CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-852

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

NEW DRUG APPLICATION

CLINICAL STUDIES

NDA/Serial Number:	21-852 / N000
Drug Name:	Dovobet® (calcipotriol, 0.005% and betamethasone, ——) ointment
Indication(s):	Psoriasis Vulgaris
Applicant:	LEO Pharmaceuticals
Dates:	Submitted: 03/09/2005 PDUFA: 01/09/2006
Review Priority:	Standard Review
Biometrics Division:	Division of Biometrics III (HFD-725)
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Keywords:	Combination Drug

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1 Executive Summary

1.1 Conclusions and Recommendations

Dovobet® Ointment is a new combination drug product consisting of the moieties calcipotriol, 0.005% and betamethasone, [redacted]. Leo Pharmaceuticals is seeking approval of this new combination drug product in the treatment of psoriasis vulgaris. In one pivotal Phase 3 clinical trial Dovobet® was found to be superior to each of its active components and vehicle. Determination of efficacy was based upon a static Investigator Global Assessment (IGA) of psoriasis. Five other trials were used to support the efficacy claim. The safety profile for Dovobet® was similar to that of betamethasone, and these two treatment arms had fewer reported AE's than the calcipotriol and vehicle arms (note that safety was assessed based on three placebo-controlled trials). The difference in the AE profiles was in large part due to the higher percentage of subjects experiencing pruritus in the calcipotriol and vehicle arms. None of the serious events or the death of one subject were claimed to be treatment related according to the study investigators.

1.2 Brief Overview of Clinical Studies

One pivotal Phase 3 safety and efficacy trial, MCB-0003-INT, was completed to compare Dovobet® to betamethasone, calcipotriol and its vehicle (note dosing frequency was once daily). The treatment duration and time point for primary analysis was 4 weeks. Study MCB-0003-INT was conducted in 91 European and 15 Canadian recruiting a total of 1603 subjects. Eligibility criteria defined in the protocol required subjects to have at least one body region be affected by psoriasis in at least 10% of the surface area and a baseline IGA score of at least mild. The objective of the trial was to show the superiority of Dovobet® to each of its components and vehicle measured by the percent of IGA successes (IGA 'clear' or 'almost clear').

1.3 Statistical Issues and Findings

The sponsor had an End of Phase 2 Meeting with the Agency and the briefing package for the meeting package only contained a summary of the Phase 3 protocol. The Agency requested a full, detailed Phase 3 protocol so as to reach agreement on the statistical design and analysis. The sponsor did not submit a final detailed Phase 3 protocol to which the Agency could provide comment prior to initiation of the Phase 3 trial. Consequently, the statistical methodology proposed by the sponsor differs from that which the Agency typically requests.

Despite these limitations, the pivotal study, MCB-0003-INT, did collect the Agency preferred primary endpoint, a static Investigator Global Assessment (IGA) dichotomized to success or failure. Also included in this trial was an endpoint for Psoriasis Area and Severity Index (PASI) score which is the primary endpoint used in many of the sponsor's Phase 3 trials to which data was submitted. While the statistical methodology used by the sponsor and that preferred by the Division differ, the superiority of Dovobet® over its

components and vehicle is clearly established using both methods (refer to Table 1) in Study MCB-0003-INT.

Table 1. Efficacy Results for Percent of Successes using the IGA* (ITT)

	Dovobet®	Betamethasone	Calcipotriol	Vehicle
N	490	476	480	157
Success (%)	276 (56.3%)	176 (37.0%)	107 (22.3%)	16 (10.2%)
p-value[1]		$p < .0001$	$p < .0001$	$P < .0001$

[1] p-value is the same for reviewer's analysis using CMH stratified by reviewer's definition of pooled center and for sponsor's logistic regression using sponsor defined pooled center.
* Success is defined as 'very mild' or 'absence' of disease which is defined by the sponsor as 'controlled disease'.
Source: Reviewer's analysis and Page 105 of MCB-0003 Study Report (5.3.5.1.1 MCB-0003-INT Appendix II).

The submission contains six studies to which efficacy was assessed using either a static IGA or percent change in PASI score. While many of these trials are not full factorial designs and the dosing frequency are not just QD, the designs did allow one to obtain estimates of IGA success and/or PASI score. These estimates are provided in Table 2 and demonstrate consistent results across studies. The table also shows that the BID regimen has higher efficacy in terms of PASI score than the QD regimen, but the difference is quite small. The collection of evidence provides support for the superiority of Dovobet® to each of its components and vehicle.

Table 2. Summary of Efficacy for the Combination Drug in 6 Phase 3 Trials

Once Daily			
	N	**IGA**	**% Change PASI**
MCB-0001	249	NA (dynamic)	65.0%
MCB-0002	645	331 (51.3%)	68.7%
MCB-0003	490	276 (56.3%)	71.3%
MCB-9905	152	NA (dynamic)	67.7%
Twice Daily			
	N	**IGA**	**% Change PASI**
MVB-9802	307	NA (dynamic)	71.7%
MCB-9904	369	NA (dynamic)	74.4%
MCB-9905	237	NA (dynamic)	72.9%

*Source: Reviewer's Analysis

The safety of Dovobet® was assessed for both the once and twice daily applications for the three placebo-controlled studies). Dovobet® had a similar AE rate as betamethasone and these were lower than the AE rates for calcipotriol and vehicle. The reason for the difference was in large part due to the increased rate of subjects reporting of pruritus in the calcipotriol and vehicle arms. A total of 22 subjects had serious adverse events out of 3471 subjects, none of which were reported as being related to study drug.

2 Introduction

2.1 Overview

Dovobet® Ointment is a combination drug product consisting of the two moieties, betamethasone dipropionate [redacted] d calcipotriol hydrate 0.005%. Dovobet® has been approved in sixty-one countries and marketed in forty-eight. Specifically, it has been on the European market since 2001. The sponsor's clinical program includes eight trials that are placebo-controlled, active-controlled or both all conducted in countries outside of the United States. The sponsor has submitted one trial, MCB-0003-INT, as the pivotal trial and the remaining seven trials as supportive. Table 3 on the following page lists these eight controlled trials. This review will thoroughly review MCB-0003-INT and use the placebo controlled trials, MCB-9802-INT and MCB-9905-INT, as supportive evidence because the duration of treatment is the same as the pivotal trial and the purpose is to examine superiority of Dovobet®. Results of the five active-controlled trials are included in the Appendix. The supportive studies use the primary endpoint of change in Psoriasis Area Severity Index (PASI score) which the Division does not regard as a primary endpoint, but rather prefer a primary endpoint based on an Investigator Global Assessment (IGA). The pivotal trial does include both a PASI score and IGA to which the sponsor relies on the percent of IGA successes as the primary endpoint.

2.2 Data Sources

The datasets for each of the above mentioned studies in Table 3 are archived in the electronic data room under \\CDSESUB1\N21852\N_000\2005-03-09\m5\datasets.

3 Statistical Evaluation

3.1 Evaluation of Efficacy

Evaluation of efficacy in the main text of the review deals mainly with Study MCB-0003-INT. Detailed results of the placebo-controlled trials and active-controlled trials can be found in the Appendix Section A.3 and A.4. Results from these trials will be borrowed in the conclusion of efficacy results in Section 3.1.7 on page 22. More detailed results of efficacy for each of the active-controlled studies described in Table 3 can be found in the Appendix.

3.1.1 Study Design and Endpoints

Study MCB-0003-INT is an international, multi-center, randomized, double-blind, four-arm parallel group study. The four treatments consist of the combination drug product Dovobet®, its two components; calcipotriol and betamethasone, and its vehicle. The duration of treatment is 4 weeks with the protocol stating, "Patients who are considered by the investigator to require no further treatment for their psoriasis before the end of

four weeks treatment will complete the study at this time." This implies subjects who achieve success prior to week 4 can withdraw from the study and are considered a success in the analysis of efficacy at week 4 in the primary analysis as LOCF is the primary imputation technique. Normally for interpreting study results, the Division typically requests that all subjects be evaluated at the same time. Examining the data, it appears that only a total of eighteen subjects dropped out of the trial prior to week 4 due to successful clearing of their psoriasis. Ten of the eighteen subjects received Dovobet® ointment, seven betamethasone, and one calcipotriol. Impacts on efficacy were not seen when imputing these subjects as treatment failures. Note that reported results for the ITT population within the review regard these subjects that withdraw early due to efficacy as successes (i.e. missing data is imputed using LOCF).

Table 3. Sponsor's Clinical Study Overview

Study	Objective	Drug Products	Number of Subjects	Treatment Duration	Date[1]
MCB-0003-INT	Superiority over all components	Dovobet® QD Calciopotriol QD Betamethasone QD Vehicle QD	490 480 476 157	4 weeks	11/21/2000 *02/01/2001 to 06/19/2001*
MCB-9905-INT	Superiority Dovobet® QD over Vehicle	Dovobet® QD Dovobet® BID Dovonex® BID* Vehicle BID	152 237 231 208	4 weeks	11/08/1999 *01/18/2000 to 08/02/2000*
MCB-9802-INT	Superiority over all components	Dovobet® BID Calciopotriol BID Betamethasone BID Vehicle BID	307 311 313 109	4 weeks	11/17/1998 *02/25/1999 to 07/29/1999*
MCB-0002-INT[2]	Comparison of 3 treatment regimens	Calcipotriol BID Combo QD→C Combo QD→C→B	327 322 323	12 weeks 8→4 weeks 28→5→2 days	11/15/2000 *02/06/2001 to 08/26/2001*
MCB-0001-INT	Superiority of Combination	Combo QD Tacalcitol® (C) QD	249 252	4 weeks 8 weeks	05/23/2001 *09/19/2001 to 01/28/2002*
MCB-0201-FR	HPA axis	Dovobet® Diprosone® (B)	12 12	4 weeks	04/03/2003 *04/15/2003 to 01/13/2004*
MCB-9904-INT	Superiority of combination	Combo C B	369 365 363	4 weeks + 4 week open follow-up	10/11/1999 *12/08/1999 to 06/22/2000*
MCB-0102-INT	Safety of 3 treatment regimens	Combo QD Combo QD→C Combo QD→C	212 213 209	52 weeks cycle 4 weeks 4→48 weeks	04/25/2002 *08/23/2002 to 04/20/2004*

[1] The first date corresponds to the date of the final protocol revision and the second dates (in italics) correspond to the start and end of the study.
[2] The arrow corresponds to the order of the treatment. For example: Combo→C→B means that first subjects received the combination then after twenty-eight days used calcipotriol alone for five days and then betamethasone alone for two days (note that the use of five days and two days was cycled four times). More details for the active-controlled trials can be found in the Appendix Section A.4.
* Note that Dovonex® BID contains only the active ingredient calcipotriol.

Subjects are randomized in a 3:3:3:1 fashion with planned recruitment of 400 subjects for each of the active arms and 130 for the vehicle arm. The objective of the study is to establish the superiority of Dovobet® over each of its components and vehicle, testing at the two-sided significance level of α=0.05. Superiority is tested based upon the primary endpoint percent of subjects that are considered to have 'controlled disease' (described in more detail below).

Enrollment eligibility criteria defined in the protocol required subjects to have at least one body region be affected by at least 10% of the surface area (i.e. psoriasis must affect at least 10% of arms, 10% of trunk, and/or 10% of legs). According to the PASI score, this requires that the extent of the PASI score must be at least two in one or more of the three body regions. In terms of IGA, subjects must have at least mild disease severity (third level of IGA).

Success on the basis of the IGA score is defined as 'controlled disease' and this occurs when a subject has very mild or absence of disease. Below in Table 4 are the six static scales of disease severity according to the IGA.

Table 4. Definition of Investigator's Global Assessment of Disease Severity

Severity of Disease	Description
Absence	The disease is controlled. No evidence of redness, no evidence of thickness, and no evidence of scaling.
Very Mild	The disease is controlled, but not entirely cleared. The overall clinical picture consists of lesions with some discoloration with absolutely minimal thickness, i.e. the edges to the lesion(s) can just be felt.
Mild	The overall clinical picture consists of lesions with light red coloration, slight thickness and a fine, thin scale layer.
Moderate	The overall clinical picture consists of lesions with red coloration, a moderate thickness and moderate, somewhat coarse scale layer.
Severe	The overall clinical picture consists of lesions with very red coloration, severe thickness and a severe, coarse thick scale layer.
Very Severe	The overall clinical picture consists of lesions with extreme deep red coloration, very severe thickness and a very severe, coarse thick scale layer.

Source: Page 44 of Protocol MCB-0003-INT (Section 5.3.5.1.1 MCB 0003 INT Appendix V).

Although the Division has not normally used PASI scores for regulatory approval, it is described here in more detail as the vast majority of the sponsor's supportive studies do not collect a static IGA score and rely on the PASI score to establish efficacy. Note that only Studies MCB-0002-INT and MCB-0003-INT record a static IGA, whereas the remaining studies listed in Table 3 do not collect an IGA or the IGA scale is dynamic in nature. The extent of the psoriatic involvement will be recorded for each of the three areas: arms, trunk and legs 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 body regions will be recorded for each of the symptoms for redness, thickness and scaliness using the scale below.

0	Absent
1	Slight
2	Moderate
3	Severe
4	Severest Possible

Define the following: R = redness score, T = thickness score, S = scaliness score and E = extent score. Using these definitions, the following formula is then used to calculate the PASI score:

- Arms: X_{arm}=.2*(R+T+S)*E
- Trunk: X_{trunk} = .3*(R+T+S)*E
- Legs: X_{leg} = .4*(R+T+S)*E

PASI is then the sum of the three body region scores: $X_{arm}+X_{trunk}+X_{leg}$. The range of PASI is from 0 to 64.8.

The protocol also lists several secondary endpoints and those that *may* have regulatory utility are provided below.

- Proportion of subjects that classified themselves as 'treatment successes' ('marked improvement' or 'cleared') at the end of treatment according to the dynamic subjects' global evaluation of treatment response (scale provided in Table 5 below).
- Distribution of IGA at each time point.

Several of the secondary endpoints listed in the protocol will not be tested for efficacy claims. Examples of endpoints stated in the protocol not included in the review for efficacy claims are: reasons for withdrawl and description of adverse events as these deal mainly with safety.

Table 5. Definition of Subjects's Global Assessment of Disease Severity

Severity of Disease	Description
Worst	Psoriasis is worse than at baseline evaluation, in severity and/or extent
Unchanged	Psoriasis has not changed
Slight Improvement	Some definite improvement (overall about 25%) however, significant signs of psoriasis remain.
Moderate Improvement	Definite improvement (overall about 50%)
Marked Improvement	Very definite improvement (overall about 75%), some evidence of psoriasis remains, further treatment required
Cleared	No evidence or very minor evidence of psoriasis remains, no treatment required.

Source: Page 44 of Protocol MCB-0003-INT (Section 5.3.5.1.1 MCB 0003 INT Appendix V).

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

3.1.2.1 Patient Disposition

Protocol MCB-0003-INT stated that all randomized subjects comprise the intent-to-treat (ITT) population and will be analyzed for efficacy. However, the protocol did not specify a per-protocol (PP) population. The Agency requested the sponsor to provide details of the PP population via fax on May 18, 2005. The sponsor responded to the request stating, "In Study MCB-0003-INT a per protocol population was not scheduled in the protocol and thus no per protocol population has been defined and no per protocol analysis has been done. As stated in the protocol, section 11.12.1, page 52 the analysis of efficacy was based on the ITT population only since the primary conclusion on efficacy would be based on the ITT analysis for a Phase 3 superiority trial." The PP population is typically used as a supportive analysis to the ITT analysis findings. As the sponsor provided no definition of a PP population, this review assumes that all subjects that completed a week 4 end of treatment visit will be included in the PP population. Based upon this definition, the two analysis populations for the pivotal trial are described in Table 6.

Table 6. Analysis Population for Study MCB-0003-INT

	Dovobet®	Betamethasone	Calcipotriol	Vehicle
ITT Population	490	476	480	157
PP Population	473 (97%)	452 (95%)	444 (93%)	136 (87%)

Source: Reviewer's Analysis

3.1.2.2 Demographic Characteristics

In Study MCB-0003-INT an analysis of the baseline characteristics for age, gender and race revealed quite homogenous subgroups across treatment arms for each of the baseline characteristics. In Study MCB-0003-INT, the vast majority of subjects had race defined as Caucasian with each treatment arm comprised of 96% or more Caucasian subjects. At a Guidance meeting with the sponsor on June 9, 2003 the clinical team advised the sponsor that the sponsor would need to provide evidence that this

[redacted]

is submitted under IND[redacted] detailed listing of the demographic characteristics for Study MCB-0003-INT can be found in the Appendix Section A.1 on page 31.

3.1.2.3 Baseline Prognostic Factors

This exploratory analysis performed by the reviewer examines disease severity at entry to determine if disease severity at entry is similar across treatment arms. The disease severity is measured by both the IGA and PASI. Results can be seen in Table 7. Results shown in the table depict that randomization created near equal baseline values of IGA and PASI for each treatment arm. Thus, efficacy claims should not be impacted by any single treatment arm having favorable baseline values.

