td>Number</td>
<td>175</td>
<td>173</td>
<td>78</td>
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<td>3.7</td>
<td>1.2</td>
</tr>
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<td>18.0</td>
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<td>0.0</td>
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<td>Number</td>
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Table 105: Mental Health scale based on the SF-36 (v2) health survey questionnaire by visit: full analysis set

<table>
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<th>VISIT</th>
<th>Mental Health Scale</th>
<th>DAIVGEBT Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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<td></td>
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<td>Mean</td>
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<td>SD</td>
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<td>Median</td>
<td>Median</td>
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<td>Minimum</td>
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<tr>
<td></td>
<td></td>
<td>Number</td>
<td>Number</td>
<td>Number</td>
</tr>
</tbody>
</table>

**VISIT 1/ DAY 0**
- Mean: 76.2, 75.2, 76.4
- SD: 18.8, 17.4, 15.9
- Median: 80.0, 80.0, 80.0
- Minimum: 15, 20, 35
- Maximum: 100, 100, 100
- Number: 182, 183, 91

**VISIT 4/ WEEK 4**
- Mean: 79.5, 75.5, 75.8
- SD: 17.6, 18.7, 17.1
- Median: 85.0, 80.0, 80.0
- Minimum: 10, 25, 30
- Maximum: 100, 100, 100
- Number: 174, 173, 78

**VISIT 6/ WEEK 8**
- Mean: 80.2, 78.1, 77.7
- SD: 17.5, 17.6, 17.6
- Median: 85.0, 85.0, 85.0
- Minimum: 15, 20, 25
- Maximum: 100, 100, 100
- Number: 170, 162, 63
Table 106: Change in Mental Health scale based on the SF-36 (v2) health survey questionnaire from baseline to week 4 and 8: full analysis set

<table>
<thead>
<tr>
<th>VISIT</th>
<th>Mental Health Change</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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<td>13.8</td>
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<td>0.0</td>
<td>0.0</td>
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<td>172</td>
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<td>161</td>
<td>63</td>
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Table 107: Reported Health Transition scale based on the SF-36 (v2) health survey questionnaire by visit: full analysis set

<table>
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<tr>
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<th>Reported Health Transition</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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<td>%</td>
<td>Number of Subjects</td>
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<td>9.9</td>
<td>10</td>
</tr>
<tr>
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<td>Somewhat better</td>
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<td>10.4</td>
<td>18</td>
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<tr>
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<td>About the same</td>
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<td>70.3</td>
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</tr>
<tr>
<td></td>
<td>Somewhat worse</td>
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<td>7.7</td>
<td>21</td>
</tr>
<tr>
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<td>Much worse</td>
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<td>1.6</td>
<td>1</td>
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<tr>
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<td>183</td>
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<tr>
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<td>9.1</td>
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<td>1</td>
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<td>18</td>
<td>10.5</td>
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<tr>
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<td>Somewhat better</td>
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Table 108: Symptoms score based on the Skindex-16 questionnaire by visit: full analysis set

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<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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<td>Median</td>
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Table 109: Change in Symptoms score based on the Skindex-16 questionnaire from baseline to week 4 and 8: full analysis set

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<th>VISIT</th>
<th>Symptoms Score Change</th>
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<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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<td>Median</td>
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<td>-4.2</td>
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<td>172</td>
<td>78</td>
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<td>Maximum</td>
<td>169</td>
<td>161</td>
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Table 110: Emotions score based on the Skindex-16 questionnaire by visit: full analysis set

<table>
<thead>
<tr>
<th>VISIT</th>
<th>Emotions Score</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitrol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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<td>0</td>
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<td>Maximum</td>
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<td>Number</td>
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<td>173</td>
<td>78</td>
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<td>VISIT 6/ WEEK 8</td>
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<td>162</td>
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Table 111: Change in Emotions score based on the Skindex-16 questionnaire from baseline to week 4 and 8: full analysis set

