CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-122

MEDICAL REVIEW(S)

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS
HFD-170, 10903 New Hampshire Avenue, Silver Spring MD 20993

CLINICAL TEAM LEADER MEMORANDUM

DATE: October 1, 2007

TO: File, NDA 22-122

FROM: Mwango A. Kashoki, M.D., M.P.H
Medical Team Leader

RE: Supervisory Review of NDA 22-122
Voltaren 1% Gel
Novartis, Inc.

Proposed indication: [redacted] of joints amenable to [redacted] treatment, such as the hands or knees.

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Novartis was advised to develop DSG as a prescription medication for the treatment of osteoarthritis (OA).

On November 3, 2003, Novartis submitted a new IND (I 64, 334) to DAAODP. A second guidance meeting was held on November 18, during which the Applicant sought advice regarding its development plan for a " indication. Two identical efficacy trials, VOSG-PN-304 and VOSG-PN-310, in patients with OA of the knee were planned. DAAODP advised Novartis that the studies should be 12 weeks long, and should have three co-primary endpoints: WOMAC[1] pain, WOMAC function, and a patient global impression of overall treatment. A "landmark" efficacy analysis at 12 weeks was required. The Applicant was cautioned against using the last observation carried forward (LOCF) method for imputation of missing data. Finally, the Applicant was reminded that instructions on how patients were to measure out gram quantities of DSG were necessary.

An End-of-Phase 2 meeting was held on June 29, 2004. The Applicant was informed that the overall design of studies VOSG-PN-304 and VOSG-PN-310 was acceptable. DAAODP recommended that a responder analysis also be performed, and that the definition of a treatment failure include use of the maximum daily dose of rescue medication for 3-4 consecutive days. Regarding the Applicant's proposed studies in patients with osteoarthritis of the hand (studies VOSG-PN-314 and VOSG-PN-315), DAAODP required that the studies be 8 weeks long, and have three co-primary endpoints that assess pain, function, and patient global impression of treatment. DAAODP stated that clinical trials in hand and knee OA would not support

Novartis then proposed an alternative indication.

A third guidance meeting was held on December 7, 2004 to discuss a potential indication. Novartis proposed two identical 6-week trials, with evaluation of efficacy at 4 weeks using three co-primary endpoints: pain intensity (as measured on a 100-mm Visual Analog Scale), patient global assessment of disease activity, and the AUSCAN[2] total score. Novartis argued that OA of the hand presents differently from knee OA, with pain often lasting up to 4 weeks. DAAODP found the endpoints acceptable, but recommended assessing efficacy at 6 weeks, and extending the trials to 8 weeks to gather more efficacy and safety data. Novartis proposed evaluating efficacy at 4 weeks for the primary efficacy analysis, and then at 6 weeks. DAAODP advised the Applicant to specify an appropriate statistical plan to accommodate this analysis. Also, use of imputation methods other than LOCF was recommended, in order to evaluate the effects of the imputation method on the results of the efficacy analysis. Regarding the proposed indication, DAAODP stated that "relief of

[1] WOMAC: Western Ontario and MacMaster Universities Osteoarthritis Index.
[2] AUSCAN: Australian/Canadian (AUSCAN) Index – evaluates pain, stiffness and functioning in patients with osteoarthritis of the hand.

was more appropriate, if supported by the data.

On December 22, 2204, Novartis submitted protocol VOSG-PE-314 for Special Protocol Assessment (SPA). The study design, duration, efficacy measures and endpoints were considered acceptable. However, the protocol lacked details regarding the proposed regression method for imputation of missing baseline values.

In 2005, following the reorganization of the Center for Drug Evaluation and Research, the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) assumed regulatory responsibility for the DSG application.

In October 2005, Novartis submitted a protocol amendment for study VOSG-PE-310 which described modification of the efficacy analysis population from the intent-to-treat (ITT) population to the "modified efficacy subpopulation" (MES). The MES comprised all randomized patients with a post-baseline score who did not have spontaneous improvement in pain in the target knee during analgesic washout, and who did not have significant pain in the contralateral knee at baseline. Use of the MES was based on the post-hoc efficacy analysis of study VOSG-PE-304, which showed that statistical significance for the primary endpoint was shown in the MES, but not in the ITT population. DAARP responded that an important issue was whether the MES sufficiently reflects the patient population that is likely to use DSG to gauge the benefit in that population.

A pre-NDA meeting was held on July 21, 2006. Novartis reiterated that the desired indication was "relief of

An indication of joints amenable to treatment, such as the hands and knees" could be considered, however a statement would be added to the label that certain joints, such as the hips and shoulders, are not included in the indication. Regarding the trials in patients with knee OA, DAARP stated that demonstration of efficacy in one knee would be generalizeable to the population of patients with OA in both knees, and that the MES population is representative of the larger OA population.

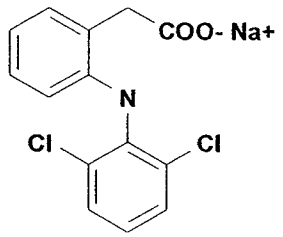
The NDA for DSG was submitted on December 19, 2006. The NDA was submitted via the 505(b)(2) route, with cross-references made to Novartis' NDAs for oral diclofenac sodium (Voltaren®) tablets: NDAs 19-201, 20-254 and 20-142. Novartis also referenced the Solaraze NDA (diclofenac sodium gel, 3%; N 21-005) for information and data pertaining to dermal carcinogenicity and photoodermal carcinogenicity. Bioglan Pharmaceuticals Corporation is the application holder for Solaraze

On May 17, 2007, Novartis informed the FDA that Bioglan and Jagotec AG had filed a complaint for patent infringement against Novartis. The complaint was dismissed without prejudice on July 26, 2007.

3. Chemistry, Manufacturing, and Controls (CMC)

The review of the CMC data was performed by Dr. Sue Ching Lin. Refer to her review for details regarding the CMC portion of the NDA.

The molecular structure of diclofenac is shown below:



The diclofenac sodium drug substance used in DSG is the same active pharmaceutical ingredient that is used in the approved Voltaren (diclofenac sodium) Enteric Coated Tablets.

The DSG drug product is a white [redacted] opaque emulsion-gel, and contains 1-g diclofenac sodium per 100 g of gel as active ingredient. The non-active ingredients are carbomer homopolymer Type C, cocoyl caprylocaprate, fragrance [redacted], isopropyl alcohol, mineral oil, polyoxyl 20 cetostearyl ether, propylene glycol, purified water, and strong ammonia solution. All of the excipients except cocoyl caprylocaprate and [redacted] are commonly used and recognized US pharmacopoeia excipients. Cocoyl caprylocaprate [redacted] is listed in the European Pharmacopoeia.

DSG is packaged in collapsible aluminum tubes with a [redacted] screw cap (100-g, [redacted] and 20-g) [redacted]. The stability data support the proposed 36-month expiration period for the drug product stored at controlled room temperature. However, the drug product should be kept from freezing because a phase separation of the drug product was observed in aluminum tubes when subjected to freeze/thaw cycles.

During the NDA review, four synthesis and/or degradant impurities of DSG were identified that exceeded the qualification threshold of [redacted]. The latter three impurities are found in the approved oral Voltaren and Voltaren-XR products, and since exposure to these impurities following DSG application would be less than that following oral exposure, no further characterization was required for this NDA. Regarding the [redacted] impurity, the Applicant agreed to lower the specification to no more than [redacted].

Although the fragrance contained in the drug product is considered novel to the Agency, it comprises less than [redacted] of the drug product and therefore, per ICH Q3B(R2) requirements, does not require toxicological qualification. Additionally, all of the ingredients that comprise the perfume are Generally Recognized As Safe (GRAS).

4. Non-Clinical Pharmacology and Toxicology

Please refer to the review by Dr. Lawrence Leshin for details regarding the non-clinical data on DSG.

The Applicant referred to its NDAs for Voltaren® Enteric-coated tablets, Cataflam tablets, and Voltaren-XR tablets for non-clinical pharmacokinetic and safety information. Reference was also made to Bioglan's NDA for Solaraze regarding information and data pertaining to dermal carcinogenicity and photocodermal carcinogenicity.

Development of DSG included local toxicity tests to assess its irritancy, photo-irritancy, sensitization and photosensitization potential. The photo-mutagenicity of diclofenac sodium was assessed in an Ames test and a chromosome aberration study. Apart from local tolerance and sensitization studies, no specific toxicity studies of the DSG formulation were conducted.

The Applicant found that the sensitization potential of DSG which was observed in the first maximization test was not reproducible in two subsequent tests. There was no evidence of diclofenac-related skin or systemic tumorigenic effects in the dermal carcinogenicity study. In the photocarcinogenicity study, there was a weak indication that diclofenac might decrease the time of onset of UV induced skin tumors. However, the effects observed were marginal and were not supported by other toxicity studies using DSG. There was no evidence that UV radiation enhanced the potential for skin irritation or sensitization.

As stated in Section 3, four DSG impurities were identified [redacted]. However, because three of these impurities are present in approved oral diclofenac formulations, and because the Applicant agreed to limit the threshold for the other impurity to NMT [redacted] no further toxicological characterization of the impurities was required.

DSG contains a novel excipient, cocoyl caprylocaprate. Although this ingredient is present in many cosmetic products, including many products that are used long-term,

there has been no determination of the carcinogenic potential, specifically the clastogenic potential. Also, the available clinical data is insufficient to inform the carcinogenic potential. Finally, dermal carcinogenicity data are required for inclusion of cocoyl caprylocaprate in the Inactive Ingredient Database. Therefore, the Pharmacology/Toxicology review team recommends that a dermal carcinogenicity study of should be conducted for cocoyl caprylocaprate to determine its carcinogenic potential. The study may be performed as a Phase 4 commitment.

Stability testing shows that photodegradants of diclofenac developed with exposure of DSG to light. Although Novartis referenced Solaraze for dermal carcinogenicity and photocarcinogenicity data, the photodegradants identified for Solaraze were not examined for toxicological effects. Thus, skin sites to which DSG is applied may, in sunlight, be exposed to uncharacterized photodegradants. The Pharmacology/Toxicology team recommends advising patients to avoid exposure of DSG-treated areas to sunlight.

5. Clinical Pharmacology

Dr. David Lee reviewed the Clinical Pharmacology data. Please refer to his review for details regarding the pharmacokinetic data for DSG.

The Applicant conducted two clinical pharmacology studies with DSG: a study comparing the absorption of diclofenac after maximal DSG exposure compared to a 50 mg oral dose of diclofenac, and a study evaluating the effects of heat and exercise on the absorption (systemic exposure) of diclofenac.

Systemic exposure with normal recommended use of DSG (applied to 1 knee, 4 times a day) is on average 17 times lower than with oral diclofenac treatment (50 mg, 3 times a day). The amount of diclofenac sodium that is systemically absorbed from DSG is on average 6% to 7% of the amount that is systemically absorbed from an oral form of diclofenac sodium. The systemic exposure with DSG is proportional to the amount that is applied.

The Applicant found that under conditions of maximal use (drug applied to both hands and knees QID), DSG produces approximately 20% of the systemic exposure of an oral dose of diclofenac of 50 mg tid. The Cmax achieved under conditions of maximal DSG use is 2% that of an oral dose of diclofenac.

In general, based on the AUC and Cmax data, 12g of DSG is approximately equivalent to 10 mg of oral diclofenac.

In the study to determine the effects of heat, moderate heat was applied to one knee for 15 minutes prior to application of DSG (4g). In the study evaluating the effects of exercise, DSG application was followed by 20 minutes of moderate exercise. The studies showed that there were no statistically significant or clinically relevant differences in the maximum concentration (Cmax), the area under the concentration-time curve from time 0

to time 24 hours (AUC_{0-24}) and the total amount excreted in diclofenac under the conditions tested.

The Applicant referenced the NDA for Voltaren® sodium enteric coated tablets for additional information on the clinical pharmacology of diclofenac.

6. Clinical Microbiology

Clinical microbiology testing was not required for this product.

7. Clinical/Statistics

Dr. Neville Gibbs conducted the primary clinical review, and Ms. Ruthanna Davi performed the statistical review.

