

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 22-185

STATISTICAL REVIEW(S)



US Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION
NEW DRUG APPLICATION
CLINICAL STUDIES

NDA/Serial Number: 22-185/SN000
Drug Name: Taclonex® (betamethasone and calcipotriene) scalp suspension
Indication(s): Psoriasis vulgaris of the scalp
Applicant: LEO Pharmaceuticals

Dates: Submitted: 06/28/2007
PDUFA: 04/28/2008

Review Priority: Standard

Biometrics Division: Division of Biometrics III
Statistics Reviewer: Mat Soukup, Ph.D.
Concurring Reviewer: Mohamed Alesh, Ph.D.

Medical Division: Division of Dermatology and Dental Products
Clinical Team: Reviewer: Brenda Carr, M.D. (DDDP)
Lead: Jill Lindstrom, M.D. (DDDP)
Project Manager: Margo Owens (DDDP)

Keywords: combination product, superiority

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STATISTICAL REVIEW AND EVALUATION ADDENDUM

NEW DRUG APPLICATION

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The sponsor initiated their clinical trials prior to receiving the Division's concurrence on the enrollment criteria for subjects and the definition of treatment success for the primary endpoint. After study enrollment, as outlined in the statistical review, the sponsor modified the inclusion criteria to exclude subjects with baseline IGA scores of 'mild'. At the Pre-NDA meeting the sponsor proposed to conduct three analyses to address the Division's concern about defining treatment success based on the IGA. This reviewer carried out the statistical review with a treatment success endpoint defined as two grade improvement as typically done in other applications. One of the sponsor's analysis corresponded to an endpoint defining success as a two grade improvement on the IGA scale along with having an IGA score of 'absence of disease' or 'very mild disease'. With the additional restriction, the number of successes in the sponsor's analysis are relatively smaller than in the reviewer analysis. Results for the sponsor's analysis are shown in Table 1.

Table 1: Sponsor's Analysis of Investigator Global Results (ITT-LOCF)^a

	Taclonex	Betamethasone	Calcipotriene	Vehicle
Study MBL 405 INT				
Sample Size	541	556	272	136
Success (%)	363 (67.1)	350 (62.9)	96 (35.3)	26 (19.1)
p-value	-	0.14 ¹	< .001 ¹	< .001 ²
Study MBL 406 INT				
Sample Size	567	562	286	-
Success (%)	362 (63.8)	324 (57.7)	111 (38.8)	-
p-value	-	0.028 ¹	< .001 ¹	-

^a Sponsor's 'FDA Analysis' with response defined as 'absence of disease' or 'very mild disease' *and* a two grade improvement.

¹ Cochran-Mantel-Haneszal test stratified by pooled site.

² Cochran-Mantel-Haneszal test stratified by country.

Source: Sponsor Table 11 and 12 in the Summary of Clinical Efficacy.

It should be noted that the change in the definition of treatment success for the primary endpoint does not impact the efficacy finding as the determination of efficacy was based on subjects with at least a baseline IGA score of 'moderate' and treatment success was defined as 'absence of disease' or 'very mild disease'.

Primary Statistical Reviewer: Mat Soukup, Ph.D.

Date: April 28, 2008

Statistical Team Leader: Mohamed Aloh, Ph.D.

cc:

Archival NDA

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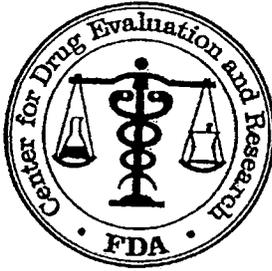
April 28, 2008

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/s/

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4/28/2008 02:54:24 PM
BIOMETRICS

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4/28/2008 05:35:27 PM
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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Taclonex[®] scalp suspension is a new combination drug product consisting of the moieties calcipotriene, 50 mcg/g and betamethasone, 0.5 mg/g. Leo Pharmaceuticals is seeking approval of this new combination drug product for the treatment of scalp psoriasis. Two pivotal Phase 3 trials were conducted; Study 405 was of full factorial design and Study 406 excluded a vehicle arm. In Study 406, Taclonex[®] scalp suspension was found to be superior to each of its active components with quite robust efficacy findings. In Study 405, Taclonex[®] scalp suspension was clearly superior to calcipotriene and vehicle, though it was not robustly significant over betamethasone. The determination of efficacy was based upon a static Investigator Global Assessment (IGA) of psoriasis. Four other active-controlled or vehicle-controlled trials were used to support the efficacy claim. The safety profile for Taclonex[®] scalp suspension was similar to that of betamethasone, and these two treatment arms had fewer reported AE's than the calcipotriol and vehicle arms. The difference in the AE profiles was in large part due to the higher percentage of subjects experiencing local skin irritation in the calcipotriene and vehicle arms. None of the serious events were claimed to be treatment related according to the study investigators.

1.2 Brief Overview of Clinical Studies

Two pivotal Phase 3 safety and efficacy trials, Study 405 and Study 406, were completed. Study 405 included Taclonex[®] scalp suspension, betamethasone, calcipotriene, and vehicle with the objective of establishing the superiority of Taclonex[®] scalp suspension to each monad and vehicle. Study 406 included Taclonex[®] scalp suspension, betamethasone, and calcipotriene with the objective of establishing the superiority of Taclonex[®] scalp suspension to each monad. The treatment duration and time point for primary analysis was 8 weeks. Study 405 was conducted in 101 centers in Europe and Canada recruiting a total of 1505 subjects. Study 406 was conducted in 98 centers in Europe and Canada recruiting a total of 1418 subjects. The objective of the trial was to show the superiority of Taclonex[®] scalp suspension to each of its components and vehicle (Study 405 only) as measured by the percent of IGA successes (IGA score of 'absence of disease' or 'very mild disease'). Including the four supportive trials to the pivotal trials, a total of 1858 subjects were treated with Taclonex[®] scalp suspension.

1.3 Statistical Issues and Findings

The sponsor initiated both pivotal trials prior to attending an End of Phase 2 (EOP2) Meeting with the Division on December 1, 2004. The initial enrollment criteria in the two pivotal trials

allowed subjects to be enrolled with an IGA score of ‘mild’ disease severity. At the EOP2 meeting the Division stated that subjects who enroll with an IGA score of ‘mild’ must achieve an IGA score of ‘absence of disease’ to be considered a treatment success as this better reflects a clinical improvement. Based upon this meeting the sponsor decided to revise the Phase 3 protocols to reflect that upon enrollment subjects must have at least an IGA score of ‘moderate’. In addition, the Division also recommended the sponsor include a vehicle arm in Study 406 to aid in the interpretation of study findings.

At the Pre-NDA Meeting held on January 30, 2007 the sponsor informed the Division that they modified the enrollment criteria of the then ongoing Phase 3 trials. Such a change in the enrollment criteria raised questions about how to define treatment success (IGA dichotomized to ‘absence of disease’ or ‘very mild disease’ or IGA dichotomized to two grade improvement) as well as what subject population to include (whether to include subjects enrolled with a baseline IGA score of ‘mild’ or exclude such subjects). Various analyses were performed throughout the review and based upon discussions with the clinical review team, it was decided to use the population which only included subjects with at least an IGA score of ‘moderate’ and to define IGA success as ‘absence of disease’ or ‘very mild disease’. This analysis population is what is referred to as the ‘Sponsor’s Amended Analysis’ throughout the body of the statistical review.

Efficacy results are provided in Table 1. In both studies, it was shown that the treatment effect comparing Taclonex[®] scalp suspension to betamethasone is much smaller than that comparing Taclonex[®] scalp suspension to calcipotriene. Based upon the above defined population and definition of treatment success, both studies were able to establish the contribution of each monad at the $\alpha = 0.05$ level. As can be seen in Table 1, the efficacy results for Study 405, namely the comparison of Taclonex[®] scalp suspension to betamethasone, were not as strong as the efficacy results in Study 406 though the lack of a vehicle arm in Study 406 makes it difficult to fully interpret study findings between trials.

An integrated summary of efficacy (ISE) was incorporated to utilize data from four other late Phase clinical trials which examined the same dosing scheme used in Studies 405 and 406. Using the same analysis population as described and the same definition of treatment success, Figure 1 depicts response rates for the two pivotal trials and the four supportive trials. Overall, the response rates are quite consistent across studies for each of the treatment groups with the following exceptions.

- The Phase 2 trial, Study 401, had higher response rates in both treatment arms than in the other studies.
- The vehicle response in Study 502 is much higher than the observed vehicle response rate in Study 405 which is explored further in Section 3.1.3.3.

Table 1: Investigator Global Results (ITT-LOCF)

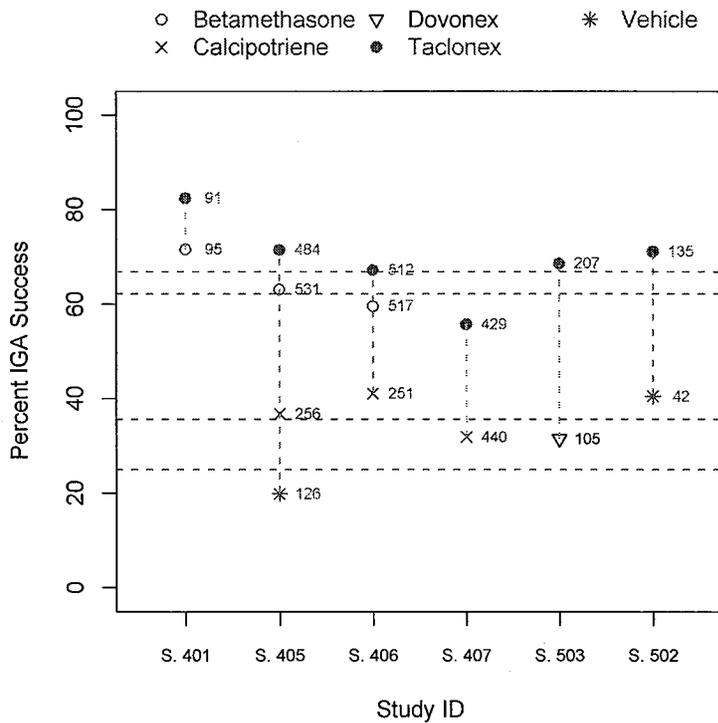
	Taclonex	Betamethasone	Calcipotriene	Vehicle
Study MBL 405 INT				
Sample Size	494	531	256	126
Success (%)	346 (70.0)	335 (63.1)	94 (36.7)	25 (19.8)
p-value ²	-	0.0205	< .001	< .001
Study MBL 406 INT				
Sample Size	512	517	251	-
Success (%)	344 (67.2)	308 (59.6)	103 (41.0)	-
p-value ¹	-	0.0089	< .001	-

¹ Cochran-Mantel-Haneszal test stratified by pooled site.

² Fisher’s Exact test due to small stratum in pooled sites.

Source: Reviewer’s Analysis of the ‘Sponsor’s Amended Analysis’.

Figure 1: Efficacy Summary for all Controlled Trials



2 INTRODUCTION

Taclonex® scalp suspension is a product containing a combination of betamethasone 0.5 mcg/g and calcipotriene 50 mg/g intended for the topical treatment of scalp psoriasis. The suspension formulation has been developed to supplement calcipotriene plus betamethasone dipropionate combination ointment (Taclonex® ointment) approved on 01/09/2006 for the treatment of psoriasis vulgaris includes the same active substances in the same concentration. The sponsor's reasoning for developing the suspension formulation is to provide a cosmetically acceptable formulation for use on the scalp as the ointment formulation tends to leave the hair greasy.

2.1 Regulatory History

The sponsor initiated both pivotal trials prior to attending an End of Phase 2 (EOP2) Meeting with the Division held on December 1, 2004. The initial enrollment criteria in the two pivotal trials allowed subjects to be enrolled with an IGA score of 'mild' disease severity. At the EOP2 meeting the Agency stated that subjects who enroll with an IGA score of 'mild' must achieve an IGA score of 'absence of disease' to be considered a treatment success as this better reflects a clinical improvement. Based upon this meeting the sponsor decided to revise the Phase 3 protocols to reflect that upon enrollment subjects must have at least a score of 'moderate' on the IGA.

Such a change in the enrollment criteria raised questions about how to define treatment success (IGA dichotomized to 'absence of disease' or 'very mild disease' or IGA dichotomized to two grade improvement) as well as what subject population to include (whether to include subjects enrolled with a baseline IGA score of 'mild' or exclude such subjects). At the Pre-NDA meeting, the sponsor proposed three analyses to address the trial design modification after study initiation (names of the analyses are based on sponsor's naming convention used at the Pre-NDA meeting).

- "Sponsor's Original Analysis": Analysis includes all subjects including those with a baseline IGA score of 'mild' and success is defined as 'controlled disease' ('absence of disease' or 'very mild disease') regardless of baseline severity.
- "Sponsor's Amended Analysis": Analysis excludes all subjects with a baseline IGA score of 'mild' and success is defined as 'controlled disease' ('absence of disease' or 'very mild disease').
- "FDA Analysis": Analysis includes all subjects including those with a baseline IGA score of 'mild' and success is defined as a two grade reduction which implies subjects enrolled with a baseline IGA score of 'mild' must reach 'absence of disease' to be considered a

success.¹

Due to the modification of the trial after study initiation the Division advised the sponsor at the Pre-NDA Meeting that the most appropriate approach for efficacy assessment is unknown and efficacy assessment will be a review issue.

In addition to the issue of the impact of baseline enrollment criteria and the subsequent defined statistical analysis population, Study 406 did not include a vehicle treatment arm. At the End of Phase 2 Meeting the following is the Biostatistics reviewer comment about not including a vehicle arm in both studies.

“The sponsor is encouraged to include a vehicle arm in both Phase 3 studies. Including a vehicle arm in the second study may make it easier to interpret the results of the second study. In addition, when all subjects are on an active treatment, there may be a tendency to overestimate response which may make it harder to establish efficacy.”

2.2 Clinical Trial Overview

The clinical development of Taclonex[®] scalp suspension includes two pivotal trials, Study 405 and Study 406, as well as several additional safety and efficacy studies. The studies pertinent to the evaluation of safety and efficacy are provided in Table 2. In the body of this review, the two pivotal trials are assessed, whereas the additional safety and efficacy studies with different objectives are provided in the Appendix.

2.3 Data Sources

The sponsor submitted data sets which comply with CDISC standards; therefore data sets which follow the Study Data Tabulation Model are submitted as well as data which follow the Analysis Data Model. The data sets used for the statistical review are located in the EDR at: <//cdsesub1/evsprod/NDA022185/0000/m5/datasets>.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The evaluation of efficacy is reported in the main body of text for the two pivotal Phase 3 trials, Study MBL 0405 INT (Study 405) and Study MBL 0406 INT (Study 406). These two Phase 3

¹Note that such a definition also would define success for a subject enrolled with a baseline IGA score of ‘severe’ and an IGA score of at least ‘mild’ at end of treatment.

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Table 2: Efficacy and Safety Studies Overview

Study	Development Objective	Drug Products	Number Subjects	Treatment Duration	Date [†]
MBL 0401 INT	Phase 2	Taclonex® QD	108	up to 8 weeks	Feb. 2004 to July 2004
	Dose ranging	Betamethasone QD	110		
MBL 0404 FR	Phase 1 Safety	Taclonex® gel + Taclonex® oint.	35	up to 8 weeks	Sept. 2005 to June 2006
MBL 0405 INT	Phase 3 Superiority	Taclonex® QD	541	up to 8 weeks	Nov. 2004 to Sept. 2005
		Betamethasone QD	556		
		Calcipotriol QD	272		
MBL 0406 INT	Phase 3 Superiority	Vehicle QD	136	up to 8 weeks	Dec. 2004 to Sept. 2005
		Taclonex® QD	568		
MBL 0407 INT	Phase 3 Superiority	Betamethasone QD	563	up to 8 weeks	Sept. 2005
		Calcipotriol QD	286		
MBL 0407 INT	Phase 3 Safety	Taclonex® QD	419	up to 52 weeks	Feb. 2005 to July 2006
		Calcipotriol QD	431		
MBL 0502 US	Phase 3 Superiority	Taclonex® QD	135	up to 8 weeks + 44 weeks open label	Dec. 2005 to Sept. 2006*
		Vehicle QD	42		
MBL 0503 INT	Phase 3 Efficacy	Taclonex® QD	207	up to 8 weeks	Sept. 2005 to May 2006
		Dovonex® BID	105		

[†] Dates correspond to the start and end of the study.