Table 7. Baseline Values across Treatment Arms for PASI and IGA

	Dovobet®	Betamethasone	Calcipotriol	Vehicle	p-value[1]
Number of Subjects	490	476	480	157	
PASI					
Mean (SD)	9.9 (6.0)	9.8 (6.1)	10.4 (6.4)	9.5 (6.3)	0.1274
IGA					
3	81 (16.5%)	90 (18.9%)	79 (16.5%)	29 (18.5%)	0.8695
4	311 (63.5%)	297 (62.4%)	300 (62.5%)	99 (63.1%)	
5	89 (18.2%)	85 (17.9%)	92 (19.2%)	28 (17.8%)	
6	9 (1.8%)	4 (.8%)	9 (1.9%)	1 (.6%)	

[1] p-values are based upon a Kruskal-Wallis test for PASI and a Chi-square test for IGA.
Source: Reviewer's Analysis

3.1.3 Statistical Methodology

The sponsor had an End of Phase 2 meeting with the Division on June 26, 2000. For this meeting the sponsor provided a summary of the Phase 3 protocol. The biostatistics team commented at this time, "...for detailed statistical comments on future Phase 3 studies the original protocols are requested. The following are some general comments related to the sponsor's submission." Comments of relevance to the NDA and included in the minutes are provided below.

- "Phase 3 study protocols are expected to provide details about sample size calculations, methods of randomization and statistical methods of analysis, including pre-specification of all covariates planned to be included in the analysis. The statistical model used for efficacy assessment needs to include all pre-specified covariates. The Cochran-Mantel-Haenszel test, with adjustment for the investigator should be used for efficacy assessment of the primary endpoint recommended by the Division (see the clinical comments)."
- "The sponsor in their data analysis indicated that they used the ANOVA model and this model included treatment and country effects (page 156). It is not clear however, whether 'country' was pre-specified in the protocol. For the ongoing Phase 3 studies the Division recommends that the investigator effect (instead of the country effect) be included in the model, and testing for treatment-by-investigator interaction should be carried out."

The final draft of Protocol MCB-0003-INT was dated November 21, 2000 with the study starting on February 2, 2001 and finishing on June 19, 2001. This draft of the protocol did not take into account some of the recommendations and also by not disclosing a detailed Phase 3 protocol for review, the Agency did not have the chance to provide feedback on all aspects of the protocol. Several design and analysis procedures included in the protocol are not consistent with the Division's usual preferences. The discrepancies in the sponsor's analysis and that which would have been endorsed by the Division are described below.

The sponsor's method of analysis of the primary endpoint, percent of subjects with controlled disease (IGA disease severity of absence of disease or very mild disease) uses

logistic regression including center as a covariate for the ITT population. As stated to the sponsor at the End of Phase 2 Meeting, the Division recommends using the Cochran-Mantel-Haenszel (CMH) test stratifying by center on the ITT population to be the primary analysis technique for a dichotomous primary endpoint. The analysis plan also does not request testing for the treatment by center interaction as requested.

Also, since the Division was not able to comment on a detailed final Phase 3 protocol, the sponsor used many centers often with centers not even recruiting a single subject to each treatment arm. Typically the Division recommends that centers plan to recruit at least eight subjects per treatment arm when treatment assignment is unbalanced between treatment arms to reduce the chance of obtaining cells with zero frequency in the efficacy analysis. The protocol should include an approach for pooling small centers if actual enrollment did not meet the above criterion. The sponsor's pooling strategy listed in the protocol states centers should enroll at least ten subjects and those that did not enroll ten subjects were combined with other smaller centers.

As supportive evidence, the Division recommends using the Per-Protocol (PP) population. In the protocol *no* statement is made about what subjects comprise the PP population and/or a definition of the PP population. The Division requested from the sponsor in the 74-day letter to have the sponsor define and include a PP analysis of the primary endpoint(s). As mentioned in Section 3.1.2.1, the sponsor did not provide a PP population and this review considers all subjects completing treatment as part of the PP population.

As the Division was not able to comment on a final Phase 3 protocol and the comments that were given to the sponsor at the End of Phase 2 meeting were ignored, this review will utilize analysis techniques that the Division typically endorses using the sponsor's analysis as supportive. The primary analysis for efficacy will be conducted on the ITT population using the reviewer's strategy for pooling the data (details provided in the next paragraph). The details of this analysis are described prior to working with the data and follow the Division's typical recommendations.

The pooling of centers is done within country and should a center recruit less than eight subjects per treatment arm, the center with the largest number of subjects not meeting this criteria is combined with the smallest center(s) such that the combined center approximately reaches the desired value of eight subjects per treatment arm. Should all centers within a country not enroll a total of eight subjects per arm, the data from this country will be combined with another similar country. Based upon this pooling strategy, 106 centers were pooled to form nineteen pooled centers in Study MCB-0003-INT. In this pooling strategy the data from Ireland and Sweden were combined to form a single pooled center.

The analysis of the percent of subjects that had controlled disease at the end of treatment will be analyzed using the CMH test stratifying by pooled center. The sponsor's results using logistic regression will be provided as supportive evidence. To test for the homogeneity of the odds ratios between pooled centers, the Breslow-Day test will be

tested at the α=.10 significance level. Should the test be significant, efficacy results will be analyzed to determine if a single pooled center drives efficacy claims by removing each center and testing for statistical significance. Testing for superiority will occur at the two-sided α=.05 level.

The sponsor proposes to test the percent change in PASI using ANOVA with design variables for center and treatment but not with a treatment-by-center interaction. This reviewer's analysis will also implement ANOVA including a test for the treatment-by-center interaction, tested at α=.10. If the interaction is significant, the same sensitivity analysis used with the analysis of percent with controlled disease will be carried out. If the interaction is not significant at the α=.10 level, the interaction term is dropped from the model and the treatment effect is tested at the two-sided α=.05 level.

The analysis of the secondary endpoint, percent of subjects with a patient global success, will be analyzed in the same way as the primary endpoint, percent with controlled disease. Success of the secondary endpoint will be tested at the two-sided α=.05 level.

3.1.4 Primary Endpoint Results (ITT Population)

To establish efficacy of Dovobet®, the sponsor must show the superiority of Dovobet® over each of its components and vehicle on the percent of subjects with controlled disease (IGA severity of absence or very mild disease) at week 4 as stated in the protocol. The percent of subjects with controlled disease is the primary endpoint of interest for FDA approval. However, the European trials often use percent reduction in PASI score as the primary endpoint. Since the vast majority of the data submitted to the NDA are European trials, PASI score is the only endpoint used in the Phase 3 trials. Thus, the review will focus on the percent of subjects with controlled disease, but also use percent reduction in PASI score so as to incorporate study results from Studies MCB-9802-INT and MCB-9905-INT in this review. Section 3.1.4.2 examines the relationship between controlled disease and PASI score.

3.1.4.1 Percent with Controlled Disease

The test of the superiority of Dovobet® to each of its components and vehicle on the basis of the percent of subjects with controlled disease showed that Dovobet® was significantly superior to each of its components and vehicle ($p < .0001$ for all comparisons). Here, controlled disease is defined as having an IGA severity of absence of disease or very mild disease by week 4 (see Section 3.1.1 for IGA definition). The statistical results are based upon a CMH test stratified by pooled centers according to the reviewer's analysis. The sponsor's results using logistic regression with covariates for treatment and their definition of pooled centers are provided in the bottom row of Table 8 and results are consistent with the reviewer's analysis. To test for homogeneity of the odds ratios across the pooled centers, a Breslow-Day was carried out for each of the superiority comparisons to which none reached statistical significance ($p > .10$). Thus, it does not appear a single center drives the statistical significance.

Table 8. Efficacy Results for Percent with Controlled Disease (ITT)

	Dovobet®	Betamethasone	Calcipotriol	Vehicle
N	490	476	480	157
Success (%)	276 (56.3%)	176 (37.0%)	107 (22.3%)	16 (10.2%)
p-value[1]		$p < .0001$	$p < .0001$	$p < .0001$
p-value[2]		$p < .0001$	$p < .0001$	$p < .0001$

[1] p-value is based upon reviewer's analysis using CMH stratified by reviewer's definition of pooled center.
[2] p-value is based upon sponsor's logistic regression using sponsor defined pooled center.
Source: Reviewer's analysis and Page 105 of MCB-0003 Study Report (5.3.5.1.1 MCB-0003-INT Appendix II).

A further examination into percent of controlled disease subjects examined response rates based upon the baseline disease severity. The results are shown in Table 9. This table reveals that Dovobet® and betamethasone have similar response rates if the initial disease severity is mild and these response rates are higher than for calcipotriol and vehicle. However, when baseline disease severity increases, Dovobet® has higher response rates of having controlled disease than either of its components or vehicle.

Table 9. Percent of Subjects with Controlled Disease by Baseline IGA Disease Severity

Success/Total (Percent Success)	Dovobet®	Betamethasone	Calcipotriol	Vehicle
Base = Mild	54/81 (66.7%)	57/90 (63.3%)	29/79 (36.7%)	5/29 (17.2%)
Base = Moderate	171/311 (55%)	101/297 (34.0%)	62/300 (20.7%)	8/99 (8.1%)
Base = Severe	48/89 (53.9%)	17/85 (20.0%)	15/92 (16.3%)	3/28 (10.7%)
Base = Very Severe	3/9 (33.3%)	1/4 (25%)	1/9 (11.1%)	0/1 (0%)
Total	276/490 (56.3%)	176/476 (37.0%)	107/480 (22.3%)	16/157 (10.2%)

Source: Page 108 of MCB-0003 Study Report (5.3.5.1.1 MCB-0003-INT Appendix II).

3.1.4.2 Modified Definition of IGA Success

As mentioned, not all the comments offered by the Agency at the End of Phase 2 Meeting were incorporated into the Phase 3 protocol. One potential issue occurring in the design of the trial is that subjects were able to enroll in the trial with mild disease (IGA level of 2) and by the end of the trial have very mild disease (IGA level of 1). Underlying the ordinal IGA scale is a latent continuous scale which is partitioned to produce an IGA ordinal scale. Thus, one considers each category on the ordinal scale to represent an interval on the underlying continuous scale. With the sponsor's proposed definition of treatment success included in the protocol, a subject might enroll in the study with a 'low' score of "mild disease" (level 2) and be assigned an 'upper' score of "very mild disease" (level 1) at the end of the study merely due to variability in the evaluator's assessment over time. As cases such as this do not reflect treatment success, the Agency would like subjects who enter the study with a score of "mild" attain a score of "clear" at the end of the study to be considered a success (that is, a 2 grade improvement is required

for defining a treatment success). Table 10 shows the results using such a modified definition for controlled disease which was not included in the sponsor's protocol. As we would expect, the percentage of subjects with controlled disease for this definition is lower than the protocol specified definition, but this new definition does *not* alter the strong finding that Dovobet® is superior to each of its components and vehicle found in the protocol definition of controlled disease.

Table 10. Efficacy Results for Percent with Controlled Disease (2 Grade Improvement)

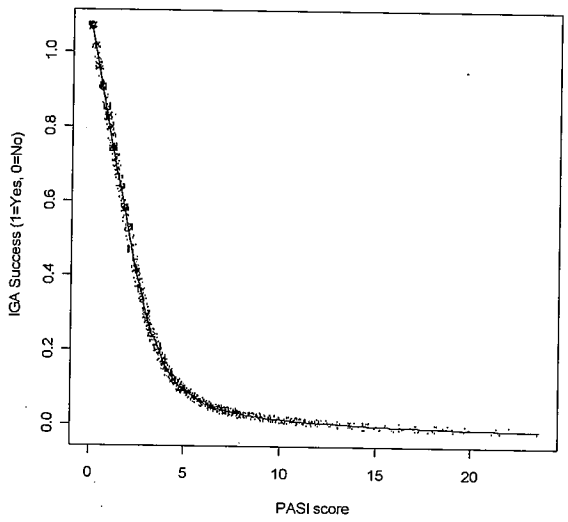
	Dovobet®	Betamethasone	Calcipotriol	Vehicle
N	490	476	480	157
Success (%)	235 (47.8%)	125 (26.3%)	79 (16.5%)	12 (7.6%)
p-value[2]		$p < .0001$	$p < .0001$	$p < .0001$

[1] p-value is based upon reviewer's analysis using CMH stratified by reviewer's definition of pooled center.
Source: Reviewer's analysis.

3.1.4.3 Relationship between Controlled Disease and PASI Score

Using the week 4 data from MCB-0003-INT, a logistic regression model was constructed to determine if PASI score could accurately predict IGA success (i.e. controlled disease). A nonparametric regression method using loess was used to obtain estimates of the relationship between PASI scores and IGA success. This relationship is shown in Figure 1 and clearly suggests a nonlinear relationship.

Figure 1. Loess fit of the Relationship of IGA Success and PASI Score



Since it is not known what transformation of PASI scores will induce linearity, a restricted cubic spline (or natural spline) with 3 knots is used. Note that cubic splines have been shown to be able to fit sharply curving shapes and made to be smooth at the knots. Also, the restricted cubic spline offers the advantage of forcing linearity in the tails

and also only requiring the estimation of the number of knots minus 1 parameters[1]. The choice of the location of the knots is based on the 10th, 50th and 90th percentiles of the PASI scores. In most situations Stone[2] has found the location of the knots is not important and the use of the above percentiles is adequate.

Thus, the estimated logistic model can be expressed as such (note that X represents PASI score)

$$P(IGA\ \ Success) = \frac{1}{1+\exp\{-X\hat{\beta}\}}, \text{ where}$$

$$X\hat{\beta} = 3.25 - 1.58X + .02(X-0.6)_+^3 - .03(X-3.3)_+^3 + .01(X-9.4)_+^3$$

$$\text{and } (x)_+ = \begin{cases} x & if \quad x > 0 \\ 0 & OW \end{cases}.$$

Note that the model with a restricted cubic spline function for X with knots at 0.6, 3.3 and 9.4 can be written as

$$f(X) = X\beta = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4 \text{ , where}$$
$$X_1 = X,\ X_2 = (X-0.6)_+^3,\ X_3 = (X-3.3)_+^3,\ X4 = (X-9.4)_+^3.$$

Then to test for overall linearity in X, we can test

$$H_0 : \beta_2 = \beta_3 = \beta_4 = 0.$$

The analysis of variance results are shown below in Table 11. The Wald statistic confirms that PASI score is *not* linearly related to IGA success (note this is the test described above). The total likelihood ratio χ^2 for the model is 1046 on 2 degrees of freedom (results not shown) which is highly significant.

Table 11. Wald Statistics for IGA success

	χ^2	*d.f.*	*P*
PASI	475.55	2	< .0001
Nonlinear	108.26	1	< .0001
TOTAL	475.55	2	< .0001

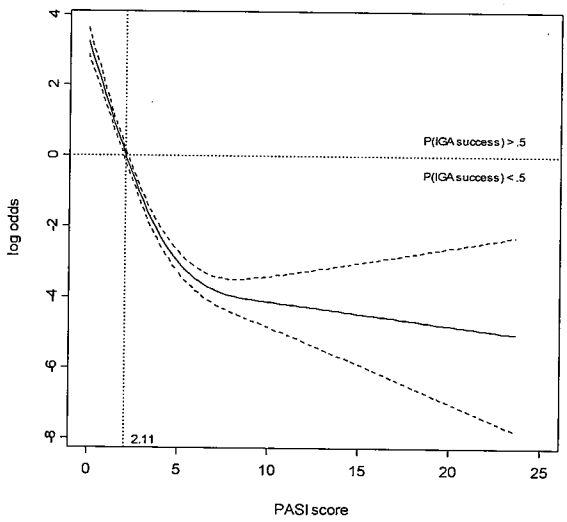
A plot of the fitted model is shown in Figure 2. A goodness-of-fit test was based on methods proposed by le Cessie and van Houwelingen[3] resulting in $p = .982$ suggesting a very strong fit of the model. The log odds listed on the y-axis of the figure correspond

[1] C.J. Stone and C. Y. Koo. Additive splines in statistics. In *Proceedings of the Statistical Computing Section ASA*, p. 45-48, Washington D.C., 1985.
[2] C.J. Stone. Comment: Generalized additive models. *Statistical Science*, 1:312-314, 1986.

[3] S. le Cessie and J. C. van Houwelingen. A goodness-of-fit test for binary regression models, based on smoothing methods. *Biometrics*, 47:1267-1282, 1991.

to $\log[P/(1-P)]$, where $P = \Pr(IGA\ success \mid PASI)$. Thus, log odds greater than 0 correspond to a $P > .5$. The outer bands of the curve correspond to 95% prediction bands.

Figure 2. Model Fit of the Logistic Model using PASI Score to Predict IGA Success



The probability of concordance, *c*, between predicted probability and response was used to measure the fitted model's predictive ability. In general, for a pair of bivariate observations (X_1, Y_1) and (X_2, Y_2), the probability of concordance, *c*, can be defined as

$$c = P(Y_2 > Y_1 \mid X_2 \geq X_1).$$

The probability of concordance is used for assessing the discriminatory power of a statistical model. A concordance probability of 1.0 represents a model that has perfect discrimination, whereas a value of 0.5 indicates that a coin flip would provide information as accurate as the statistical model.