7.1. Efficacy

7.1.1. General discussion of study design and endpoints

The FDA draft guidance, *Guidance for Industry – Clinical Development Programs for Drugs, Devices, and Biological Products for the Treatment of Osteoarthritis (OA)*, describes the Agency's current thinking regarding the development of OA therapies. The guidance states that trials intended to demonstrate symptom improvement should be at least 3 months in duration. Efficacy outcome measures should evaluate effects of treatment on pain, function, and patient's global assessment of treatment. Pain measures include the Likert scale and 100-mm visual analog scale (VAS). The Lequesne index and the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index have been validated as a measure of pain, function, and stiffness in the hip and knee of OA patients. The Lequesne index includes the measurement of pain (5 questions), walking distance (1 question), and activities of daily living (4 questions), with versions available for the hip and knee. The WOMAC is a 24-item questionnaire assessing pain (5 items), physical function (17 items) and stiffness (2 items).

The guidance does not specifically address measures of function in patients with OA of the hand. The Applicant used the Australian/Canadian (AUSCAN) Index to assess hand function. The AUSCAN is a self-administered questionnaire that assesses the three dimensions of pain, disability and joint stiffness in hand osteoarthritis using a battery of 15 questions. The instrument is scaled on either a 5-point Likert scale or a 100mm VAS. For this NDA, Novartis modified the AUSCAN (VAS version) to allow for assessment of symptoms in the left and right hands separately (see Appendix 1).

Although the guidance does not specify what primary efficacy endpoint should be used, the Agency has traditionally required three co-primary endpoints of pain, function and patient global, to be assessed at the end of the study period. For evidence in support of a claim, efficacy is demonstrated based on statistically significant improvement compared with control, and on a satisfactory overall risk-benefit analysis.

7.1.2. Efficacy Findings

The Applicant submitted the results of four efficacy trials in the NDA: VOSG-PN-304 and -310, as well as VOSG-PE-314, and -315.

Two trials, -310 and -315, were submitted in support of the efficacy of DSG. Studies -304 and -314 were considered failed trials (a statistically significant difference was not shown between DSG and placebo with respect to the three co-primary endpoints).

7.1.2.1.Study VOSG-PN-310 – Knee OA

Study design and conduct

This was a 12-week, randomized, double-blind, placebo-controlled trial in adult patients with OA of the knee. Eligible subjects were those who met the American College of Rheumatology criteria for a diagnosis of OA, had symptoms for at least 6 months, and had a baseline VAS pain score of at least 50-mm on movement of the target knee. Patients had to have a pain intensity score of less than 20 mm in the contralateral knee. Subjects were excluded if they had advanced arthritic disease on x-ray, had secondary osteoarthritis, or had a history of rheumatoid arthritis. The use of intra-articular treatments, analgesics, or any other therapies for OA was not permitted. Patients were allowed up to 4 g of acetaminophen per day, for rescue medication.

Subjects were to apply 4 g of gel to the target knee four times daily. Drug was to be applied on the lateral and medial aspects of the knee, as well as proximally and distally. A dosing card was to be used to standardize the amount of drug applied. Subjects were to rate their assessment of pain intensity on movement (POM) at the end of each day or before the first use of rescue medication that day. Pain assessments were to be made for both the target and contralateral knee. The function and global assessments were to be recorded at the clinic visits. The full WOMAC function scale was to be completed for the target knee, and a subset of the WOMAC questions (2 for pain, 2 for function) for the contralateral knee.

Statistical analysis

The protocol specified three primary efficacy outcomes: WOMAC pain, WOMAC physical function, and patient global rating of disease. A comparison between DSG and placebo at 12 weeks was to be performed, with statistical significance required on all three outcomes (2-sided α=0.05) to avoid the issue of multiple comparisons.

The protocol delineated a complex imputation scheme. If one or consecutive visits were skipped in the middle of the study, the efficacy outcome would be imputed by averaging the value of the visit immediately prior to and after the missed visit(s). If there is no subsequent visit after a missed visit, LOCF imputation would be used. If a patient discontinued due to lack of efficacy, the imputed value would be the maximum of the last non-missed visit and the baseline value.

Sensitivity analyses were to be conducted on the primary efficacy outcomes to assess the impact of the imputation strategy. These would include substituting in the active group for each missing value at Visit X, the mean of all non-missing values in the active group at Visit X, and correspondingly in the placebo group. The reverse process would also be

performed, where the mean of all of the non-missing values in the placebo group would be used to impute missing values in the active group.

Secondary efficacy outcomes included a comparison of response rates, where response was defined (using the Osteoarthritis Research Society International (OARSI) responder index) as either of the following:

- ≥ 50% improvement in pain and an absolute change of ≥ 20, *or*
- improvement in function of ≥ 50% and absolute change of ≥ 20, or at least two of the following:
    - (a) improvement in pain ≥ 20% and absolute change ≥ 10
    - (b) improvement in function ≥ 20% and absolute change ≥ 10
    - (c) improvement in global rating ≥ 20% and absolute change ≥ 10

Another definition of treatment response was non-use of rescue medication in the 3 days prior to the study visit, and a decrease in pain of ≥ 20 mm.

As discussed in Section 2, the Applicant amended the protocol based on the findings from study VOSG-PN-304. Post-hoc analyses of VOSG-PN-304 found that efficacy was demonstrated in a subset of the ITT population, namely those who did not demonstrate a decrease of POM in the target knee between the screening and the baseline visit and who had a score of < 2 (out of 8) on the abridged WOMAC pain index for the contralateral knee at the baseline visit. This modified efficacy subset (MES) would be used as the primary population for the efficacy analyses in study VOSG-PN-310.

Of note, the Applicant held a "blind data review meeting" after the study was complete but prior to unblinding. Several changes were made to the planned analyses which are documented in the statistical analysis plan. Although the changes were not incorporated into the protocol as a formal amendment, Dr. Davi considered it unlikely that any of these changes would have negatively impacted the robustness of the study conclusions.

One important change was the presentation of the WOMAC pain endpoint on a scale from 0 to 20 (instead of a 0-100 mm scale). The statistical analysis plan describes the change as follows: "The protocol indicated that WOMAC subscale scores would be standardized to a 0-100 scale. Instead they are reported in the original integer scales (0-20 for pain, 0-68 for physical function). This was done to avoid creating the mistaken impression that the subjects had assessed the VAS version of the WOMAC." Dr. Davi considered this change to be acceptable because, in the end, the pain assessment was done using the original scale in which it was measured.

Study efficacy results

A total of 492 patients were in the randomized, ITT population (254 in the DSG group and 238 in the placebo group). There were 246 patients in the MES population (127 DSG patients, and 119 placebo patients). The two populations were similar with respect to demographic and baseline disease characteristics (refer to Dr. Gibbs' review for details).

The FDA results of primary efficacy analysis of the MES population are shown in the table that follows. Also shown are the results of the protocol-specified sensitivity analyses including analysis imputing the baseline value for missing data (BOCF imputation).

Table 1: Primary Efficacy Results – Study VOSG-PN-310 – Knee OA

Primary Efficacy Analysis				
Endpoint	**DSG**	**Placebo**	**LS mean difference (Placebo-DSG)**	**p-value**
WOMAC pain (0-20)	5.9	7.3	1.3	0.02
WOMAC function	20.2	25.9	5.7	0.003
Global rating of disease	34.1	42.6	8.5	0.02
Analysis using BOCF imputation				
WOMAC pain	6.4	7.9	1.5	0.02
WOMAC function	21.2	27.4	6.2	0.001
Global rating of disease	35.4	44.1	8.6	0.02
Analysis using "mean of the same group" imputation				
WOMAC pain	5.5	5.9	0.5	0.37
WOMAC function	18.8	22.2	3.4	0.04
Global rating of disease	30.2	35.7	5.6	0.07
Analysis using "mean of the other group" imputation				
WOMAC pain	5.6	5.6	0.0	>0.99
WOMAC function	19.4	20.9	1.5	0.37
Global rating of disease	31.2	33.5	2.3	0.46

The table shows that, in the primary analysis, DSG was superior to placebo with respect to all three co-primary endpoints. At 12 weeks, the difference in WOMAC pain score between the DSG and placebo groups was 1.3 ($p = 0.023$). The difference in WOMAC function scores was 5.7, ($p=0.003$) and the difference in the global rating of disease was 8.5 ($p = 0.018$).

The protocol's pre-specified sensitivity analyses do not unequivocally support the finding of the primary efficacy analysis: a statistically significant difference between treatment groups was not found for all 3 co-primary endpoints. Nevertheless, the sensitivity analyses provide some numerical support of the primary efficacy results. Additionally, the analysis using BOCF imputation, a very conservative imputation method, showed a statistically significant difference on all co-primaries.

The Applicant also performed a comparison of the OARSI response, based on the WOMAC pain index and site-assessed POM in the MES (Table 2). The proportion of OARSI responders based on the WOMAC pain index was higher in the DSG group than in the vehicle group at each assessment week. The differences between the treatment groups were statistically significant at each assessment week. Similar results were found when the proportion of OARSI responders based on the site-assessed POM.

Table 2: OARSI Response Rates - Study VOSG-PN-310 – Knee OA (Applicant's analysis)

Table 9-10 OARSI response – MES

OARSI response rate n (%)	DSG N = 127	Vehicle N = 119	p-value
WOMAC pain index normalized to 100-pt scale			
Week 1	87 (68.5)	59 (49.6)	0.005
Week 4	94 (74.0)	72 (60.5)	0.043
Week 8	95 (74.8)	70 (58.8)	0.013
Week 12	94 (74.0)	70 (58.8)	0.024
Site-assessed pain on movement on 100 mm VAS			
Week 1	89 (70.1)	57 (47.9)	< 0.001
Week 4	95 (74.8)	66 (55.5)	0.001
Week 8	94 (74.0)	72 (60.5)	0.06
Week 12	92 (72.4)	66 (55.5)	0.013

All p-values based on the Cochran-Mantel-Haenszel (CMH) Chi-squared test of association, stratified by center

(Source: Applicant's study report for Study VOSG-PE-310, p. 57, Table 9-10)

A continuous responder analysis was also performed. For all primary efficacy outcomes, the percentage of responders in the DSG group exceeded the percentage in the vehicle group by up to 24 percentage points in all categories (except for the 2 highest categories in the WOMAC pain analysis, ≥ 90% and 100%). Separation in percentage of responders between DSG and vehicle groups was widest in the categories ≥ 30%, ≥ 40% and ≥ 50%. The overall differences between the DSG and vehicle in the continuous response curves were statistically significant for all 3 primary efficacy outcomes: WOMAC pain, p=0.013; WOMAC function, p=0.03); patient global p=0 039. The responder curves are appended (Appendix 2).

7.1.2.2.Study VOSG-PE-315 – Hand OA

Study design and conduct

This was an 8-week, randomized, double-blind, placebo-controlled trial in adult patients with OA of the hand. Eligible subjects were those who met the ACR criteria for a diagnosis of primary hand OA, had symptoms for at least 12 months, and had a baseline VAS pain score of at least 40-mm in the target (dominant) hand. Following analgesic washout, pain had to increase by at least 15 mm in 24 h. Patients had to have a pain intensity score at least 20 mm in the non-dominant hand. Subjects were excluded if they had advanced arthritic disease on x-ray, had secondary osteoarthritis, had symptomatic OA at locations other than the hand that required treatment, or had a history of

rheumatoid arthritis. Patients were allowed up to 4 g of acetaminophen per day, for rescue medication.

Subjects were to apply 2 g of gel to the target/dominant hand, and 2 g to the non-dominant hand four times daily. Drug was to be applied to the base of the thumb and all five fingers, with particular attention to the affected joints. A dosing card was to be used to standardize the amount of drug applied. Subjects were to rate their assessment of pain intensity at the end of each day, separately for the dominant and non-dominant hand. The function and global assessments were to be recorded at the clinic visits. The AUSCAN index would be used to evaluate function, using the function sub-scale for the dominant hand only.

Statistical analysis
The protocol specified three primary efficacy outcomes: WOMAC pain score, AUSCAN total score, and patient global rating of disease. A step-wise comparison between DSG and placebo at weeks 4 and 6 was to be performed, with statistical significance required on all three outcomes (2-sided α=0.05 to avoid the issue of multiple comparisons). Also, each patient would be categorized (based on baseline data) into one of three OA categories: (1) having pain only in the first carpometacarpal (CMC-1) joint; (2) having pain in the CMC-1 joint and at least one distal interphalangeal (DIP) or proximal interphalangeal (PIP) joint; or (3) having only interphalangeal (IP) or PIP joint pain .