* Dates corresponds to the date of first subject enrolled until date of last double-blind visit.

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trials are of similar design though Study 406 does *not* include a vehicle arm. The efficacy results of the four supportive trials are provided in the appendix. The section on efficacy concludes with an integrated summary of all efficacy results.

Note that primary efficacy results are presented for each of the three analysis populations when appropriate. Based on discussions with the clinical review team, it was decided that the ‘Sponsor’s Amended Analysis’ may be the most relevant population for labeling. Thus, for sensitivity analyses as well as the integrated summary of efficacy, results are presented only for the ‘Sponsor’s Amended Analysis.’

3.1.1 Study MBL 0405 INT

3.1.1.1 Study Design Study 405 was an international, multi-center, prospective, randomized, double-blind, 4-arm, parallel group, 8-week study in patients with scalp psoriasis. The study was conducted at 101 centers (Canada 15; Denmark 4; France 25; Norway 10; Portugal 2; Spain 10; Sweden 11; United Kingdom 24). Patients enrolled were randomized in a 4:4:2:1 ratio to receive once daily treatment for up to 8 weeks with either Taclonex[®] scalp suspension, betamethasone scalp suspension, calcipotriene scalp suspension, or vehicle scalp suspension. The study enrolled a total of 1505 subjects; 541 subjects randomized to Taclonex[®] scalp suspension, 556 randomized to betamethasone scalp suspension, 272 randomized to calcipotriene scalp suspension, and 136 randomized to the vehicle scalp suspension.

As mentioned in Section 2.1, the sponsor initiated trials prior to the End of Phase 2 (EOP2) meeting with the Division held on December 1, 2004, and at this time subjects could be enrolled into the trial with an IGA score of ‘mild’ disease severity. At the EOP2 meeting the Agency stated that subjects who enroll with a baseline IGA score of ‘mild’ must reach an IGA score of ‘absence of disease’ at the end of treatment to be considered a treatment success as to better reflect a clinical improvement. Based upon the Division’s comments at the EOP2 meeting, on January 20, 2005 the sponsor revised the protocol to reflect that upon enrollment subjects must have at least an IGA score of ‘moderate’.

Visits to the investigative site were performed on Day 0 (Visit 1), Day 7 (Visit 2), Day 14 (Visit 3), Day 28 (Visit 4), Day 42 (Visit 5), and Day 56 (Visit 6). A follow-up visit took place 14 days after the subjects’s last on-treatment visit if a treatment related adverse event was ongoing.

3.1.1.2 Endpoints Efficacy assessments including the Investigator’s Global Assessment (IGA), extent of scalp psoriasis, assessment of the clinical signs (redness, thickness and scaliness) were performed at all visits (1 to 6) and the patient’s overall assessment of response to treatment at visits 2 to 6.

3.1.1.2.1 Primary Endpoint The protocol defined primary endpoint is defined as subjects with ‘controlled disease’ (‘absence of disease’ or ‘very mild disease’) according to the IGA at end of treatment (Week 8). A description of the IGA is shown below in Table 3. As the sponsor initiated the trials prior to the End of Phase 2 Meeting this impacted the Division’s preferred definition of treatment success based on the IGA scale. Typically, the Division prefers that to be considered a treatment success based upon a dichotomized IGA scale, subjects who enroll with a ‘mild’ rating on the IGA scale should reach a score of ‘clear’ by end of treatment. Further discussion of the definition of the primary endpoint and the method of analysis is described in more detail in Section 2.1.

Table 3: Description of Investigator Global Assessment

Absence of disease:	No evidence of redness, no evidence of thickness and no evidence of scaliness on the scalp.
Very mild disease:	The overall clinical picture consists of lesions with the presence of minimum erythema.
Mild disease:	The overall clinical picture consists of lesions with light red coloration, slight thickness and a fine, thin scale layer.
Moderate disease:	The overall clinical picture consists of lesions with red coloration, a moderate thickness and a moderate scaled layer.
Severe disease:	The overall clinical picture consists of lesions with red coloration, severe thickness and a severe, coarse thick scale layer.
Very severe disease:	The overall clinical picture consists of lesions with red coloration, very severe thickness and a very severe, coarse thick scale layer.

3.1.1.2.2 Secondary Endpoints The following are the seven protocol (based on Amendment No. 2) defined secondary endpoints.

- The total sign score at Week 8 will be dichotomized to success (score = 0 or 1) and failure (score greater or equal to 2).
- The score for scaliness, redness and thickness at Week 8 will be dichotomized to success (score = 0) and failure (score greater or equal to 1).
- The proportion of patients who achieve ‘controlled disease’ (‘absence of disease’ or ‘very mild disease’) according to the IGA at Week 2 and 4.
- The proportion of patients who achieve ‘treatment success’ (‘almost clear’ or ‘cleared’) according to patients overall assessment of disease severity at Week 8.

3.1.1.3 Patient Disposition and Baseline Characteristics

3.1.1.3.1 Patient Disposition The disposition of subjects randomized into Study 405 is tabulated in Table 4. In Study 405 the rate of withdrawn subjects is highest in the calcipotriene and vehicle arms with the most prevalent reasoning being lack of efficacy and unacceptable adverse events in subjects receiving calcipotriene and lack of efficacy in the vehicle group.

Table 4: Subject Disposition – Study 405

	Taclonex (N = 541)	Betamethasone (N = 556)	Calcipotriene (N = 272)	Vehicle (N = 136)
Completed all trial visits	434 (80.2)	473 (85.1)	210 (77.2)	106 (77.9)
Efficacy prior to week 8 [†]	47 (8.7)	37 (6.7)	5 (1.8)	0 (0.0)
Discontinued*	60 (11.1)	46 (8.3)	57 (21.0)	30 (22.1)
Exclusion criteria emerged	3 (0.6)	3 (0.5)	2 (0.7)	3 (2.2)
Unacceptable adverse event(s)	8 (1.5)	6 (1.1)	20 (7.4)	7 (5.1)
Unacceptable treatment efficacy	2 (0.4)	9 (1.6)	19 (7.0)	16 (11.8)
Lost to follow-up	16 (3.0)	9 (1.6)	7 (2.6)	0 (0.0)
Voluntary (and no other reason)	10 (1.8)	10 (1.8)	10 (3.7)	3 (2.2)
Other	23 (4.3)	14 (2.5)	8 (2.9)	7 (5.1)

[†] Subjects had a treatment response prior to Week 8 and thus did not have a week 8 visit.

* Subjects can have more than one reason for discontinuation.

Source: Table 2 of the Sponsor's Study Report; results reproduced by reviewer.

3.1.1.3.2 Baseline Demographic Factors The baseline demographic factors collected in the trial were: age, race, gender, and country. A summary of these four factors by treatment group did not reveal any differences between the treatment groups at baseline. Table 19 in Appendix Section A.1.1 contains the tabulated results. As the study was conducted in Europe and Canada the prevailing race was Caucasian which accounted for more than 95% of the enrolled subjects.

3.1.1.3.3 Baseline Prognostic Factors The following baseline prognostic factors were evaluated to assess for any imbalance between the treatment groups which might impact efficacy: IGA, extent of scalp psoriasis, redness of the scalp, scaliness of the scalp, plaque thickness of the scalp, and duration of scalp psoriasis. Tabled results are provided in Appendix Section A.1.2 on page 46. The tabled results show that subjects randomized to Taclonex[®] scalp suspension had the highest percentage of subjects with a baseline IGA score of 'mild' and the shortest duration

of scalp psoriasis. Overall, the majority of subjects had a baseline IGA score of 'moderate' or 'severe' psoriasis which was balanced between treatment groups.

3.1.1.4 Statistical Methodology For all analyses of the primary variable, Taclonex[®] scalp suspension will be compared to the three other treatment groups: betamethasone scalp suspension, calcipotriene scalp suspension, and vehicle scalp suspension. The efficacy of Taclonex[®] scalp suspension will be established if all three comparisons reach statistical significance at the two-sided $\alpha = 5\%$ significance level.

The primary analysis will be conducted on the full analysis set defined as all subjects randomized to treatment (note this review defines this population as the ITT population). The per protocol analysis set is considered supportive and consists of those patients in the full analysis set who have applied study medication, who provide efficacy data following start of treatment and who meet all inclusion/disease definition criteria as described in the protocol.

The protocol defined method for the assessment of the proportion of patients who achieve 'absence of disease' or 'very mild disease' according to the IGA at end of treatment (Week 8) will be compared between the treatment groups using the Cochran-Mantel-Haenszel test adjusting for the effect of center. In Protocol Amendment No. 2 a provision to allow for pooling of centers within a country is included for centers with small numbers of subjects enrolled yet the definition of small is not included. The statistical analysis plan states that comparisons of Taclonex[®] scalp suspension to vehicle will be pooled on country as few subjects randomized to vehicle were enrolled in a given center.

Recall that at the Pre-NDA Meeting the sponsor proposed multiple analysis populations due to the modification of the inclusion criteria of the ongoing trial. As it was not clear which analysis population was most appropriate the review of Study 405 includes primary analysis results from all three proposed populations.

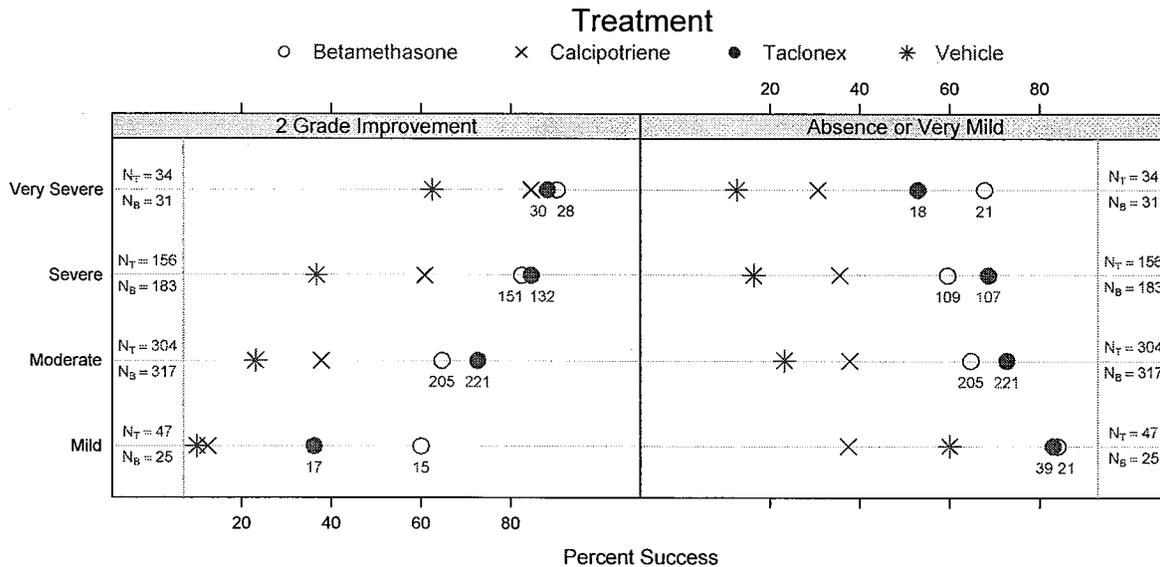
Per the protocol (Amendment No. 2), the analyses of the seven secondary variables will use a 0.01 level of significance to account for multiplicity. This level is greater than a conservative Bonferroni multiplicity adjustment of 0.007. The sponsor stated this multiplicity adjustment was based on the fact that some of the endpoints are correlated and as a result a Bonferroni adjustment of $\alpha = 0.007$ would be too severe. In communication with the sponsor, the Division provided the following comment about the choice of secondary endpoints and multiplicity adjustments.

"The sponsor should note that the magnitude of the adjustment depends on the extent of the correlation. The sponsor should get estimates of correlation among endpoints and adjust accordingly as the correlation is not expected to be the same for all endpoints. The sponsor might consider only a few secondary endpoints which are clinically relevant _____ to reduce the impact of mul-

b(4)

Since results of the ‘FDA Analysis’ differs from the other two analyses proposed by the sponsor, it appears that the baseline severity and definition of success have an impact on the efficacy conclusion for the comparison of Taclonex[®] scalp suspension to betamethasone. Figure 2 depicts the percent of subjects classified as success based on the baseline IGA score as well as the definition of treatment success. The numbers included in the plot below the corresponding plotting characters represent the number of subjects enrolled per treatment group and baseline IGA level who are defined as success based on the given definition of IGA success (note that numeric values are depicted only for Taclonex[®] scalp suspension and betamethasone). Additionally, the marginal sample sizes for Taclonex[®] scalp suspension and betamethasone are provided in the margins of the plot.

Figure 2: Efficacy According to Baseline IGA Score – Study 405



This plot clearly shows trends by treatment group. Specifically, the trends can be summarized as follows for each definition of success.

- *Defining success as a two grade improvement*
 1. The trend shows that as baseline severity increases the proportion of subjects defined as success also increases regardless of treatment.
 2. With the exception of subjects enrolled with baseline IGA scores of ‘mild’ and ‘very severe’, which showed a higher response rate for subjects treated with betamethasone than Taclonex[®] scalp suspension, there is only a minimal treatment effect be-

tween Taclonex[®] scalp suspension and betamethasone when the baseline IGA score is 'moderate' or 'severe'.

3. Subjects with a baseline IGA score of 'mild' had a higher proportion of successes when treated with betamethasone than Taclonex[®] scalp suspension which was enough to reduce the overall treatment effect to a level which does not reach statistical significance.

- *Defining success as absence or very mild disease*

1. The trend shows that as baseline severity increases the proportion of subjects defined as success decreases slightly regardless of treatment.
2. In general, Taclonex[®] scalp suspension tends to show the highest response rate for subjects with a baseline IGA score of 'moderate' or 'severe'.

Due to the observed reversed treatment effect between subjects treated with Taclonex[®] scalp suspension and betamethasone with baseline IGA scores of 'very severe' further analysis was conducted on these subjects. Of the 65 subjects treated with Taclonex[®] scalp suspension or betamethasone with baseline IGA scores of 'very severe' 55% were enrolled in Canada and 26% in France. One site in Canada, CA122, which listed Dr. Lyn Guenther² as the primary investigator enrolled a total of 13 subjects (6 Taclonex[®] scalp suspension, and 7 betamethasone) with a baseline IGA score of 'very severe'. 1 out of 6 subjects (16.7%) treated with Taclonex[®] scalp suspension was rated a treatment success at end of treatment compared to 6 out of 7 subjects (85.7%) treated with betamethasone was rated a treatment at end of treatment. Overall, such a difference in treatment effects cannot be explained from the sponsor's submission.

This section summarized the efficacy of Study 405 when looking at the ITT population with imputation of missing data using LOCF. The results of the multiple analyses showed that the baseline IGA score, mainly subjects with mild IGA scores, as well as the definition of the success criteria impacted study conclusions. As results are based upon subgroup analyses which were not pre-specified and the multiplicity adjustment not pre-specified, consistency of efficacy findings among the other pivotal study, Study 406, and other supportive studies will be examined in more detail in the integrated summary of efficacy found in Section 3.1.3.

3.1.1.6 Primary Endpoint Results (PP-LOCF) The per protocol analysis set consists of those patients in the full analysis set who have applied study medication, who provide efficacy data following start of treatment, and who meet all inclusion/disease definition criteria as described in the protocol. Other reasons for excluding patients or patient data from the per protocol analysis set were the following.

²Address: Guenther Dermatology Research Centre, 835 Richmond Street, London, Ontario N6A3H7 Canada

- No efficacy after the first baseline visit.
- Failure to take study medication.
- No IGA assessment at baseline or end of treatment.
- The extent of scalp psoriasis did not meet inclusion criteria (i.e. at least 10%)
- Use of prohibited treatment therapies.
- Failure to apply enough of prescribed treatment.
- Failure to attend final visit within one week of planned final visit.