Rather than using the raw estimate of the probability of concordance, a bias-corrected estimate is used to assess the discriminatory power of the model (techniques proposed by Bradley Efron). The method involves fitting the model to all the data consisting of *n* observation and variables X and Y. Then construct a bootstrapped sample of size *n* and derive the model on this data. This model is then applied to the original sample data. The accuracy index, in this case *c*, from the bootstrapped sample minus the index computed on the original sample is an estimate of optimism. This process was repeated for 150 bootstrap replications to yield an estimate of the optimism. The optimism estimate is then subtracted from the original estimate of *c* to obtain the bias-corrected estimate of *c*. The bias-corrected estimate of $c = .973$ indicating a very high level of predictability of the above fitted model.

Based upon this model, several PASI scores along with the estimated probability of IGA success are provided in Table 12. From this estimated model, it appears that once PASI scores start to exceed 2.11, there is a higher probability that IGA is a failure.

Table 12. Prediction Results for a Given PASI Score

PASI score	Pr(IGA success)	Pr(IGA failure)
0	.96	.04
.5	.92	.08
1	.84	.16
2	.54	.46
5	.05	.95
10	.02	.98
20	.01	.99

The only other Phase 3 trial that collected both a static IGA and PASI score was Study MCB-0002-INT. Following similar modeling strategies as that used above, results from Study MCB-0002-INT were consistent with results from Study MCB-0003-INT (note that only data from week 4 was again used in this analysis). Based upon the Wald test statistics, all tests were highly significant ($p < .0001$) as was also shown in Table 11 for Study MCB-0003-INT. In addition, the bias-corrected estimate of $c = .895$ indicates a high level of predictability for the model (not shown) in MCB-0002-INT. Studies MCB-0001-INT and MCB-9904-INT also collected a dynamic IGA (i.e. grade levels required one to refer to baseline assessments) and percent change in PASI. The relationship of the dynamic IGA and percent change in PASI is provided for these two studies in the Appendix Section A. 5 on page 54.

In conclusion, results from Study MCB-0003-INT and MCB-0002-INT suggest that the relation between PASI score and IGA success is quite strong at week 4. Thus, should efficacy based upon PASI scores show strong statistical significance it is likely that efficacy would also have been established using IGA as an endpoint. However, if the p-value based upon PASI scores is marginal, it would be hard to determine if a trial that also collected IGA would meet statistical significance for IGA success. It is worth noting that while the above results are for PASI scores, the same methodological procedures were also done comparing percent change in PASI scores to IGA success with very similar results.

3.1.4.4 Percent Reduction in PASI

The analysis of the percent reduction in PASI scores at week 4 shows a highly significant difference between Dovobet® and its components and vehicle in Study MCB-003-INT. The results of this analysis are shown in Table 13 along with the point estimate of the mean percent reduction at week 4 for each group (Note that a positive value implies end of treatment PASI score is below baseline PASI score). The p-values were based upon an ANOVA model with design variables for treatment and pooled center.

Table 13. Efficacy Results for Percent Reduction in PASI: Study MCB-0003-INT.

	Dovobet® QD	Betamethasone QD	Calcipotriol QD	Vehicle QD
N	490	476	480	157
Mean (SD)	71.3% (25.7%)	57.2% (29.8%)	46.1% (30.9%)	22.7% (33.5%)
p-value[1]		$p < .0001$	$p < .0001$	$p < .0001$

[1] p-value is based upon reviewer's analysis using ANOVA with design variables for treatment and reviewer's definition of pooled center.

When comparing Dovobet® to its vehicle, the ANOVA model showed a significant treatment by pooled center interaction. This interaction appeared to be an artifact of one of the French pooled centers as it showed a large overall percent reduction in PASI in comparison to other pooled centers. However, the percent change in PASI for the Dovobet® arm was still better than that of the vehicle group. Thus, the interaction term was dropped and the ANOVA model with main effects only was fit for comparing Dovobet® to vehicle. Note that when the ANOVA model was fit using the sponsor's definition of pooled centers, both the comparison of Dovobet® to betamethasone and vehicle showed significant interaction effects. This is not surprising as many of the pooled centers in the sponsor's definition consist of only a total of 10 subjects per pooled center and it is possible by chance to have one arm perform better than another arm when sample sizes are so small.

3.1.5 Primary Endpoint Results (PP Population)

As mentioned, no PP population was defined in the protocol and the sponsor stated that analysis on a PP population was not planned. As a result, no analysis on a PP population was performed. For supportive evidence, the review team has decided to define the PP population as all subjects that completed an end of treatment visit.

Results on both the percent of subjects with controlled disease and percent change in PASI scores are consistent with results from the ITT population. All tests are highly significant (p-values < .0001) and shown in Table 14.

Table 14. Efficacy Results for the PP population (Study MCB-0003-INT)

	Dovobet®	Betamethasone	Calcipotriol	Vehicle
N	473	452	444	136
Controlled Disease				
Success (%)	266 (56%)	169 (37%)	106 (24%)	16 (12%)
p-value[1]		$p < .0001$	$p < .0001$	$p < .0001$
Percent Change PASI				
Mean (SD)	72.0% (24.5%)	58.4% (28.3%)	48.8% (29.7%)	26.8% (31.3%)
p-value[2]		$p < .0001$	$p < .0001$	$p < .0001$

[1] p-value is based upon reviewer's analysis using CMH stratified by reviewer's definition of pooled center.

[2] p-value is based upon reviewer's analysis using ANOVA with design variables for treatment and reviewer's definition of pooled center.

3.1.6 Secondary Endpoint Results

The protocol states the following as secondary endpoints: the distribution of the investigator's global assessment of disease severity at each visit and end of treatment along with percent of treatment subject based upon subject rating. Since the primary endpoint percent with controlled disease at end of week 4 needs to reach statistical significance in order to test the secondary endpoints, the total number of secondary endpoints examined is three. As the Division typically does not require a multiplicity adjustment for a small number of secondary endpoints, no multiplicity adjustment is applied in the testing of these three secondary endpoints.

3.1.6.1 Distribution of Controlled Disease for each Visit

The sponsor includes in their proposed draft label the percent of subjects with controlled disease across time for each treatment arm. The sponsor proposes to use a bar plot with an error bar corresponding to an upper 95% confidence interval above each bar in the draft labeling. A similar plot excluding the error bars is provided in Figure 3. From this figure it is apparent that by the end of week 2, there is clearly a higher percentage of subjects with controlled disease for the Dovobet® arm versus any other arm.

Figure 3. Percent with Controlled Disease across Time

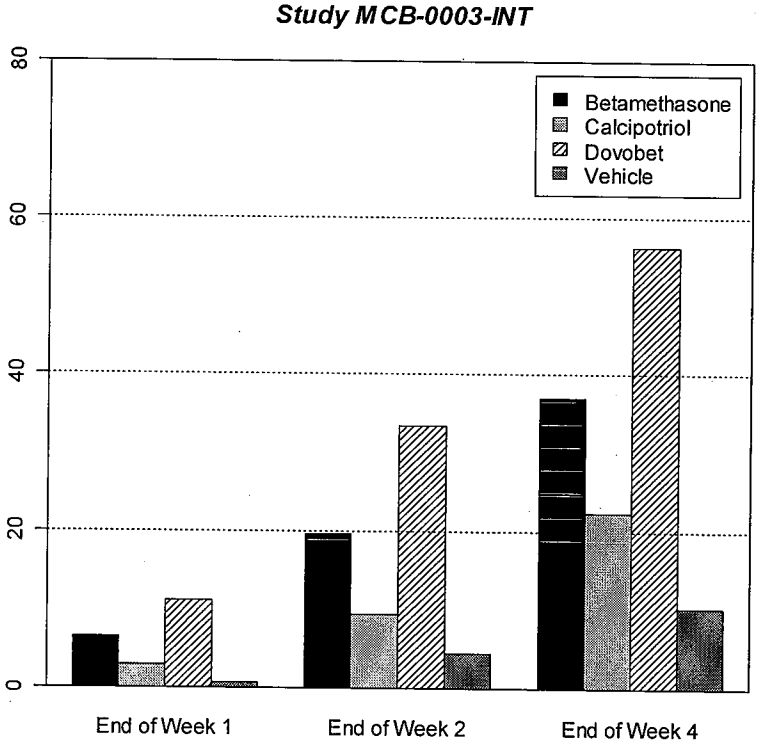


Table 15 below shows the p-values comparing Dovobet® to each of its components and vehicle at the *end of week 2*. Thus, each of these comparisons is significant at the unadjusted α=.05 significance level.

Table 15. Efficacy results for Percent with Controlled Disease at the *end of Week 2.*

	Dovobet®	Betamethasone	Calcipotriol	Vehicle
N	490	476	480	157
Success (%)	164 (33.5%)	93 (19.5%)	45 (9.4%)	7 (4.5%)
p-value[1]		$p < .0001$	$p < .0001$	$p < .0001$

[1] p-value is based upon reviewer's analysis using CMH stratified by reviewer's definition of pooled center.

Results for the comparisons at the *end of week 1* are provided in Table 16. As with the end of week 2 data, Dovobet® is significantly superior to each of its components and vehicle when testing at the unadjusted α=.05 level.

Table 16. Efficacy results for Percent with Controlled Disease at the *end of Week 1.*

	Dovobet®	Betamethasone	Calcipotriol	Vehicle
N	490	476	480	157
Success (%)	54 (11.0%)	31 (6.5%)	14 (2.9%)	1 (.6%)
p-value[1]		$p = .0172$	$p < .0001$	$p = .0001$

[1] p-value is based upon reviewer's analysis using CMH stratified by reviewer's definition of pooled center.

Protocol MCB-0003-INT does not list a formal statistical testing procedure for examining the secondary endpoint of the speed of controlled disease of Dovobet® as compared to each of its components and vehicle. As a result on the basis of the percent with controlled disease, Dovobet® was superior to each of its components and vehicle at the end of week 1 and end of week 2. However, since the protocol did not pre-specify a testing procedure for comparing Dovober® to each of its components and vehicle *across time*, it does not seem appropriate to include a graph such as Figure 3 in labeling of Dovober®.

3.1.6.2 Percent 'Treatment Success', Subject's Rating

The sponsor defines a treatment success when subjects rate their improvement of disease symptoms as 'marked improvement' or 'cleared' according to the Subject's Global Assessment of Disease Severity (refer to Table 5). The analysis based upon a CMH test stratifying by pooled center showed Dovobet® has a significantly higher proportion of treatment successes as its components and vehicle (all p-values < .0001). Results are provided in Table 17.

Table 17. Efficacy results for Percent with Treatment Success: Study MCB-0003-INT.

	Dovobet®	Betamethasone	Calcipotriol	Vehicle
N	490	476	480	157
Success (%)	316 (64.5%)	216 (45.4%)	137 (28.5%)	15 (9.6%)
p-value[1]		$p < .0001$	$p < .0001$	$p < .0001$

[1] p-value is based upon reviewer's analysis using CMH stratified by reviewer's definition of pooled center.
Source: Reviewer's analysis.

3.1.7 Efficacy Conclusion

In Study MCB-0003-INT consistent results were found on the basis of two endpoints

1. Percent with controlled disease by week 4 and
2. Percent reduction in PASI scores by week 4 from baseline PASI score.

Specifically, Study MCB-0003-INT showed Dovobet® to have the highest response rate followed by betamethasone, calcipotriol and then vehicle for BOTH endpoints.

3.1.7.1 Summary of Primary Endpoint Efficacy for Dovobet® (6 Studies)

The percent change in PASI scores shows how the clinical development of Dovobet® tended toward a once daily treatment regimen based upon efficacy. The other component, safety, will be explored in Section 3.2. Study MCB-9802-INT (Appendix Section A.3.2 on page 33) established that a twice daily regimen of Dovobet® was significantly better than each of its components and vehicle. Study MCB-9905-INT (Appendix Section A.3.1 on page 32) then established that a once daily regimen of Dovobet® was significantly better than calcipotriol BID and vehicle BID (but significantly inferior to Dovobet® BID). Then study MCB-0003-INT compared Dovobet® QD to each of its components and vehicle all with a single dosing. This study clearly established the superiority of Dovobet® over its components and vehicle (all p-values < .0001) on the basis of percent reduction in PASI scores at week 4. To further support the superiority of Dovobet®, the percent of subjects with controlled disease was also highly significant in the comparison of Dovobet® to each of its components and vehicle (all p-values < .0001). Thus, based upon the collective evidence, Study MCB-0003-INT has met its study objectives in establishing the superiority of Dovobet® QD over its components and vehicle.

The estimates of efficacy for Dovobet® from the pivotal trial combined with the two supportive placebo-controlled trials (Appendix Section A.3) and 3 active-controlled trials (Appendix Section A.4) are provided in Table 18 below. Note that all reported results are after 4 weeks of treatment and based on the ITT population imputing missing data with LOCF. Within dosing frequency results are quite consistent across each of the trials with the pivotal trial MCB-0003-INT showing slightly higher efficacy estimates than the other trials. Also based upon the percent change in PASI, the trials suggest only small efficacy gains are made by using a BID dosing frequency over a QD dose frequency.

Table 18. Summary of Efficacy for the Combination Drug in 6 Phase 3 Trials

Once Daily			
	N	**IGA**	**% Change PASI**
MCB-0001	249	NA (dynamic)	65.0%
MCB-0002	645	331 (51.3%)	68.7%
MCB-0003	490	276 (56.3%)	71.3%
MCB-9905	152	NA (dynamic)	67.7%
Twice Daily			
	N	**IGA**	**% Change PASI**
MVB-9802	307	NA (dynamic)	71.7%
MCB-9904	369	NA (dynamic)	74.4%
MCB-9905	237	NA (dynamic)	72.9%

3.2 Evaluation of Safety

The safety of Dovobet® along with its components and vehicle is analyzed in two sections. Section 3.2.1 examines the once daily dosing regimen which combines the safety information from Studies MCB-0003-INT and MCB-9905-INT. Section 3.2.2 combines the safety information from Studies MCB-9905-INT and MCB-9802-INT to examine the twice daily dosing regimens of the four treatment arms. The final section, Section 3.2.3 concludes the safety information provided in these three studies.

3.2.1 Once Daily Application Safety

The percent of subjects experiencing an adverse event in the Dovobet® treatment arm is similar to that of the betamethasone treatment arm and significantly smaller than the calcipotriol and vehicle treatment arms according to a CMH test. Number of AE's, percents and corresponding p-values in comparing Dovobet® to its components and vehicle are shown in Table 19. In the table a higher percentage of subjects experience AE's in the less efficacious treatment arms, calciopotriol and vehicle, than the more efficacious treatment arms, Dovobet® and betamethasone. To examine why more AE's occur in calcioptriol and vehicle, the AE's were summarized by the MedDRA system organ class.

Table 19. Adverse Experiences for Once Daily Application

	Dovobet® QD	Betamethasone QD	Calcipotriol QD	Vehicle QD	Total
N	642	476	480	157	1755
# with AE	158 (24.6%)	117 (24.6%)	157 (32.7%)	53 (33.8%)	485 (27.6%)
p-value[1]		$p = .9905$	$p = .0028$	$p = .0198$	

[1] p-value is based upon a CMH test for the 2x2 contingency table.
Source: Reviewer's analysis.

The safety profiles using the MedDRA system organ class classification broken down by treatment are listed in Table 20 on the following page. Note that subjects may have more than one system organ class classification AE as provided in the table. In the system of General disorders and administrative site conditions, both the calcipotriol and vehicle arms (shaded cells in Table 20) tend to have higher application site irritation factors such as burning and pruritus than Dovobet® and betamethasone. Similarly, in the skin and subcutaneous tissue disorders system, the discrepancies are mainly due to a larger percentage of subjects experiencing pruritus NOS in the calcipotriol and vehicle arms (shaded cells in Table 20). Dovobet® also has three subjects that are listed under investigations (shaded cells) whereas the other three treatment arms have zero subjects under this system. In these three cases; one subject had a pre-planned gastroscopy (ID: MCB0003_5732_IE004), and two subjects in Sweden for Study MCB-9905-INT had elevated blood calcium levels (ID: MCB9905_8677_SE005 and MCB9905_8695_SE096).

Table 20. Adverse Events by MedDRA System Organ Class Classification.