<table>
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<tr>
<th>VISIT</th>
<th>Emotions Score Change</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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<td>Mean</td>
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<td>172</td>
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<td></td>
<td></td>
<td>Number</td>
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Table 112: Functioning score based on the Skindex-16 questionnaire by visit: full analysis set

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<th>VISIT</th>
<th>Functioning Score</th>
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<th>Gel Vehicle (n=91)</th>
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<td>Number</td>
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<td>Number</td>
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Table 113: Change in Functioning score based on the Skindex-16 questionnaire from baseline to week 4 and 8: full analysis set

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<tr>
<th>VISIT Functioning Score Change</th>
<th>DAIVOBET Gel (n=183)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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<tr>
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<td>161</td>
<td>63</td>
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Safety

Table 114: Adverse events reported in the treatment phase by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class¹</th>
<th>Preferred Term¹</th>
<th>DAIVOBET Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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<td>%</td>
<td>Number of Subjects</td>
<td>%</td>
</tr>
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<td></td>
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¹ MedDRA primary system organ class and preferred term: safety analysis set.
Table 114: Adverse events reported in the treatment phase by MedDRA primary system organ class and preferred term: safety analysis set

<table>
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<tr>
<th>System Organ Class¹ Preferred Term¹</th>
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<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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<tbody>
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<td>Number of Subjects</td>
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<td>1</td>
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<tr>
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<td>0</td>
</tr>
<tr>
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Table 114: Adverse events reported in the treatment phase by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>DAIVOBBT Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
<td>%</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
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<tr>
<td>Chest pain</td>
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<td>0</td>
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<tr>
<td>Fatigue</td>
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<td>0.5</td>
</tr>
<tr>
<td>Inflammation localised</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Oedema peripheral</td>
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<td>0.0</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Pain</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Pain exacerbated</td>
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<td>0.5</td>
<td>0</td>
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</tr>
<tr>
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</tr>
<tr>
<td>Pyrexia</td>
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<td>0</td>
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<tr>
<td>Immune system disorders</td>
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</tr>
<tr>
<td>Hypersensitivity</td>
<td>1</td>
<td>0.5</td>
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</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body tinea</td>
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<td>0.5</td>
</tr>
<tr>
<td>Bronchitis</td>
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<td>1</td>
<td>0.5</td>
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<td>Folliculitis</td>
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<tr>
<td>Gastroenteritis</td>
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<td>1.1</td>
<td>6</td>
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</tr>
<tr>
<td>Gastroenteritis viral</td>
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<td>2</td>
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</tbody>
</table>
Table 114: Adverse events reported in the treatment phase by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>DAIVOBST Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
<td>%</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Influenza</td>
<td>3</td>
<td>1.6</td>
<td>2</td>
<td>1.1</td>
</tr>
<tr>
<td>Nail tinea</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>11</td>
<td>6.0</td>
<td>6</td>
<td>3.3</td>
</tr>
<tr>
<td>Otitis externa</td>
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<td>0.0</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Otitis media</td>
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<td>0.5</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Pharyngitis streptococcal</td>
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<td>0</td>
<td>0.0</td>
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<tr>
<td>Pneumonia</td>
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<td>0.5</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>1</td>
<td>0.5</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Tinea pedis</td>
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<td>0.0</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Tooth abscess</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Tooth infection</td>
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<td>0.0</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>8</td>
<td>4.4</td>
<td>10</td>
<td>5.4</td>
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</table>
Table 114: Adverse events reported in the treatment phase by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class¹ Preferred Term¹</th>
<th>DAIVOBBT Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Viral upper respiratory tract infection</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back injury</td>
<td>2</td>
<td>1.1</td>
<td>1</td>
</tr>
<tr>
<td>Contusion</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Excoriation</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
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<tr>
<td>Fall</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Foot fracture</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Fractured coccyx</td>
<td>0</td>
<td>0.0</td>
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<tr>
<td>Joint injury</td>
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<td>1</td>
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<tr>
<td>Joint sprain</td>
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</tr>
<tr>
<td>Limb injury</td>
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<td>0.0</td>
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<tr>
<td>Skin laceration</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Sunburn</td>
<td>0</td>
<td>0.0</td>
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</tbody>
</table>
Table 114: Adverse events reported in the treatment phase by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class†</th>
<th>Preferred Term*</th>
<th>DAIVO BBT Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
<td>%</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin B12 decreased</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1</td>
<td>0.5</td>
<td>2</td>
<td>1.1</td>
</tr>
<tr>
<td>Back pain</td>
<td>1</td>
<td>0.5</td>
<td>2</td>
<td>1.1</td>
</tr>
<tr>
<td>Bursitis</td>
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<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Localised osteoarthritis</td>
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<td>1</td>
<td>0.5</td>
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<tr>
<td>Monoarthritis</td>
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<td>0</td>
<td>0.0</td>
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<tr>
<td>Muscle cramp</td>
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<td>1.1</td>
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</tr>
<tr>
<td>Muscle spasms</td>
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<td>1</td>
<td>0.5</td>
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<tr>
<td>Pain in extremity</td>
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<td>1</td>
<td>0.5</td>
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<tr>
<td>Psoriatic arthropathy</td>
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<td>0.5</td>
<td>0</td>
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</tbody>
</table>