Initially, the protocol specified that analysis would be done using the ITT population (all randomized patients with at least 1 post-baseline score). However, during a "blind data review" meeting, the Applicant determined that subjects with a baseline scores which allowed little or no room for improvement would be excluded from the analysis. This resulted in five exclusions (3 DSG and 2 placebo). Ms. Davi concluded that due to the large size of the study, exclusion of these subjects would not have a great impact on the legitimacy of the study results.

Several sensitivity analyses were conducted on the primary outcomes in the final study model, including an assessment of the impact of imputing by LOCF for early termination:

1. At each Visit X, missing values in the diclofenac group due to early termination were imputed (replaced) by the mean of all non-missing values in the diclofenac group, and correspondingly for vehicle.
2. At each Visit X, missing values in the diclofenac group due to early termination were imputed by the mean of all non-missing values in the vehicle group, and vice versa.

Regarding missing data, the protocol was amended to state that if a post-baseline visit or several consecutive visits or individual efficacy assessments from a visit were missed, each efficacy outcome was imputed by averaging the values of the last visit and the subsequent non-missed visit. If there was no later non-missed visit, efficacy results in all subsequent missed visits were imputed by LOCF. If a patient discontinued because of lack of efficacy, either LOCF or BOCF imputation (whichever had the maximum value) was used.

In her review of Study VOSG-PE-315, Ms. Davi found a significant treatment—by OA category interaction. This interaction was therefore included in the ANOVA model for the primary efficacy analysis.

Study efficacy results
A total of 385 patients were in the randomized (198 in the DSG group and 187 in the placebo group) (refer to Dr. Gibbs' review for details).

Table 3a shows the results of Ms. Davi's primary efficacy results at Week 4, using the modified ITT population (i.e. excluding the aforementioned 5 subjects). Included in Table 3a are the Applicant's findings for the AUSCAN function sub-scale, to further inform how DSG treatment may have impacted patient's experience of treatment.

Table 3b illustrates the Applicant's results of the protocol-specified sensitivity analyses, and an additional sensitivity analysis that was requested by the Agency, in which the baseline value was imputed for missing data (BOCF imputation). These analyses were done without factoring in a treatment-by-OA category interaction.

The tables show that at Week 4, the DSG group had statistically significantly lower pain and function scores than the placebo group. No difference between the groups was found for the patient global endpoint.

None of the sensitivity analyses showed that DSG was superior to placebo on all three co-primary endpoints. The findings for the individual endpoints were inconsistent.

Table 3a: Week 4 Efficacy Results (FDA analysis) – Study VOSG-PN-315 – Hand OA

Primary Efficacy Analysis (modified ITT population)				
Endpoint	**DSG N=198**	**Placebo N=187**	**LS mean difference (Placebo-DSG)**	**p-value**
WOMAC pain (0-100)	42.6	49.7	6.9	0.011
AUSCAN total	43.7	50.2	6.3	0.011
AUSCAN function*	44.7	50.8	6.6	0.010
Global rating of disease	37.5	41.9	4.9	0.08

* Applicant's analysis, dominant hand only. (Source: Applicant's Study Report for VOSG-PE-315 and Appendix 5, Section 5.1.2).

Table 3b: Week 4 Sensitivity Analysis Results (Applicant's Analysis) – Study VOSG-PN-315 – Hand OA

Sensitivity Analysis (modified ITT population)				
Endpoint	**DSG N=198**	**Placebo N=187**	**LS mean difference (Placebo-DSG)**	**p-value**
Analysis using BOCF imputation				
WOMAC pain	44.3	49.7	5.5	0.03
AUSCAN total	45.2	50.6	5.4	0.03
Global rating of disease	39.3	43.8	4.5	0.08
Analysis using "mean of the same group" imputation				
WOMAC pain	41.6	46.4	4.8	0.048
AUSCAN total	43.2	47.6	4.4	0.06
Global rating of disease	37.2	40.8	3.6	0.14
Analysis using "mean of the other group" imputation				
WOMAC pain	42.1	46.0	3.9	0.11
AUSCAN total	43.5	47.3	3.8	0.11
Global rating of disease	37.5	40.5	3.0	0.23

Source: Applicant's Study Report for VOSG-PE-315 and Appendix 5, Section 5.1.2

Table 4 (below) shows the results of Ms. Davi's primary efficacy analysis at Week 6. Her analysis found that, at Week 6, DSG was superior to placebo on all three co-primary endpoints.

Table 4: Week 6 Efficacy Results (FDA analysis) – Study VOSG-PE-315 – Hand OA

Primary Efficacy Analysis				
Endpoint	**DSG N=198**	**Placebo N=187**	**LS mean difference (Placebo-DSG)**	**p-value**
WOMAC pain (0-100)	39.9	46.9	7.0	0.014
AUSCAN total	41.4	48.5	7.1	0.006
Global rating of disease	35.2	40.4	6.0	0.023

Although the protocol for Study VOSG-PN-315 pre-specified that if a statistically significant difference was not demonstrated on all 3 primary outcomes at Week 4, then it would be concluded that efficacy of DSG had not been demonstrated regardless of any results at Week 6, the Week 6 data suggest that longer term treatment of this chronic condition do result in favorable effects.

The OARSI response in the ITT population is summarized in Table 5. The proportion of OARSI responders was higher in the DSG group than in the placebo group at each assessment week. The difference between the DSG and vehicle groups in OARSI response rate was highest at Week 1 (13.9%) and Week 4 (12.3%), and ranged between 8.8% and 9.0% at the other visits.

Table 5: OARSI Response Rates - Study VOSG-PE-315 – Hand OA (Applicant's analysis)

Table 9-4 OARSI response - ITT population

OARSI Response Rate – n (%)				
Week	DSG (N = 198)	Vehicle (N = 187)	% Difference (V-D)	p-value
1	110 (55.6)	78 (41.7)	13.9	0.008
2	117 (59.1)	94 (50.3)	8.8	0.06
4	124 (62.6)	94 (50.3)	12.3	0.013
6	127 (64.1)	103 (55.1)	9.0	0.054
8	130 (65.7)	106 (56.7)	9.0	0.06

All p-values based on a logistic regression model with main effects of treatment and hand OA category.

(Source: Applicant's Table 9.4, Study report for VOSG-PE-315, p. 56)

With respect to the continuous responder analyses that were performed, for OA pain intensity, the percentage of responders in the DSG group exceeded the percentage in the vehicle group in all categories from ≥ 0% through ≥ 90% by up to about 15 percentage points at Week 4 and Week 6. The separation between DSG and vehicle continuous responder curves was statistically significant at both week 4 (p=0.004) and week 6 (p=0.01).

For the total AUSCAN score, the percentage of responders in the DSG group exceeded the percentage in the vehicle group at Week 4 over all categories from ≥ 0% to ≥ 70% by up to 11 percentage points. Similarly, the percentage of responders in the DSG group exceeded the percentage in the vehicle group at Week 6 over all categories from ≥ 0% to ≥ 90% by up to 14 percentage points. The separation between DSG and vehicle continuous responder curves was statistically significant at both week 4 (p=0.011) and week 6 (p=0.008).

For the global rating of disease, the percentage of responders in the DSG group exceeded the percentage in the vehicle group at Week 4 over all categories from ≥ 0% to ≥ 50% by up to 14 percentage points. The percentage of responders in the DSG group exceeded the percentage in the vehicle group at Week 6 over all categories from ≥ 0% to ≥ 80% by up to 12 percentage points. The separation between DSG and vehicle continuous responder curves was statistically significant at Week 6 (0.013) but not at Week 4 (p=0.45).

See Appendix 3 for figures showing the Week 4 and Week 6 continuous responder analyses.

7.1.2.3.Efficacy conclusions

The Applicant conducted four efficacy trials, two of which were deemed failed trials (studies -304 and -314) and the remaining two were submitted in support of efficacy of DSG.

Per the division's analysis, Study -310 (knee OA) demonstrated that DSG was superior to placebo with respect to all three co-primary endpoints of pain, function, and patient global assessment of treatment. This finding was supported by sensitivity analysis using BOCF imputation, and by responder analyses.

Study -315 (hand OA) failed to meet its primary endpoint. At Week 4, superiority of DSG versus placebo was shown only for the pain and function endpoints, not the patient global assessment. None of the sensitivity analyses showed a benefit of DSG over placebo at Week 4. Also, a continuous responder analysis at Week 4 did not show a significant difference of DSG from placebo on the patient global endpoint (although statistically significant differences were shown for the pain and function endpoints). However, results of the primary analysis at Week 6 showed that DSG was statistically significantly superior to placebo on all 3 co-primary endpoints. The same was true upon continuous responder analysis.

Even though the protocol specified that if a statistically significant difference was not demonstrated on all 3 primary outcomes at Week 4, then it would be concluded that efficacy of DSG had not been demonstrated (regardless of any results at Week 6), the Week 6 data provide support the efficacy of DSG. The Week 6 data suggest that, for a topical therapy intended to treat the symptoms of osteoarthritis of the hands, evaluation of effect after 4 weeks may not be appropriate. Instead, as was initially recommended by the Agency, assessment of efficacy at after a longer duration of treatment may be necessary.

Overall, therefore, data from the two studies provide evidence efficacy of DSG in the

7.2. Safety

The following information was reviewed to evaluate the safety of DSG:

- Pooled data from the 4 placebo-controlled trials. These data comprised the primary safety database.
- One open label long term study (VOSG-PN-309).
- Three (3) dermal trials evaluating DSG's potential for skin sensitization, irritation and photo-toxicity.

Although the Applicant submitted post-marketing safety surveillance data for the European topical formulation of diclofenac (Voltaren® Emulgel™; diclofenac diethylamine (DEA)), these data were not considered to be strongly relevant to establishing the safety of DSG. This is because the DEA formulation is different from DSG, and many of the adverse reactions associated with DEA could be related to the diethylamine excipient, and not to specifically diclofenac. Diethylamine is a secondary amine that is manufactured from ethanol and ammonia. It is corrosive to the eyes, mucous membranes, and skin. Skin contact can cause irritation, dermatitis, blistering and necrosis. Diethylamine is not approved for use in drug products in the US.

Similarly, the data from the short-term, limited-dose clinical pharmacology studies were not considered to be strongly relevant to establishing the safety of DSG, and so were not reviewed for safety.

The dermal safety trials were evaluated separately from the primary safety database. The review was performed by the Division of Dermatology and Dental Products and the findings are discussed under the section on dermal adverse events.

Regarding the trials in the primary safety database, two of the controlled trials have already been discussed. The remaining two controlled trials and the open-label trial are summarized below:

Table 5: Additional studies comprising the primary safety database

Study ID	Study Design	Doses
VOSG-PN-304	12-week, randomized, placebo-controlled, 2-arm, parallel group safety and efficacy study. Identical design and endpoints to study VOSG-PN-310	DSG 4g QID Placebo QID
VOSG-PE-314	8-week, randomized, placebo-controlled, two-arm, parallel group safety and efficacy study. Adults with OA of the hand Identical design and endpoints to study VOSG-PE-315	DSG 2g QID (dominant hand) DSG 2g QID (non-dominant hand) Placebo (both hands) QID
VOSG-PN-309	12-month, open-label, safety study Adults with OA of the knee	DSG to one (4g QID) or both (8g QID) knees

7.2.1. Exposure

Overall 2,223 subjects were treated with study medication in the OA population: 1,347 subjects were treated with DSG and 876 were treated with vehicle (placebo). These totals include all subjects from the controlled clinical trials as well as the long-term safety trial. A total of 142 subjects originally treated with vehicle in studies VOSG-PN-304 and VOSG-PN-310 went on to enter the open-label study, and were then treated with DSG. These subjects are counted in both the DSG and vehicle totals.

With respect to the clinical pharmacology trials, 76 healthy volunteers were exposed to DSG.

7.2.2. Deaths

There was a single death in the course of the clinical trials conducted with DSG that was not considered to be related to the administration of study medication.

> Subject 236/4469 was a 76-year-old male participant in Study VOSG-PN-310 (knee OA). The patient had a history of hypercholesterolemia and hypothyroidism (treated with levothyroxine). He was randomized to treatment with DSG and died on Day 5 of therapy, following an episode of ventricular fibrillation.