	Dovobet® (N = 642)		Betamethasone (N = 476)		Calcipotriol (N = 480)		Vehicle (N = 157)	
System	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**
Blood and lymphatic system disorders	1	0.2%	0	0.0%	0	0.0%	0	0.0%
Cardiac disorders	1	0.2%	2	0.4%	3	0.6%	1	0.6%
Ear and labyrinth disorders	0	0.0%	0	0.0%	2	0.4%	0	0.0%
Eye disorders	1	0.2%	3	0.6%	5	1.0%	0	0.0%
Gastrointestinal disorders	16	2.5%	18	3.8%	17	3.5%	8	5.1%
General disorders and administration site conditions	17	2.6%	7	1.5%	22	4.6%	13	8.3%
Immune system disorders	0	0.0%	1	0.2%	0	0.0%	0	0.0%
Infections and infestations	45	7.0%	43	9.0%	28	5.8%	11	7.0%
Injury and poisoning	4	0.6%	5	1.1%	7	1.5%	0	0.0%
Investigations	3	0.5%	0	0.0%	0	0.0%	0	0.0%
Metabolism and nutrition disorders	0	0.0%	1	0.2%	1	0.2%	0	0.0%
Musculoskeletal, connective tissue and bone disorders	18	2.8%	11	2.3%	8	1.7%	4	2.5%
Neoplasms benign and malignant (including cysts and polyps)	1	0.2%	0	0.0%	0	0.0%	0	0.0%
Nervous system disorders	26	4.0%	20	4.2%	25	5.2%	5	3.2%
Pregnancy, puerperium and perinatal conditions	0	0.0%	0	0.0%	1	0.2%	0	0.0%
Psychiatric disorders	2	0.3%	3	0.6%	5	1.0%	1	0.6%
Renal and urinary disorders	1	0.2%	2	0.4%	0	0.0%	0	0.0%
Reproductive system and breast disorders	2	0.3%	1	0.2%	1	0.2%	0	0.0%
Respiratory, thoracic and mediastinal disorders	8	1.2%	3	0.6%	10	2.1%	0	0.0%
Skin & subcutaneous tissue disorders	56	8.7%	26	5.5%	60	12.5%	22	14.0%
Surgical and medical procedures	1	0.2%	2	0.4%	2	0.4%	0	0.0%
Vascular disorders	2	0.3%	1	0.2%	0	0.0%	1	0.6%

Source: Reviewer's analysis.

3.2.1.1 Serious Adverse Events Once Daily

Thirteen subjects (.7% of all subjects) experienced a serious AE for those included in the once daily application safety population. Of these thirteen subjects, the sponsor reported that none of them appeared to be treatment related. One subject (ID: MCB0003_6279_CA136) did die from myocardial infarction, but this was also believed to be unrelated to treatment according to the sponsor. Listings of serious AE's are depicted in Table 21 on the following page.

Table 21. Reported Serious Adverse Events

ID	Dictionary Term	Treatment	Death	Reported Relatedness
MCB0003-5012-FR308	Cerebrovascular Disorder NOS	Betamethasone	No	Unlikely
MCB0003-5192-SE012	Chest Pain NEC	Calcipotriol	No	Unlikely
MCB0003-5236-CA040	Myocardial Infarction	Calcipotriol	No	Unlikely
MCB0003-5305-CA140	Operation NOS/Facial Bones Fracture	Betamethasone	No	Unlikely
MCB0003-5732-IE004	Pilonidal Abscess	Dovobet	No	Unlikely
MCB0003-5811-DE061	Appendicitis	Betamethasone	No	Unlikely
MCB0003-6037-UK531	Angina Pectoris	Vehicle	No	Unlikely
MCB0003-6279-CA136	Myocardial Infarction	Calcipotriol	Yes	Unlikely
MCB0003-6287-CA134	Myocardial Infarction	Betamethasone	No	Unlikely
MCB0003-6804-FR171	Cerebrovascular Disorder NOS	Calcipotriol	No	Unlikely
MCB0003-6971-ES027	Ileitis	Calcipotriol	No	Unlikely
MCB9905-8885-CA038	Dysphasia	Dovobet	No	Unlikely
MCB9905-9165-UK512	Mouth Ulceration	Dovobet	No	Unlikely

Source: Reviewer's Analysis

3.2.2 Twice Daily Application Safety

Comparing Dovobet® BID to each of its components and vehicle, all applied BID, in terms of the percent of subjects that experienced an AE, as with the once daily application, Dovobet® has a smaller percentage of AE's than calcipotriol and vehicle and a similar percentage as betamethasone. The number of subjects and the percent experiencing an AE are provided in Table 22.

Table 22. Adverse Events for Twice Daily Application

	Dovobet® BID	Betamethasone BID	Calcipotriol BID	Vehicle BID	Total
N	544	313	542	317	1716
# with AE	149 (27.4%)	90 (28.8%)	199 (36.7%)	104 (32.8%)	542 (31.6%)
p-value[1]		$p = .6682$	$p = .0009$	$p = .0925$	

[1] p-value is based upon a CMH test for the 2x2 contingency table.
Source: Reviewer's analysis.

As with the once daily application, both calcipotriol and vehicle tend to have a higher percentage of subjects classified to the general disorders and administration site conditions system and the skin and subcutaneous tissue disorders system (refer to the shaded cells in Table 23) than the Dovobet® and betamethasone treatment arms. Again, a large reason for the differences is in the percentage of subjects reporting AE's associated with pruritus. Listings of serious AE's for the twice daily application according to the MedDRA System Organ Class are provided in Table 23 on the following page.

3.2.2.1 Serious Adverse Events Twice Daily

Nine subjects (.5% of all subjects) experienced a serious adverse event when applying the drug product twice daily. The sponsor classified all of these serious adverse events as

unrelated to treatment. None resulted in death. Listings are provided in Table 24 on the following page.

Table 23. Adverse Events by MedDRA System Organ Class Classification.

	Dovobet® (N = 544)		Betamethasone (N = 313)		Calcipotriol (N = 542)		Vehicle (N = 317)	
System	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**
Blood and the lymphatic system	0	0.0%	0	0.0%	1	0.2%	0	0.0%
Cardiac disorders	0	0.0%	4	1.3%	2	0.4%	1	0.3%
Ear and labyrinth disorders	2	0.4%	2	0.6%	0	0.0%	1	0.3%
Eye disorders	0	0.0%	1	0.3%	4	0.7%	0	0.0%
Gastrointestinal disorders	16	2.9%	10	3.2%	13	2.4%	7	2.2%
General disorders and administration site conditions	8	1.5%	5	1.6%	18	3.3%	7	2.2%
Hepato-biliary disorders	0	0.0%	2	0.6%	1	0.2%	0	0.0%
Infections and infestations	23	4.2%	29	9.3%	41	7.6%	23	7.3%
Injury and poisoning	8	1.5%	4	1.3%	8	1.5%	0	0.0%
Investigations	1	0.2%	4	1.3%	0	0.0%	1	0.3%
Metabolism and nutrition disorders	4	0.7%	2	0.6%	2	0.4%	3	0.9%
Musculoskeletal, connective tissue and bone disorders	13	2.4%	7	2.2%	9	1.7%	8	2.5%
Neoplasms benign and malignant (including cysts and polyps)	0	0.0%	0	0.0%	2	0.4%	0	0.0%
Nervous system disorders	12	2.2%	0	0.0%	8	1.5%	14	4.4%
Neurological disorders	15	2.8%	15	4.8%	19	3.5%	5	1.6%
Psychiatric disorders	1	0.2%	1	0.3%	4	0.7%	2	0.6%
Reproductive system and breast disorders	2	0.4%	2	0.6%	0	0.0%	0	0.0%
Respiratory, thoracic and mediastinal disorders	1	0.2%	5	1.6%	9	1.7%	8	2.5%
Skin & subcutaneous tissue disorders	61	11.2%	31	9.9%	113	20.8%	49	15.5%
Surgical and medical procedures	1	0.2%	2	0.6%	0	0.0%	0	0.0%
Vascular disorders	2	0.4%	0	0.0%	3	0.6%	0	0.0%

Source: Reviewer's analysis.

3.2.3 Safety Conclusion

Comparing the safety profiles of the once daily application to the twice daily application, with the exception of the vehicle, the percentage of subjects experiencing an AE is decreased when the application is once daily. Neither the twice daily nor the once daily application resulted in serious AE's according to the sponsor's submission. Thus, because of the reduced rate of AE's in the once daily application, the safety profile of Dovobet® QD appears to be better tolerated than Dovobet® BID.

Table 24. Reported Serious Adverse Events

ID	Dictionary Term	Treatment	Death	Reported Relatedness
MCB9802-4227-CA125	Rib Fracture	Calcipotriol	No	Unlikely
MCB9802-4950-IE004	Infection NOS	Calcipotriol	No	Unlikely
MCB9905-8376-NL003	Oral Cavity Cancer	Calcipotriol	No	Unlikely
MCB9905-8100-FR014	Arthralgia	Dovobet	No	Unlikely
MCB9905-8303-UK159	Cholecystectomy	Dovobet	No	Unlikely
MCB9905-8608-UK512	Intestinal Obstruction NOS	Dovobet	No	Unlikely
MCB9905-8105-FR014	Depression	Vehicle	No	Unlikely
MCB9905-8940-FI051	Tachycardia NOS	Vehicle	No	Unlikely
MCB9905-8968-FI034	Deafness NOS	Vehicle	No	Unlikely

Source: Reviewer's Analysis

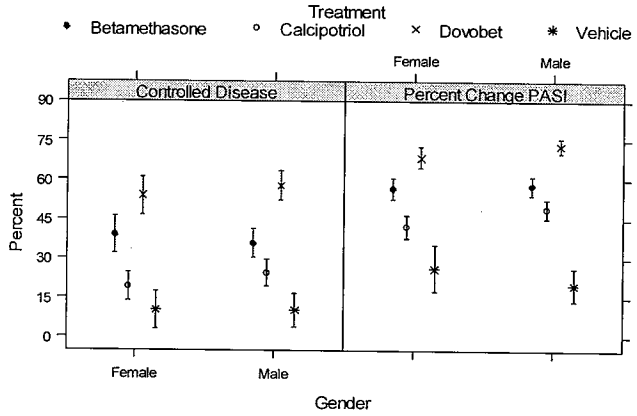
4 Findings in Special/Subgroup Populations

Efficacy results across subgroups is performed for Study MCB-0003-INT only as this study is the only one to use an endpoint based upon an Investigator Global Assessment and includes the proposed to be marketed once daily application. Results are presented in both the percent change in PASI and percent controlled disease. Note that positive scores in the percent change in PASI imply improvement in the PASI score. The results are presented as figures for gender, race and age with tables included in the Appendix Section A.2 on page 31. The error bars in the figures correspond to upper and lower 95% confidence bounds for the point estimate.

4.1 Gender, Race, and Age

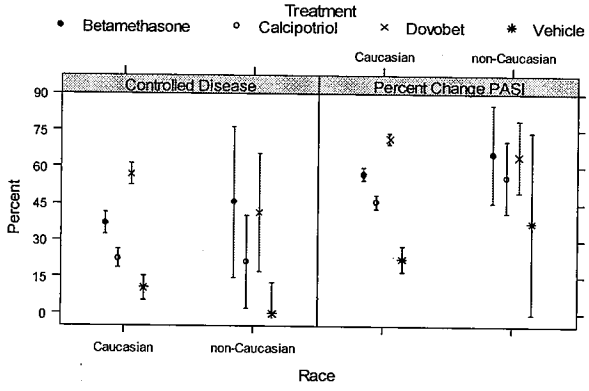
Figure 4 on the following page depicts the efficacy results for percent with controlled disease and percent change in PASI (positive implies improvement). This figure shows that females and males tended to have very similar response rates for controlled disease and percent change in PASI for all treatment arms.

Figure 4. Efficacy results for each Gender



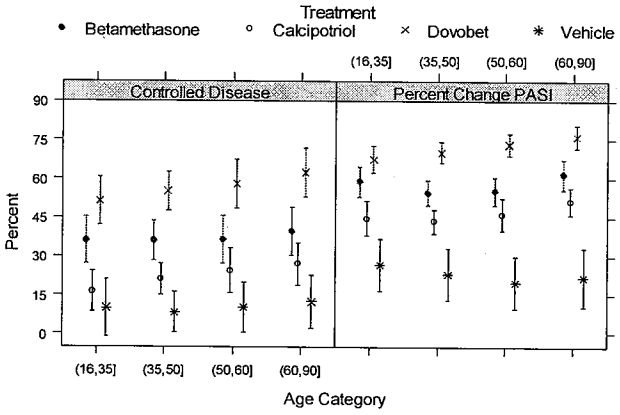
Race is broken down into two groups: Caucasian and Non-Caucasian as at least 96% of subjects within a treatment arm are classified as Caucasian. The Non-Caucasian group is composed of Black, Asian and Other subjects of which the overall percent representation is small in number. Thus, this group is combined to form the Non-Caucasian group. Figure 5 shows the results for each of the two race subgroups. Overall, efficacy is consistent across racial subgroups.

Figure 5. Efficacy Results for each Race



Age is broken into four categories and these were defined to mimic the categories the sponsor provided in its MCB-0003-INT Study Report. The categories are: 35 and younger (17 is the minimum enrolled subject age), 36 to 50, 51 to 60, and older than 61 (90 is the oldest enrolled subject). Figure 6 depicts results across the age subgroups. This figure shows that efficacy trends are very consistent across the different age categories.

Figure 6. Efficacy Results for each Age Category



4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

The sponsor's submission contained one large pivotal Phase 3 trial that established the superiority of Dovobet® to each of its components and vehicle based upon IGA (and also PASI score). In addition, 5 supportive trials showed consistent estimates of efficacy for Dovobet® providing further support for the superiority claim. The Agency comments to the sponsor regarding the protocol for Study MCB-0003-INT were not all incorporated into the protocol and hence the sponsor's analysis of efficacy differed from that typically requested by the Agency. However, regardless of the analysis method, efficacy conclusions remained unchanged.

Study MCB-0003-INT established the superiority of Dovobet® to each of its components and vehicle. Results for IGA and PASI scores (although this endpoint is not considered to be primary) for the pivotal trial are provided in Table 25.

Table 25. Efficacy Results for the ITT population (Study MCB-0003-INT)

	Dovobet®	Betamethasone	Calcipotriol	Vehicle
N	490	476	480	157
Controlled Disease				
Success (%) p-value[1]	276 (56.3%)	176 (37.0%) $p < .0001$	107 (22.3%) $p < .0001$	16 (10.2%) $p < .0001$
Percent Change PASI				
Mean (SD) p-value[2]	71.3% (25.7%)	57.2% (29.8%) $p < .0001$	46.1% (30.9%) $p < .0001$	22.7% (33.5%) $p < .0001$

[1] p-value is based upon reviewer's analysis using CMH stratified by reviewer's definition of pooled center.

[2] p-value is based upon reviewer's analysis using ANOVA with design variables for treatment and reviewer's definition of pooled center.

Also in Study MCB-9905-INT the once daily application of Dovobet® was superior to twice daily applications of Calcipotriol (p=.0005) and vehicle ($p < .0001$) for percent reduction in PASI scores. Further, based on percent reduction in PASI scores twice daily application of Dovobet® was superior to each of its components, applied twice daily in Study MCB-9802-INT (p-values below .0001) and MCB-9904-INT (p-values below .0001) after 4 weeks of treatment. The active-controlled trials included in the Appendix Section A.4 on page 35 also provide estimates of IGA and/or PASI scores which are consistent with those found in the pivotal trial. Thus, the collective evidence supports the claim that Dovobet® is superior to each of its components and vehicle.

The safety of Dovobet® was assessed for both the once and twice daily applications for the three placebo-controlled studies. Dovobet® had a similar AE rate as betamethasone and these were lower than the AE rates for calcipotriol and vehicle. The reason for the difference was in large part due to the increased rate of subjects reporting of pruritus in the calcipotriol and vehicle arms. A total of 22 subjects had serious adverse events out of 3471 subjects, none of which were reported by the study investigator as being related to study drug.

5.2 Conclusions and Recommendations

The efficacy analysis of the single pivotal Phase 3 trial showed Dovobet® Ointment is statistically superior to each of its components and vehicle in the treatment of psoriasis vulgaris. In addition, efficacy claims were supported by 5 additional trials. The pivotal trial relied on the percent of IGA successes, whereas the supporting studies relied on percent reduction in PASI scores. The former is considered by the Agency to be primary and the latter is typically not used for regulatory utility. As the pivotal study showed significant efficacy findings for both IGA and PASI scores, efficacy results from the other studies which used PASI scores only were used as supportive.

Thus, from a statistical perspective, the collective evidence establishes the superiority of Dovobet® Ointment over each of its components and vehicle.

Appendix

A.1 Baseline Demographic Characteristics

Table A.1.1: Demographic Characteristics for MCB-0003-INT

	Dovobet®	Betamethasone	Calcipotriol	Vehicle	p-value[1]
Number of Subjects	490	476	480	157	
Age					
Mean (SD)	47.6 (14.4)	48.2 (15.0)	48.9 (14.7)	49.8 (14.4)	.2939
Gender					
Male	62.9%%	61.1%	59.0%	56.0%	.3920
Female	37.1%	38.9%	41.0%	44.0%	
Race					
African-American	.61%	.21%	1.04%	0%	.4863
Asian	2.24%	1.68%	2.71%	1.27%	
Caucasian	96.53%	97.69%	96.04%	97.45%	
Other	.61%	.42%	.21%	1.27%	

[1] p-values are based upon a Kruskal-Wallis test for continuous variables and a Chi-square test for categorical variables.
Source: Tab 5.3.5.1.1 MCB 0003 INT Study Report, page 9.