*Preferred term
†System organ class

continued...
Table 114: Adverse events reported in the treatment phase by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class¹ Preferred Term</th>
<th>DAIVOBBT Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Neoplasm skin</td>
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<td>0.0</td>
<td>1</td>
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<tr>
<td>Squamous cell carcinoma</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burning sensation</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
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<tr>
<td>Carpal tunnel syndrome</td>
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<td>Headache</td>
<td>5</td>
<td>2.7</td>
<td>2</td>
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<tr>
<td>Migraine</td>
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<td>0</td>
</tr>
<tr>
<td>Neuralgia</td>
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<td>1</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Stress symptoms</td>
<td>1</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematuria</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
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</table>

¹MedDRA (Medical Dictionary for Regulatory Activities)
Table 114: Adverse events reported in the treatment phase by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>DAIVOBST Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Cervical dysplasia</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
<td>0 (0.0)</td>
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<tr>
<td></td>
<td>Dysmenorrhoea</td>
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<td>1 (0.5)</td>
<td>0 (0.0)</td>
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<tr>
<td></td>
<td>Prostatic hypertrophy</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Asthma</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td></td>
<td>Pharyngolaryngeal pain</td>
<td>1 (0.5)</td>
<td>0 (0.0)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td></td>
<td>Productive cough</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td></td>
<td>Rhinitis allergic</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>Sinus congestion</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Dermatitis contact</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td></td>
<td>Dermatitis exfoliative</td>
<td>1 (0.5)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>Dry skin</td>
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<td>0 (0.0)</td>
<td>0 (0.0)</td>
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<tr>
<td></td>
<td>Erythema</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
<td>0 (0.0)</td>
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</tbody>
</table>
Table 114: Adverse events reported in the treatment phase by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class¹ Preferred Term¹</th>
<th>DAIVOBET Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hyperhidrosis</td>
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<td>0.5</td>
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<tr>
<td>Milia</td>
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</tr>
<tr>
<td>Onychomadesis</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Pruritus</td>
<td>6</td>
<td>3.3</td>
<td>13</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>1</td>
<td>0.5</td>
<td>3</td>
</tr>
<tr>
<td>Rash</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Rash macular</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Rash scaly</td>
<td>1</td>
<td>0.5</td>
<td>3</td>
</tr>
<tr>
<td>Skin burning sensation</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Skin desquamation</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
</tr>
<tr>
<td>Skin inflammation</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Skin irritation</td>
<td>6</td>
<td>3.3</td>
<td>4</td>
</tr>
<tr>
<td>Urticaria</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Surgical and medical procedures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mole excision</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Nail avulsion</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
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</tbody>
</table>