Although NSAIDs have been associated with an increased risk of cardiovascular thrombotic events and myocardial infarction, it is unlikely that this patient experienced significant enough systemic exposure of diclofenac in the 5-day treatment period to have caused this event. Additionally, the patient had pre-existing cardiac risk factors, and was taking levothyroxine, a medication that can have adverse cardiovascular effects such as an increase in heart rate, cardiac wall thickness, and cardiac contractility and may precipitate angina or arrhythmias.

7.2.3. Serious Adverse Events

Primary safety database (controlled efficacy studies)

As shown in Table 6, of the 1788 patients in the controlled efficacy trials, 19 subjects (10 in the DSG group (1%), and 9 in the placebo group (1%)) reported 22 SAEs. The most frequent SAEs were diarrhea and depression (n=2 patients each, both in the DSG group). A clear and consistent pattern of SAEs was not evident, and the incidence of AEs did not appear to be notably greater for the DSG group compared to the placebo group. No serious dermal adverse reactions were reported. Dr. Gibbs reviewed the narratives describing each of the SAEs and did not consider any to be related to treatment with study drug.

Table 6: Serious adverse events – Controlled, short-term studies

MedDRA Preferred Term	DSG (N=912)	Placebo (N=876)
	N	N
DEPRESSION	2	0
DIARRHOEA	2	0
ATRIAL FIBRILLATION	1	0
DEEP VEIN THROMBOSIS	1	0
ESCHERICHIA SEPSIS	1	0
FOREARM FRACTURE	1	0
POSTMENOPAUSAL HAEMORRHAGE	1	0
PULMONARY EMBOLISM	1	0
VENTRICULAR FIBRILLATION	1	0
VOMITING	1	0
ABDOMINAL MASS	0	1
ANGINA PECTORIS	0	1

Table 6 (contd.): Serious adverse events – Controlled, short-term studies

MedDRA Preferred Term	DSG (N=912)	Placebo (N=876)
	N	N
CORONARY ARTERIAL STENT INSERTION	0	1
DIABETIC NEPHROPATHY	0	1
FACIAL PALSY	0	1
INTERVERTEBRAL DISC PROTRUSION	0	1
MIGRAINE	0	1
SYNCOPE	0	1
WRIST FRACTURE	0	1

Open-label safety study
In Study -309, of the 578 patients who were treated, 350 dosed one knee (4g DSG QID) and 228 dosed both knees (8g DSG QID). A total of 29 patients reported at least one SAE (13 treated with 4g QID, and 16 treated with 8 g QID). The SAEs occurred in very low frequency (no more than 2 cases each) and did not suggest a dose-response relationship. No serious dermal adverse reactions were reported. The SAEs were not considered related to study drug. Refer to Dr. Gibbs' review for details regarding the SAEs in the open-label study.

7.2.4. Adverse Events of Interest

7.2.4.1.Dermal Adverse Events

To calculate the skin-related AEs which occurred with the use of DSG, the skin-related AEs were consolidated from the three System Organ Classes (SOCs): General disorders and administration site conditions; Skin and subcutaneous tissue disorders; and Injury, poisoning, and procedural complications. The non-serious dermal AEs are shown Table 7, below. Note that the table omits several preferred terms that are included in the SOCs but are not likely to be related to topical drug application (Table 7, footnote 1).

Note also that this approach to enumerating the skin-related AEs is different from Norvartis' and Dr. Gibbs' approach. They consolidated AEs from two SOCs only: "General disorders and administration site conditions," and "Skin and subcutaneous tissue disorders." This review includes the "Injury, poisoning, and procedural complications" SOC to capture the incidence of blisters on the fingers of two patients who were being treated for hand OA.

Application site reactions were the most frequently reported dermal AE in both groups: 6.8% (62/912) of DSG-treated patients, and 2.2% (19/876) of placebo patients. Among the application site reactions, dermatitis was the most common, with a rate of 3.5% in the DSG group, versus 0.7% in the placebo group.

Table 7: Non-serious dermal adverse events – Controlled Trials[1]

Body System	MedDRA Preferred Term	DSG N=912		Placebo N=876	
		N	%	N	%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE ...				
	BURNING	0	0.00	1	0.11
	DERMATITIS	**32**	**3.51**	**6**	**0.68**
	DRYNESS	4	0.44	3	0.34
	ECZEMA	0	0.00	1	0.11
	ERYTHEMA	6	0.66	3	0.34
	IRRITATION	2	0.22	0	0.00
	PAPULES	1	0.11	0	0.00
	PARAESTHESIA	5	0.55	3	0.34
	PRURITUS	7	0.77	1	0.11
	REACTION	2	0.22	0	0.00
	URTICARIA	0	0.00	1	0.11
	VESICLES	3	0.33	0	0.00
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	BLISTER	1	0.11	1	0.11
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	ACNE	0	0.00	1	0.11
	DERMAL CYST	1	0.11	0	0.00
	DERMATITIS	3	0.33	1	0.11
	DERMATITIS ALLERGIC	2	0.22	1	0.11
	DERMATITIS CONTACT	5	0.55	2	0.23
	DRY SKIN	5	0.55	0	0.00
	ECCHYMOSIS	2	0.22	1	0.11
	ECZEMA	1	0.11	0	0.00
	ERYTHEMA	1	0.11	0	0.00
	ONYCHORRHEXIS	2	0.22	0	0.00
	PRURITUS	6	0.66	3	0.34
	RASH	7	0.77	5	0.57
	RASH PAPULAR	1	0.11	1	0.11
	SKIN BURNING SENSATION	1	0.11	0	0.00
	SKIN DESQUAMATION	1	0.11	0	0.00
	SKIN HYPERPIGMENTATION	0	0.00	1	0.11
	SKIN IRRITATION	3	0.33	0	0.00
	SKIN LESION	3	0.33	1	0.11
	URTICARIA	1	0.11	0	0.00

[1] The table omits the following preferred terms: angioneurotic edema, skin laceration, wound secretion, meniscus lesion, excoriation, contusion, tenderness, pitting edema, peripheral edema, edema, swelling face, burns second degree, open wound, rosacea.

When each type of application site reaction is considered individually, it appears as though there was no considerable difference between the DSG and placebo groups. The

total number of application site reactions in each group was calculated to evaluate whether the same conclusion could be drawn in that instance. Table 8 (below) shows that 7% of DSG patients experienced an application site reaction compared to 2% of placebo patients.

Table 8: All application site reactions – Controlled Trials[1]

Adverse Reaction[†]	Voltaren Gel N = 913	Placebo (vehicle) N = 876
	N (%)	N (%)
Any application site reaction	62 (6.8)	19 (2.1)
Application site dermatitis	32 (4)	6 (1)
Application site pruritus	7 (0.8)	1 (0.1)
Application site erythema	6 (0.7)	3 (0.3)
Application site paresthesia	5 (0.6)	3 (0.3)
Application site dryness	4 (0.4)	3 (0.3)
Application site vesicles	3 (0.3)	0 (0)
Application site irritation	2 (0.2)	0 (0)
Application site papules	1 (0.1)	0 (0)

[†]Preferred Term according to MedDRA 9.1.

7.2.4.2. Special dermal safety studies

Three Phase 1 clinical studies were conducted to evaluate the (1) cumulative irritation potential, (2) phototoxicity potential, and (3) skin sensitizing potential of DSG. The studies were reviewed by the Division of Dermatology and Dental Products.

The review found that, under conditions of the dermal safety studies, clinically significant potential for irritation, sensitization, or phototoxicity was not identified. Because photoallergenicity studies were not been conducted with DSG, the Division of Dermatology and Dental Products recommended that product labeling should reflect that adequate precautions should be taken to minimize sunlight exposure. Additionally, an evaluation of the photocontact allergic potential of DSG was recommended as a post-marketing study.

Refer to the review by Dr. Brenda Vaughn for details of the design and results of the dermal safety studies.

7.2.4.3. Adverse events in patients taking concomitant oral NSAIDs

The use of concomitant NSAIDs was prohibited in all of the studies. However, at the request of the Agency, the Applicant evaluated the number of patients who used an NSAID post-baseline and their type and frequency of AEs.

Altogether, 2.6% of DSG patients (24/912) and 3.9% of placebo patients (34/876) used a prohibited NSAID (Applicant's Table 3-10, Summary of Clinical Safety – data not shown). Table 8 provides a listing of the AEs with a frequency > 1 for the subjects who ingested NSAIDs during the knee or hand OA controlled efficacy trials. None of the AEs suggest synergistic or additive toxicity for the oral NSAID when topical diclofenac is used. In particular, there are no gastrointestinal or cardiovascular AEs among the most commonly reported AEs for the group.

Table 9. Most common AEs in patients taking concomitant oral NSAIDs – Controlled trials

Table 4-23 Most frequently reported (total incidence > 1) adverse events for subjects who used oral NSAIDs during the controlled clinical trials – major safety population

		Knee		Hand		Overall	
		DSG	Vehicle	DSG	Vehicle	DSG	Vehicle
	Total number of subjects studied	513	493	400	383	913	876
	Number of subjects with AEs - n (%)	14 (2.7)	24 (4.9)	4 (1.0)	2 (0.5)	18 (2.0)	26 (3.0)
	Total number of AE terms	37	51	5	2	42	53
SOC	MedDRA Preferred Term - n (%)						
Nerv	Headache	5 (1.0)	5 (1.0)			5 (0.5)	5 (0.6)
Musc	Arthralgia	6 (1.2)	3 (0.6)			6 (0.7)	3 (0.3)
Musc	Back pain		5 (1.0)			0 (0.0)	5 (0.6)
Musc	Myalgia	1 (0.2)	3 (0.6)			1 (0.1)	3 (0.3)
Musc	Pain in extremity	2 (0.4)	2 (0.4)			2 (0.2)	2 (0.2)
Infec	Sinusitis	2 (0.4)	2 (0.4)			2 (0.2)	2 (0.2)
Infec	Bronchitis		3 (0.6)			0 (0.0)	3 (0.3)
Inj&P	Back injury		2 (0.4)			0 (0.0)	2 (0.2)
Resp	Cough		1 (0.2)	1 (0.3)		1 (0.1)	1 (0.1)
Metab	Hypercholesterolemia	1 (0.2)	1 (0.2)			1 (0.1)	1 (0.1)
Infec	Influenza	1 (0.2)	1 (0.2)			1 (0.1)	1 (0.1)
Musc	Neck pain	1 (0.2)	1 (0.2)			1 (0.1)	1 (0.1)
Gastr	Toothache		1 (0.2)		1 (0.3)	0 (0.0)	2 (0.2)
Infec	Upper respiratory tract infection	1 (0.2)	1 (0.2)			1 (0.1)	1 (0.1)

(Applicant's Table 4-23, Summary of Clinical Safety, p. 68)

7.2.5. Common Adverse Events

In the controlled efficacy trials, there were 835 patients who reported a non-serious AE: 451 (49.5%) in the DSG group and 384 (43.8%) in the placebo group. Table 9 lists the AEs that occurred in at least 1% of DSG-treated patients, and with greater frequency than the placebo group. The table excludes AEs that are unlikely to be related to drug treatment (Table 9, footnote 1).

The table shows that dermal AEs were the most common adverse reactions, such as dermatitis, pruritis, and erythema.

Table 10: Common adverse reactions occurring in at least 0.5% of the DSG group and at a greater frequency than placebo – Controlled Trials[1]

MedDRA Preferred Term	DSG (N=912)		Placebo (N=876)	
	N	%	N	%
APPLICATION SITE DERMATITIS	32	3.51	6	0.68
RASH	7	0.77	5	0.57
APPLICATION SITE PRURITUS	7	0.77	1	0.11
APPLICATION SITE ERYTHEMA	6	0.66	3	0.34
PRURITUS	6	0.66	3	0.34
APPLICATION SITE PARAESTHESIA	5	0.55	3	0.34
BURSITIS	5	0.55	3	0.34
ABDOMINAL PAIN UPPER	5	0.55	2	0.23
DYSPEPSIA	5	0.55	2	0.23
DERMATITIS CONTACT	5	0.55	2	0.23
DRY SKIN	5	0.55	0	0

[1] The table excludes the following AEs which occurred in > 0.5% of DSG patients and in higher frequency than placebo patients, but are considered unlikely to be related to study drug: arthralgia, back pain, pain in extremity, upper respiratory tract infection, sinusitis, pain, neck pain, myalgia, pharyngolaryngeal pain, joint sprain, sinus headache, sinus congestion, contusion, muscle strain, nausea, ear pain, dizziness.