A.2 Efficacy Results by Subgroup (MCB-0003-INT)

These tables contain efficacy results by subgroup. Values within the tables correspond to mean (SD).

Table A.2.1. Efficacy Results by Gender

	Dovobet®	Betamethasone	Calcipotriol	Vehicle
Percent Controlled Disease				
Female	53.8% (50.0%)	38.9% (48.9%)	19.3% (39.6%)	10.1% (30.4%)
Male	57.8% (49.5%)	35.7% (48.0%)	24.4% (43.0%)	10.2% (30.5%)
Percent Reduction PASI				
Female	68.4% (27.6%)	56.4% (28.8%)	41.9% (31.3%)	26.2% (37.5%)
Male	73.1% (24.4%)	57.7% (30.5%)	49.0% (30.3%)	20.0% (30.0%)

Table A.2.2. Efficacy Results by Race

	Dovobet®	Betamethasone	Calcipotriol	Vehicle
Percent Controlled Disease				
Caucasian	56.9% (48.3%)	36.8% (41.7%)	22.3% (49.6%)	10.5% (30.7%)
Non-Caucasian	41.2% (52.2%)	45.5% (41.9%)	21.1% (50.7%)	0.0% (0.0%)
Percent Reduction PASI				
Caucasian	57.0% (29.7%)	45.7% (30.8%)	71.6% (25.5%)	22.3% (33.4%)
Non-Caucasian	65.5% (34.0%)	55.9% (32.8%)	64.4% (30.9%)	37.1% (38.0%)

Table A.2.3. Efficacy Results by Age Category

	Dovobet®	Betamethasone	Calcipotriol	Vehicle
Percent Controlled Disease				
(0, 35]	51.3% (50.2%)	36.2% (48.3%)	16.5% (37.3%)	10.0% (30.5%)
(35, 50]	55.1% (49.9%)	36.1% (48.2%)	21.1% (40.9%)	8.3% (27.9%)
(50, 60]	57.9% (49.6%)	36.4% (48.4%)	24.5% (43.2%)	10.3% (30.7%)
(60, 90]	62.4% (48.7%)	39.4% (49.1%)	27.0% (44.6%)	12.5% (33.5%)
Percent Reduction PASI				
(0, 35]	67.2% (28.3%)	58.8% (30.2%)	44.6% (31.9%)	26.7% (28.6%)
(35, 50]	70.0% (26.5%)	54.4% (29.8%)	43.6% (31.3%)	23.1% (35.4%)
(50, 60]	73.2% (23.1%)	55.2% (28.6%)	46.2% (31.7%)	19.9% (32.1%)
(60, 90]	76.2% (23.3%)	61.6% (30.4%)	51.2% (28.4%)	21.9% (36.7%)

A.3 Placebo-Controlled Results

As the Division did not have the opportunity to comment on the design of the supportive studies, the pooling strategy described for the Study MCB-0003-INT is also incorporated into the analysis of Studies MCB-9802-INT and MCB-9905-INT.

A.3.1 Study MCB-9905-INT

Title:
Calcipotriol/Betamethasone Once and Twice Daily in Psoriasis Vulgaris

Treatment Groups:
The Sponsor describes this as an international, multi-center, prospective, randomized, double-blind, four arm parallel group study.

1. Dovobet® once daily
2. Dovobet® twice daily
3. Dovonex® (active calcipotriol) twice daily
4. Vehicle twice daily.

Main Inclusion/Exclusion Criteria:
Baseline PASI score for extent of at least 2, i.e., psoriasis affecting at least 10% of arms, trunk, or legs.

Study Design:
At 57 centers in France, Canada, Denmark, Great Britain, Netherlands, Spain, Sweden and Finland 152 subjects were assigned to Dovobet® QD, 237 to Dovobet® BID, 231 to Calcipotriol BID and 208 to vehicle. Subjects are assessed at baseline and after 1, 2 and 4 weeks. All patients randomized were included in the intent to treat population.

Dates of Study:
18 January 2000 - 02 August 2000
Final Protocol Draft: 08 November 1999

Endpoints:
1. Percent Change in PASI score (Refer to Section 3.1.1)

Method of Analysis:
ANOVA including terms for treatment and pooled site

Results:
Using Dovobet® QD as the treatment to compare to the other treatment arms, Dovobet® QD is significantly better than calcipotriol BID and vehicle BID according to the percent change in PASI scores, results shown in Table A.3.1.1. However, the twice daily application of Dovobet® is significantly better than the once daily application. Note that the percent change between these two applications only differs by about 5 percent. The point estimates of percent reduction in Study MCB-0003-INT and MCB-9905-INT for Dovobet® QD are quite similar, 71.3% and 67.7%, respectively implying that Study MCB-9905-INT supports the PASI score claims found in MCB-0003-INT.

Table A.3.1.1 Efficacy Results for Percent Reduction in PASI: Study MCB-9905-INT.

	Dovobet® QD	Dovobet® BID	Calcipotriol BID	Vehicle BID
N	152	237	231	208
Mean (SD)	67.7% (24.7%)	72.9% (22.4%)	57.7% (29.4%)	26.4% (31.2%)
p-value[1]		$p = .0208$[2]	$p = .0005$	$p < .0001$

[1] p-value is based upon reviewer's analysis using ANOVA with design variables for treatment and reviewer's definition of pooled center (this is defined as in Study MCB-0003-INT).
[2] Dovobet® BID is significantly better than Dovobet® QD.

A.3.2 Study MCB-9802-INT

Title:
Calcipotriol/Betamethasone Twice Daily in Psoriasis Vulgaris

Treatment Groups:
The Sponsor describes this as an international, multi-center, randomized, double-blind, four arm parallel group study.

1. Dovobet® twice daily
2. Betamethasone twice daily
3. Calcipotriol twice daily
4. Vehicle twice daily.

Main Inclusion/Exclusion Criteria:
Baseline PASI score for extent of at least 2, i.e., psoriasis affecting at least 10% of arms, trunk, or legs.

Study Design:
At 75 centers in Belgium, Canada, Denmark, Finland, France, Germany, Ireland, Netherlands, Norway, Sweden, Switzerland and United Kingdom recruiting 307 subjects assigned to Dovobet® BID, 313 assigned to Betamethasone BID, 311 to Calcipotriol BID and 109 to vehicle. Subjects are assessed at baseline and after 1, 2 and 4 weeks. All patients randomized were included in the intent to treat population.

Dates of Study:
25 February 1999 – 29 July 1999
Final Protocol Draft: 17 November 1998

Endpoints:
1. Percent Change in PASI score (Refer to Section 3.1.1)

Method of Analysis:
ANOVA including terms for treatment and pooled site

Results:
In Study MCB-9802-INT all treatment arms use twice daily dosing regimens. The objective of this trial was to establish the superiority of Dovobet® BID over each of its components and vehicle. Based upon the percent reduction in PASI score, Dovobet® BID was significantly superior to each of its components and vehicle (results shown in Table A.3.1.2).

Table A.3.1.2 Efficacy Results for Percent Reduction in PASI: Study MCB-9802-INT.

	Dovobet® BID	Betamethasone BID	Calcipotriol BID	Vehicle BID
N	307	313	311	109
Mean (SD)	71.7% (27.0%)	62.9% (26.8%)	48.3% (32.2%)	28.2% (30.7%)
p-value[1]		$p < .0001$	$p < .0001$	$p < .0001$

[1] p-value is based upon reviewer's analysis using ANOVA with design variables for treatment and reviewer's definition of pooled center (this is defined as in Study MCB-0003-INT).

A.3.3 Limitations of Studies MCB-9905-INT and MCB-9802-INT

In the previous section, using results from Studies MCB-9905-INT and MCB-9802-INT to support the efficacy claim of Study MCB-0003-INT, it was concluded that Dovobet® QD was significantly better than each of its components and vehicle. As with the protocol for Study MCB-0003-INT, the Division did not have an opportunity to comment on the Phase 3 protocols used in Studies MCB-9905-INT and MCB-9802-INT. As a result, several deficiencies in these studies may inhibit their regulatory utility, but because the Division is first made aware of these deficiencies after completion of the studies, any conclusions reached are based upon post hoc analyses. As with Study MCB-0003-INT, the two Studies MCB-9905-INT and MCB-9802-INT use many centers with very few recruiting at least eight subjects per treatment arm. The remedy for this situation was to pool centers as was described in Section 3.1.3 for Study MCB-0003-INT.

More importantly, the randomization of these two studies does not appear to be well preserved. In Study MCB-9905-INT subjects were to be randomized in a 2:2:2:1 fashion (Dovobet® QD, Dovobet® BID, Calcipotriol BID, and Vehicle) according to the protocol. However, if you look at the actual number of subjects enrolled 152, 237, 231 and 208, this does not appear to be the case. The protocol also stated that randomization was to be carried out within center, yet many centers failed to recruit a single patient in one or more treatment arms yet recruited up to eight subjects for one of the arms. For

example, in a site in Spain (defined as site ES023), eight subjects were assigned to Dovobet® BID, four subjects to calcipotriol BID, eight subjects to vehicle, and zero subjects to Dovobet® QD.

In a similar manner, the randomization of Study MCB-9802-INT also does not appear to be preserved. The protocol for this study states that subjects will be assigned to calcipotriol BID, betamethasone BID, Dovobet® BID and vehicle BID in a 3:3:3:1 fashion. The randomization was also to be carried out within center. The actual recruitment within many centers showed one of the treatment arms to have zero enrolled subjects while the other arms had 4 or more subjects.

The impact on efficacy claims of not following the randomization scheme is not discernable based upon the submitted data to the NDA. A general conclusion for these two studies is that as stand alone studies they do not warrant regulatory utility as the randomization does not appear to be preserved and the primary endpoint is not agreed upon with the Division. However, if these Phase 3 trials are regarded as Phase 2 type trials, they do provide supportive evidence in the selection of the Dovobet® QD dose and its superiority over each of its components and vehicle in terms of efficacy. The next section explores if the choice of a once daily treatment regimen of Dovobet® provides an increased safety profile over a twice daily treatment regimen.

A.4 Active-Controlled Study Results

The following analyses apply to the active control studies provided by the Sponsor. The following might be noted:

i. For convenience the Intent-to-Treat (ITT) population used was that defined by the sponsor. Thus in Study MCB-9904 the sponsor used a different definition of the ITT population than was used in the other studies.
ii. Further, for the statistical analysis, in studies MCB-0001, MCB-0002, and MCB-9904 it was felt that the pooling of centers provided by the sponsor was insufficient and still resulted in a number of small pooled centers. Hence further centers were pooled. All pooling was conducted within country with the objective of generally having 8 or more subjects per arm per pooled center. This would not change means but would have an effect on reported significance levels in the analyses.
iii. Also note that except for studies MCB-0002 *and* MCB-0102 the Sponsor's definition of the investigator global assessment (IGA) was dynamic and used only post-baseline data. The PASI only required baseline data. Thus we would expect the data set using LOCF would be larger for the PASI scores than for the dynamic IGA. This seems to be the reason for the small discrepancies in the numbers of patients used in the analyses. In Study MCB-9904 the data sets have include scores for four more patients using the dynamic change from baseline in the investigator and patient evaluations than have computed PASI scores. This discrepancy also appears in the Sponsor's analysis without comment. Note four cases out a 1000 should have no impact on conclusions, but should be noted.

A.4.1 Study MCB-0001-INT

Title:
Calcipotriol/betamethasone Once Daily versus Tacalcitol Once Daily in Psoriasis Vulgaris

Treatment Groups:
The Sponsor describes that as a mult-icenter, prospective, double-blind, parallel group, eight week, Phase 3b study comparing two treatment regimens in psoriasis vulgaris:

1. Combination ointment of calcipotriol 50μg/g plus betamethasone dipropionate 0.50mg/g once daily for 4 weeks followed by calcipotriol ointment 50μg/g once daily for 4 weeks with,
2. Tacalcitol ointment 4μg/g once daily for 8 weeks.

Main Inclusion/Exclusion Criteria:

1. The entry criteria require a clinical diagnosis of psoriasis amenable to treatment with a maximum of 50g of medication per week,
2. Baseline PASI score for extent of at least 2, i.e., psoriasis affecting at least 10% of arms, trunk, or legs.

Study Design:
At 39 centers in France, Germany, Spain, and the United Kingdom 249 patients were randomized to the combination followed by calcipotriol and 252 patients to Tacalcitol. Patients are assessed at baseline and after 2, 4, 6, and 8 weeks. The week 6 and 8 evaluations were only conducted on patients who did not clear by week 4 and did not withdraw from the study. All patients randomized were included in the intent to treat population. Note the sponsor describes this study as incorporating a pharmacoeconomic evaluation, however this aspect is ignored here. The Intent-to-Treat (ITT) population consisted of all patients randomized and dispensed treatment.

Dates of Study:
19 September 2001 - 28 January 2002
Final Protocol Draft: 23 April 2001

Endpoints:
1. PASI score (Refer to Section 3.1.1)

2. Investigator's/Patient's Overall Efficacy Assessment

Scale	Description
Worse	Psoriasis is worse than at baseline evaluation, in severity and/or extent
Unchanged	Psoriasis has not changed
Slight improvement	Some definite improvement (overall about 25%), however significant signs of psoriasis remain
Moderate improvement	Definite improvement (overall about 50%)
Marked improvement	Very definite improvement (overall about 75%), some evidence of psoriasis remains, further treatment required
Clearance	No or very minor evidence of psoriasis remains, no treatment required

3. Primary Endpoint:
Percentage reduction in PASI score from baseline to up to four weeks. Not that this endpoint was not defined at a fixed time point.

4. Secondary Endpoints:
   i. Percentage change in PASI to the end of treatment up to 8 weeks,
   ii. Percentage change in PASI to week 2,
   iii. Percentage of investigator/patient scores showing at least "marked improvement" (these are defined as "responders"),
   iv. Amount of study medication used.

Methods of Analysis:
1. Primary endpoint:
ANOVA with treatment and center as factors.

2. Secondary endpoints:
ANOVA as above and CMH responders versus nonresponders.

Results:
As shown in the following table, week 4 differences in the primary endpoint in the ITT-LOCF population are statistically significant ($p < 0.0001$).

Note that other test results using this endpoint are for rough guidance only.

Table A.4.1.1 Percent Change from Baseline and Change from Baseline

	Week 0[1]	Week 2	Week 2 ITT-LOCF	Week 4	Week 4* ITT-LOCF
%Chng Comb (SD)[2]		-50.5 (26.1)	-48.6 (27.3)	-66.7 (27.8)	-65.0 (29.1)
Tacal (SD)[2]		-24.5 (27.3)	-23.9 (27.2)	-35.0 (40.1)	-33.3 (39.4)
Diff (SE)[3]		-25.7 (2.3)	-24.3 (2.3)	-30.7 (3.1)	-31.5 (3.0)
Test of diff[4]				< 0.0001	< 0.0001
Change Comb (SD)	9.7 (6.1)	-4.8 (3.9)	-4.7 (3.9)	-6.4 (4.7)	-6.2 (4.7)
Tacal (SD)	9.9 (6.0)	-2.4 (2.9)	-2.3 (2.9)	-3.4 (4.4)	-3.2 (4.3)
Diff (SE)	-0.2 (0.5)	-2.4 (0.3)	-2.3 (0.3)	-2.8 (0.4)	-2.9 (0.4)
Test of diff				< 0.0001	< 0.0001

*- Percent change at Week 4 in ITT-LOCF population is primary endpoint.
[1]- Week 0 nominal change values correspond to baseline PASI score.
[2]- SD denotes simple standard deviation of treatment PASI score
[3]- SE denotes standard error of difference adjusted for sites.
[4]– Test of treatment differences adjusted for sites.

	Week 6	Week 8 ITT-LOCF
%Chng Comb (SD)	-61.1 (33.1)	-59.0 (38.7)
Tacal (SD)	-40.6 (40.1)	-38.4 (46.4)
Diff (SE)	-20.0 (3.4)	-20.4 (3.7)
Test of diff		< 0.0001
Change Comb (SD)	-5.9 (5.0)	-5.4 (5.2)
Tacal (SD)	-3.9 (4.7)	-3.9 (5.1)
Diff (SE)	-1.8 (0.4)	-1.5 (0.4)
Test of diff		0.0004

Thus at week 4, the differences between the Combination product and the Tacalcitol ointment, using both the percent change from baseline (as per protocol) and the actual change, were statistically significant (both $p < 0.0001$). Note that the percentage change in PASI scores to the end of treatment up to 8 weeks and the percentage change in PASI scores to week 2 were secondary endpoints, and both showed statistically significant differences ($p \leq 0.0004$ and $p < 0.0001$, respectively).

Note that the Clin/Stat team has some question about the regulatory utility of the PASI scores. However, it was felt that a PASI score of 0 was clinically interpretable. The following table shows the incidence of subjects with zero scores, plus the significance level of the corresponding chi-square test of homogeneity in proportions.