This resulted in the exclusion of 76 subjects from the PP analysis population and consequently a total of 1429 subjects were evaluated for efficacy in the PP population. Efficacy results of the PP analysis population are provided in Table 6. Results from the PP analysis are similar to those of the ITT analysis population namely that the “FDA Analysis” failed to demonstrate the statistical significance of Taclonex® scalp suspension over betamethasone. The comparisons of Taclonex® scalp suspension to calcipotriene and vehicle were both highly significant ($p < 0.001$) in all analyses.

Table 6: Investigator Global Results (PP-LOCF) – Study 405

	Taclonex	Betamethasone	Calcipotriene	Vehicle
Sponsors Original Analysis				
Sample Size	513	531	254	131
Success (%)	374 (72.9)	347 (65.3)	98 (38.6)	31 (23.7)
p-value ¹	-	0.0074	< .001	< .001
Sponsors Amended Analysis				
Sample Size	468	507	240	121
Success (%)	336 (71.8)	326 (64.3)	92 (38.3)	25 (20.7)
p-value ²	-	0.0134	< .001	< .001
FDA Analysis				
Sample Size	513	531	254	131
Success (%)	390 (76)	388 (73.1)	123 (48.4)	40 (30.5)
p-value ¹	-	0.2221	< .001	< .001

¹ Cochran-Mantel-Haneszal test stratified by pooled site.

² Fisher’s Exact test due to small stratum in pooled sites.

Source: Reviewer’s analysis (see reviewer comment).

Reviewer Comment: *Results of the PP-LOCF efficacy analysis based on the ‘Sponsor’s Original Analysis’ differ slightly from Table 60 of the Study Report in terms of the number of defined successes though the denominators in both are the same.³ The study report does not make it clear how the missing data were handled and this is one potential reason for the discrepant results. Overall, the p-values in both analyses are quite similar.*

3.1.1.7 Missing Data Sensitivity Analysis The following strategy was used to perform a sensitivity analysis on the missing data for the analysis population which *excludes* subjects with baseline IGA scores of ‘mild’. Subjects that dropped out of the trial early due to any of the following reasons had efficacy data considered missing at week 8.

- Exclusion criteria developed
- Lost to follow-up
- Voluntary (no other reason)
- Other

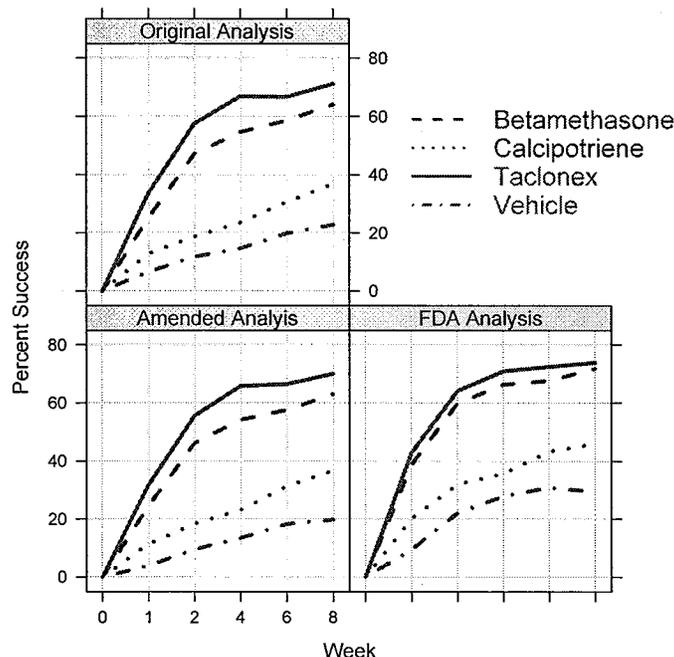
Additionally, subjects that dropped out of the trial early due to an unacceptable AE or unacceptable efficacy were considered week 8 treatment failures. Subjects that dropped out of the trial early due to efficacy response were considered a treatment response.

Rather than imputing the data using LOCF, three alternative imputation scenarios are proposed. These are to impute the missing data as all failures, all successes, and impute using the overall mean of those completing the trial for a given treatment arm. Using the ‘Sponsor’s Amended Analysis’ population and the above definitions of missing, 49, 34, 22, and 10 subjects have missing Week 8 efficacy observations for Taclonex® scalp suspension, betamethasone, calcipotriene, and vehicle, respectively.

Table 7 contains the results for the sensitivity analyses. Efficacy results in the comparison of Taclonex® scalp suspension to calcipotriene and vehicle are highly significant for all methods of data imputation. Due to the higher proportion of missing subjects in Taclonex® scalp suspension than betamethasone, the imputation strategies of imputing the mean response rate or as treatment success were more favorable to Taclonex® scalp suspension which reached the nominal 5% significance level. However, when all missing data were treated as failures this reduces the treatment effect and thereby resulting in a p-value less than the nominal 5% significance level. Note that results from this sensitivity analysis show that treatment effects from the ITT-LOCF population comparing Taclonex® scalp suspension to betamethasone fall between the imputation strategies of imputing the missing data based on the mean and imputing as successes.

³The study report lists 2 additional successes for Taclonex® scalp suspension, 4 fewer successes for betamethasone, 1 additional success for calcipotriene, and 1 additional success for vehicle.

Figure 3: Efficacy Across Time – Study 405



3.1.2 Study MBL 0406 INT

3.1.2.1 Study Design Study 406 was an international, multi-center, prospective, randomized, double-blind, three-arm, parallel group, 8-week study in patients with scalp psoriasis. The study was conducted at 98 centers (Belgium 11; Canada 6; Finland 7; France 7; Germany 14; Ireland 4; Netherlands 8; United Kingdom 41). Subjects enrolled were randomized in a 2:2:1 ratio to receive once daily treatment for up to 8 weeks with either Taclonex® scalp suspension, betamethasone scalp gel, or calcipotriene scalp gel (i.e. this trial did not include a vehicle treatment arm). The study enrolled a total of 1418 subjects; 568 patients to Taclonex® scalp suspension, 563 to betamethasone scalp gel, and 286 to calcipotriene scalp gel.

As with Study 405, the sponsor initiated Study 406 which included subjects with baseline IGA scores of 'mild' prior to the End of Phase 2 (EOP2) meeting with the Agency held on December 1, 2004. On January 20, 2005 the sponsor revised the protocol to reflect that upon enrollment subjects must have at least an IGA score of 'moderate'.

Visits to the investigative site were performed on Day 0 (Visit 1), Day 7 (Visit 2), Day 14 (Visit 3), Day 28 (Visit 4), Day 42 (Visit 5), and Day 56 (Visit 6). A follow-up visit took place 14 days after the subjects's last on-treatment visit if a treatment related (possible, probable or not assessable relationship to treatment) adverse event was ongoing.

3.1.2.2 Endpoints The protocol defined primary and secondary endpoints for Study 406 are the same as those defined in Study 405. As with Study 405 being initiated prior to the End of Phase 2 Meeting with the Agency, the same difficulties about the relationship between the baseline severity level and definition of the primary endpoint are also relevant to Study 406. As such, efficacy evaluations again are presented using the three analyses as proposed by the sponsor. Additionally, as previously mentioned, Study 406 did not include a vehicle arm.

3.1.2.3 Patient Disposition and Baseline Characteristics

3.1.2.3.1 Patient Disposition The disposition of subjects randomized into Study 406 is tabulated in Table 8. In Study 406 the rate of withdrawn subjects is highest in the calcipotriene arm with the most prevalent reasoning being lack of efficacy, unacceptable adverse events, and other. Subjects randomized to Taclonex[®] scalp suspension had the lowest rate of dropouts with ‘Other’ listed as the most common reason for dropout.⁴

Table 8: Subject Disposition – Study 406

	Taclonex [®] scalp suspension (N = 568)	Betamethasone (N = 563)	Calcipotriene (N = 286)
Completed all trial visits	469 (82.6)	465 (82.6)	244 (85.3)
Efficacy prior to week 8 [†]	51 (9.0)	32 (5.7)	4 (1.4)
Discontinued*	48 (8.5)	66 (11.7)	38 (13.3)
Exclusion criteria emerged	2 (0.4)	4 (0.7)	0 (0.0)
Unacceptable adverse event(s)	4 (0.7)	7 (1.2)	8 (2.8)
Death	0 (0.0)	0 (0.0)	1 (0.3)
Unacceptable treatment efficacy	7 (1.2)	9 (1.6)	8 (2.8)
Lost to follow-up	12 (2.1)	17 (3.0)	6 (2.1)
Voluntary (and no other reason)	9 (1.6)	6 (1.1)	4 (1.4)
Other	16 (2.8)	25 (4.4)	15 (5.2)

[†] Subjects had a treatment response prior to Week 8 and thus did not have a week 8 visit.

* Subjects can have more than one reason for discontinuation.

Source: Table 2 of the Sponsor’s Study Report; results reproduced by reviewer.

3.1.2.3.2 Baseline Demographic Factors The baseline demographic factors collected in the trial were: age, race, gender, and country. A summary of these four factors by treatment

⁴‘Other’ reasons included items such as dissatisfaction with the cosmetic effect, withdrawing consent, and product recall.

group did not reveal any differences amongst the treatment groups at baseline. Table 20 in Appendix Section A.1.1 contains the tabulated results. With the trial being conducted in Europe and Canada the prevailing race was Caucasian which was recorded in greater than 95% of enrolled subjects.

3.1.2.3.3 Baseline Prognostic Factors The following baseline prognostic factors were evaluated to assess for any imbalance between the treatment groups which might impact efficacy: IGA, extent of scalp psoriasis, redness of the scalp, scaliness of the scalp, plaque thickness of the scalp, and duration of scalp psoriasis. Tabled results are provided in Appendix Section A.1.2 on page 46. All prognostic factors appear to be similar across the treatment arms. Overall, the majority of subjects had an IGA score of ‘moderate’ or ‘severe’ scalp psoriasis at baseline.

3.1.2.4 Statistical Methodology The statistical methodology for Study 406 is the same as that for Study 405. Again, three analyses are performed as the sponsor’s trials were initiated prior to obtaining concurrence from the Agency. The primary analysis is based on the full analysis set (i.e. ITT) with missing week 8 data imputed using LOCF. In this trial a vehicle is not included and in order to demonstrate statistical significance the comparisons of Taclonex[®] scalp suspension to both betamethasone and calcipotriene are compared at the two-sided $\alpha = 0.05$ significance level.

3.1.2.5 Primary Endpoint Results (ITT-LOCF) Results for the primary endpoints based on the three analyses is provided in Table 9. Unlike Study 405, all three analyses demonstrated that Taclonex[®] scalp suspension was statistically significant in comparison to betamethasone and calcipotriene at the two-sided $\alpha = 0.05$ significance level.

Figure 4 depicts efficacy results for subjects based on the baseline IGA score as well as the definition of the primary endpoint. For all baseline IGA scores, Taclonex[®] scalp suspension has a higher response rate than betamethasone when the IGA endpoint success criteria is defined as ‘absence of disease’ or ‘very mild disease’. The majority of subjects who enrolled with an IGA score of ‘moderate’ or ‘severe’, the response rate is higher in subjects treated with Taclonex[®] scalp suspension than betamethasone or calcipotriene. However, as was seen in Study 405, when defining success as a two grade improvement, the response rate is higher in subjects treated with betamethasone than Taclonex[®] scalp suspension when enrolled with a baseline IGA score of ‘mild’.

Recall, that in Study 405 subjects enrolled with a baseline IGA score of ‘very severe’ had a higher response rate when treated with betamethasone than with Taclonex[®] scalp suspension when defining treatment success as ‘absence of disease’ or ‘very mild disease’. This finding may have been the result of a single center as discussed in Section 3.1.1.5. Using the same population in Study 406, this time Taclonex[®] scalp suspension has a higher response rate than

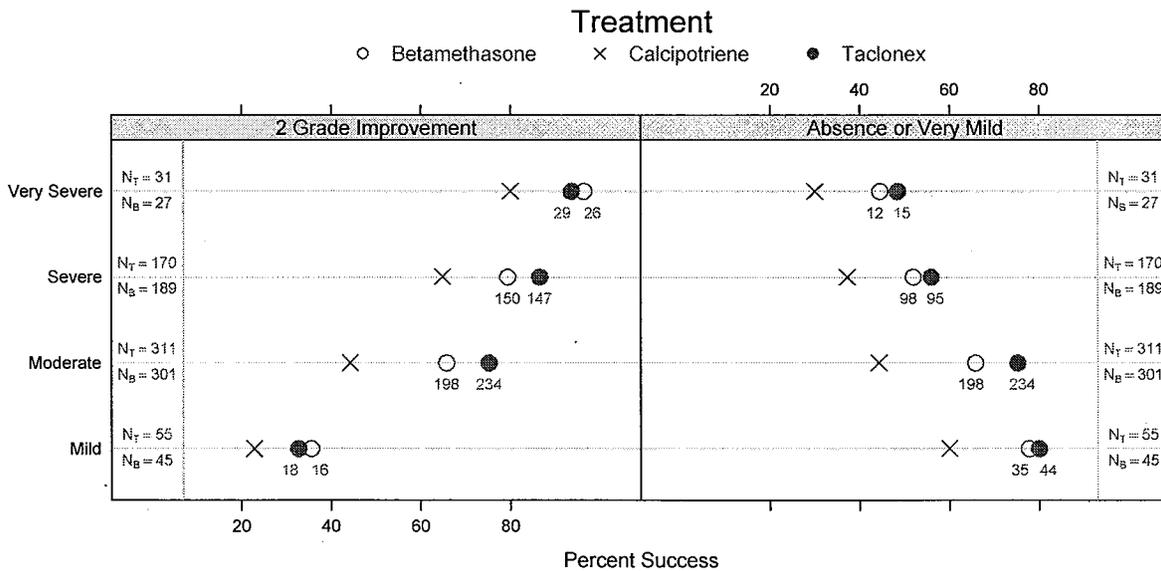
Table 9: Investigator Global Results at Week 8 (ITT-LOCF) – Study 406

	Taclonex	Betamethasone	Calcipotriene
Sponsors Original Analysis			
Sample Size	567	562	286
Success (%)	388 (68.4)	343 (61.0)	124 (43.4)
p-value ¹	-	0.0079	< .001
Sponsors Amended Analysis			
Sample Size	512	517	251
Success (%)	344 (67.2)	308 (59.6)	103 (41.0)
p-value ¹	-	0.0089	< .001
FDA Analysis			
Sample Size	567	562	286
Success (%)	428 (75.5)	390 (69.4)	142 (49.7)
p-value ¹	-	0.0181	< .001

¹ Cochran-Mantel-Haenszel test stratified by pooled site.

Source: Sponsor’s Original Analysis is a reproduction of Table 15 of the Study Report. All other analyses performed by statistical reviewer.

Figure 4: Efficacy According to Baseline IGA Score – Study 406



betamethasone. In Study 406 enrollment of subjects with ‘very severe’ baseline IGA scores was balanced across countries and no individual site recruited more than a total of 5 subjects with a ‘very severe’ IGA score. In addition, a comparison was made between Taclonex[®] scalp suspension and betamethasone according to demographic and baseline prognostic factors. This comparison showed a very similar baseline distribution on all demographic and baseline prognostic factors.

3.1.2.6 Primary Endpoint Results (PP-LOCF) The per protocol analysis set consists of those patients in the full analysis set who have applied study medication, who provided efficacy data following start of treatment and who meet all inclusion/disease definition criteria as described in the protocol. Other reasons for excluding patients or patient data from the per protocol analysis set in Study 406 were the following.

- No efficacy after the first baseline visit.
- The subject did not use any trial medication.
- The subject did not meet inclusion/exclusion criteria.
- Use of prohibited treatment therapies.
- Noncompliance including violating visit window time frames.