7.2.6. Adverse Events Leading to Discontinuation

In the controlled efficacy trials, 4.9% (45/912) DSG patients and 2.7 (24/876) placebo patients discontinued participation due to an adverse event. Adverse dermal effects were the main reason for treatment discontinuation. Refer to Dr. Gibbs' review for details regarding subject disposition.

7.2.7. Safety Conclusions

Overall, the safety data from the short-term controlled and longer-term open-label studies suggest that treatment with DSG is primarily associated with application site reactions, of which application site dermatitis is the most common. Application site reactions were the most frequent reason for treatment discontinuation. Most adverse reactions to DSG were non-serious. With respect to NSAID-related events, the data do not show that patients treated for up to one year with DSG experienced clinically concerning cardiovascular, gastrointestinal, renal, or hepatic reactions.

8. Advisory Committee

An Advisory Committee meeting was not required for this product.

9. Other regulatory issues

9.1. 505(b)(2) NDA issues

Refer to Section 2 – Background/Regulatory History

9.2. Pediatric studies

Included within this NDA was a request for full waiver from the requirements for data on the safety and efficacy of DSG in pediatric patients. The basis for this request was that there are no data to show the incidence of OA of superficial joints in patients less than 18 years of age.

9.3. Proprietary name

Novartis proposed Voltaren Gel as the proprietary name for DSG. The Division of Medication Errors and Technical Support (DMETS) had no objections to this name

10. Labeling

This section discusses general recommended changes for the product label, if DSG is approved for marketing.

The data show that treatment with DSG results in systemic diclofenac exposure (refer to Section 5). Under conditions of maximal use (DSG applied to both hands and knees QID), DSG produces approximately 20% of the systemic exposure of an oral dose of diclofenac of 50 mg tid. As such, the product label for DSG should include the standard language from the NSAID labeling template that describes the potential risks of NSAID treatment.

The proposed indication is ' , such as the hands and knees." DSG provides symptomatic relief of osteoarthritis, and but does not modify the disease process. The INDICATION language should be changed to include the p'

The DOSAGE AND ADMINISTRATION section should be rewritten to more clearly describe how patients are to measure out gram quantities of DSG for application.

The table of common adverse reactions should be revised to reflect only those adverse events that occurred more frequently in the DSG group than in the placebo group, and should exclude reactions that are unlikely to be related to study drug (e.g.

The DRUG INTERACTIONS section should list all of the drug-drug interactions described in the NSAID template.

The [redacted] section should be deleted [redacted]

The CLINICAL STUDIES section should be revised to reflect only the results from the clinical trials that showed efficacy of DSG. [redacted]

The PATIENT COUNSELING INFORMATION section should contain the standard language from the "Information For Patients" section of the NSAID template.

There are multiple instances throughout the product label of language describing the [redacted]

Labeling reviews by other disciplines:
The Division of Medication Errors and Technical Support (DMETS) reviewed the container labels, carton labeling and a preliminary version of the package insert for DSG. Recommendations included those listed below, and will be implemented.

- DMETS provided general comments regarding the modification of the size and location of the established name, and the prominence of the graphic next to the tradename.
- DMETS also required that the word "topical" be deleted from the established name, since "topical gel" is not part of the recognized dosage form.
- The route of administration is to be included under the established name. For example,

  "(diclofenac sodium) gel 1%
  For Topical Use Only"

- As currently written, the dosing cards do not clearly explain how to correctly administer the prescribed dose. DMETS recommends that each dosing card provide only one designated area on which to apply Voltaren Gel to avoid dosing errors. The dosing card should also provide instructions for how patients are to apply the gel to the affected area. The dosing instructions should make it more apparent which side of each dosing sheet is the printed side, should tell patients not to use a dosing card more than once and should instruct patients to measure out each application with a new card..

The Division of Drug Marketing, Advertising, and Communications also reviewed the labeling for DSG. Recommendations made included those listed below. The recommendations will be implemented.

- The indication be changed to reflect tha
- Instructions for use not
- Addition of the oral NSAIDs to the list of products for which concomitant use with DSG has not been studied.
- Deletion of the statement that
- Deletion of the data from the
- Deletion of the

11. Comments to Applicant

1. An evaluation of the photocontact allergic potential of Voltaren Gel has not been performed. We recommended that you conduct this study as a post-marketing commitment, following approval of the product.

2. A dermal carcinogenicity study should be conducted for the cocoyl caprylocaprate excipient, to determine its carcinogenic potential. The study may be performed as a Phase 4 commitment.

12. Appendix

12.1. Appendix 1: Modified AUSCAN index

3. AUSCAN Osteoarthritis Hand Index for the right hand and for the left hand

The AUSCAN® index (Bellamy et al 2002a, Bellamy et al 2002b) consists of 15 questions grouped into 3 sections (pain, stiffness and difficulty performing daily activities). It focuses on functional status of the hand during the previous 24 hours. The VAS version of the AUSCAN index will be used. All questions in the AUSCAN index are modified to refer separately to the right hand and to the left hand, rather than to the hands considered together (Table 3.5.2).

Table 3.4.2 Modification of the wording of the AUSCAN index to assess the right hand and the left hand separately

Pain subscale	
Amount of pain experienced in your left hand	**Amount of pain experienced in your right hand**
How much pain do you have in your left hand?	How much pain do you have in your right hand?
1. At rest (i.e. when not using your left hand)	1. At rest (i.e. when not using your right hand)
2. When gripping objects with your left hand	2. When gripping objects with your right hand
3. When lifting objects with your left hand	3. When lifting objects with your right hand
4. When turning objects with your left hand	4. When turning objects with your right hand
5. When squeezing objects with your left hand	5. When squeezing objects with your right hand
Stiffness subscale	
Amount of joint stiffness experienced in your left hand	**Amount of joint stiffness experienced in your right hand**
6. How severe is stiffness in your hands after first wakening in the morning	6. How severe is stiffness in your right hand after first wakening in the morning
Function subscale	
Degree of difficulties experienced in your left hand	**Degree of difficulties experienced in your right hand**
7. Turning taps/faucets on	7. Turning taps/faucets on
8. Turning a round door/knob or handle	8. Turning a round door/knob or handle
9. Doing up buttons	9. Doing up buttons
10. Fastening jewellery	10. Fastening jewellery
11. Opening a new jar	11. Opening a new jar
12. Carrying a full pot with your left hand	12. Carrying a full pot with your right hand
13. Peeling vegetables/fruits	13. Peeling vegetables/fruits
14. Picking up large heavy objects	14. Picking up large heavy objects
15. Wringing out washcloths	15. Wringing out washcloths

These assessments will be performed at all visits. However, **the function subscale (Questions 7 to 15) will be completed for the dominant hand only.** The investigator or designee should assist the patients in case of questions and check the completion of the questionnaire before the patient leaves the study site.

12.2. Appendix 2: Continuous Responder Analyses – Study VOSG-PN-310

(Source: Applicant's study report for VOSG-PE-310, Post-text supplement 3, p. 117, 119, 121)

Figure 9.15.1 Continuous Responder Analysis
Successive % Improvement Rates By Treatment for WOMAC Pain Index
(Patients in Modified Efficacy Subpopulation)

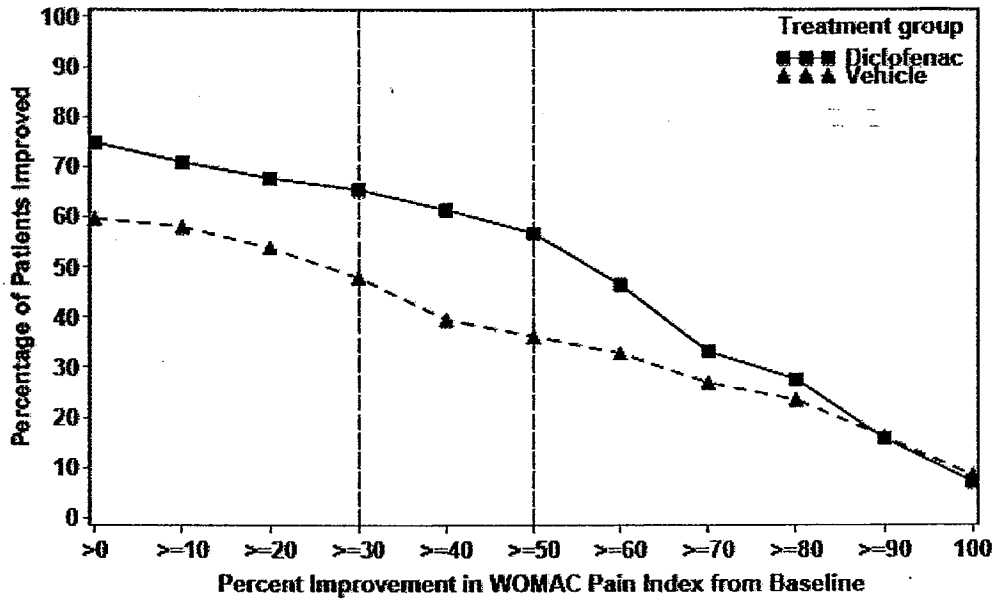
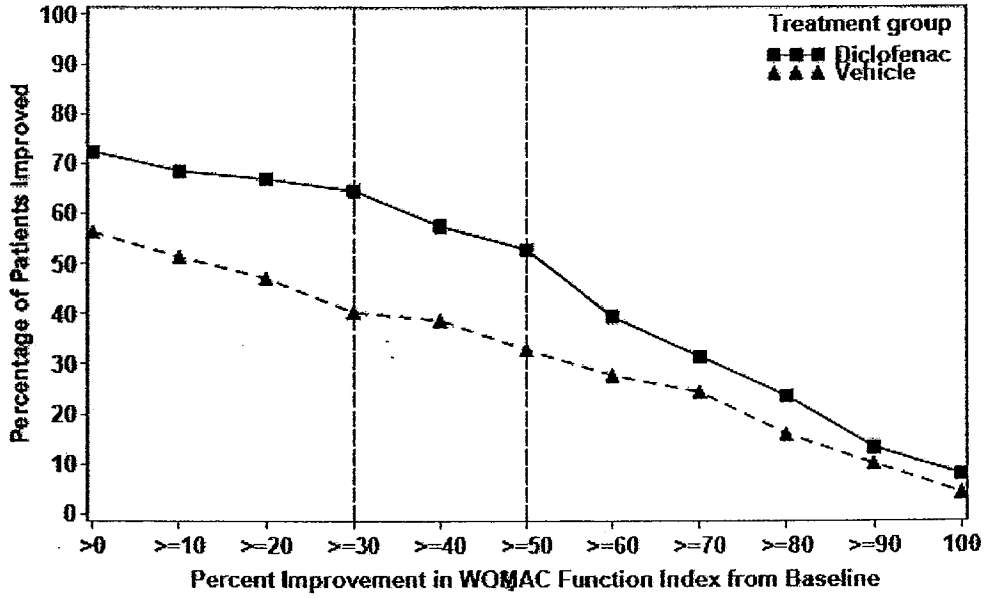
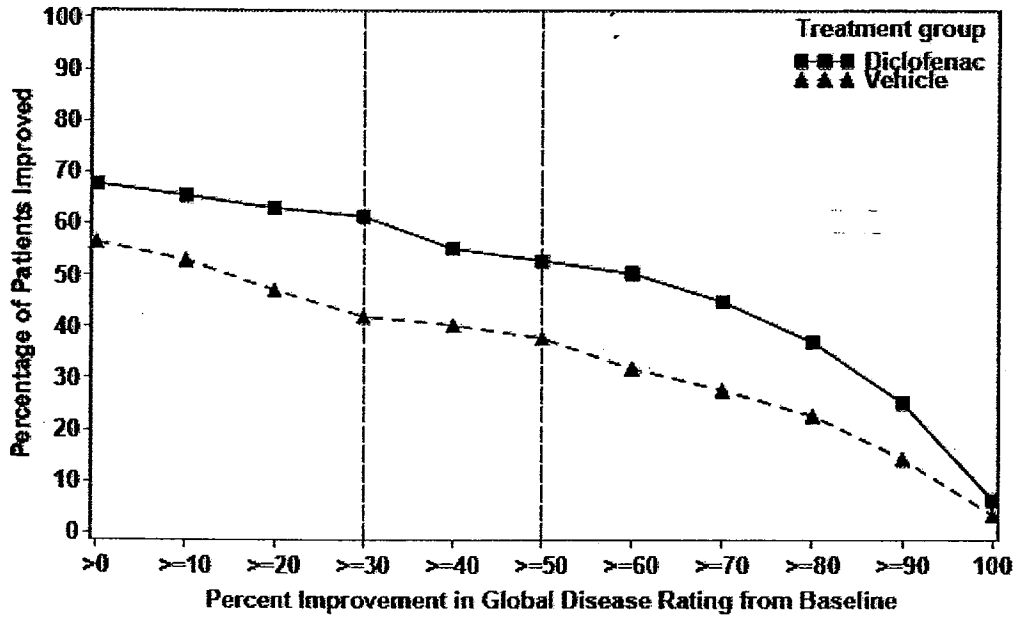