Table A.4.1.2 Proportions of Patients with PASI score = 0

PASI =0 # resp/N (%)	Week 2[1]	Week 4	Week 4 ITT-LOCF	Week 6	Week 8 ITT-LOCF
Combination	0/240	10/238 (4.2%)	10/249 (4.0%)	4/222 (1.8%)	23/249 (9.2%)
Tacal	0/246	3/236 (1.3%)	3/252 (1.2%)	0/210	4/252 (1.6%)
Test of differences			0.0353		<0.0001

Note this is a post hoc analysis and the study was not powered for this endpoint. Since success proportions are so low, CMH tests are not appropriate, i.e. a center with zero successes in both treatment groups would not be counted in the computation of the test statistic. Also, non-stratified chi-square tests were used to test homogeneity in the proportion of PASI scores equal to zero. Because the PASI score is at least partly subjective one might expect positive within center correlation of these scores. Then the actual scores will have some degree of over dispersion, and thus the simple chi-square tests used above are likely to be to some extent anti-conservative. However, they may still be indicative.

It may also be relevant to see the proportion of the cases where the PASI is small:

Table A.4.1.3 Proportions of Patients with PASI score ≤ 1

PASI =0 # resp/N (%)	Week 2[1]	Week 4	Week 4 ITT-LOCF	Week 6	Week 8 ITT-LOCF
Combination	24/240 (10.0%)	60/238 (25.2%)	61/249 (24.5%)	57/222 (25.7%)	75/249 (30.1%)
Tacal	8/246 (3.3%)	23/236 (9.7%)	23/252 (9.1%)	19/210 (9.0%)	36/252 (14.3%)

Note the combination drug is uniformly superior to Tacalcitol ointment at each endpoint. However the exact meaning of a PASI score between 0 and 1 is not clear. Note the primary endpoint is at Week 4.

Two other secondary endpoints are the percentages of investigator and patient "responder" scores (i.e. scored as at least "marked improvement" on the overall efficacy assessment).

Table A.4.1.4 Investigator Overall Assessments Responders versus Non-Responders

Invest. Assessment # resp/N (%)	Week 2[1]	Week 4	Week 4 ITT-LOCF	Week 6	Week 8 ITT-LOCF
Combination	94/240 (39.2%)	139/238 (58.4%)	141/245 (57.6%)	123/222 (55.4%)	125/246 (50.8%)
Tacal	17/246 (6.9%)	42/236 (17.8%)	42/247 (17.0%)	46/210 (21.9%)	58/247 (23.5%)
Test of differences			< 0.0001		< 0.0001

Again, note the numbers of patients differ slightly from those in the PASI scores since these evaluations require a second visit. The tests of differences are CMH tests stratifying on pooled investigator/center.

Table A.4.1.5 Patient Overall Assessments Responders versus Non-Responders

Invest. Assessment # resp/N (%)	Week 2[1]	Week 4	Week 4 ITT-LOCF	Week 6	Week 8 ITT-LOCF
Combination	102/240 (42.5%)	141/238 (59.2%)	143/245 (58.4%)	129/222 (58.1%)	129/246 (52.4%)
Tacal	21/246 (8.5%)	43/236 (18.2%)	43/247 (17.4%)	47/210 (22.4%)	67/247 (27.1%)
Test of differences			< 0.0001		< 0.0001

Thus Week 4 differences in both of these secondary endpoints in the ITT-LOCF population were statistically highly significant ($p < 0.0001$).

The protocol specified analyses in this study showed statistically significant differences between the combination ointment of calcipotriol 50µg/g plus betamethasone dipropionate 0.50mg/g once daily for 4 weeks was statistically significantly better than Tacalcitol ointment 4µg/g once daily for 4 weeks (all $p < 0.0001$). The differences at the end of the second 4 weeks between calcipotriol ointment 50µg/g and Tacalcitol ointment 4µg/g used once daily for the second 4 weeks remained statistically significant ($p < 0.0001$).

A.4.2 Study MCB-0002-INT

Title:
Different Treatment Regimes with Calcipotriol/betamethasone Ointment and Calcipotriol Ointment in Psoriasis Vulgaris

Treatment Groups:
The sponsor describes this as a multi-center, prospective, partly double-blind, three arm, parallel group, Phase 3 study comparing three treatments for psoriasis vulgaris:

1. Calcipotriol ointment applied twice daily for up to 12 weeks or clearing,
2. Calcipotriol/betamethasone ointment applied once daily for up to 8 weeks followed by calcipotriol ointment applied once daily for up to 4 weeks, and
3. Calcipotriol/betamethasone ointment applied once daily for up to 4 weeks followed by calcipotriol ointment applied once daily on weekdays (5 days) and

calcipotriol/ betamethasone ointment applied once daily on weekends (two days) all for up to 8 weeks.

Note that at Week 4, the primary comparison endpoint for this application, both combination groups, i.e. the two calcipotriol/betamethasone ointment treatment groups is establishing equivalence. Then any differences between them at this time point should be only due to randomization.

Main Inclusion/Exclusion Criteria:

1. The entry criteria require a baseline PASI score for extent of at least 2, i.e., affecting at least 10% of arms, trunk, or legs,
2. Investigators global assessment of severity of at least mild.

Study Design:

At 62 centers in Canada, Denmark, Finland, France, Germany, Norway, Spain, Sweden, and the United Kingdom 322, 323, and 327 patients were randomized (1:1:1) to the treatment groups1., 2., and 3. above. Evaluations are to be conducted at baseline, and weeks 1, 2, 4, 5, 8, and 12 weeks. The ITT population consisted of all patients randomized and dispensed treatment.

Study Dates:

6 February 2001 - 26 August 2001.
Final Protocol Draft: 15 November 2000

Endpoints:

1. PASI score (see description in section 3.1.1 in the main body of report)
2. Investigator's global assessment (IGA) of disease severity

Investigator's Global Assessment of Disease Severity

Scale	Description
Absence of Disease	The disease is controlled. No evidence of redness, no evidence of infiltration, and no evidence of scaling.
Very Mild Disease	The disease is controlled, but not entirely cleared. The overall clinical picture is consisting of lesions with some discoloration with absolutely discrete infiltration.
Mild Disease	The overall clinical picture is consisting of lesions with light red coloration, a slight infiltration, and a fine, thin scale layer.
Moderate Disease	The overall clinical picture is consisting of lesions with red coloration, a moderate infiltration, and a moderate, somewhat coarse scale layer.
Severe Disease	The overall clinical picture is consisting of lesions with very red coloration, thick infiltration, and a severe, coarse thick scale layer.
Very Severe Disease	The overall clinical picture is consisting of lesions with extreme deep red coloration, very thick infiltration and very severe, coarse thick scale layer.

3. Patient's overall efficacy assessment

Patient's Overall Efficacy Assessment

Scale	Description
Worse	Psoriasis is worse than at baseline evaluation, in severity and/or extent
Unchanged	Psoriasis has not changed
Slight improvement	Some definite improvement (overall about 25%), however significant signs of psoriasis remain
Moderate improvement	Definite improvement (overall about 50%)
Marked improvement	Very definite improvement (overall about 75%), some evidence of psoriasis remains, further treatment required
Clearance	No or very minor evidence of psoriasis remains, no treatment required

4. Primary endpoints:
   i. Percentage reduction in PASI score from baseline to the end of treatment eight weeks.
   ii. Proportion with controlled disease at week 8 (defined as a score on IGA of very mild disease or absence).

5. Secondary endpoints:
   i. Percentage and absolute change in PASI score to the end of treatment up to 8 weeks.
   ii. Change in severity scores for extent, redness, thickness and scaliness from baseline to each subsequent visit and to the end of treatment.
   iii. Proportion of patients with controlled disease (from IGA) at each visit and to the end of treatment.
   iv. Distribution of IGA at each visit and to the end of treatment.
   v. The percentage of patient overall efficacy scores showing at least "marked improvement" (these defined "responders").
   vi. Distribution of patient overall efficacy scores at each visit and to the end of treatment.

Methods of Analysis:

1. Primary endpoints:
   i. PASI score ANOVA with treatment and center as factors. Contrasts with calcipotriol.
   ii. CMH for controlled disease or not
2. Secondary endpoints :
   Analyzed descriptively.

Efficacy Results:

Note most results are given both for Week 4 and the protocol specified Week 8. The table on the following page displays the PASI score results.

Table A.4.2.1 Percent Change from Baseline and Change from Baseline

Mean (SD)	Treatment	Week 0[1]	Week 2	Week 4	Week 4* ITT-LOCF
% Change	Calc BID 12 wks		-45.7 (23.2)	-57.2 (24.0)	-55.0 (25.7)
	Comb QD 4 wks		-58.1 (23.4)	-68.7 (23.6)	-67.6 (24.7)
	Comb QD 8 wks		-58.2 (21.8)	-70.3 (21.2)	-69.8 (21.8)
	Calc – Comb 4wks p-value		12.1 (1.7) < 0.0001	11.3 (1.7) < 0.0001	12.4 (1.7) < 0.0001
	Calc – Comb 8wks p-value		12.3 (1.7) < 0.0001	13.0 (1.7) < 0.0001	14.6 (1.7) < 0.0001
Change	Calc BID 12wks	10.3 (5.8)	-5.0 (3.8)	-6.3 (4.6)	-6.2 (4.7)
	Comb QD 4wks	10.4 (5.9)	-6.1 (4.1)	-7.2 (4.5)	-7.1 (4.8)
	Comb QD 8wks	10.3 (5.6)	-5.9 (3.6)	-7.2 (4.7)	-7.2 (4.5)
	Calc – Comb 4wks p-value	0.53 (0.42) 0.2060	1.01 (0.28) 0.0003	0.77 (0.34) 0.0237	0.94 (0.34) 0.0053
	Calc – Comb 8wks p-value	0.61 (0.42) 0.1536	0.88 (0.28) 0.0014	0.83 (0.34) 0.0145	1.10 (0.33) 0.0011

Mean (SD)	Treatment	Week 8	Week 8 ITT-LOCF	Week 12 ITT-LOCF
% Change	Calc BID 12wks	-68.0 (27.9)	-64.1 (30.7)	-65.9 (33.1)
	Comb QD 4wks	-69.6 (24.9)	-68.2 (26.1)	-69.0 (28.5)
	Comb QD 8wks	-74.4 (22.6)	-73.3 (23.8)	-64.6 (21.8)
	Calc – Comb 4wks p-value	1.27 (1.94) 0.5124	4.12 (2.00) 0.0398	3.17 (2.35) 0.1763
	Calc – Comb 8wks p-value	6.31 (1.94) 0.0012	9.17 (2.00) < 0.0001	-1.22 (2.35) 0.6012
Change	Calc BID 12wks	-7.7 (5.5)	-7.2 (5.5)	-7.4 (5.8)
	Comb QD 4wks	-7.4 (5.0)	-7.2 (5.0)	-7.2 (5.0)
	Comb QD 8wks	-7.7 (5.0)	-7.7 (5.0)	-6.7 (5.3)
	Calc – Comb 4wks p-value	-0.37 (0.39) 0.3484	0.03 (0.38) 0.9303	-0.17 (0.40) 0.6759
	Calc – Comb 8wks p-value	-0.02 (0.39) 0.9688	0.45 (0.38) 0.2305	-0.63 (0.40) 0.1125

*- Percent change at Week 4 in ITT-LOCF population is primary endpoint.
[1]- Week 0 nominal change values correspond to baseline PASI score.
[2]- SD denotes simple standard deviation of treatment PASI score
[3]- SE denotes standard error of difference adjusted for sites.
[4]– Test of treatment differences adjusted for sites.

At week 4, for both the percent change and the change from baseline, both combination treatment groups are statistically significantly better than the BID Calcipotriol ointment treatment group (all four $p \leq 0.0053$). Note that "Comb 8 wks" denotes the treatment group where Calcipotriol/betamethasone ointment is applied once daily for up to 8 weeks followed by calcipotriol ointment applied once daily for up to 4 weeks. Similarly "Comb 4 wks" denotes the treatment where the combination ointment is applied once daily for up to 4 weeks followed by calcipotriol ointment applied once daily on weekdays (5 days) and calcipotriol/ betamethasone ointment applied once daily on weekends (two days) all for up to a further 8 weeks.

The following table shows the incidence of subjects with zero scores, plus the significance level of the corresponding chi-square test of homogeneity in proportions.

Table A.4.2.2 Proportions of Patients with PASI score = 0

PASI =0 # resp/N (%)	Week 2[1]	Week 4	Week 4 ITT-LOCF	Week 8	Week 8 ITT-LOCF	Week 12 ITT-LOCF
Calc BID 12wks	0/318	2/305 (0.7 %)	2/327 (0.6 %)	11/294 (3.7 %)	11/327 (3.4 %)	19/327 (5.8 %)
Comb QD 4wks	2/319 (0.6 %)	11/314 (3.5 %)	11/323 (3.4 %)	16/311 (5.1 %)	16/323 (5.0 %)	26/323 (8.0 %)
Comb QD 8wks	3/318 (0.9 %)	6/314 (1.9 %)	6/322 (1.9 %)	21/308 (6.8 %)	22/322 (6.8 %)	24/322 (7.5 %)
Calc – Comb 4wks p-value			0.0110			
Calc – Comb 8wks p-value			0.1485			

For this study both Combination treatment groups are uniformly better than the BID Calcipotriol ointment treatment group. However the difference between the Calcipotriol ointment group and the treatment group with Calcipotriol/betamethasone ointment applied once daily for up to 8 weeks was not statistically significant. Note that at Week 4 both Combination treatment groups were identical, so the difference in efficacy is either due to a Type 1 or Type 2 error or a secular trend in one of these groups.

Table A.4.2.3 displays the proportion of patients with controlled disease (based on the IGA) at each visit and to the end of treatment.

Table A.4.2.3 Investigator Global Assessments Proportion with Controlled Disease

Invest. Assess. # resp/N (%)	Week 2[1]	Week 4	Week 4 ITT-LOCF	Week 8	Week 8 ITT-LOCF	Week 12 ITT-LOCF
Calc BID 12wks	47/323 (14.8 %)	87/305 (28.5 %)	89/326 (27.3 %)	130/294 (44.2 %)	133/326 (40.8 %)	149/326 (45.7 %)
Comb QD 4wks	104/319 (32.6 %)	165/314 (52.5 %)	166/322 (51.6 %)	152/311 (48.9 %)	154/322 (47.8 %)	175/322 (54.3 %)
Comb QD 8wks	100/318 (31.4 %)	163/314 (51.9 %)	165/320 (51.6 %)	176/308 (57.1 %)	178/320 (55.6 %)	129/320 (40.3 %)
Calc – Comb 4wks p-value			<0.0001		0.0479	
Calc – Comb 8wks p-value			<0.0001		<0.0001	

The results in Table A.4.2.3 show that at Week 4 both combination treatments, which are actually equivalent at Week 4, are significantly better than the Calcipotriol ointment group (both $p < 0.0001$). Note that differences are still statistically significant at Week 8, but the treatment group with calcipotriol/betamethasone ointment applied once daily for up to 4 weeks followed by calcipotriol ointment applied once daily on weekdays (5 days) and calcipotriol/ betamethasone ointment applied once daily on weekends (two days) all for up to 8 weeks was barely statistically significantly better than the calcipotriol ointment applied twice daily for up to 12 weeks ($p \leq 0.0479$).

Using the Sponsor's definition of controlled disease, a few cases that had mild disease at baseline would be counted as controlled if the patient had only a one step improvement to very mild. For such measures the Division has sometimes requested that "success" be

defined to require at least a two step improvement. Such a definition of controlled disease would require a score of absence of disease or very mild and at least a two step improvement. Results using this definition are given in the following table.

Table A.4.2.4 Proportions with Controlled Disease Using Division Definition

Invest. Assess. # resp/N (%)	Week 2[1]	Week 4	Week 4 ITT-LOCF	Week 8	Week 8 ITT-LOCF	Week 12 ITT-LOCF
Calc BID 12wks	41/318 (12.9 %)	76/305 (24.9 %)	78/327 (23.9 %)	120/294 (40.8 %)	123/326 (37.7 %)	135/326 (41.4 %)
Comb QD 4wks	80/319 (25.1 %)	139/314 (44.3 %)	140/322 (43.5 %)	126/311 (40.5 %)	128/322 (39.8 %)	156/322 (48.4 %)
Comb QD 8wks	77/318 (24.2 %)	136/314 (45.3 %)	137/320 (42.8 %)	151/308 (49.0 %)	153/320 (47.8 %)	109/320 (34.1 %)
Calc – Comb 4wks p-value			<0.0001		0.5225	
Calc – Comb 8wks p-value			<0.0001		0.0061	

From CMH tests on the endpoint defined using the Division definition corresponding to controlled disease, at Week 4, the Combination treatment groups were statistically significantly better than the calcipotriol ointment treatment group (both $p < 0.0001$). At Week 8, the time of the final endpoint specified in the protocol, results were more equivocal. Note that at Week 8 the Combination treatment groups are no longer equivalent. In this study, at Week 8, the complicated treatment regimen starting with 4 weeks of the Combination drug is no longer statistically significantly better than the calcipotriol ointment treatment group ($p \leq 0.5225$). However the somewhat simpler treatment starting with 8 weeks of the Combination drug is still statistically significantly better than the calcipotriol ointment treatment group ($p \leq 0.0061$).