²Continued...
Table 114: Adverse events reported in the treatment phase by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class' Preferred Term'</th>
<th>DAIVOBST Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td>Surgical and medical procedures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tooth extraction</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>3</td>
<td>1.6</td>
<td>1</td>
</tr>
<tr>
<td>Hypotension</td>
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<td>0.0</td>
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</tr>
<tr>
<td>Total number of adverse events'</td>
<td>98</td>
<td>39.6</td>
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<tr>
<td>Total number of subjects</td>
<td>72</td>
<td>39.6</td>
<td>83</td>
</tr>
</tbody>
</table>

1) Classification according to MedDRA version 6.1
2) Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
Table 115: Relationship of adverse events reported in the treatment phase to study medication by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class\Preferred Term</th>
<th>DAIWOBT Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not related</td>
<td>Possible</td>
<td>Probable</td>
</tr>
<tr>
<td>Blood and lymphatic system</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear pain</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Meniere's disease</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vertigo</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 115: Relationship of adverse events reported in the treatment phase to study medication by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class¹ Preferred Term²</th>
<th>DAVOBET Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not-related</td>
<td>Possible</td>
<td>Probable</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Enteritis</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gastritis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gastrooesophageal reflux disease</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Haemorrhoids</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Oral discomfort</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tooth disorder</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Toothache</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
| Vomiting                             | 0         | 0        | 0        | 0          | 2        | 0        | 0          | 0        | 0        | 0          

¹ System Organ Class
² Preferred Term

DAIVOBET Gel (n=182) Tacalcitol (n=184) Gel Vehicle (n=91)
Table 115: Relationship of adverse events reported in the treatment phase to study medication by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class\Preferred Term</th>
<th>DAIVOBET Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not-related</td>
<td>Possible</td>
<td>Probable</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Application site burning</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Application site dryness</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Application site pruritus</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chest pain</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Inflammation localised</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Oedema peripheral</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pain</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pain exacerbated</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pitting oedema</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

MMADK 22/03-09:10:53:25 rel_tr.doc Continued...
Table 115: Relationship of adverse events reported in the treatment phase to study medication by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class\Preferred Term\</th>
<th>DAIVOBET Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not related</td>
<td>Possible</td>
<td>Probable</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body tinea</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Folliculitis</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gastroenteritis viral</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Influenza</td>
<td>3</td>
<td>0</td>
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</tbody>
</table>

MMADK 23JUN09 10:53:28 gel_tr.doc continued...
Table 115: Relationship of adverse events reported in the treatment phase to study medication by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>DAIVOBE® Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not-related</td>
<td>Possible</td>
<td>Probable</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nail tinea</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Otitis externa</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Otitis media</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pharyngitis streptococcal</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tinea pedis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tooth abscess</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tooth infection</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Viral upper respiratory tract infection</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 115: Relationship of adverse events reported in the treatment phase to study medication by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>DAIIVOBET Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not related</td>
<td>Possible</td>
<td>Probable</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back injury</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Contusion</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Excoriation</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fall</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Foot fracture</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fractured coccyx</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Joint injury</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Joint sprain</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Limb injury</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin laceration</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sunburn</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 115: Relationship of adverse events reported in the treatment phase to study medication by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class¹ Preferred Term¹</th>
<th>DAIVOBET Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not related</td>
<td>Possible</td>
<td>Probable</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin B12 decreased</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Back pain</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bursitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Localised osteoarthritis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Monoarthritis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Muscle cramp</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

¹ Not related, Possible, Probable

MMADK 23JUN09 16:53:26 rel_tr.doc Continued...
Table 115: Relationship of adverse events reported in the treatment phase to study medication by MedDRA primary system organ class and preferred term: safety analysis set