This resulted in the exclusion of 59 subjects from the PP analysis population and consequently a total of 1356 subjects were evaluated for efficacy on the PP population. Efficacy results of the PP analysis population are provided in Table 10. Results from all three analyses using the PP analysis population reach the nominal two-sided $\alpha=0.05$ significance level.

Reviewer Comment: *Similar to Study 405, the Study Report results for the PP population are slightly different in Study 406 than the reviewer’s analysis by one or two additional treatment successes for each arm. Overall, this difference does not alter the efficacy finding.*

3.1.2.7 Missing Data Sensitivity Analysis As described in Section 3.1.1.7 for Study 405, a similar sensitivity analysis was implemented for Study 406 to assess the impact of the method of imputation on the efficacy conclusions. To reiterate the procedure; the following strategy was used to perform a sensitivity analysis on the missing data for the analysis population which *excludes* subjects with mild IGA scores. Subjects that dropped out of the trial early due to any of the following reasons had efficacy data considered missing at week 8.

- Exclusion criteria
- Lost to follow-up

Table 10: Investigator Global Results at Week 8 (PP-LOCF) – Study 406

	Taclonex	Betamethasone	Calcipotriene
Sponsors Original Analysis			
Sample Size	547	539	270
Success (%)	381 (69.7)	335 (62.2)	123 (45.6)
p-value ¹	-	0.0077	< .001
Sponsors Amended Analysis			
Sample Size	496	501	241
Success (%)	338 (68.1)	303 (60.5)	102 (42.3)
p-value ¹	-	0.0085	< .001
FDA Analysis			
Sample Size	547	539	270
Success (%)	421 (77.0)	384 (71.2)	141 (52.2)
p-value ¹	-	0.0232	< .001

¹ Cochran-Mantel-Haenszel test stratified by pooled site.

Source: Reviewer's analysis (see reviewer comment).

- Voluntary (no other reason)
- Other

Additionally, subjects that dropped out of the trial early due to an unacceptable AE or unacceptable efficacy were considered week 8 treatment failures. Subjects that dropped out of the trial early due to efficacy response were considered a treatment response.

Rather than imputing the data using LOCF, three alternative imputation scenarios are proposed. These are to impute the missing data as all failures, all successes, and impute using the overall mean of those completing the trial for each treatment arm. Using the 'Sponsor's Amended Analysis' population and the above definitions of missing, 33, 41, and 16 subjects have missing Week 8 efficacy observations for Taclonex® scalp suspension, betamethasone, and calcipotriene, respectively. Table 11 contains the results for the sensitivity analysis. In Study 406 all alternate methods of imputation resulted in a p-value less than the nominal 5% significance level for the comparison of Taclonex® scalp suspension to both betamethasone and calcipotriene.

3.1.2.8 Secondary Endpoint Results Recall that the sponsor listed seven secondary endpoints in the protocol without adequately addressing multiplicity per the request from the Division. Of the seven protocol-listed secondary endpoints two were to assess the percent success based on the IGA at weeks 2 and 4.

b(4)

Table 11: Imputation Sensitivity Analysis - Study 406

	Taclonex (N = 512)	Betamethasone (N = 517)	Calcipotriene (N = 251)
Subjects Missing Data [†]	33	41	16
Imputed Failures			
Success (%)	333 (65.0)	295 (57.1)	101 (40.2)
p-value*	-	0.0089	< 0.001
Imputed Mean			
Success (%)	354 (69.1)	318 (61.5)	107 (42.6)
p-value*	-	0.0107	< 0.001
Imputed Successes			
Success (%)	366 (71.5)	336 (65.0)	117 (46.6)
p-value*	-	0.0272	< 0.001

[†] Note that sample sizes differ from Table 8 as this analysis excludes mild subjects.

* Fisher's Exact Test.

Source: Reviewer's analysis.

Figure 5 depicts the response rates across time for each of the three analyses. b(4)

As the multiplicity adjustment was not adequately addressed as requested by the Division a priori for testing of secondary endpoints, it is unclear if the Type I error is fully controlled when assessing efficacy at earlier time points. Tables of response rates and 95% confidence intervals for the difference of Taclonex® scalp suspension from each comparator are provided in the Appendix Section A.1.3. Overall, the comparisons using the "Original Analysis" and "Amended Analysis" tend to show more favorable results than the "FDA Analysis".

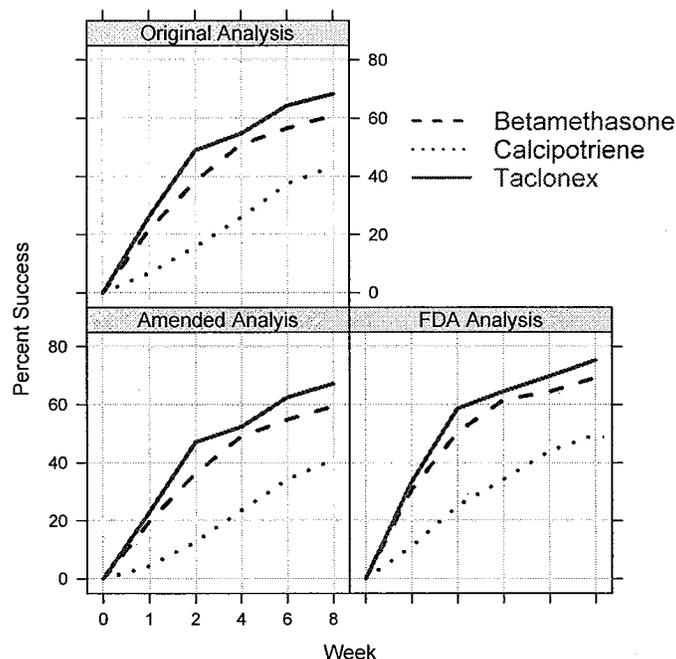
3.1.3 Integrated Summary of Efficacy

Six studies are included in the integrated summary of efficacy (ISE) which consists of two studies with a vehicle control, Study 405 and Study 502, as well as four trials which do not include vehicle but active control; Study 401, Study 406, Study 407, and Study 503⁵. While the objectives of the 6 trial might differ, each of these 6 trials included a treatment of once daily for at least 8 weeks with an evaluation visit at Week 8.

The (ISE) is based on the population of subjects with at least a baseline IGA score of

⁵Study 405 and Study 406 are considered the primary efficacy Phase 3 trials which are assessed in the body of the review. Studies 502, 401, 401, and 503 are considered supportive and further details are provided in the Appendix Section A.2

Figure 5: Efficacy Across Time – Study 406



‘moderate’. The primary endpoint is defined as the percent of subjects who have an IGA score of ‘absence of disease’ or ‘very mild disease’ at week 8. The analysis population is the ITT population with missing data imputed using LOCF.

Table 12 depicts the sample size of each trial along with the observed response rate for each treatment arm. In trials where a treatment arm is not included the table denotes such exclusions as ‘-’. Overall, the clinical development of Taclonex® scalp suspension using these 6 studies results in a total of 1858, 1143, 947, 168, and 105 subjects randomized to Taclonex® scalp suspension, betamethasone, calcipotriene, vehicle, and Dovonex, respectively.

3.1.3.1 Summary of Response Rates for Phase 3 Trials The six trials included in the ISE are not of identical design, however the trials are of similar design through the Week 8 efficacy assessment. To visualize the response rates for the individual studies Figure 6 was constructed. The order of the study listed on the *x*-axis is based upon the date the trial was initiated starting with earliest to latest. Overall, the response rates are quite consistent across studies for each of the treatment groups with the exception of the vehicle which is explored further in Section 3.1.3.3 and the increased response seen in both treatment arms of the Phase 2 study (Study 401).

As Figure 6 demonstrated quite consistent response rates for treatment the treatment groups,

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Table 12: Integrated Summary of Efficacy (ITT-LOCF)

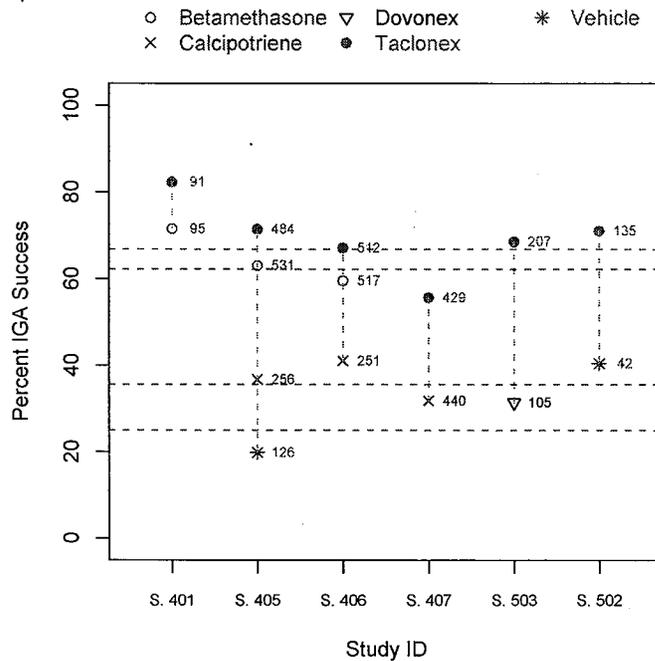
	Taclonex	Betamethasone	Calcipotriene	Vehicle	Dovonex
Study 401					
Sample Size	108	110	-	-	-
Success (%)	90 (83.3)	82 (74.5)	-	-	-
Study 405†					
Sample Size	494	531	256	126	-
Success (%)	346 (70.0)	335 (63.1)	94 (36.7)	25 (19.8)	-
Study 406†					
Sample Size	512	517	251	-	-
Success (%)	344 (67.2)	308 (59.6)	103 (41.0)	-	-
Study 407					
Sample Size	429	-	440	-	-
Success (%)	239 (55.7)	-	140 (31.8)	-	-
Study 502					
Sample Size	135	-	-	42	-
Success (%)	96 (71.1)	-	-	20 (47.6)	-
Study 503					
Sample Size	207	-	-	-	105
Success (%)	142 (68.6)	-	-	-	33 (31.4)

† Trial is considered primary Phase 3 trial

Source: Reviewer's analysis.

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Figure 6: Efficacy Summary for all Controlled Trials



the response rates from Table 12 are combined for each treatment arm and then divided by the total sample size for the given treatment arm to give a weighted mean response. The overall sample size and weighted mean for each treatment arm in the six studies included in the ISE is provided in Table 13.⁶ Results from this table clearly show that the treatment between Taclonex® scalp suspension and betamethasone is much smaller than treatment effects comparing Taclonex® scalp suspension to calcipotriene, vehicle, and Dovonex.

Table 13: Integrated Summary of Efficacy (ITT-LOCF)

	Taclonex (N = 1858)	Betamethasone (N = 1143)	Calcipotriene (N = 947)	Vehicle (N = 168)	Dovonex (N = 105)
Weighted Mean	66.8%	62.2%	35.6%	25.0%	31.4%
Difference	-	4.6%	31.3%	41.8%	35.4%

Source: Reviewer’s analysis.

⁶Note that the weighted mean response is depicted in Figure 6 as horizontal, dotted lines for each treatment group.

3.1.3.2 Percent Contribution of Monads The identity proposed by Karl E. Peace[1, 2] shown in Equation 1 provides estimates of the effectiveness of Taclonex, betamethasone, calcipotriene, and the interaction of betamethasone and calcipotriene.

$$E(\text{Taclonex}) = E(\text{betamethasone}) + E(\text{calcipotriene}) + E(\text{Interaction}) \quad (1)$$

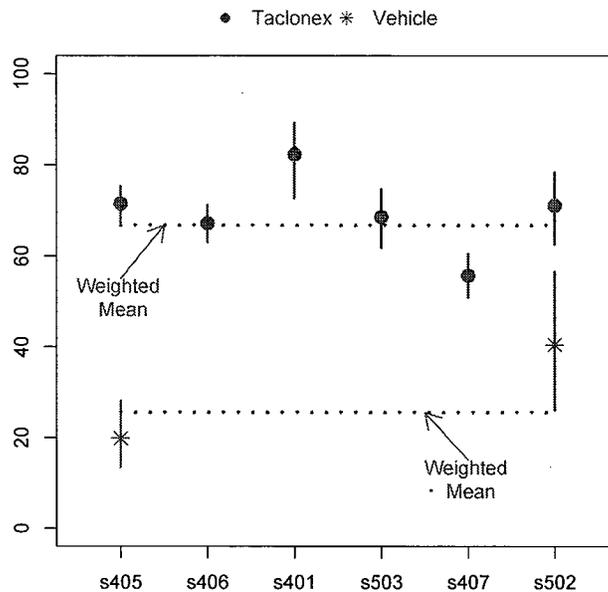
Using the above identity and the weighted means from Table 12 the percent contribution of each of the monads (e.g. $P(\text{betamethasone})$ is interpreted as percent of the effectiveness of Taclonex contributed by betamethasone) and the interaction are estimated as follows.

- $P(\text{betamethasone}) = 100 \times [E(\text{betamethasone})/E(\text{Taclonex})] = 89.0\%$
- $P(\text{calcipotriene}) = 100 \times [E(\text{calcipotriene})/E(\text{Taclonex})] = 25.3\%$
- $P(\text{Interaction}) = 100 \times [E(\text{Interaction})/E(\text{Taclonex})] = -14.3\%$

These calculations show that betamethasone has a higher contribution to the effectiveness of Taclonex[®] scalp suspension than calcipotriene. In addition, as the interaction term is negative this implies that the two monads in the combination are antagonistic meaning the effectiveness of the combination is less than the sum of its parts.

3.1.3.3 Summary of Vehicle Controlled Trials Figure 7 contains response rates and unadjusted 95% confidence intervals for each of the trials focusing only on subjects treated with Taclonex[®] scalp suspension or vehicle. The weighted mean across each of the trials for each treatment arm is shown as a horizontal dotted line. In Study 502 the vehicle did have a higher response rate than in Study 405 (difference of 27.8%) though the number of subjects treated in Study 502 was not large ($N = 42$). The lower confidence bound of the response rate in subjects treated with Taclonex[®] scalp suspension is above the weighted mean response of subjects treated with vehicle for all studies. As seen in Table 13 the difference in weighted means of Taclonex[®] scalp suspension and vehicle is more than 40%.

In Figure 7 the response rate of vehicle in Study 502 are much higher than in Study 405. The baseline prognostic factors for each of these studies are provided in Table 21 and Table 33. Examination of the two tables suggests that subjects enrolled in Study 502 had lower severity ratings of the clinical signs of psoriasis at baseline than subjects enrolled in Study 405. Thus, this might be one explanation for the higher proportion of successes for vehicle treated subjects in Study 502.

Figure 7: Efficacy Response for Taclonex[®] scalp suspension and Vehicle

3.2 Evaluation of Safety

3.2.1 Adverse Events

Study MBL 0401, Study MBL 0405, Study MBL 0406, and Study MBL 0503 all included treatment periods of 8 weeks. These four controlled-trials are used in the tabulations of adverse events. In addition, the tabulations only include those subjects in the electronic data sets with a flag indicating eligibility for safety evaluation. This results in a safety population of 1406, 1214, 548, and 135 subjects treated with Taclonex[®] scalp suspension, betamethasone, calcipotriene, and vehicle, respectively. The adverse events are coded using the MedDRA dictionary version 6.1.

Results are presented in Table 14 which includes both the MedDRA preferred term (PT) as well as the system organ classification (SOC) when the preferred term is reported in at least 3% of subjects. Note that for subjects that reported an AE on more than one occasion only a single instance was used in the tabulation. Based on Table 14, Taclonex[®] scalp suspension does not appear to show an increase incidence in adverse events to either of its monads or vehicle. In fact, for the skin and subcutaneous disorders SOC both subjects treated with calcipotriene and vehicle reported a higher incidence of PT's than Taclonex[®] scalp suspension and betamethasone.