The following table displays the percentage of patient overall efficacy scores showing at least "marked improvement" (these defined "responders").

Table A.4.2.5 Patient Overall Assessments Responders versus Non-Responders

Invest. Assess. # resp/N (%)	Week 2[1]	Week 4	Week 4 ITT-LOCF	Week 6	Week 8 ITT-LOCF	Week 12 ITT-LOCF
Calc BID 12wks	73/323 (23.0 %)	105/305 (34.4 %)	108/327 (33.1 %)	149/294 (50.7 %)	152/326 (46.6 %)	184/326 (56.4 %)
Comb QD 4wks	118/319 (37.0 %)	184/314 (58.6 %)	185/322 (57.5 %)	177/311 (56.9 %)	181/322 (56.2 %)	209/322 (64.9 %)
Comb QD 8wks	118/318 (37.1 %)	176/314 (56.1 %)	177/320 (55.3 %)	204/308 (66.2 %)	208/320 (65.0 %)	173/320 (54.1 %)
Calc – Comb 4wks p-value			<0.0001		0.0141	
Calc – Comb 8wks p-value			<0.0001		<0.0001	

Again at Week 4 both equivalent combination treatments were significantly better than the Calcipotriol ointment group (both $p < 0.0001$).

A.4.3 Study MCB-0102-INT

Title:
Repeated Courses of Calcipotriol/betamethasone Dipropionate in Psoriasis Vulgaris

Treatment Groups:
The Sponsor describes this as a Phase 3 multi-center, prospective, randomized, three arm, parallel group safety study comparing the safety of two treatment regimens of the combination calcipotriol 50 µg/g plus betamethasone dipropionate 0.5 mg/g,with calcipotriol 50 µg/g treatment:

1. Once daily combination for 52 weeks,
2. Alternating 4 week periods of once daily combination and once daily calcipotriol use,
3. Once daily combination for 4 weeks followed by 48 weeks of once daily calcipotriol treatment.

Main Inclusion/Exclusion Criteria:
1. Affects no more than 30% of body surface area,
2. Investigators global assessment of severity of at least moderate.

Study Design:
At 67 centers in Belgium, Canada, Denmark, Finland, France, Germany, Ireland, Norway, Spain, Sweden, and the United Kingdom 212, 213, and 209 patients were randomized (1:1:1) to the treatment groups 1., 2., and 3. above. Evaluations are to be conducted at baseline, and every four weeks up to week 52 (14 visits).

Study Dates:
23 August 2002 – 20 April 2004.
Final Protocol Draft: 25 April 2002

Efficacy Endpoints (both as in Study MCB-0002-INT):
1. Investigator's global assessment (IGA) of disease severity defined as in Study MCB-0002-INT. A category of at least mild (i.e., mild, very mild, or absence) is classified as "satisfactory," otherwise "not satisfactory."

2. The protocol specified a patient global assessment of study treatment with two categories: "satisfactory" or "not satisfactory."

3. Primary endpoint (from Protocol):
   i. any adverse drug reaction
   ii. any adverse drug reaction associated with long term steroid use

4. Secondary endpoints (from Protocol):
   i. any AE.
   ii. IGA,
   iii. Patient's global assessment of study treatment.
   iv. weight of study medication used.

v. reason's for withdrawal

Protocol Specified Methods of Analysis:

1. Primary endpoints:
   Adverse events compared by chi-square tests of homogeneity of event proportions.
2. Secondary endpoints:
   AE's analyzed similarly.

However for this report only the efficacy results are investigated.

3. Efficacy (ITT-LOCF)
   Satisfactory IGA and patient's global assessment of study treatment (i.e., binary endpoints) analyzed using ANOVA over treatments. (Note due to heterogeneous variances this is generally not an appropriate analysis.)

Efficacy Results:

The following tables on the next page display the efficacy results over the year long study.

Table A.4.3.1 Investigator Overall Assessments Satisfactory versus Not Satisfactory

IGA # resp/N (%)	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28
Comb qd	150/212 (70.8 %)	145/212 (68.4 %)	153/212 (72.2 %)	151/212 (71.2 %)	145/212 (68.4 %)	140/212 (66.0 %)	141/212 (66.5 %)
Comb/Calc 4/48 wks	164/209 (78.5 %)	119/209 (56.9 %)	150/209 (62.2 %)	122/209 (58.4 %)	125/209 (59.8 %)	126/209 (60.3 %)	126/209 (60.3 %)
Comb/Calc 4/4 Alt.	147/213 (69.0 %)	118/213 (55.4 %)	154/213 (72.3 %)	121/213 (56.8 %)	149/213 (70.0 %)	121/213 (56.8 %)	147/213 (69.0 %)

IGA # resp/ N (%)	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Comb qd	136/212 (64.2 %)	139/212 (65.6 %)	141/212 (66.5 %)	139/212 (65.6 %)	138/212 (65.1 %)	134/212 (63.2 %)
Comb/Calc 4/48 wks	127/209 (60.8 %)	120/209 (57.4 %)	124/209 (59.3 %)	123/209 (58.9 %)	117/209 (56.0 %)	117/209 (56.0 %)
Comb/Calc 4/4 Alt.	123/213 (57.7 %)	146/213 (68.5 %)	126/213 (59.2 %)	135/213 (63.4 %)	122/213 (57.3 %)	132/213 (62.0 %)

At the end of four weeks all three groups have had the same treatment, so any differences just reflect differences in patients. Since the primary interest is in this time point, only descriptive review was performed. After the first four weeks, the combination group generally (though not uniformly) dominates the other treatment groups. In the alternating treatment group weeks 4, 12, 20, 28, 36, 44, and 52 correspond to the end of a four week treatment with the combination product. Except for Weeks 4 and 8, this alternating treatment group is somewhat superior to the treatment group with the once daily combination for 4 weeks followed by 48 weeks of once daily calcipotriol treatment.

Recall that in this study the protocol specified a patient global assessment of treatment with two categories: "satisfactory" or "not satisfactory." The following tables display the profiles of this response:

Table A.4.3.2 Patient Success Satisfactory versus Not Satisfactory

IGA # resp/ N (%)	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28
Comb qd	192/212 (90.6 %)	158/212 (74.5 %)	159/212 (75.0 %)	156/212 (73.6 %)	156/212 (73.6 %)	152/212 (71.7 %)	147/212 (69.3 %)
Comb/Calc 4/48 wks	198/209 (94.7 %)	125/209 (59.8 %)	141/209 (67.5 %)	140/209 (67.0 %)	141/209 (67.5 %)	129/209 (61.7 %)	138/209 (66.0 %)
Comb/Calc 4/4 Alt.	197/213 (92.5 %)	122/213 (57.3 %)	181/213 (85.0 %)	136/213 (63.8 %)	167/213 (78.4 %)	121/213 (56.8 %)	163/213 (76.5 %)

IGA # resp/ N (%)	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Comb qd	140/212 (66.0 %)	141/212 (66.5 %)	147/212 (69.3 %)	137/212 (64.6 %)	140/212 (66.0 %)	137/212 (64.6 %)
Comb/Calc 4/48 wks	134/209 (64.1 %)	127/209 (60.8 %)	128/209 (61.2 %)	133/209 (63.6 %)	127/209 (60.8 %)	127/209 (60.8 %)
Comb/Calc 4/4 Alt.	135/213 (63.4 %)	158/213 (74.2 %)	128/213 (60.1 %)	151/213 (70.9 %)	127/213 (59.6 %)	143/213 (67.1 %)

Again, Week 4 differences just reflect differences in patients. Thereafter, by this measure, the combination group is uniformly better than the treatment group with the once daily combination followed by 48 weeks of calcipotriol. Again, weeks 4, 12, 20, 28, 36, 44, and 52 in the alternating treatment group correspond to the end of a four week treatment with the combination product. Except for Week 4 the alternating group is somewhat superior to the treatment group with the first 4 weeks followed by 48 weeks of once daily calcipotriol treatment.

A.4.4 Study MCB-9904-INT

Title:
Calcipotriol/betamethasone versus Calcipotriol alone versus Betamethasone alone in Psoriasis Vulgaris

Treatment Groups:
The Sponsor describes this as a multi-center, prospective, randomized, double-blind, three arm,parallel group Phase 3 study comparing three twice daily treatments for up to four weeks for psoriasis vulgaris:

1. Calcipotriol 50 µg/g plus betamethasone (as dipropionate) 0.5 mg/g ointment,
2. Calcipotriol ointment 50 µg/g,
3. Betamethasone (as dipropionate) 0.5 mg/g ointment.

(Note this not the proposed dosing schedule for the to-be-marketed version).

Main Inclusion/Exclusion Criteria:

1. Baseline PASI score for extent of at least 2, affecting at least 10% of arms, trunk, or legs,
2. Minimum score of at least one for each of redness, thickness, and scaliness scores.

Study Design:
At 79 centers in Belgium, Canada, Denmark, France, Germany, Ireland, Norway, Spain, Sweden, and the United Kingdom 372, 369, and 365 patients were randomized (1:1:1) to the treatment groups 1., 2., and 3. above. The Phase 1, four week, double-blind evaluations are made at baseline, and weeks 1,2, and 4. The Phase 2, four week, open-label phase continues the originally blinded treatment and has evaluations at weeks 5 and 8. Patients whose psoriasis clears before four weeks are evaluated and immediately enter the Phase 2 period. The ITT population was defined as those subjects who were randomized and used medication AND had at least one on-treatment efficacy evaluation. For convenience the Sponsor's definition of the ITT was used.

Study Dates:
8 December 1999 – 22 June 2000.
Final Draft Protocol: 11 October 1999

Endpoints:
1. PASI score (refer to Section 3.1.1)
2. Investigator's/Patient's overall efficacy assessment

The definition of these variables is given below.

Investigator's/Patient's Overall Efficacy Assessment

Scale	Description
Worse	Psoriasis is worse than at baseline evaluation, in severity and/or extent
Unchanged	Psoriasis has not changed
Slight improvement	Some definite improvement (overall about 25%), however significant signs of psoriasis remain
Moderate improvement	Definite improvement (overall about 50%)
Marked improvement	Very definite improvement (overall about 75%), some evidence of psoriasis remains, further treatment required
Clearance	No or very minor evidence of psoriasis remains, no treatment required

Note that the Investigator's/Patient's overall efficacy assessments were only evaluated during Phase 1.

3. Investigator's assessment of target lesion (summarized):

Redness		**Thickness**		**Scaliness**	
0	No existing redness	0	No evidence above skin level	0	No evidence
1		1		1	
2	Light red coloration	2	Slight elevation	2	Fine scales
3		3		3	
4	Red coloration	4	Moderate elevation, rounded	4	Moderate scaling
5		5		5	
6	Very red coloration	6	Marked elevation, sharp edges	6	Severe coarse thick scales
7		7		7	
8	Extreme red coloration	8	Very marked elevation, very hard sharp edges	8	Very severe coarse thick scales

4. Primary endpoint:
Percentage reduction in PASI score from baseline to the end of Phase 1 treatment

5. Secondary endpoints:
   i. percentage change in psoriasis grading of thickness of the target lesion from baseline to subsequent assessments and the end of treatment in Phase 1,
   ii. percentage change in PASI score to week 2,
   iii. percentage of patients with investigator/patient scores showing at least "marked improvement" in Phase 1 (these defined "responders").

Methods of Analysis:

1. Primary endpoint:

ANOVA with percentage reduction in PASI score at Week 4 with treatment and country as factors.

2. Secondary endpoints
   i. Percentage change in psoriasis grading of thickness of the target lesion using ANOVA with treatment and country as factors.
   ii. Proportions of responders from the investigator's or patient's assessments analyzed using logistic regression with factor for country and presumably treatment. The overall six level variables were also to be analyzed using a cumulative logit model.

Results:

The following tables show the results for the endpoints above.

Table A.4.4.1 Percent Change from Baseline and Change from Baseline

	Treatment	Week 0[1]	Week 1	Week 2	Week 4	Week 4* ITT-LOCF
% Change	Combination	N Mean (Std Dev)	362 -47.4 (21.5)	357 -64.7 (22.0)	343 -74.6 (21.2)	366 -74.4 (22.3)
	Calcipotriol		362 -31.0 (20.6)	352 -44.4 (24.3)	348 -57.5 (27.6)	365 -55.3 (29.1)
	Betamethasone		358 -39.8 (23.0)	353 -52.3 (23.4)	347 -61.0 (27.4)	362 -61.3 (27.9)
p-values	Calc – Comb				<0.0001	<0.0001
	Beta – Comb				<0.0001	<0.0001
Change	Combination	370 10.8 (5.9)	362 -5.1 (3.7)	357 -7.1 (4.8)	343 -8.3 (5.9)	366 -8.2 (5.3)
	Calcipotriol	369 10.9 (6.1)	362 -3.4 (2.9)	352 -4.9 (4.0)	348 -6.4 (5.0)	365 -6.1 (5.0)
	Betamethasone	364 10.5 (5.6)	358 -4.3 (3.6)	353 -5.6 (4.2)	347 -6.5 (4.9)	362 -6.6 (4.9)
p-values	Calc – Comb				<0.0001	<0.0001
	Beta – Comb				<0.0001	<0.0001

*- Percent change at Week 4 in ITT-LOCF population is primary endpoint.
[1]- Week 0 nominal change values correspond to baseline PASI score.
[2]- SD denotes simple standard deviation of treatment PASI score
[3]- SE denotes standard error of difference adjusted for sites.
[4]– Test of treatment differences adjusted for sites.

Table A.4.4.1 (cont.) Percent Change from Baseline and Change from Baseline

		Open Treatment		
	Treatment	Week 5	Week 8	Week 8 LOCF
% Change	Combination	337 -74.1 (22.1)	328 -64.7 (29.6)	362 -64.7 (31.0)
	Calcipotriol	328 -62.1 (25.3)	317 -64.3 (30.4)	362 -63.1 (31.0)
	Betamethasone	339 -63.4 (26.2)	326 -60.9 (29.9)	343 -59.7 (31.0)
p-values	Calc – Comb			0.4521
	Beta – Comb			0.2667
Change	Combination	337 -8.2 (5.4)	328 -7.1 (5.1)	362 -7.1 (5.1)
	Calcipotriol	328 -7.0 (5.2)	317 -7.4 (5.4)	362 -7.3 (5.5)
	Betamethasone	339 -6.7 (4.7)	326 -6.4 (4.8)	343 -6.4 (4.9)
p-values	Calc – Comb			0.7859
	Beta – Comb			0.1055

Thus at week 4, both the change from baseline and the percent change from baseline showed statistically significant differences between the Combination treatment and each of its constituents (all $p \leq 0.0001$). Note the percentage change in PASI score to week 2 is a secondary endpoint.

The following table shows the incidence of subjects with zero scores, plus the significance level of the corresponding chi-square test of homogeneity in proportions.

Table A.4.4.2 Proportions of Patients with PASI score = 0

PASI =0 # resp/N (%)	Week 1	Week 2	Week 4	Week 4 ITT-LOCF	Week 5	Week 8	Week 8 ITT-LOCF
Combination	0/362	5/357 (1.4 %)	28/343 (8.2 %)	33/366 (9.0 %)	33/304 (9.8 %)	21/328 (6.4 %)	22/341 (6.5 %)
Calcipotriol	0/362	0/352	11/348 (3.2 %)	11/365 (3.0 %)	10/328 (3.0 %)	16/317 (5.0 %)	16/332 (4.8 %)
Betamethasone	1/358 (0.3 %)	4/353 (1.1 %)	19/347 (5.5 %)	24/362 (6.6 %)	16/339 (4.7 %)	12/326 (3.7 %)	12/331 (3.5 %)
Calc – Comb			0.0044	0.0006			0.3590
Beta – Comb			0.1612	0.2307			0.0756

Note this is a post hoc analysis and the study was not powered for this endpoint. Again, with some zero marginals highly likely, CMH tests are not appropriate, hence chi-square tests are used. Because of over dispersion we would expect the test statistics to be anticonservative.

Patients with investigator/patient scores on the overall efficacy assessment of at least "marked improvement" in Phase 1 are defined as "responders" in the corresponding efficacy assessment. Results for these assessments are presented in the following two tables.

Table A.4.4.3 Investigator Overall Efficacy Assessments Responders vs. Non-Responders

Invest. Assess. # resp/N (%)	Week 1	Week 2	Week 4	Week 4 ITT-LOCF
Combination	101/365 (27.7 %)	186/359 (51.8 %)	235/345 (68.1 %)	251/369 (68.0 %)
Calcipotriol	34/362 (9.4 %)	75/352 (21.3 %)	142/348 (40.8 %)	142/365 (38.9 %)
Betamethasone	64/359 (17.8 %)	105/354 (29.7 %)	160/348 (46.0 %)	169/363 (46.6 8 %)
Calc – Comb			<0.0001	<0.0001
Beta – Comb			<0.0001	<0.0001

The significance levels above are from Cochran-Mantel-Haenszel tests of treatment differences at the specified visit. The protocol specified an analysis using logistic regression with factor for country and presumably treatment. Using this simple logistic regression model and dummy indicators of effects, at week 4 in the ITT-LOCF population, differences between the Combination treatment and both Calcipotriol and Betamethasone were both statistically significant (Wald statistics: p <0.0001 and $p \leq 0.0205$, respectively). As also specified in the protocol was a supporting analysis using the overall six level ordinal responses with cumulative logits. Results were similar, with differences between the Combination treatment and both Calcipotriol and Betamethasone both statistically significant (Wald statistics: $p < 0.0001$ and $p \leq 0.0098$, respectively).