<table>
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<th>DAIVOST Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not related</td>
<td>Possible</td>
<td>Probable</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Psoriatic arthropathy</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoplasm skin</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burning sensation</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Carpal tunnel syndrome</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Migraine</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Neuralgia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
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</table>
Table 115: Relationship of adverse events reported in the treatment phase to study medication by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class' Preferred Term</th>
<th>DAIVOBET Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
</table>
|                                                        | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not 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Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | 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related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probable | Not related | Possible | Probability: Not related, Possible, Probable | MMADK 22/05/09:10:53:26 rel_tr.doc Continued...
Table 115: Relationship of adverse events reported in the treatment phase to study medication by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class\Preferred Term\</th>
<th>DAIIVOBET Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not related</td>
<td>Possible</td>
<td>Probable</td>
</tr>
<tr>
<td>Respiratory, thoracic and</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharyngolaryngeal pain</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Productive cough</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rhinitis allergic</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sinus congestion</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatitis contact</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dermatitis exfoliative</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dry skin</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Erythema</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Milia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Onychomadesis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

MMADK 23/JUN09:16:53:26 rel_tr.doc Continued...
Table 115: Relationship of adverse events reported in the treatment phase to study medication by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class¹</th>
<th>Preferred Term²</th>
<th>DAIVOBET Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Not-related</td>
<td>Possible</td>
<td>Probable</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Psoriasis</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Rash macular</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Rash scaly</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Skin burning sensation</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Skin desquamation</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Skin inflammation</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Skin irritation</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Urticaria</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Surgical and medical procedures</td>
<td>Mole excision</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Nail avulsion</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Tooth extraction</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

MMADK 23/08/09 10:52:26 rel_tr.doc continued...
Table 115: Relationship of adverse events reported in the treatment phase to study medication by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>DAIVOBBT Gel (n=182)</th>
<th>Tacalcitol (n=184)</th>
<th>Gel Vehicle (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Not related</td>
<td>Possible</td>
<td>Probable</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypotension</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total number of adverse events</td>
<td>78</td>
<td>8</td>
<td>11</td>
<td>1</td>
</tr>
</tbody>
</table>

1) Classification according to MedDRA version 6.1
2) Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
Table 116: Adverse events reported in the observation phase by MedDRA primary system organ class and results of statistical analysis: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class†</th>
<th>DAI伏BET Gel (n=68)</th>
<th>Tacalcitol (n=35)</th>
<th>Gel Vehicle (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Congenital, familial and genetic disorders</td>
<td>0 0.0</td>
<td>1 2.9</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>1 1.5</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>1 1.5</td>
<td>1 2.9</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>1 1.5</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>8 11.8</td>
<td>9 25.7</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>0 0.0</td>
<td>1 2.9</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>1 1.5</td>
<td>3 8.6</td>
<td>1 20.0</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>1 1.5</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>4 5.9</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>1 1.5</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Total number of adverse events†</td>
<td>19</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Total number of subjects</td>
<td>15 22.1</td>
<td>14 40.0</td>
<td>1 20.0</td>
</tr>
<tr>
<td>P-value†</td>
<td>0.055</td>
<td>0.91</td>
<td></td>
</tr>
</tbody>
</table>

1) Classification according to MedDRA version 6.1
2) Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes
3) Chi-squared test
Table 117: Adverse events reported in the observation phase by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class and Preferred Term</th>
<th>DAIVOBBT Gel (n=68)</th>
<th>Tacalcitol (n=35)</th>
<th>Gel Vehicle (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td>Congenital, familial and genetic disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermoid cyst</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Bye disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bye swelling</td>
<td>1</td>
<td>1.5</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Malaise</td>
<td>1</td>
<td>1.5</td>
<td>0</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug hypersensitivity</td>
<td>1</td>
<td>1.5</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellulitis</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Hordeolum</td>
<td>1</td>
<td>1.5</td>
<td>0</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>1</td>
<td>1.5</td>
<td>2</td>
</tr>
<tr>
<td>Otitis media</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 117: Adverse events reported in the observation phase by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class\Preferred Term\</th>
<th>DAIVOBT Gel (n=68)</th>
<th>Tacalcitol (n=35)</th>
<th>Gel Vehicle (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
<td>Number of Subjects</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
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<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Wound infection</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Back pain</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Localised osteoarthritis</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tendonitis</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 117: Adverse events reported in the observation phase by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class¹</th>
<th>Preferred Term¹</th>
<th>DAIVOBBT Gel (n=68)</th>
<th>Tacalcitol (n=35)</th>
<th>Gel Vehicle (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>%</td>
<td>Number of Subjects</td>
<td>%</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal cyst</td>
<td>1</td>
<td>1.5</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermal cyst</td>
<td>1</td>
<td>1.5</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1</td>
<td>1.5</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Rash</td>
<td>1</td>
<td>1.5</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Skin burning sensation</td>
<td>1</td>
<td>1.5</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>1.5</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total number of adverse events¹</td>
<td>19</td>
<td>22.1</td>
<td>15</td>
<td>40.0</td>
</tr>
<tr>
<td>Total number of subjects</td>
<td>15</td>
<td>22.1</td>
<td>14</td>
<td>40.0</td>
</tr>
</tbody>
</table>