Table 14: Adverse Events by System Organ Class and Preferred Term[†]

	Taclonex (N = 1406)	Betamethasone (N = 1214)	Calcipotriene (N = 548)	Vehicle (N = 135)
Gastrointestinal disorders				
Diarrhoea	9 (0.6)	4 (0.3)	5 (0.9)	2 (1.5)
General disorders and administration site conditions				
Pain	5 (0.4)	3 (0.2)	4 (0.7)	3 (2.2)
Infections and infestations				
Nasopharyngitis	70 (5.0)	70 (5.8)	27 (4.9)	9 (6.7)
Upper respiratory tract infection	33 (2.3)	27 (2.2)	13 (2.4)	3 (2.2)
Influenza	19 (1.4)	24 (2.0)	11 (2.0)	1 (0.7)
Musculoskeletal and connective tissue disorders				
Back pain	19 (1.4)	14 (1.2)	5 (0.9)	1 (0.7)
Nervous system disorders				
Headache	46 (3.3)	46 (3.8)	12 (2.2)	4 (3.0)
Skin and subcutaneous tissue disorders				
Pruritus	38 (2.7)	30 (2.5)	49 (8.9)	9 (6.7)
Psoriasis	37 (2.6)	25 (2.1)	18 (3.3)	4 (3.0)
Erythema	6 (0.4)	5 (0.4)	18 (3.3)	1 (0.7)
Skin irritation	6 (0.4)	6 (0.5)	17 (3.1)	4 (3.0)

[†] Results are presented as counts with percentages in parentheses.

Source: Reviewer's Analysis.

3.2.2 Serious Adverse Events

A total of 29 serious adverse events (SAEs) were reported from 23 subjects. Of these 29 SAEs: 13, 6, 9, and 1 were reported in subjects treated with Taclonex[®] scalp suspension, betamethasone, calcipotriene, and vehicle, respectively. The 13 SAEs reported by subjects treated with Taclonex[®] scalp suspension occurred in 9 subjects of which all were recorded as being not related to study treatment by the site investigator. Table 15 contains a list of all the SAEs reported in subjects treated with Taclonex[®] scalp suspension.

Table 15: Serious Adverse Events by System Organ Class and Preferred Term†

	Taclonex (N = 1406)	Betamethasone (N = 1214)	Calcipotriene (N = 548)	Vehicle (N = 135)
Gastrointestinal disorders				
Diverticulitis	1 (0.1)	0 (0)	0 (0)	0 (0)
Infections and infestations				
Groin abscess	1 (0.1)	0 (0)	0 (0)	0 (0)
Pneumonia	1 (0.1)	0 (0)	1 (0.2)	0 (0)
Injury, poisoning and procedural complications				
Hand fracture	1 (0.1)	0 (0)	0 (0)	0 (0)
Joint injury	1 (0.1)	0 (0)	0 (0)	0 (0)
Road traffic accident	1 (0.1)	0 (0)	0 (0)	0 (0)
Tibia fracture	1 (0.1)	0 (0)	0 (0)	0 (0)
Wrist fracture	1 (0.1)	0 (0)	0 (0)	0 (0)
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain	1 (0.1)	0 (0)	0 (0)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Anal cancer	1 (0.1)	0 (0)	0 (0)	0 (0)
Nervous system disorders				
Convulsion	1 (0.1)	0 (0)	0 (0)	0 (0)
Syncope	1 (0.1)	0 (0)	0 (0)	0 (0)
Vascular disorders				
Circulatory collapse	1 (0.1)	0 (0)	0 (0)	0 (0)

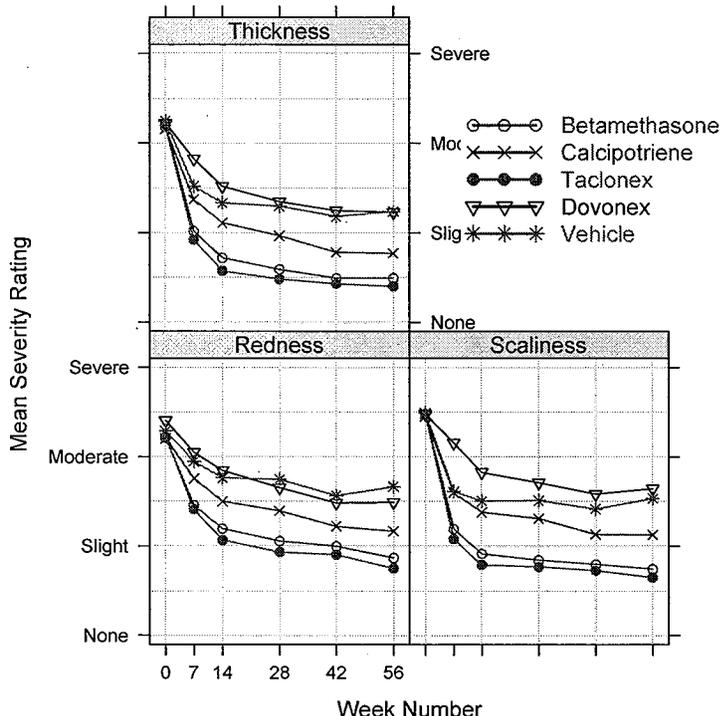
† Results are presented as counts with percentages in parentheses.

Source: Reviewer's Analysis.

3.2.3 Local Skin Reaction Signs

To assess the signs of scalp psoriasis, investigator's rated the redness, scaliness, and thickness on a 5 point scale with 0 = no sign, 1 = slight signs, 2 = moderate signs, 3 = severe signs, and 4 = very severe signs. The mean score was calculated for each visit from baseline to week 8 for the same four studies included in the presentation of adverse events by SOC and PT. The mean profile for each of the treatment groups is presented in Figure 8. For all treatment arms a rapid decrease occurs from baseline to day 14 and then only a slight decrease is seen thereafter. Comparatively the mean profile of Taclonex® scalp suspension shows a lower score for each skin sign than the other treatment arms though the difference is not large in comparison to betamethasone.

Figure 8: Local Skin Reaction Signs Across Time



3.2.4 HPA Axis Suppression

Study MBL 0404 FR was a multi-center trial to assess the effect of Taclonex[®] scalp suspension to treat scalp psoriasis plus Taclonex[®] ointment to treat body psoriasis on HPA axis and calcium metabolism. In this trial, subjects were treated once daily for up to 8 weeks for scalp psoriasis in addition to treatment of body psoriasis as needed. Subjects cleared of scalp psoriasis at week 4 were allowed to discontinue from the study.

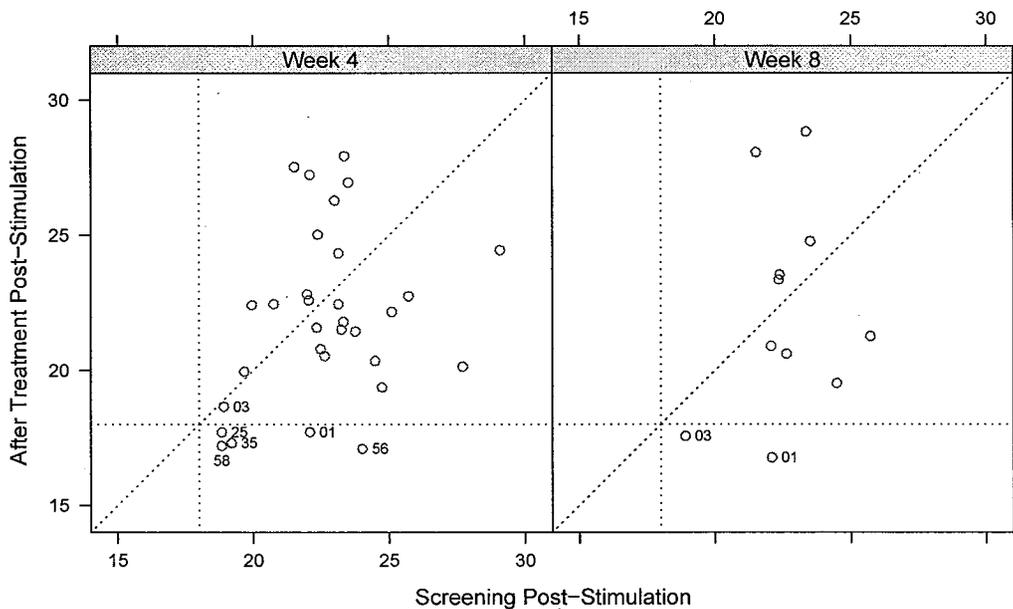
The primary response of interest was the adrenal response to the adrenocorticotrophic hormone (ACTH) stimulation test defined as serum cortisol level obtained after 30 minutes. The assessment of adrenal response was measured at baseline, week 4, and week 8 for subjects who did not discontinue at week 4. Cortisol levels at 30 minutes post-stimulation below 18 mcg/dL were considered to have HPA axis suppression.

Thirty-two subjects were included in the week 4 evaluation and eleven subjects were included in the week 8 evaluation. Note that subjects who had clearance of their scalp psoriasis at Week 4 were allowed to discontinue from the trial. Figure 9 depicts the screening post-stimulation values and the after treatment post-stimulation values (note that the *x* and *y*-axis are truncated

to exclude an outlying subject with baseline post-stimulation value near 50 and week 4 post-stimulation value near 40).

Subjects below the horizontal line of 18 are considered to have HPA axis suppression. Based upon this threshold, five out of 32 subjects (15.6%) were suppressed at week 4 and 2 out of 11 subjects (18.2%) were suppressed at week 8. One subject, ID 0001, was suppressed at both week 4 and week 8 with a lower post-stimulation value at week 8 than at week 4.

Figure 9: HPA Axis Suppression Assessment – Study 404



The general trend for both 4 week and 8 weeks tends to cluster around the 45° lines implying no change between baseline and post treatment visits though the number of subjects with 8 weeks of data is small from which to draw any definitive conclusion. Also, in looking at the bivariate distribution of the week 4 and week 8 post-stimulation values (not shown), the general trend appears to cluster around the 45° line.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

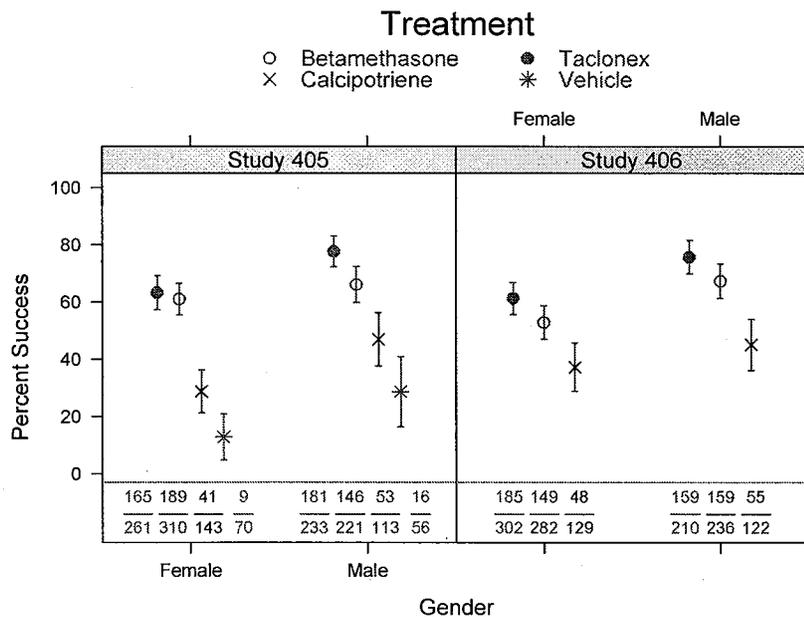
Section 4.1 provides a graphical assessment of efficacy by subgroup as well tabular information listed in the lower section of each graph for Study 405 and Study 406. The efficacy summaries by gender, race, and age correspond to the ‘Sponsor’s Amended Analysis’ (i.e. the analysis includes subjects with at least an IGA score of ‘moderate’ at baseline and success is defined as ‘absence of disease’ or ‘very mild disease’). Note that the protocol did not pre-specify any subgroup analysis which controlled the overall Type I error rate.

4.1 Gender, Race, and Age

4.1.1 Gender

Figure 10 depicts efficacy results according to gender along with unadjusted 95% confidence intervals. In both studies, Taclonex® scalp suspension had higher response rates than each of the monads and vehicle for both genders. For each treatment group the response rates for males tended to be higher than in females which was observed in both pivotal trials.

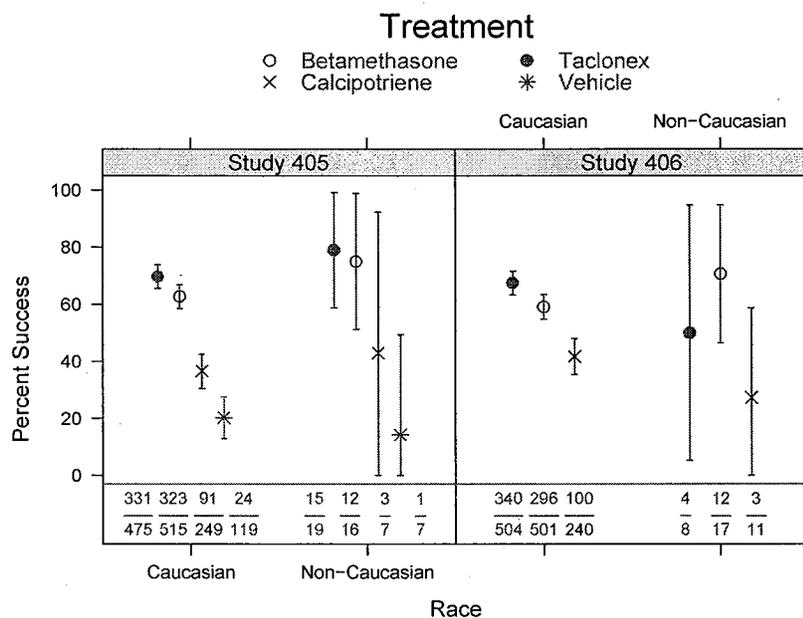
Figure 10: Efficacy Results According to Gender



4.1.2 Race

Due to such a small percentage of subjects enrolled with race recorded as Black, Asian, or Other (refer to Tables 19 and 20) race was dichotomized into two categories: Caucasian and Non-Caucasian. Figure 11 depicts the mean response rates along with unadjusted 95% confidence intervals by race. Even with collapsing race into two categories, due to the small percentage of Non-Caucasian subjects enrolled it is difficult to draw any conclusions on these subjects. Since a large portion of the subjects enrolled were Caucasian efficacy results within this subgroup were very similar to the findings found in the primary analyses.

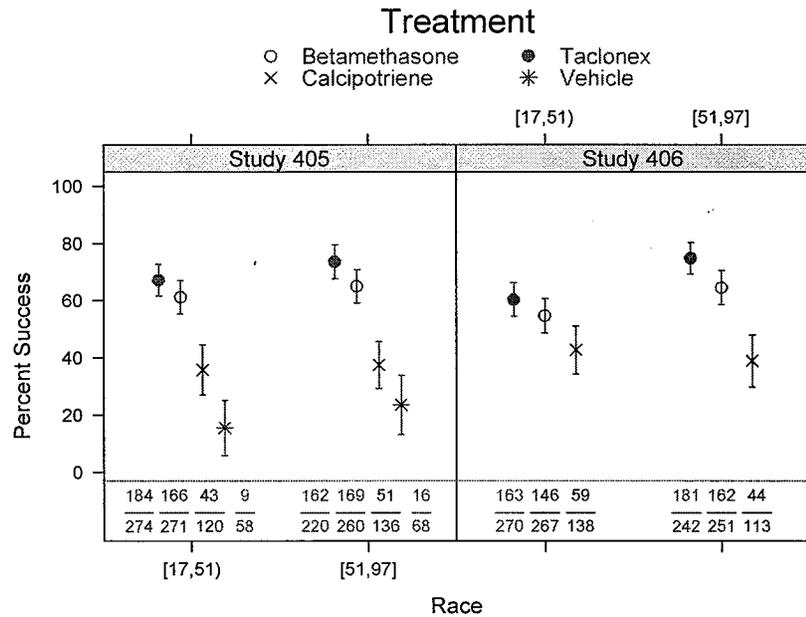
Figure 11: Efficacy Results According to Race



4.1.3 Age

The age of subjects was dichotomized into two categories which was based on the split of the overall median age of the two studies which was 50 years old. Results depicted in Figure 12 show that Taclonex® scalp suspension had higher response rates than each of the monads and vehicle for both age groups in each study. For each treatment group the response rates tended to be higher in the older cohort than the younger cohort which was seen in both pivotal trials.