Table A.4.4.4 Patient Overall Efficacy Assessments Responders versus Non-Responders

Patient Assess. # resp/N (%)	Week 1	Week 2	Week 4	Week 4 ITT-LOCF
Combination	128/365 (35.1 %)	199/359 (55.4 %)	232/345 (67.3 %)	248/369 (67.2 %)
Calcipotriol	52/362 (14.4 %)	88/352 (25.0 %)	140/348 (40.2 %)	140/365 (38.4 %)
Betamethasone	93/359 (25.9 %)	115/354 (32.5 %)	173/348 (49.7 %)	183/363 (49.6 %)
Calc – Comb			<0.0001	<0.0001
Beta – Comb			<0.0001	<0.0001

As before, the significance levels above are from Cochran-Mantel-Haenszel tests of treatment differences at the specified visit. The protocol specified logistic regression also showed statistically significant differences between the Combination treatment and Calcipotriol (Wald statistic, $p < 0.0001$) but not with Betamethasone (Wald statistic, $p \leq 0.3932$). Again, the analysis comparing the Combination treatment and Calcipotriol with the six level ordinal responses was also statistically significant (Wald statistic, $p < 0.0001$), however the comparison with Betamethasone was not (Wald statistic, $p \leq 0.1629$).

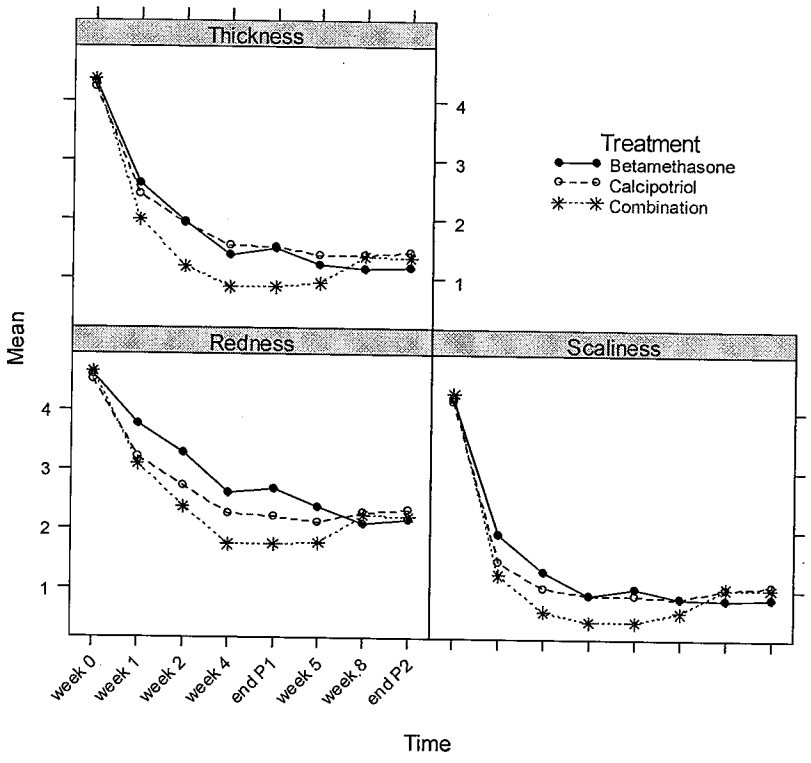
Target Lesions

Note that the grading of thickness of the target lesion is the basis of a secondary endpoint. In particular, the percentage change in psoriasis grading of thickness of the target lesion is to be analyzed using ANOVA with treatment and country as factors.

The contrasts in the ANOVA with pooled center and treatment as factors comparing the proportion of the Combination drug to either Calcipotriol or Betamethasone all treatment differences at Week 4, End of Phase 1, were statistically significant (all $p \leq 0.0001$). Cochran-Mantel-Haensel tests comparing the proportion of the combination drug to either Calcipotriol or Betamethasone at the same endpoint were also statistically significant (both $p \leq 0.0001$).

In addition to thickness, other factors related to the target lesion were redness and scaliness. The plot of the means for each treatment group across time paneled by factor is shown in Figure A.4.4.1. This graphic shows the rapid decrease in means up until the end of Phase 1 for all treatment arms. Interestingly after Phase 1, the Dovobet® group tended to start having increased mean values for each of the target lesion assessments in Phase 2. In contrast, the Calcipotriol and Betamethasone arms tend to continue to decrease slightly or level off in Phase 2.

Figure A.4.4.1 Mean Scores for each Factors of the Target Lesions



A.4.5 Study MCB-0201-FR

Title:
Effect of Calcipotriol/betamethasone Dipropionate Ointment Compared to Betamethasone Dipropionate on the HPA axis in Patients with Psoriasis Vulgaris.

Treatment Groups:
The sponsor describes that as a single center, prospective, randomized 1:1, active controlled, double-blind, two arm, parallel group, four week study, with a two week run-in period, comparing two treatment regimens in psoriasis vulgaris:

1. Combination ointment of calcipotriol 50μg/g plus betamethasone dipropionate 0.50mg/g once daily for 4 weeks,
2. Diprosone® (betamethasone dipropionate 0.50mg/g) ointment.

Main Inclusion/Exclusion Criteria:

1. The entry criteria require a clinical diagnosis of psoriasis on trunk or limbs with lesions involving 15-30% of body surface area.
2. Patient's with normal HPA axis function.

Study Design:
Adrenal function was one assessed within the first week and at day 28 using a rapid standard dose ACTH stimulation test. Patients were assessed at twice during the two week run-in period and at the beginning and end of the four week treatment period.

Dates of Study:
15 April 2003 - 13 January 2004
Final Protocol Draft: 03 April 2003

Endpoints:
1. Primary endpoint:
Adrenal response, defined as the maximum serum cortisol concentration at 30 or 60 minutes.

2. Secondary endpoint:
   i. Adrenal response, defined as the maximum rise in serum cortisol concentration from time 0 to 30 or 60 minutes after injection.
   ii. 8:00 AM serum cortisol concentration before injection.
   iii. Mean change in PASI score from the beginning to the end of the four week treatment period.

For this analysis only the treatment differences in change from baseline in PASI score are analyzed.

Results:
The following table summarizes the efficacy results using the PASI scores.

Table A.4.5.1 Results on PASI Score

	Baseline		Week 4		
	N	PASI	PASI	Change in PASI	% Change
Dovobet	12	11.9	3.7	8.2	69.8
Diprosone	12	14.3	5.0	9.3	63.6

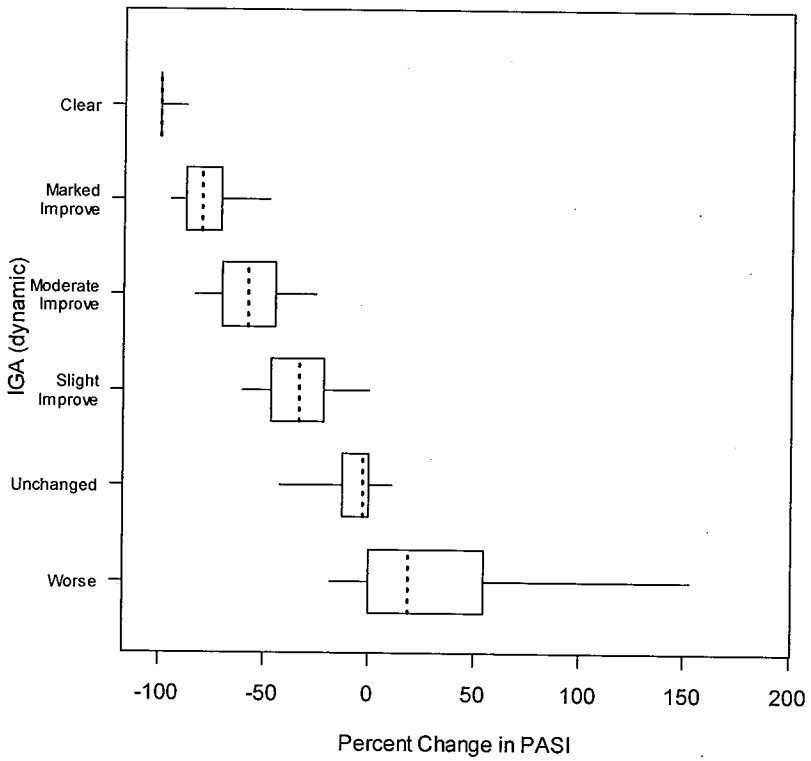
The simple t-test comparing change from baseline in PASI score between the two treatment groups was not statistically significant ($p \leq 0.5331$). These results are identical to those computed by the sponsor.

A.5 PASI vs. IGA (Active-Controlled Results)

The following plots display the comparison between the static IGA and the PASI score and the "dynamic" IGA and the percent change from baseline in PASI score at Week 4. Plots at earlier and later weeks were similar.

In Study MCB-0001-INT the IGA measures change from baseline (i.e. the scaling for IGA is dynamic), so it makes sense to evaluate the relation between the percent change from baseline in the PASI score and the IGA. Note that a negative percent change from baseline in PASI scores implies disease improvement. Figure A.5.1 summarizes the distribution of percent change from baseline in the PASI score at each level of improvement of the IGA. The boxes in the plot indicate the quartiles, while medians are connected by lines. Lines extending from the quartiles correspond to the 5th and 95th percentiles of the percent change from baseline in PASI scores.

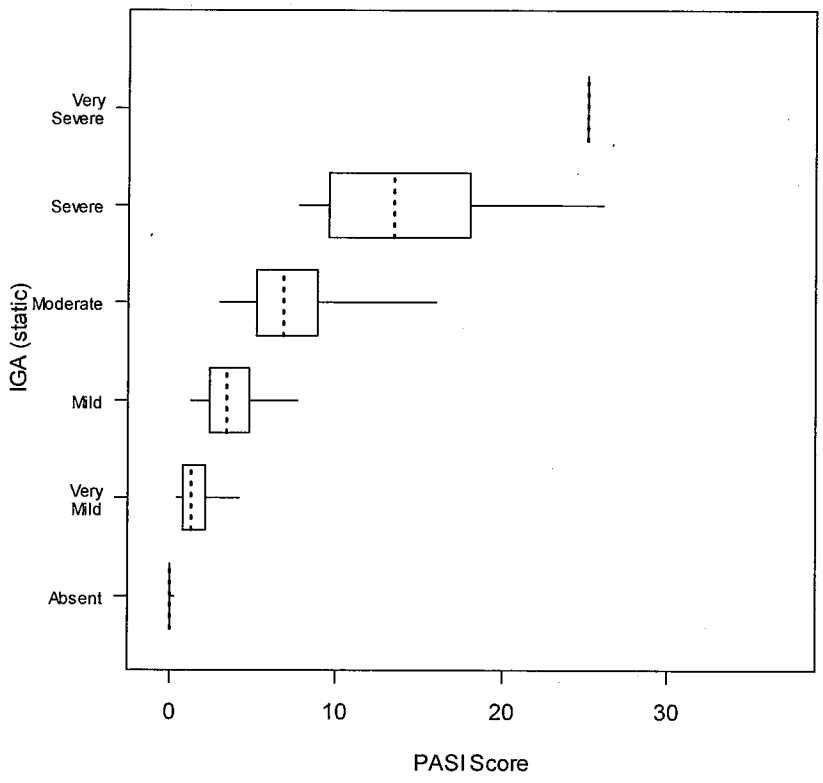
Figure A.5.1 Relation of Percent Change in PASI and IGA (Study MCB-0001-INT)



The relation between scores and the IGA is apparent. Note that the interquartile segments, denoted by the blocks, barely overlap. This suggests the PASI score populations are rather separated at successive levels of the IGA. Treating the percent change in PASI scores as ordinal, the Spearman rank correlation "rho" was -0.8329, and Kendall's concordance correlation "tau-b" was -0.7038, both quite strong correlations. At other time points plots were similar. Correlations were large (in absolute magnitude) and quite strong (At the different times, $-0.8487 \leq \text{rho} \leq -0.7881$ and $-0.7180 \leq \text{tau-b} \leq -0.6471$).

Recall that Study MCB-0002-INT collected a static IGA as did Study MCB-0003-INT. Thus, rather than look at the relationship of IGA and the percent change from baseline PASI score, the relationship between IGA and PASI score at week 4 is examined as was performed with the pivotal trial. Figure A.5.2 graphically illustrates the distribution of the PASI scores for a given IGA grade. In the figure boxes correspond to quartiles and lines extending from them correspond to the 5^{th} and 95^{th} percentiles. Note the increasing trend in PASI score over the levels of the IGA implying that as the PASI score increases the IGA grade also increases.

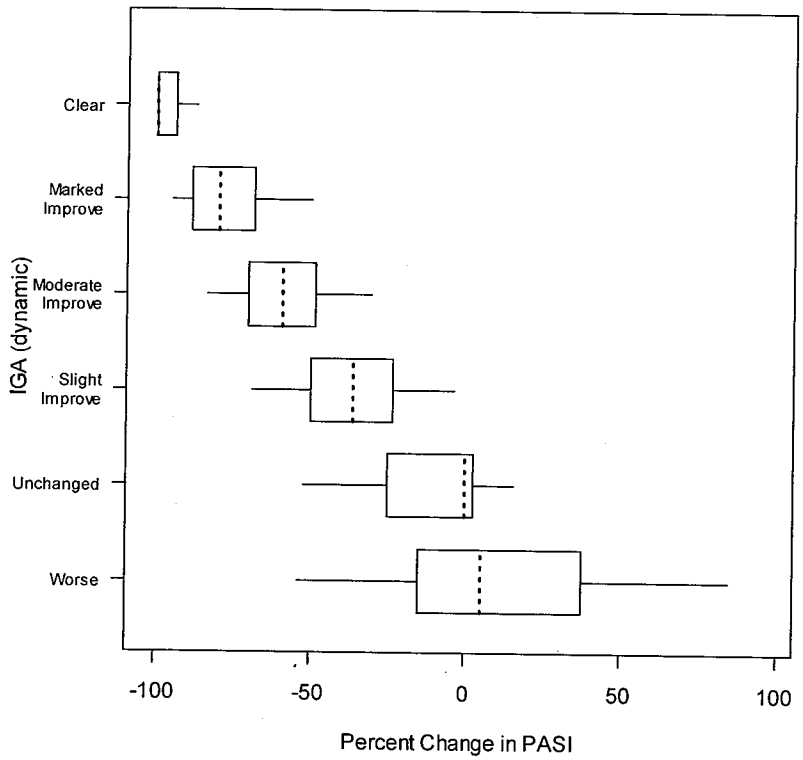
Figure A.5.2 Relation of PASI score and IGA (Study MCB-0002-INT)



In addition to the modeling of week 4 IGA success using PASI scores as mentioned in Section 3.1.4.3 on page 15, the following statistics are calculated to assess the relationship of the static IGA and PASI scores. Treating the PASI score as ordinal, the Spearman rank correlation "rho" was 0.7660, and Kendall's concordance correlation "tau-b" was 0.6432, both strong correlations. At other time points plots were similar; correlations were still large (in absolute magnitude) and rather strong (at the different times, $0.6182 \leq \text{rho} \leq 0.8350$ and $0.5081 \leq \text{tau-b} \leq 0.7166$).

In Study MCB-9904-INT the IGA measures percent change from baseline, so again it seems most appropriate to compare the percent change from baseline in the PASI score to the IGA. Note that negative percent change from baseline in PASI scores implies disease improvement. Figure A.5.3 depicts this relationship.

Figure A.5.3 Relation of Percent Change in PASI and IGA (Study MCB-9904-INT)



Again this plot suggests a strong a relation between the PASI scores, both direct and computed as change from baseline and the IGA assessed as a "static score" and as a change from baseline, "dynamic" score. Note treating the percent change in PASI score as ordinal, the Spearman rank correlation "rho" was -0.7996, and Kendall's concordance

correlation "tau-b" was -0.6708, both quite strong correlations. At other time points plots were similar, although correlations were slightly smaller (in absolute magnitude), but still quite strong (All rho ≤ -0.6998, tau-b ≤ -0.5835).

To borrow evidence from some of the supportive studies, efficacy was determined using PASI scores as no static IGA was collected. As the Division regards a static IGA as the clinically meaningful endpoint, the examination of the relationship between IGA and PASI scores was done in order to borrow evidence from studies that did not collect a static IGA. The plots and correlations shown above indicate that the percent change in PASI score is strongly related to the dynamic IGA in Studies MCB-0001 and 9904 and that the actual PASI score is strongly related to the static IGA in Study MCB-0002. Note that the above examination does not address the issue of whether or not the PASI score is itself an interpretable measure.

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10/28/05

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