Figure 9.15.2 Continuous Responder Analysis
Successive % Improvement Rates By Treatment for WOMAC Function Index
(Patients in Modified Efficacy Subpopulation)



Diclofenac Sodium Gel 1% Protocol VOSG-PN-31

Figure 9.15.3 Continuous Responder Analysis
Successive % Improvement Rates By Treatment for Global Disease Rating
(Patients in Modified Efficacy Subpopulation)



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ON ORIGINAL

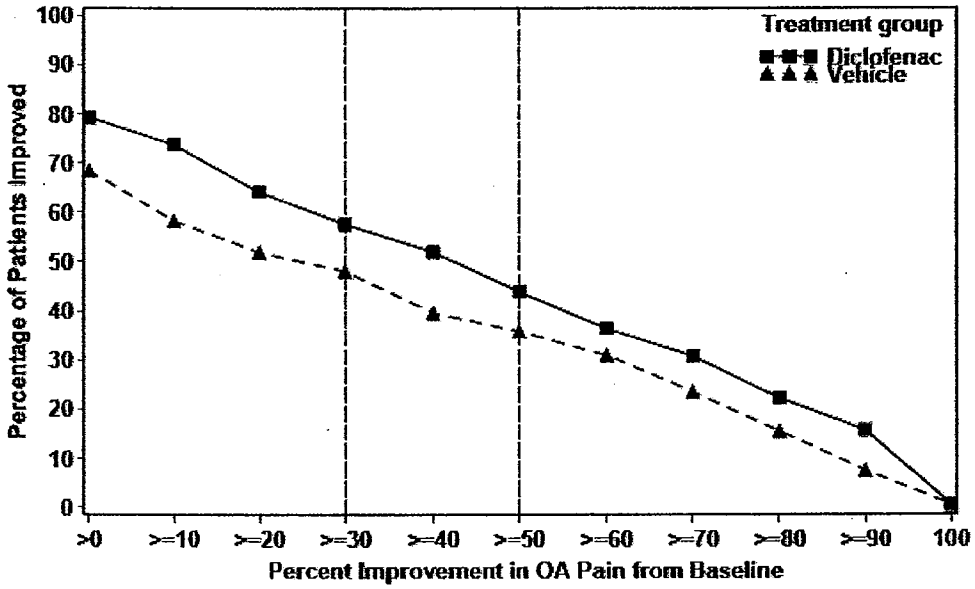
12.3. Appendix 3: Continuous Responder Analyses – Study VOSG-PE-315

(Source: Applicant's study report for VOSG-PE-315, Post-text supplement 3, p. 76-81)

Week 4 Analyses:

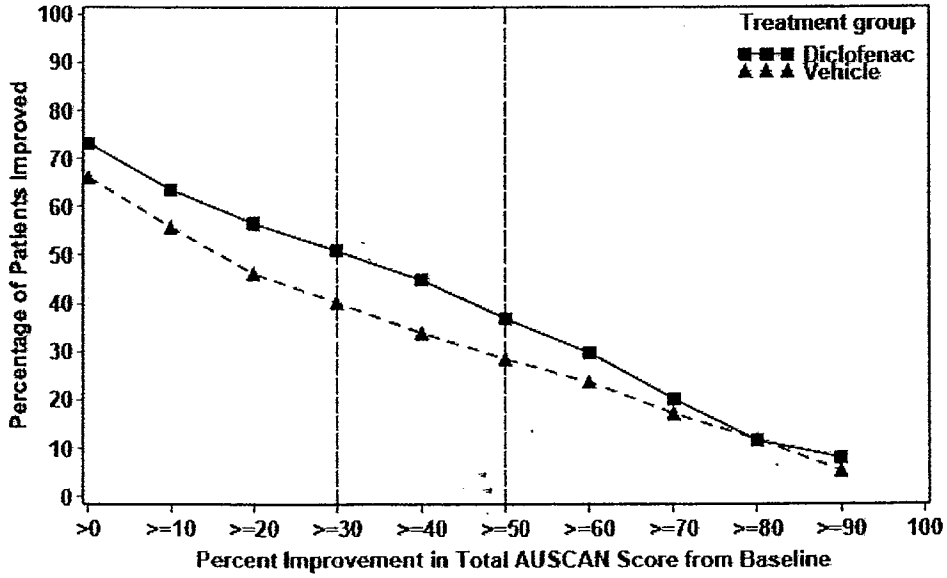
Diclofenac Sodium Gel 1% Protocol VOSG-PE-31

Figure 9.18.1.1 Continuous Responder Analysis
Successive % Improvement Rates By Treatment for OA Pain (Week 4)
(Patients in ITT Efficacy Population)



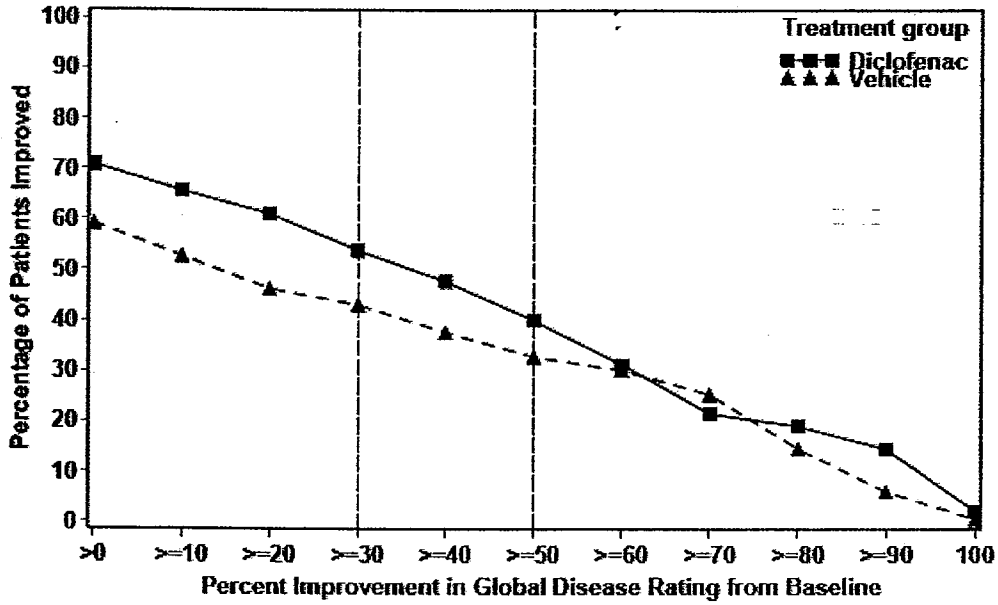
Diclofenac Sodium Gel 1% Protocol VOSG-PE-31

Figure 9.18.2.1 Continuous Responder Analysis
Successive % Improvement Rates By Treatment for Total AUSCAN Score (Week 4)
(Patients in ITT Efficacy Population)



Diclofenac Sodium Gel 1% Protocol VOSG-PE-31

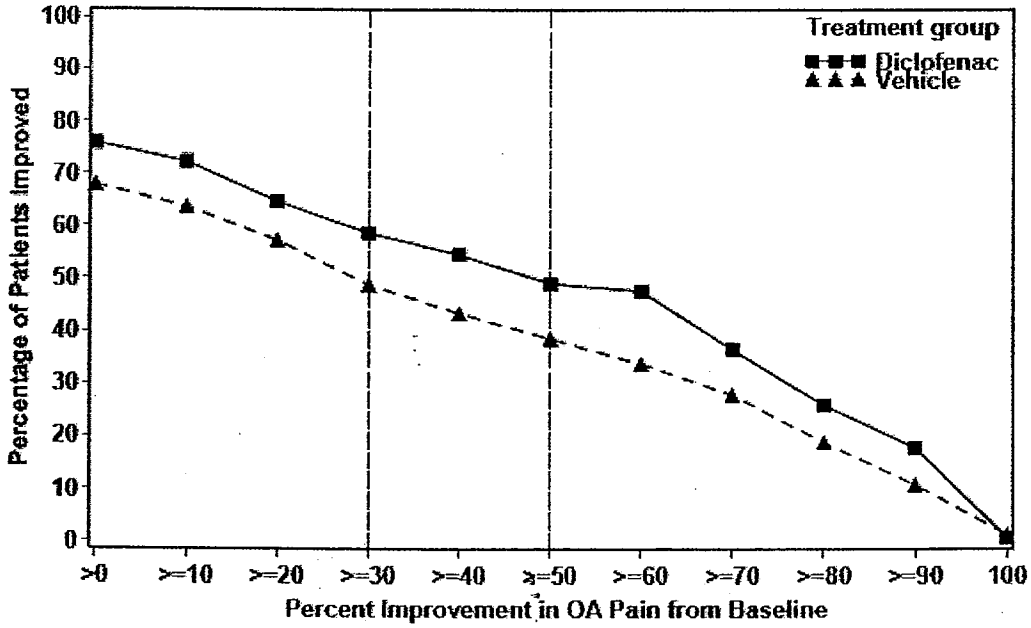
Figure 9.18.3.1 Continuous Responder Analysis
Successive % Improvement Rates By Treatment for Global Disease Rating (Week 4)
(Patients in ITT Efficacy Population)



Week 6 Analyses:

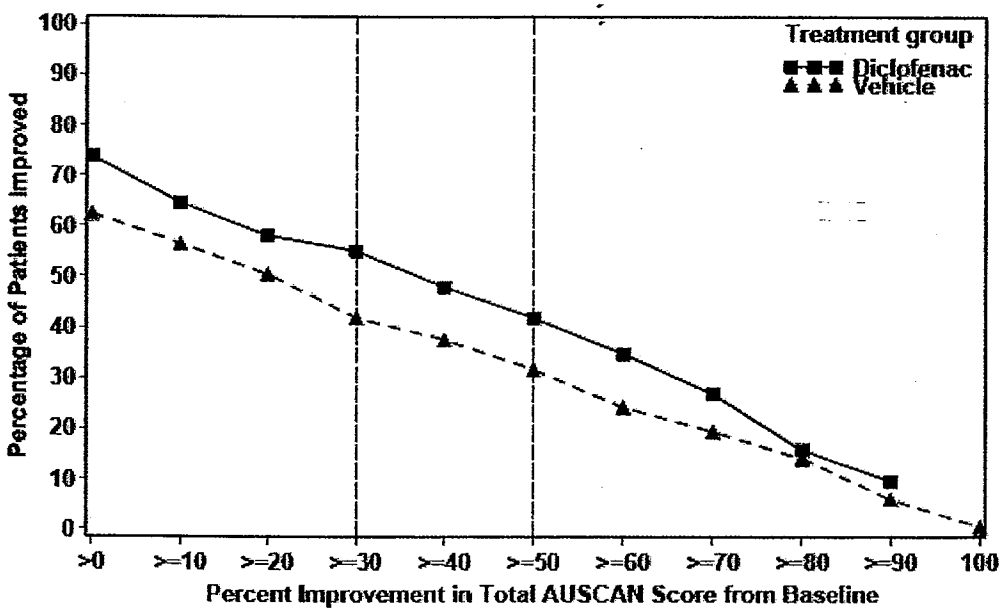
Diclofenac Sodium Gel 1% Protocol VOSG-PE-31

Figure 9.18.1.2 Continuous Responder Analysis
Successive % Improvement Rates By Treatment for OA Pain (Week 6)
(Patients in ITT Efficacy Population)