Figure 12: Efficacy Results According to Age

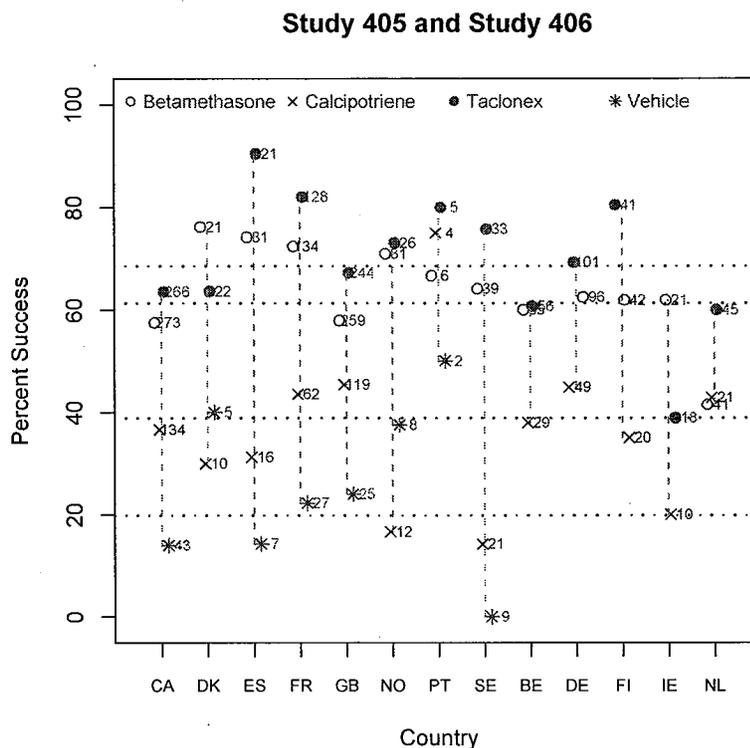


4.2 Other Special/Subgroup Populations

4.2.1 Efficacy by Country

To examine efficacy results by country, the data from Studies 405 and 406 were used jointly to depict the treatment effect for each country (vertical gray dotted lines) as well as the overall success rate (horizontal dotted lines) as shown in Figure 13. Sample size for a given treatment arm within a country is provided next to the plotting character of each treatment arm. Based upon this figure, there does not appear to be any country with a large deviation from the general trend. However in Denmark and Ireland, the success rate was higher in subjects treated with betamethasone than with Taclonex® scalp suspension.

Figure 13: Efficacy Results According to Country



5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The sponsor initiated both pivotal trials prior to attending an End of Phase 2 (EOP2) Meeting with the Division on December 1, 2004. The initial enrollment criteria in the two pivotal trials allowed subjects to be enrolled with an IGA score of 'mild' disease severity. At the EOP2 meeting the Division stated that subjects who enroll with an IGA score of 'mild' must achieve an IGA score of 'absence of disease' to be considered a treatment success as this better reflects a clinical improvement. Based upon this meeting the sponsor decided to revise the Phase 3 protocols to reflect that upon enrollment subjects must have at least an IGA score of 'moderate'. In addition, the Division also recommended the sponsor include a vehicle arm in Study 406 to aid in the interpretation of study findings.

At the Pre-NDA Meeting held on January 30, 2007 the sponsor informed the Division that they modified the enrollment criteria of the then ongoing Phase 3 trials. Such a change in the enrollment criteria raised questions about how to define treatment success (IGA dichotomized to 'absence of disease' or 'very mild disease' or IGA dichotomized to two grade improvement) as

well as what subject population to include (whether to include subjects enrolled with a baseline IGA score of ‘mild’ or exclude such subjects). Various analyses were performed throughout the review and based upon discussions with the clinical review team, it was decided to use the population which only included subjects with at least an IGA score of ‘moderate’ and to define IGA success as ‘absence of disease’ or ‘very mild disease’. This analysis population is what is referred to as the ‘Sponsor’s Amended Analysis’ throughout the body of the statistical review.

Efficacy results are provided in Table 16. In both studies, it was shown that the treatment effect comparing Taclonex[®] scalp suspension to betamethasone is much smaller than that comparing Taclonex[®] scalp suspension to calcipotriene. Based upon the above defined population and definition of treatment success, both studies were able to establish the contribution of each monad at the $\alpha = 0.05$ level. As can be seen in Table 16, the efficacy results for Study 405, namely the comparison of Taclonex[®] scalp suspension to betamethasone, were not as strong as the efficacy results in Study 406 though the lack of a vehicle arm in Study 406 makes it difficult to fully interpret study findings between trials.

Table 16: Investigator Global Results (ITT-LOCF)

	Taclonex	Betamethasone	Calcipotriene	Vehicle
Study MBL 405 INT				
Sample Size	494	531	256	126
Success (%)	346 (70.0)	335 (63.1)	94 (36.7)	25 (19.8)
p-value ²	-	0.0205	< .001	< .001
Study MBL 406 INT				
Sample Size	512	517	251	-
Success (%)	344 (67.2)	308 (59.6)	103 (41.0)	-
p-value ¹	-	0.0089	< .001	-

¹ Cochran-Mantel-Haneszal test stratified by pooled site.

² Fisher’s Exact test due to small stratum in pooled sites.

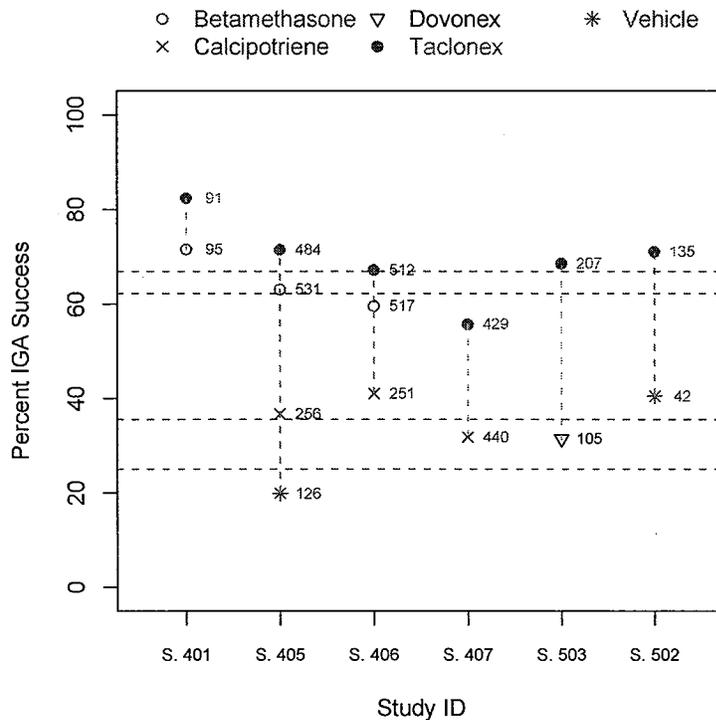
Source: Reviewer’s Analysis of the ‘Sponsor’s Amended Analysis’.

An integrated summary of efficacy (ISE) was incorporated to utilize data from four other late Phase clinical trials which examined the same dosing scheme used in Studies 405 and 406. Using the same analysis population as described and the same definition of treatment success, Figure 14 depicts response rates for the two pivotal trials and the four supportive trials. Overall, the response rates are quite consistent across studies for each of the treatment groups with the following exceptions.

- The Phase 2 trial, Study 401, had higher response rates in both treatment arms than in the other studies.

- The vehicle response in Study 502 is much higher than the observed vehicle response rate in Study 405 which is explored further in Section 3.1.3.3.

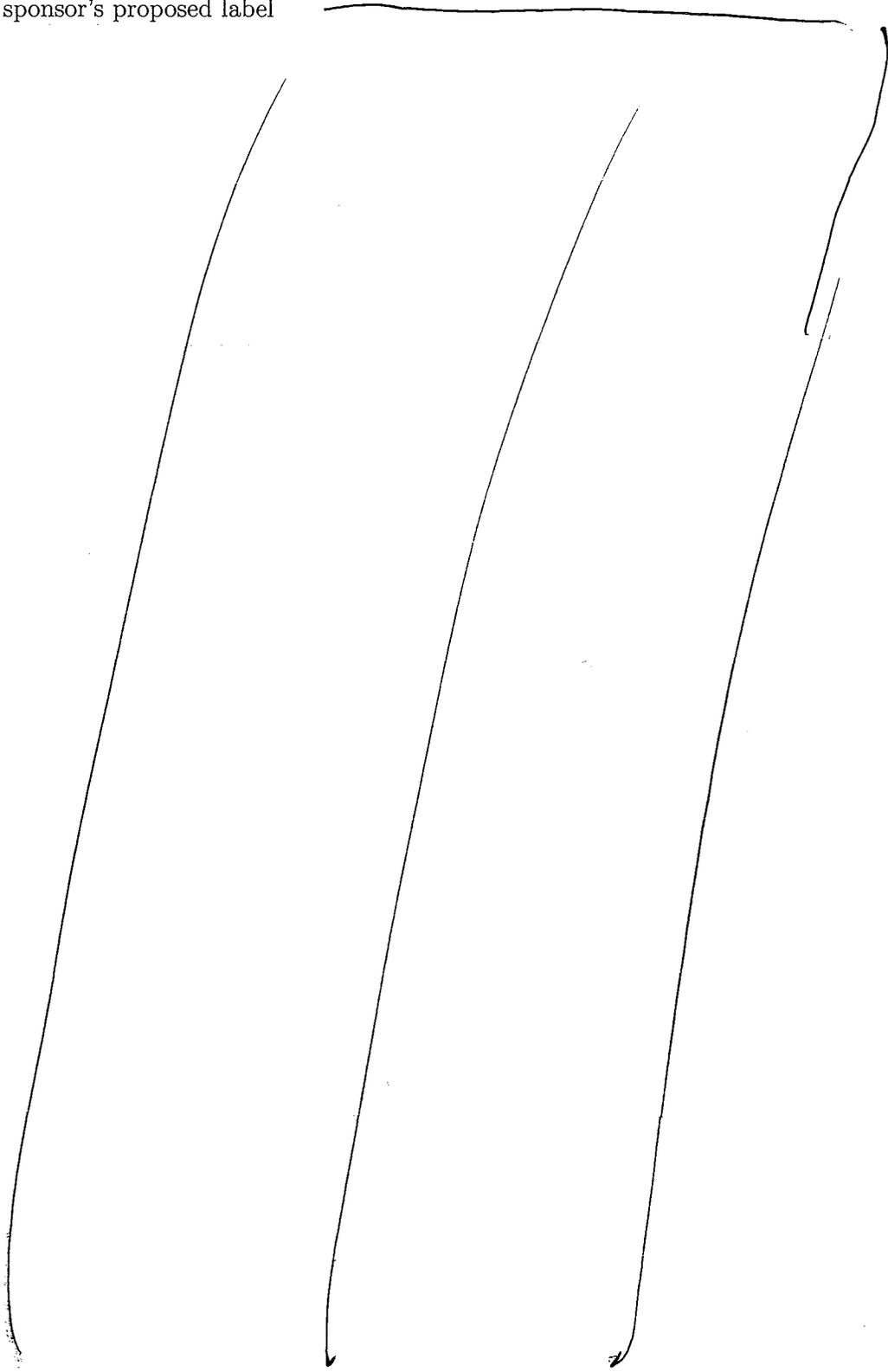
Figure 14: Efficacy Summary for all Controlled Trials



5.2 Conclusions and Recommendations

Overall, 4,116 subjects from six trials were treated with a once daily application of either Taclonex[®] scalp suspension, betamethasone, calcipotriene, or vehicle. Of the 4,116 subjects, 2,920 were enrolled in either Study 405 or Study 406. Of the pivotal trial enrollment of 2,920 subjects a total of 2,687 subjects had a baseline IGA score of ‘moderate’ of which 1,006 were exposed to Taclonex[®] scalp suspension. Using the analysis population which includes all subjects with at least a baseline IGA score of ‘moderate’ and defining a treatment success as the percent of subjects with an IGA score of ‘absence’ or ‘very mild’ both studies established the superiority of Taclonex[®] scalp suspension over each of its components and in turn also established the superiority over vehicle in Study 405. The efficacy findings were further supported from four additional additional safety and efficacy trials.

The sponsor's proposed label



b(4)

References

- [1] Peace, K.E. (1986) "Some Thoughts on Combination Drug Development", In *Proceedings of the Biopharmaceutical Section*, American Statistical Association.
- [2] Peace, K.E. (1989) "Considerations in Combination Drug Development", In *Statistical Issues in Pharmaceutical Drug Development*, Marcek Dekker, Inc., New York.
- [3] Statistical Analysis and Graphics produced with R software. R Development Core Team (2007). *R: A language and environment for statistical computing*. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL <http://www.R-project.org>.

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APPENDIX

A.1 Supplementary Information for Study 405 and Study 406

A.1.1 Baseline Demographic Tables

The following tables present tabulated data for the demographic factors (age, race, sex, and country) for the two pivotal Phase 3 trials.

Table 19: Baseline Factors by Treatment – Study 405

	Taclonex (N = 541)			Betamethasone (N = 556)			Calcipotriene (N = 272)			Vehicle (N = 136)		
	37.00	49.00	59.00	38.00	50.00	62.00	37.00	51.00	62.00	37.00	51.50	60.25
Age (years)												
Sex : Male	48% (259)			42% (233)			44% (121)			45% (61)		
Race : Caucasian	96% (518)			97% (538)			97% (265)			95% (129)		
Black	1% (4)			0% (2)			0% (1)			1% (2)		
Asian	3% (14)			2% (12)			2% (5)			2% (3)		
Other	1% (5)			1% (4)			0% (1)			1% (2)		
Country : Canada	38% (203)			36% (202)			38% (102)			35% (48)		
Denmark	4% (22)			4% (21)			4% (10)			4% (5)		
Spain	5% (25)			6% (31)			6% (16)			5% (7)		
France	21% (111)			21% (115)			19% (52)			21% (28)		
United Kingdom	20% (110)			20% (109)			19% (53)			21% (28)		
Norway	5% (29)			6% (32)			4% (12)			6% (8)		
Portugal	1% (5)			1% (6)			1% (4)			1% (2)		
Sweden	7% (36)			7% (40)			8% (23)			7% (10)		

a b c represent the lower quartile *a*, the median *b*, and the upper quartile *c* for continuous variables. Numbers after percents are frequencies.

Source: Reviewer's analysis which coincides with several of the Study Report tables.

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Table 20: Baseline Factors by Treatment – Study 406

	Taclonex (N = 568)			Betamethasone (N = 563)			Calcipotriene (N = 286)		
Age (years)	35.00	49.00	61.00	34.00	50.00	60.00	37.00	48.50	59.75
Sex : Male	42% (238)			46% (260)			48% (137)		
Race : Caucasian	98% (559)			97% (545)			96% (274)		
Black	0% (1)			0% (2)			1% (3)		
Asian	1% (4)			1% (7)			2% (7)		
Other	1% (4)			2% (9)			1% (2)		
Country : Belgium	10% (59)			10% (57)			10% (30)		
Canada	14% (79)			14% (81)			14% (39)		
Denmark	19% (106)			18% (100)			19% (53)		
Finland	8% (47)			8% (47)			8% (22)		
France	5% (28)			5% (29)			5% (15)		
United Kingdom	32% (182)			32% (182)			33% (94)		
Ireland	4% (21)			4% (21)			4% (11)		
Netherlands	8% (46)			8% (46)			8% (22)		

a b c represent the lower quartile *a*, the median *b*, and the upper quartile *c* for continuous variables. Numbers after percents are frequencies.

Source: Reviewer's analysis which coincides with several of the Study Report tables.

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A.1.2 Baseline Prognostic Factors

This sections contains the tabulated results of the baseline examination of prognostic factors which have the potential to impact efficacy conclusions for the two pivotal studies.