1) Classification according to MedDRA version 6.1
2) Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes
Table 118: Relationship of adverse events reported in the observation phase to study medication by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class' Preferred Term</th>
<th>DAIVOBET Gel (n=68)</th>
<th>Tacalcitol (n=35)</th>
<th>Gel Vehicle (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not related</td>
<td>Possible</td>
<td>Probable</td>
</tr>
<tr>
<td>Congenital, familial and genetic disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermoid cyst</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye swelling</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Malaise</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug hypersensitivity</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellulitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hordeolum</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>
Table 118: Relationship of adverse events reported in the observation phase to study medication by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class\Preferred Term\</th>
<th>DAIIOET Gel (n=68)</th>
<th>Tacalcitol (n=35)</th>
<th>Gel Vehicle (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not related</td>
<td>Possible</td>
<td>Probable</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Otitis media</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Wound infection</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Back pain</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Localised osteoarthritis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tendonitis</td>
<td>0</td>
<td>0</td>
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</table>

MMADK 13MAY09:12:13:14 rel.obs.doc Continued...
Table 118: Relationship of adverse events reported in the observation phase to study medication by MedDRA primary system organ class and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>DAIVOBET Gel (n=68)</th>
<th>Tacalcitol (n=35)</th>
<th>Gel Vehicle (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Not related</td>
<td>Possible</td>
<td>Probable</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Renal cyst</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Dermal cyst</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Pruritus</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Skin burning sensation</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total number of adverse events</td>
<td></td>
<td>15</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

1) Classification according to MedDRA version 6.1
2) Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
19 REFERENCES


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30. **DAIVONEX/DOVONEX** gel compared to **DAIVONEX/DOVONEX** scalp solution in patients with scalp psoriasis. LEO Pharma, Clinical Development 04-JAN-2007, Study No MBL 0503 INT.


32. **Clinical Study Report. Calcipotriol plus Betamethasone Dipropionate Gel Compared to Betamethasone Dipropionate in the Gel Vehicle. Calcipotriol in the Gel Vehicle and the Gel Vehicle alone in Psoriasis Vulgaris.** LEO Pharma, Medical Department, 11-APR-2007, Study No. MBL 0202 INT.


38. **EMEA Guideline on Clinical Investigation of Medicinal Products Indicated for the Treatment of Psoriasis 2004.**


20 LIST OF APPENDICES

Appendix I: Study Protocol and Amendments
Appendix II: Case Report Form
Appendix III: Statistical Analysis Plan
Appendix IV: Statistical Appendix
Appendix V: Representative Patient Information and Consent
Appendix VI: List of IECs/IRBs consulted and copy of all approvals/favourable opinions
Appendix VII: List of Investigators and Summary CVs
Appendix VIII: List of Subinvestigators
Appendix IX: List of LEO staff members contributing to the trial
Appendix X: Audit Certificate(s)
Appendix XI: Individual Patient Data
Appendix XII: Confirmation of Statistical Information Form
Appendix XIII: Authentication Form
### Approvals

<table>
<thead>
<tr>
<th>Name</th>
<th>Type</th>
<th>Reason for signature</th>
<th>Date for signature</th>
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