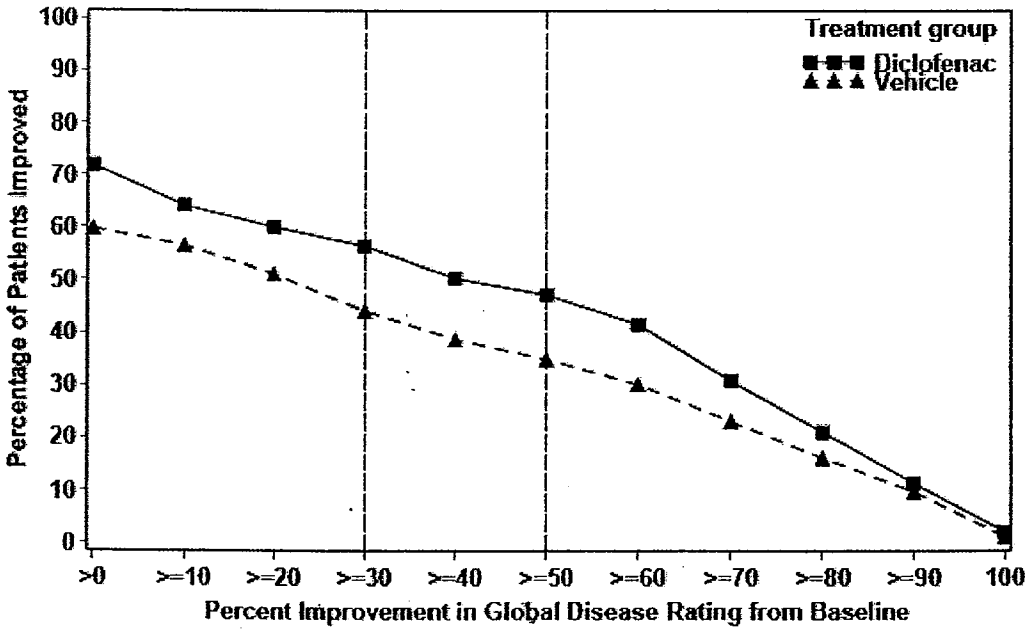
Diclofenac Sodium Gel 1% Protocol VOSG-PE-31

Figure 9.18.2.2 Continuous Responder Analysis
Successive % Improvement Rates By Treatment for Total AUSCAN Score (Week 6)
(Patients in ITT Efficacy Population)



Diclofenac Sodium Gel 1% Protocol VOSG-PE-31

Figure 9.18.3.2 Continuous Responder Analysis
Successive % Improvement Rates By Treatment for Global Disease Rating (Week 6)
(Patients in ITT Efficacy Population)



13. Appendix 4 - Common adverse events in > 1% of DSG patients

	DSG (N=913)		Placebo (N=876)	
Preferred Term	**N**	**%**	**N**	**%**
HEADACHE	114	12.50	114	13.01
ARTHRALGIA	64	7.02	52	5.94
BACK PAIN	58	6.36	54	6.16
NASOPHARYNGITIS	33	3.62	33	3.77
APPLICATION SITE DERMATITIS	32	3.51	6	0.68
PAIN IN EXTREMITY	31	3.40	25	2.85
UPPER RESPIRATORY TRACT INFECTION	24	2.63	24	2.74
SINUSITIS	21	2.30	19	2.17
PAIN	17	1.86	16	1.83
NECK PAIN	16	1.75	5	0.57
MYALGIA	13	1.43	11	1.26
TOOTHACHE	11	1.21	11	1.26
INFLUENZA	11	1.21	14	1.60
PHARYNGOLARYNGEAL PAIN	11	1.21	4	0.46
JOINT SPRAIN	10	1.10	8	0.91
SINUS HEADACHE	10	1.10	1	0.11
SINUS CONGESTION	10	1.10	1	0.11
CONTUSION	8	0.88	5	0.57
COUGH	8	0.88	14	1.60
DIARRHOEA	7	0.77	10	1.14
APPLICATION SITE PRURITUS	7	0.77	1	0.11
OEDEMA PERIPHERAL	7	0.77	7	0.80
BRONCHITIS	7	0.77	8	0.91
RASH	7	0.77	5	0.57
HYPERTENSION	7	0.77	7	0.80
EAR PAIN	6	0.66	0	0.00
NAUSEA	6	0.66	1	0.11
APPLICATION SITE ERYTHEMA	6	0.66	3	0.34
MUSCLE STRAIN	6	0.66	3	0.34
PRURITUS	6	0.66	3	0.34
ABDOMINAL PAIN UPPER	5	0.55	2	0.23
DYSPEPSIA	5	0.55	2	0.23

Appendix 4 (contd.) - Common adverse events in > 1% of DSG patients

	DSG (N=913)		Placebo (N=876)	
Preferred Term	**N**	**%**	**N**	**%**
APPLICATION SITE PARAESTHESIA	5	0.55	3	0.34
LIMB INJURY	5	0.55	1	0.11
BURSITIS	5	0.55	3	0.34
DIZZINESS	5	0.55	4	0.46
DERMATITIS CONTACT	5	0.55	2	0.23
DRY SKIN	5	0.55	0	0.00

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/s/

Mwango Kashoki
10/2/2007 09:34:47 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type: NDA 22-122
Submission Number: 0000
Submission Code: 0000

Letter Date: 2006-12-19
Stamp Date: ~~2007-10-19~~ 2006-12-20
PDUFA Goal Date: 2007-10-18 20

Reviewer Name: Neville A Gibbs, MD, MPH
Team Leader Name: Mwango Kashoki, MD, MPH
Review Completion Date: 2007-08-20

Established Name: Diclofenac sodium topical gel, DSG 1%
(Proposed) Trade Name: Voltaren —
Therapeutic Class: NSAID
Applicant: Novartis Consumer Health, Inc

Priority Designation: Standard

Formulation: Gell
Dosing Regimen: 2 g qid for hand OA; 4 g qid for knee OA

Proposed Indication: ——— joints amenable to — treatment, such as the hands and knees

Intended Population: Patients with mild to moderate OA pain

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends the approval of voltaren topical diclofenac sodium gel, or (DSG 1%) and with the trade name Voltaren Gel at a dosage of 2 gm qid for the ——— ——— the hand, or 4 gm qid fo — ne knees.

This recommendation is based on review of the efficacy and safety data submitted by Novartis Pharmaceutical, Inc for this New Drug Application (NDA) in a population of patients with mild to moderate pain of osteoarthritis of the knee and hands is based on analysis of the data. There is a favorable risk benefit ratio which outweighs any currently identified risk associated with use of topical DSG 1%.

No deficiencies were identified in the NDA submission that would preclude the approval of this product.

Voltaren was studied primarily in two adequate and controlled Phase 3 clinical trials and VOSG-PN-310 (knee OA) and VOSG-PE-315 (hand OA). These studies enrolled nearly identical subjects with mild to moderate OA pain.

Independent FDA review analyses confirmed the applicants conclusion that DSG 1% was superior to a comparator vehicle control arm (in achieving the WOMAC Pain , WOMAC Function endpoints and the Global rating of disease at Week 12 in the knee OA study; and the OA pain, Total AUSCAN and Global rating of disease at Week 8 in hand OA study.

Results of sensitivity analyses also confirmed the primary efficacy outcome analysis. This treatment effect was consistent across gender, race, age, and geographic region.

The post hoc efficacy analysis of supportive study VOSG-PN-304 (knee OA) provided the data that allowed the recognition of subjects most likely to respond to topical diclofenac therapy and the subsequent identification and definition of the modified efficacy subpopulation (MES) used for the efficacy analysis of data in Study VOSG-PN-310.

The FDA review of the Voltaren safety data found voltaren or Voltaren Gel safe for its intended use in patients with OA of joints amenable to — treatment, such as hands and knees.

The overall type and incidence of non-serious and serious adverse events and the rate of discontinuation due to AEs did not differ relevantly or systematically for the subgroups by age, gender, race and geographic region.

The main safety concern identified during the safety review of DSG 1% was the difference in the proportion of subjects in the DSG arm reporting application site reaction compared to the proportion of subjects in the vehicle arm reporting application site reactions in the vehicle arm. These reactions included the following application site dermatitis and application site erythema.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

None

1.2.2 Required Phase 4 Commitments

1. Photocontact allergic potential studies (as per Dermatology consult)

1.2.3 Other Phase 4 Requests

None

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The applicant has proposed the trade name of Voltaren Gel. Voltaren Gel (to be referred to as diclofenac sodium gel [DSG 1%] for the remainder of this review) contains the NSAID diclofenac sodium in a topical delivery system for joints amenable to — treatment, such as the hands and knees. DSG 1% is intended for qid use in adult subjects with mild to moderate pain.

Novartis Consumer Health Inc submitted four controlled Phase 3 clinical trials which compared the efficacy and safety of DSG 1% against vehicle control in subjects with mild to moderate pain of osteoarthritis. Additionally, an uncontrolled long-term trial was conducted for long term safety analysis.

1.3.2 Efficacy

Of the four submitted trials, studies VOSG-PN-310 (knee OA) and VOSG-PN-3105 (hand OA)provide evidence of treatment effect across all primary efficacy endpoints that topical DSG 1% is effective therapy for symptoms of hand and knee OA. Multiple secondary endpoints analyses also supported the conclusions of efficacy over 12 weeks of dosing

(knee OA), and 8 weeks of dosing (hand OA).

The FDA's Statistical Reviewer verified the applicants' analysis of the primary and secondary endpoints.

The study design of the knee OA study was based on accumulated data from the identical Study VOSG-PN-304 (knee OA). Post hoc analyses from the latter study were used to prospectively modify aspects of the design of the pivotal Study-310. This modification or adaptation of the design of Study VOSG-PN-310 did not appear to undermine the validity, or the integrity of the effectiveness of the trial medication.

1.3.3 Safety

The safety of DSG was demonstrated in the pooled safety population of the four placebo controlled Phase 3 trials (two knee OA and two hand OA trials) and one long term safety trial in patients with knee OA. A total of 1347 subjects were treated with DSG in the course of the clinical work conducted in support of this submission.

The incidence rate of AEs in the controlled Phase 3 studies was generally slightly higher ate of AEs in the knee studies than in the hand studies. This may be explained, in part, by the fact that the knee studies were of 50% longer duration than the hand

Oral diclofenac has been the subject of a previously approved NDA (NDA 19-201) submitted by the Novartis Corporation. The safety profile for oral diclofenac is well characterized. At typical oral doses (50 mg TID) the systemic exposure of oral diclofenac is approximately 17 x higher than that observed for typical doses (4 g QID) of topical DSG. Therefore, the risk of adverse events due to systemic exposure from DSG was anticipated to be relatively lower than with oral diclofenac. The safety data from the DSG found that, apart from evidence of greater cutaneous sensitivity of DSG 1% compared to vehicle (placebo), the topical formulation presented here did not produce any unexpected AEs.

In the controlled Phase 3 studies, the most common AEs were headache, arthralgia, back pain, nasopharyngitis and sinusitis, occurring in equal proportions in the DSG and vehicle (control) arms of the Phase 3 controlled studies. Application site skin reactions of various sorts were reported in 10.1 % of subjects treated with DSG compared to 3.8 % in the vehicle-treated subjects in the controlled Phase 3 trials. Dermal AE's were associated with 41% of the discontinuation because of AE's in the DSG 1% group, whereas the corresponding fraction for the vehicle group was 25.8%.

In the long-term uncontrolled safety study, distribution of AE's was similar to that of the controlled studies, and data from patients with up to 12 months of exposure did not reveal any new safety concerns with increasing duration of exposure. The incidence of any skin-related AEs over the 12 months was 17.8%, with a declining incidence over successive quarters. The dermal AE incidence rate in the first quarter was 11.8% declined over

subsequent quarters. This rate was comparable to the overall dermal AE rate in the DSG exposed population of the pooled controlled Phase 3 trials. Skin-related AEs accounted for 57% of all reported AEs associated with discontinuations.

SAE's were equally distributed between active drug and vehicle.

Subgroup analyses showed no differences in safety profile with age, sex or race, and dose adjustment was not required in long-term studies.

Three special safety studies related to the potential for skin irritation, sensitization, and photo-toxicity were conducted early in the development program and did not demonstrate significant potential for photo-toxicity, irritation or sensitization.