Table 21: Baseline Prognostic Factors by Treatment – Study 405

	Taclonex (N = 541)	Betamethasone (N = 556)	Calcipotriene (N = 272)	Vehicle (N = 136)
Baseline IGA : Mild	9% (47)	4% (25)	6% (16)	7% (10)
Moderate	56% (304)	57% (317)	57% (156)	51% (69)
Severe	29% (156)	33% (183)	32% (87)	36% (49)
Very severe	6% (34)	6% (31)	5% (13)	6% (8)
Baseline Extent Scalp Psoriasis : <10%	0% (0)	1% (3)	0% (0)	0% (0)
10-29%	36% (194)	31% (174)	39% (105)	34% (46)
30-49%	27% (144)	26% (144)	25% (67)	29% (39)
50-69%	14% (76)	15% (83)	12% (32)	15% (20)
70-89%	13% (70)	15% (85)	14% (38)	12% (16)
90-100%	11% (57)	12% (67)	11% (30)	11% (15)
Baseline Redness Scalp : Slight	17% (93)	15% (85)	15% (40)	11% (15)
Moderate	51% (276)	52% (289)	51% (139)	54% (74)
Severe	27% (147)	29% (163)	29% (79)	29% (40)
Very severe	5% (25)	3% (19)	5% (14)	5% (7)
Baseline Scaliness Scalp : None	0% (0)	0% (1)	0% (0)	0% (0)
Slight	11% (61)	10% (53)	10% (26)	9% (12)
Moderate	48% (262)	45% (250)	49% (133)	46% (63)
Severe	30% (160)	35% (192)	32% (87)	32% (44)
Very severe	11% (58)	11% (60)	10% (26)	12% (17)
Baseline Thickness Scalp : Slight	21% (111)	18% (101)	18% (48)	21% (29)
Moderate	52% (279)	49% (272)	53% (145)	43% (59)
Severe	22% (119)	28% (158)	24% (64)	26% (35)
Very severe	6% (32)	4% (25)	6% (15)	10% (13)
Baseline Total Sign Score:	6 6 8	6 6 6	6 7 8	5 6 8
Duration of Psoriasis (years)	5.00 10.00 21.00	7.00 14.00 26.00	5.00 14.00 23.25	5.00 13.00 25.00

a b c represent the lower quartile *a*, the median *b*, and the upper quartile *c* for continuous variables.

Numbers after percents are frequencies.

Source: Reviewer's Analysis.

Table 22: Baseline Prognostic Factors by Treatment – Study 406

	Taclonex N = 568	Betamethasone N = 563	Calcipotriene N = 286
Baseline IGA : Mild	10% (56)	8% (45)	12% (35)
Moderate	55% (311)	54% (302)	51% (147)
Severe	30% (170)	34% (189)	33% (94)
Very severe	5% (31)	5% (27)	3% (10)
Baseline Extent Scalp Psoriasis : <10%	0% (1)	0% (0)	0% (0)
10-29%	36% (207)	33% (188)	33% (95)
30-49%	28% (158)	28% (155)	29% (83)
50-69%	15% (86)	16% (89)	19% (53)
70-89%	11% (64)	12% (69)	11% (32)
90-100%	9% (52)	11% (61)	8% (23)
Baseline Redness Scalp : None	0% (0)	0% (1)	0% (0)
Slight	17% (94)	14% (78)	20% (58)
Moderate	54% (307)	54% (305)	48% (136)
Severe	26% (145)	28% (159)	28% (80)
Very severe	4% (22)	3% (19)	4% (12)
Baseline Scaliness Scalp : None	0% (1)	0% (0)	0% (0)
Slight	6% (36)	6% (31)	7% (19)
Moderate	46% (263)	46% (261)	48% (137)
Severe	36% (204)	39% (220)	37% (106)
Very severe	11% (64)	9% (50)	8% (24)
Baseline Thickness Scalp : None	0% (2)	0% (0)	0% (1)
Slight	20% (115)	19% (107)	21% (60)
Moderate	49% (280)	47% (266)	49% (139)
Severe	24% (137)	29% (161)	26% (73)
Very severe	6% (34)	5% (28)	5% (13)
Baseline Total Sign Score	5 6 8	6 7 8	5 7 8
Duration of Psoriasis (years)	5.00 12.00 22.00	5.00 11.00 25.00	6.00 12.00 22.75

a b c represent the lower quartile *a*, the median *b*, and the upper quartile *c* for continuous variables. *N* is the number of non-missing values. Numbers after percents are frequencies.

A.1.3 Primary Endpoint Results Early Time Points

The following tabulations provide efficacy results for the two pivotal studies, Study 405 and Study 406 at weeks 2, 4, and 6. As with the depiction of efficacy results for the primary time point, week 8, each of the three analysis is presented.

Table 23: Investigator Global Results @ Week 2 (ITT-LOCF) – Study 405

	Taclonex	Betamethasone	Calcipotriene	Vehicle
Sponsors Original Analysis				
Sample Size	541	556	272	136
Success (%)	311 (57.5)	262 (47.1)	51 (18.8)	16 (11.8)
95% C.I. ¹	-	(4.3, 16.4)	(32.2, 45.2)	(38.4, 53)
Sponsors Amended Analysis				
Sample Size	494	531	256	126
Success (%)	274 (55.5)	245 (46.1)	47 (18.4)	12 (9.5)
95% C.I. ¹	-	(3.0, 15.6)	(30.4, 43.9)	(38.7, 53.2)
FDA Analysis				
Sample Size	541	556	272	136
Success (%)	347 (64.1)	333 (59.9)	87 (32.0)	30 (22.1)
95% C.I. ¹	-	(-1.7, 10.2)	(25.0, 39.3)	(33.6, 50.6)

¹ 95% Confidence interval of the difference in the percentage of Taclonex® scalp suspension successes from comparator successes.

Source: Reviewer's analysis.

Table 24: Investigator Global Results @ Week 2 (ITT-LOCF) – Study 406

	Taclonex	Betamethasone	Calcipotriene
Sponsors Original Analysis			
Sample Size	567	562	286
Success (%)	278 (49.0)	216 (38.4)	45 (15.7)
95% C.I. ¹	-	(4.7, 16.5)	(27.1, 39.5)
Sponsors Amended Analysis			
Sample Size	512	517	251
Success (%)	241 (47.1)	188 (36.4)	32 (12.7)
95% C.I. ¹	-	(4.5, 16.9)	(28.0, 40.6)
FDA Analysis			
Sample Size	567	562	286
Success (%)	333 (58.7)	284 (50.5)	72 (25.2)
95% C.I. ¹	-	(2.2, 14.2)	(26.8, 40.3)

¹ 95% Confidence interval of the difference in the percentage of Taclonex® scalp suspension successes from comparator successes.

Source: Reviewer's analysis.

Table 25: Investigator Global Results @ Week 4 (ITT-LOCF) – Study 405

	Taclonex	Betamethasone	Calcipotriene	Vehicle
Sponsors Original Analysis				
Sample Size	541	556	272	136
Success (%)	362 (66.9)	304 (54.7)	64 (23.5)	20 (14.7)
95% C.I. ¹	-	(6.3, 18.2)	(36.7, 50.1)	(44.6, 59.8)
Sponsors Amended Analysis				
Sample Size	494	531	256	126
Success (%)	325 (65.8)	288 (54.2)	59 (23.0)	17 (13.5)
95% C.I. ¹	-	(5.4, 17.7)	(35.8, 49.7)	(44.5, 60.1)
FDA Analysis				
Sample Size	541	556	272	136
Success (%)	384 (71.0)	369 (66.4)	97 (35.7)	38 (27.9)
95% C.I. ¹	-	(-1.1, 10.3)	(28.2, 42.5)	(34.1, 52.0)

¹ 95% Confidence interval of the difference in the percentage of Taclonex® scalp suspension successes from comparator successes.

Source: Reviewer's analysis.

Table 26: Investigator Global Results @ Week 4 (ITT-LOCF) – Study 406

	Taclonex	Betamethasone	Calcipotriene
Sponsors Original Analysis			
Sample Size	567	562	286
Success (%)	311 (54.9)	287 (51.1)	74 (25.9)
95% C.I. ¹	-	(-2.2, 9.8)	(22.2, 35.8)
Sponsors Amended Analysis			
Sample Size	512	517	251
Success (%)	268 (52.3)	254 (49.1)	59 (23.5)
95% C.I. ¹	-	(-3.1, 9.5)	(21.7, 35.9)
FDA Analysis			
Sample Size	567	562	286
Success (%)	367 (64.7)	347 (61.7)	98 (34.3)
95% C.I. ¹	-	(-2.8, 8.8)	(23.4, 37.5)

¹ 95% Confidence interval of the difference in the percentage of Taclonex® scalp suspension successes from comparator successes.

Source: Reviewer's analysis.

Table 27: Investigator Global Results @ Week 6 (ITT-LOCF) – Study 405

	Taclonex	Betamethasone	Calcipotriene	Vehicle
Sponsors Original Analysis				
Sample Size	541	556	272	136
Success (%)	361 (66.7)	326 (58.6)	83 (30.5)	27 (19.9)
95% C.I. ¹	-	(2.2, 14)	(29.2, 43.3)	(38.6, 55.1)
Sponsors Amended Analysis				
Sample Size	494	531	256	126
Success (%)	328 (66.4)	306 (57.6)	80 (31.2)	23 (18.3)
95% C.I. ¹	-	(2.7, 14.9)	(27.8, 42.5)	(39.7, 56.6)
FDA Analysis				
Sample Size	541	556	272	136
Success (%)	392 (72.5)	376 (67.6)	118 (43.4)	42 (30.9)
95% C.I. ¹	-	(-0.8, 10.4)	(21.8, 36.3)	(32.5, 50.7)

¹ 95% Confidence interval of the difference in the percentage of Taclonex[®] scalp suspension successes from comparator successes.

Source: Reviewer's analysis.

Table 28: Investigator Global Results @ Week 6 (ITT-LOCF) – Study 406

	Taclonex	Betamethasone	Calcipotriene
Sponsors Original Analysis			
Sample Size	567	562	286
Success (%)	365 (64.4)	318 (56.6)	107 (37.4)
95% C.I. ¹	-	(1.9, 13.7)	(19.8, 34.1)
Sponsors Amended Analysis			
Sample Size	512	517	251
Success (%)	320 (62.5)	284 (54.9)	86 (34.3)
95% C.I. ¹	-	(1.4, 13.8)	(20.7, 35.7)
FDA Analysis			
Sample Size	567	562	286
Success (%)	397 (70.0)	363 (64.6)	126 (44.1)
95% C.I. ¹	-	(-0.2, 11.1)	(18.8, 33.1)

¹ 95% Confidence interval of the difference in the percentage of Taclonex[®] scalp suspension successes from comparator successes.

Source: Reviewer's analysis.

A.2 Supportive Trial Efficacy Results

In addition to the primary Phase 3 trials, Study 405 and Study 406, the sponsor's clinical development of Taclonex[®] scalp suspension also included four other supportive trials: Study 401, Study 401, Study 502 and Study 503. These trials are included in the ISE analysis and the following sections contain a brief review of each trial.

A.2.1 Study MBL 0401 INT

The Phase 2 study, Study 401, was not a formal dose ranging trial in which dose level, dose frequency, or duration of dosing were all explored. Rather, Study 401 compared once daily dosing of Taclonex[®] scalp suspension to betamethasone at week 8. The rationale for only including a single monad of the combination product appears to be driven by previous data in the development of Taclonex[®] ointment which showed that betamethasone had a higher response rate than calcipotriene in the treatment of psoriasis vulgaris.

The study was designed as an international, multi-center, prospective, randomized, double-blind, two-arm, parallel group, 8-week study. A total of 218 patients were enrolled and randomized at visit 1 (Taclonex[®] scalp suspension: 108; betamethasone: 110). The extent of involvement was planned to be more than 10% of the scalp. Disease severity should be graded as mild, moderate, severe, or very severe according to the investigator's global assessment of disease severity.

Similar to the analysis of the three pivotal trials, three analyses are performed:

'Sponsor's Original Analysis' : Success = 'absence of disease' or 'very mild disease' and baseline IGA *includes* subjects with mild scores.

'Sponsor's Amended Analysis' : Success = 'absence of disease' or 'very mild disease' and baseline IGA *excludes* subjects with mild scores.

'FDA Analysis' : Success = two grade improvement from baseline IGA and baseline IGA *includes* subjects with mild scores.

The efficacy results at Week 8 are provided in Table 29. Results show that the largest treatment effect occurred when using the 'Sponsor's Amended Analysis' ($\delta = 10.8\%$).

To further explore the efficacy conclusions seen in Table 29 treatment effects were explored based upon the baseline IGA score. Figure 15 depicts the efficacy results for both definitions of IGA success according to the baseline IGA score (y-axis). This figure shows the 'Sponsor's Amended Analysis' has the largest treatment effect as subjects with a baseline IGA score of 'mild' and treated with betamethasone have higher response rates than subjects treated with Taclonex[®] scalp suspension.

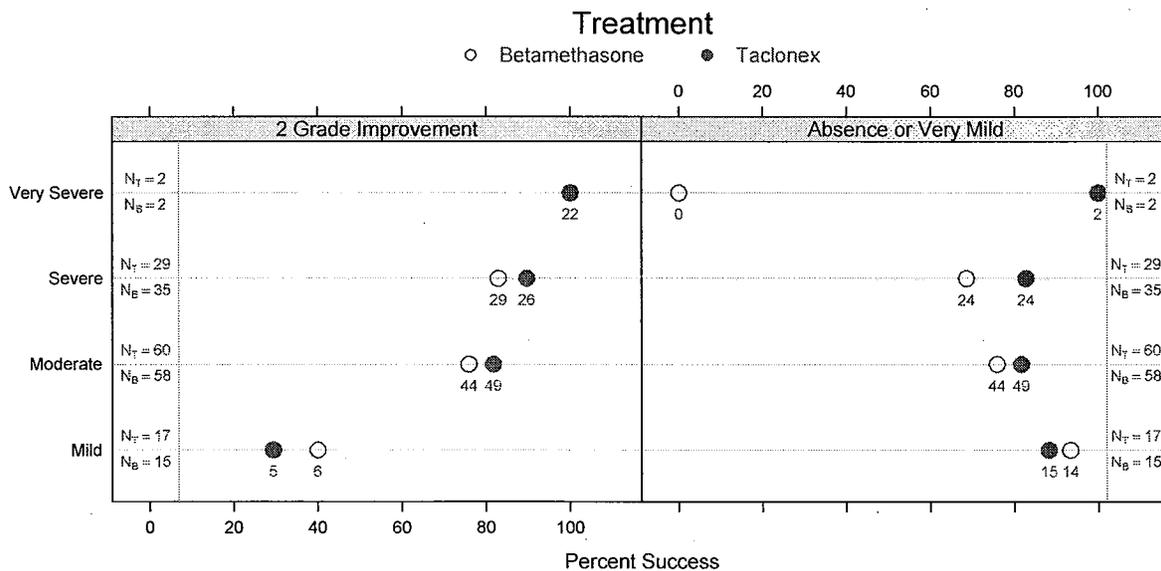
Table 29: Investigator Global Results at Week 8 (ITT-LOCF) – Study 401

	Taclonex	Betamethasone
Sponsors Original Analysis		
Sample Size	108	110
Success (%)	90 (83.3)	82 (74.5)
p-value ¹	-	0.1356
Sponsors Amended Analysis		
Sample Size	91	95
Success (%)	75 (82.4)	68 (71.6)
p-value ¹	-	0.0852
FDA Analysis		
Sample Size	108	110
Success (%)	82 (75.9)	81 (73.6)
p-value ¹	-	0.7561

¹ Fisher's Exact Test.

Reviewer's Analysis.

Figure 15: Efficacy According to Baseline IGA Score – Study 401



A.2.2 Study MBL 0503 INT

The primary objective of Study 503 was to compare the efficacy of 8 weeks, once daily treatment of Taclonex® scalp suspension with twice daily treatment of Dovonex® (calcipotriene) scalp solution. In addition, as a secondary objective, the goal was to investigate the occurrence of, and time to, relapse in subjects with 'Controlled disease' (IGA score of 'absence of disease' or 'very mild disease'). For those subjects with 'controlled disease' at or before week 8, follow-up visits occurred at week 12 and week 16.

A total of 312 patients were enrolled and randomized: 207 patients to Taclonex® scalp suspension and 105 patients to Dovonex® scalp solution. Inclusion criteria required a disease severity based on the IGA scale to be at least moderate. Consequently, the analysis of this study excludes the 'Sponsor's Amended Analysis'. Efficacy results are presented in Table 30 which clearly demonstrates the statistical significance of Taclonex® scalp suspension over Dovonex® scalp solution.

Table 30: Investigator Global Results at Week 8 (ITT-LOCF) – Study 503

	Taclonex® scalp suspension	Dovonex® scalp solution
Sponsors Original Analysis		
Sample Size	207	105
Success (%)	142 (68.6)	33 (31.4)
p-value ¹	-	< .001
FDA Analysis		
Sample Size	207	105
Success (%)	160 (77.3)	39 (37.1)
p-value ¹	-	< .001

¹ Fisher's Exact test due to small stratum in pooled sites.

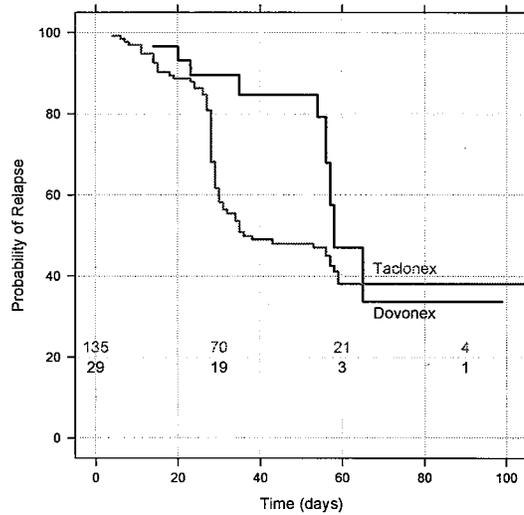
Source: Sponsor's Original Analysis is a reproduction of Table 18 of the Study Report.

'FDA Analysis' performed by the statistical reviewer.

164 subjects provided data on the time to relapse, 135 initially randomized to Taclonex® scalp suspension and 29 initially randomized to Dovonex® scalp solution. The time to relapse is calculated as the number of days in which a subject returns to a IGA score of at least 'mild'. Figure 16 depicts the number of subjects at risk at a given time point and the overall survival curves which depict the time to relapse. The figure shows that subjects treated with Dovonex® scalp solution tended to relapse to at least an IGA score of 'mild' sooner than subjects treated with Taclonex® scalp suspension prior to 60 days. After 60 days there are few subjects with observed data so any conclusions reached beyond this time point may not be justified. While the study was not powered to detect for a significance difference in the time to relapse, the reviewer

conducted a log-rank test to test for treatment differences which resulted in a p-value of 0.079.

Figure 16: Time to Relapse – Study 503



Rebound is defined for subjects who reach ‘clear’ or ‘almost clear’ at Week 8 but later have an increase of at least one grade from their baseline IGA score. Of the 135 subjects assessed initially treated with Taclonex® scalp suspension, 2 (1.5%) had a rebound of their scalp psoriasis. None of the 29 subjects treated with Dovonex® scalp solution had a rebound.

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A.2.3 Study MBL 0407 INT

Study 407 was a long-term trial to study the safety and efficacy of Taclonex® scalp suspension when used for up to 52 weeks. The control arm received calcipotriene, and randomization was performed in a 1:1 ratio to Taclonex® scalp suspension and calcipotriene. The study enrolled a total of 869 subjects from 57 centers in Europe and Canada. Visits were scheduled every 4 weeks, between Weeks 0 and 52 with safety and efficacy evaluations performed at each visit. At baseline the protocol inclusion criteria called for an extent of scalp psoriasis involving more than 10% of the total scalp area and a baseline IGA score of at least ‘moderate’.

Efficacy results at Week 8 (Visit 3) are presented in Table 31. Note that due to the inclusion criteria requiring subjects to have at least moderate disease, the ‘Sponsor’s Amended Analysis’ is not relevant. In Study 407, Taclonex® scalp suspension is statistically superior to calcipotriene for both analyses.

Table 31: Investigator Global Results at Week 8 (ITT-LOCF) – Study 407

	Taclonex® scalp suspension	Calcipotriene
Sponsors Original Analysis		
Sample Size	429	440
Success (%)	239 (55.7)	140 (31.8)
p-value ¹	-	< .001
FDA Analysis		
Sample Size	429	440
Success (%)	297 (69.2)	197 (44.8)
p-value ¹	-	< .001

¹ Fisher’s Exact test due to small sites.

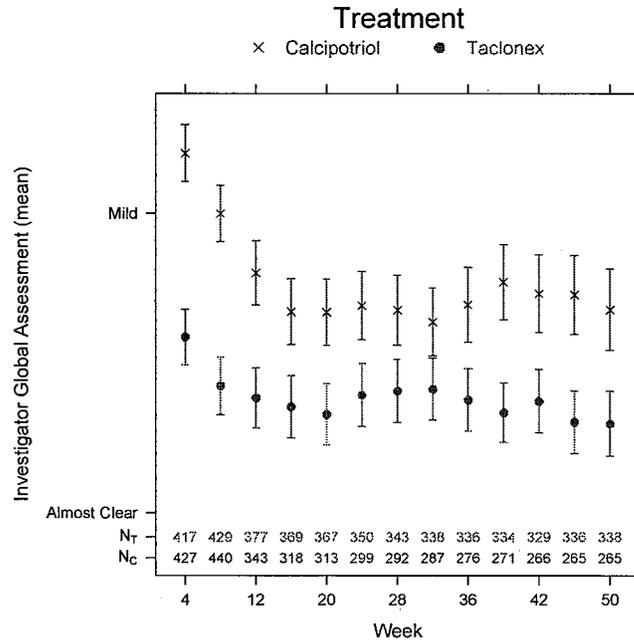
Source: Sponsor’s Original Analysis is a reproduction of Table 14 of the Study Report.

‘FDA Analysis’ performed by the statistical reviewer.

In addition to assessing the short-term efficacy, the long-term efficacy is assessed at each of the analysis visit time points. At each visit, an unadjusted 95% confidence interval of the mean IGA score is calculated. The results are shown in Figure 17 which includes the number of subjects who had IGA evaluations at each of the visits. Based upon the figure, the mean IGA score decreases sharply through Week 20 for both treatment groups, however the mean score of subjects treated with Taclonex® scalp suspension is below that of calcipotriene. After Week 20 the the mean tends to be quite stable with some variation as seen in both treatment arms. Of interest, is that the number of subjects who drop out of the study is much higher for subjects randomized to calcipotriene than those randomized to Taclonex® scalp suspension. Of the subjects treated with calcipotriene who dropped out, 51 (11.8%) subjects dropped out due

to unacceptable treatment efficacy and 44 (10.2%) of subjects dropped out due to unacceptable adverse events.

Figure 17: Long Term Efficacy – Study 407



**APPEARS THIS WAY
ON ORIGINAL**

A.2.4 Study MBL 0502 US

Study 502 was conducted in 18 U.S. centers enrolling a total of 177 subjects. Subjects were randomized in a 3:1 ratio to Taclonex® scalp suspension or vehicle. In addition all subjects had psoriasis vulgaris of the trunk and limbs for which they received Taclonex® ointment⁷. Visits were planned to occur every 2 weeks with Week 8 as the designated analysis for the analysis of the primary endpoint, a dichotomized IGA of ‘absence of disease’ or ‘very mild disease’.

The following baseline prognostic factors were evaluated in Study 502 which could have an impact on efficacy: IGA, extent of scalp psoriasis, redness of the scalp, scaliness of the scalp, plaque thickness of the scalp, and duration of scalp psoriasis. The tabulated results are shown in Table 33 on the following page. Comparing these results to Study 405 as shown in Table 21, a higher proportion of subjects with milder scores of several prognostic factors are included in Study 502 than in Study 405. As it is expected that milder cases of scalp psoriasis are easier to treat, this is one potential explanation for a higher response rate of the vehicle in Study 502 than the vehicle response rate observed in Study 405.

Table 32 contains the efficacy results for Study 502. Note that only two analyses are conducted as the baseline IGA score was to be at least moderate in severity. Both analyses show that Taclonex® scalp suspension is statistically superior to its vehicle with a treatment effect greater than 25%.

Table 32: Investigator Global Results at Week 8 (ITT-LOCF) – Study 502

	Taclonex® scalp suspension	Vehicle
Sponsors Original Analysis		
Sample Size	135	42
Success (%)	96 (71.1)	17 (40.5)
p-value ¹	-	< .001
FDA Analysis		
Sample Size	135	42
Success (%)	100 (74.1)	20 (47.6)
p-value ¹	-	0.0022

¹ Fisher’s Exact test due to small stratum in pooled sites.

Source: Sponsor’s Original Analysis is a reproduction of Table 28 of the Study Report.

‘FDA Analysis’ performed by the statistical reviewer.

⁷FDA approved drug for psoriasis comprised of betamethasone and calcipotriene.

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ON ORIGINAL**

Table 33: Baseline Prognostic Factors by Treatment – Study 502

	Taclonex <i>N</i> = 135	Vehicle <i>N</i> = 42
Baseline IGA : Moderate	81% (110)	76% (32)
Severe	17% (23)	24% (10)
Very Severe	1% (2)	0% (0)
Baseline Extent Scalp Psoriasis : 10-29%	56% (76)	57% (24)
30-49%	17% (23)	17% (7)
50-69%	11% (15)	12% (5)
70-89%	7% (9)	7% (3)
90-100%	9% (12)	7% (3)
Baseline Redness Scalp : Slight	19% (26)	26% (11)
Moderate	56% (76)	57% (24)
Severe	24% (32)	14% (6)
Very Severe	1% (1)	2% (1)
Baseline Scaliness Scalp : Slight	16% (22)	2% (1)
Moderate	49% (66)	74% (31)
Severe	31% (42)	19% (8)
Very Severe	4% (5)	5% (2)
Baseline Thickness Scalp : Slight	24% (32)	24% (10)
Moderate	53% (72)	52% (22)
Severe	20% (27)	21% (9)
Very severe	3% (4)	2% (1)
Duration of Psoriasis (years)	4.25 8.00 15.00	5.25 10.00 15.00

a b c represent the lower quartile *a*, the median *b*, and the upper quartile *c* for continuous variables. *N* is the number of non-missing values.

Numbers after percents are frequencies.

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SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Mat Soukup, Ph.D.

Date: February 21, 2008

Statistical Team Leader: Mohamed Aloh, Ph.D.

cc:

Archival NDA

DDDP/Walker

DDDP/Lindstrom

DDDP/Carr

DDDP/Owens

OBIO/Patrician

DB3/Wilson

DB3/Aloh

DB3/Soukup

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/s/

Matt Soukup
3/31/2008 10:41:18 AM
BIOMETRICS

Mohamed Alesh
3/31/2008 12:16:24 PM
BIOMETRICS

STATISTICAL REVIEW AND EVALUATION

FILEABILITY REVIEW

NDA/Serial Number: 22-185/SN000
Drug Name: Taclonex® scalp gel
Indication(s): Scalp psoriasis
Applicant: LEO Pharmaceutical

Dates: Submitted: 07/02/2007
PDUFA: 05/02/2008

Review Priority: Standard

Biometrics Division: Division of Biometrics III
Statistics Reviewer: Mat Soukup, Ph.D.
Concurring Reviewer: Mohamed Aloh, Ph.D.

Medical Division: Division of Dermatology and Dental Products
Clinical Team: Brenda Carr, M.D. (DDDP)
Project Manager: Margo Owens (DDDP)

1 INTRODUCTION

NDA 21-185 is a full eCTD submission which contains both SDTM as well as ADaM data sets. The sponsor is seeking the indication of scalp psoriasis. Taclonex® ointment is approved for the treatment of psoriasis of the body. The clinical development of Taclonex® scalp gel includes two pivotal trials, Study 405 and Study 406, as well as several additional safety and efficacy studies.

2 ORGANIZATION AND DATA REPRESENTATION

1. Is there a comprehensive table of contents with adequate indexing and pagination?
Yes - the structure follows eCTD specifications and contains a properly functioning XML backbone file.
2. Are the original protocols, protocol amendments, and proposed label provided?
Yes, protocols and amendments are submitted in the appendix. The label is submitted in module 1 which includes a MS Word version.

3. Are the following tables/listings provided in each study report?
 - (a) Patient profile listings by center for all enrolled subjects.
Results by center can be ascertained by electronic data sets.
 - (b) Discontinued subject tables by center (includes reason and time of loss).
This can be performed using the ADDS.XPT data set.
 - (c) Subgroup analysis summary tables (gender, race, age, etc.).
Subgroup results are presented in the study reports and can be assessed with electronic data sets.
 - (d) Adverse event listings by center and time of occurrence.
Either the analysis or tabulation AE data set will allow for such an assessment.
4. Have the data been submitted electronically?
 - (a) Has adequate documentation of the data sets been provided?
Yes.
 - (b) Do the data appear to accurately represent the data described in the study reports?
Yes.
 - (c) Can the data be easily merged across studies and indications?
Yes based on the variable USUBJID.

3 STATISTICAL METHODOLOGY

1. Are all primary efficacy studies of appropriate design to meet basic approvability requirements within current Division policy or to the extent agreed upon previously with the sponsor by the Division?
At the Pre-NDA meeting there was discussion about the patient population and the definition of a success based on the global assessment. This was due to the sponsor initiating the two pivotal trials prior to the End of Phase 2 Meeting with the Agency. The Agency told the sponsor that efficacy assessment will be a review issue at the Pre-NDA Meeting.
2. For each study, is there a comprehensive statistical summary of the efficacy which covers the intent-to-treat population and per protocol population?
The study reports for the two pivotal trials, MBL-0405-INT and MBL-0406-INT, appear to have adequate documentation of efficacy.
3. Based on the summary analyses of each study:

- (a) Are the analyses appropriate for the type of data collected, the study design, and the study objectives (based on protocol objectives and proposed labeling claims)?

As stated above, this will be a review issue.

- (b) Are the intent-to-treat and per protocol patient analyses properly performed?

The definitions of ITT and PP appear to be acceptable.

- (c) Has missing data been appropriately handled?

The primary method of imputation is LOCF.

- (d) Have multiplicity issues (regarding endpoints, timepoints, or dose groups) been adequately addressed?

For the seven secondary endpoints, the protocol lists a significance level of 0.01 without providing justification for the choice of the level. In review of the protocols in SN011, the Agency stated that the choice of significance level should be statistically justified or limit the number of secondary endpoints. No such justification or reduction in the number of secondary endpoints occurred.

- (e) If interim analyses were performed, were they planned in the protocol and appropriate significance level adjustments made?

NA

4. Were sufficient and appropriate references included for novel statistical approaches?

NA

5. Are all pivotal studies complete?

Yes.

6. Has the safety data been comprehensively and adequately summarized?

The electronic data sets should allow for thorough safety examination.

4 FILEABILITY CONCLUSIONS

From a statistical perspective this submission, or indications therein, is reviewable with no further input from the sponsor.

5 74-DAY LETTER COMMENTS

No comments are needed at the time of the filing date.

Mat Soukup, Ph.D.

Mathematical Statistician, Biometrics 3

Concur: Mohamed Aloh, Ph.D.
Team Leader, Biometrics 3

Cc:

Orig. NDA 22,185/SN000

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DDDP/Carr

DDDP/Owens

OBIO/Patrician

DBIII/Wilson

DBIII/Aloh

DBIII/Soukup

August 13, 2007

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/s/

Matt Soukup
8/16/2007 05:50:00 PM
BIOMETRICS

Mohamed Alesh
8/20/2007 10:45:00 AM
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