The proposed product has the same active moiety in the same concentration as Voltaren® Emulgel™ (diclofenac ethylamine gel). This product has been available in Europe for over 20 years and is approved in over 115 countries. Based on the clinical data available from the trials presented in this document, topical DSG appears to have a more moderate safety profile compared to that demonstrated for Voltaren® Emulgel™, particularly with regard to dermal adverse reactions.

1.3.4 Dosing Regimen and Administration

The applicant proposes that DSG be applied to osteoarthritic joints amenable to — treatment, such as the hands and knees, as follows:

- Lower extremities, including the knees, ankles, and feet:
  Apply the gel (4 g) to the affected area 4 times daily. Voltaren® AT should be gently massaged into the skin ensuring application to the entire affected area. Do not use more than 16 g daily per lower area.

- Upper extremities, including the elbows, wrists, and hands:
  Apply the gel (2 g) to the affected area 4 times daily Voltaren® AT should be gently massaged into the skin ensuring application to the entire affected area. Do not use more than 8 g daily per upper area.

Total usage should not exceed 32 g per day, over all affected joints.

1.3.5 Drug-Drug Interactions

DSG 1% is a topical product with minimal systemic absorption; therefore the risk of drug-drug interaction is low. Nevertheless, because some drug is systemically available, it can be

assumed that the drug-drug interactions known to occur with oral diclofenac may also occur with DSG.

Oral NSAIDS were prohibited during the studies, therefore the potential for any additive effect from the combination of oral NSAIDs and topical DSG 1 % is not known.

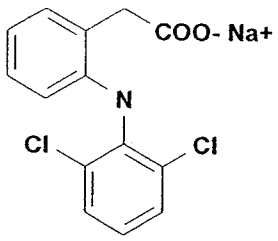
1.3.6 Special Populations

Special population studies were not performed as part of this 505(b) (2) application. Explorations of the safety data based on race, gender and age did not show an effect of these factors on the safety profile of this topically applied product.

2. INTRODUCTION AND BACKGROUND

2.1 Product Information

Voltaren® AT is a non selective nonsteroidal anti-inflammatory drug (NSAID). Its chemical name is diclofenac sodium. The structural formula is:



Diclofenac sodium topical gel, 1%, contains the active ingredient, diclofenac sodium, in an opaque, white gel base. Diclofenac sodium is a white to slightly yellow crystalline powder. Diclofenac sodium is a benzene–acetic acid derivative. The chemical name is 2-[2,6-dichlorophenyl]amino] benzeneacetic acid, monosodium salt. The molecular weight is 318.14. Its molecular formula is $C_{14}H_{10}Cl_2NNaO_2$

2.2 Currently Available Treatment for Indications

Currently several groups of medications are available for treatment of primary osteoarthritis of the knee(s) and hand(s); these include topical, oral, and intra-articular treatments.

Topical treatments include capsaicin cream (Zostrix®), topical salicylates, such as (Aspercreme®), which are available over-the-counter.

Orally administered medications include non-steroidal anti-inflammatory drugs (including oral diclofenac sodium, Voltaren® approved on July 28, 1988); acetaminophen-based products, and analgesics (including opioid analgesics) are available for treatment of primary OA.

Intra-articularly administered corticosteroids (Kenalog®) and visco supplementation (Synvisc®, Hyalgan®) are available as intra-articular treatments for knee OA.

2.3 Availability of Proposed Active Ingredient in the United States

In the United States, DSG 1% is currently an investigational new drug. Its active ingredient, diclofenac sodium, is presently marketed in the United States for treatment of signs and symptoms of OA as an oral formulation under the trade names Voltaren® (Novartis Pharmaceuticals; approved on July 28, 1988), Voltaren XR® (Novartis Pharmaceuticals; approved on November 24, 1993), Cataflam® (Novartis Pharmaceuticals; approved on March 8, 1996) and Arthrotec® (Searle & Co; approved December 24, 1997).

Another topical product containing 3% diclofenac sodium (Solaraze®, Bradley Pharmaceuticals) was approved for treatment of actinic keratosis on October 16, 2000 and is currently marketed in the US for this indication. Also, Flector Patch (diclofenac 1.3% partch) is approved for the treatment of strains, sprains and contusions in adults.

2.4 Important Issues With Pharmacologically Related Products

With oral diclofenac and other NSAIDs, major safety concerns include increased risk of thromboembolic cardiovascular and cerebrovascular events, increase in blood pressure, liver toxicity related to the hepatic metabolism, renal toxicity due to effects on renal prostaglandins, and an irritative effect on the GI tract mucosa with an increased risk of subsequent GI ulceration, bleeding and perforation. Additionally, fluid retention and edema have been observed in some patients receiving oral diclofenac.

Potential hematological effects include anemia (possibly related to GI loss, fluid retention or unknown effects on erythropoiesis) and interference with platelet function and vascular responses to bleeding related to inhibition of prostaglandin biosynthesis. Exacerbation of conditions with underlying broncho-constriction has also been observed in patients treated with oral diclofenac. Severe allergic reactions are of the same degree of concern as with other NSAIDs. These safety concerns are also potential concerns with topical diclofenac sodium, although the degree of risk should be lessened based on the reduced systemic

levels following topical application. As with the 3% topical diclofenac gel (Solaraze®) approved for treatment of actinic keratosis on October 16, 2000, major safety concerns for skin toxicity associated including contact dermatitis, pruritis, rash, skin desquamation and exfoliation.

Diclofenac diethylamine (DEA) gel, 1.16%, was first approved in Europe in 1985 under various trade names including Voltaren® and Cataflam®. It is currently marketed by Novartis in over 115 countries, of which the majority permits its sale as an over-the-counter (OTC) medication. The DEA gel formulation has been approved for relief of pain, inflammation, and swelling in post-traumatic inflammation of tendons, ligaments, muscles and joints (e.g., due to sprains, strains or bruises), localized forms of soft-tissue rheumatism (e.g., tendonitis, epicondylitis, shoulder-hand syndrome and periarthropathy), and the local management of degenerative joint conditions (e.g., osteoarthritis of the peripheral joints and of the vertebral column).

The concentration of diclofenac DEA in Voltaren® Emulgel™ 1.16% is equivalent to Diclofenac sodium (DSG 1%). However, the FDA does not permit approval of products containing diethylamine (DEA), as this compound is suspected to possess immunotoxicant, neurotoxicant, respiratory toxicant, and skin and/or sense organs toxicant properties.

Foreign labeling documents submitted by the sponsor include mention of the following adverse reactions and the frequency of their occurrence:

TABLE 2.4.1: SHOWING THE FREQUENCY OF OCCURENCE OF COMMON, RARE AND VERY RARE AE'S LISTED IN FOREIGN LABEL OF VOLTAREN/EMUGEL

SOC	ADVERSE EVENT	FREQUENCY
INFECTIONS AND INFESTATIONS	Rash pustular	< 1/10,000
IMMUNE SYSTEM DISORDERS	Hypersensitivity, angioneurotic edema	< 1/10,000
RESPIRATORY, THORACIC & MEDIASTINAL DISORDERS	Asthma	< 1/10,000
SKIN AND SUBCUTANEOUS DISORDERS	Rash, eczema, erythema, dermatitis	≥ 1/100, < 1/10
	Dermatitis bullous	≥ 1/10,000, <1/1000
	Photosensitivity reaction	< 1/10,000

Source: FDA compilation of data submitted by the applicant

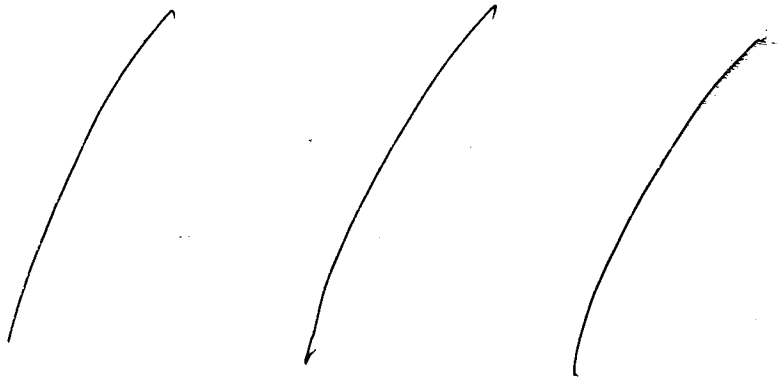
The dermal reactions are considered secondary to the DEA component and not to

diclofenac.

2.5 Presubmission Regulatory Activity

Diclofenac sodium gel 1% was studied under IND 64,334. Initially, review of the IND was the responsibility of the Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products (DAAODP).

At a Preliminary IND (PIND) Meeting held with DAAODP on February 10th 2003, the Division expressed concerns related to



The IND was submitted on November 3rd, 2003. The desired indication was the relief

An End-of Phase 2 Meeting was held on 6/29/04. The objective of the meeting was to reach concurrence on the adequacy of the clinical development plan of DSG 1% for the stated indication. DAAODP agreed to the following::

- The design of the proposed Phase 3 protocols VOSG-PE-304 and VOSG-PE-310 (Studies of 12 weeks) duration was adequate to support the proposed indication, should the results be considered positive.
- The design of the proposed VOSG-PE-314 and VOSG-PE-315 in hand OA was appropriate to the proposed indication, if these studies were at least of 8 weeks duration, should the results be considered adequate.
- That safety data with up to 12 months of patient exposure was required at time of NDA submission.

A second Guidance Meeting was held on December 7th 2004 to discuss the proposed Phase 3 development plan for hand OA. DAAODP agreed to the following:

- Accepted the sponsor's suggestion to designate the treatment of both hands as acceptable.

- Conduct of one of the hand OA studies in the USA
- Evaluation of co-primary end-points in hand OA at 4 and 6 weeks,
- Consider changing the presently worded indication of

to

The sponsor explored whether (pending review of the hand and knee OA studies) an indication for was acceptable. DAAODP claimed that

The sponsor submitted a Special Protocol Assessment (SPA) for two identical placebo-controlled 8 week primary hand OA protocols, VOSG-PE-314 and VOSG-PE-315 to the IND in February 2005. Although DAAODP considered the studies safe to proceed, the sponsor was informed that the studies would support a indication for

The applicant had previously been advised to use a true ITT analysis. On January 19th 2006 information from the completed companion (knee OA) study of identical design (VOSG-PN-304) was used to define a subset of the ITT population, the modified efficacy subpopulation (MES), which was used as the primary population for efficacy analyses in Study ongoing VOSG-PN-310. Subjects in the MES were required to have no decline in POM score between the screening and baseline visits and had a score of 0 or 1 on the WOMAC abridged pain index for the contralateral knee. This modification of efficacy analysis population was filed with the FDA in the form of an Information Amendment after completion of the study and was implemented in the Statistical Analysis Plan prior to unblinding of the study. The division agreed to the MES analysis (See 12/22/05 advice letter).

There was further protocol modification of the ITT population in Study 310, by excluding patients with spontaneous improvement of pain in target knee during the washout period and patients with significant pain in the contralateral knee at baseline.

Following the reorganization of the Office of New Drugs in 2005, the Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) became the responsible review division.

The minutes of the Pre-NDA Meeting of July 26th 2006 reflected that the statistical methods for the determination of safety and efficacy were considered to be generally acceptable by the Division.

The Division stated that efficacy analysis should include a continuous responder analysis and a baseline observation carried forward (BOCF) analysis as strategies for the handling of missing data. A rigorous assessment of rescue medication use was also recommended.

On September 9th 2006, the Division received a Letter of Authorization from the sponsor linking their application to the following NDA's:

- NDA 19-201 Voltaren (diclofenac sodium) Enteric Coated Tablets
- NDA 20-254 Voltaren-XR (diclofenac sodium) Tablets
- NDA 20-142 Cataflam (diclofenac potassium) Tablets

Since August 2006, the applicant initiated negotiations with DMETS about the choice of Trade name; discussions continue at the time of writing.

On December 19th 2006, DSG 1% was submitted to DAARP under NDA 22,122. Application was submitted under 505(b) (2), with a cross reference to Novartis NDA 19-201 for Voltaren®(diclofenac sodium) Enteric-coated tablets (and NDA's 20-254 and 20-142). Reference was also made to Solaraze NDA 21-005 via the 505(b)(2) route, for information and data pertaining to dermal carcinogenicity and photocodermal carcinogenicity.

2.6 Other Relevant Background Information

None.

3. SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Please refer to review of Dr Sue-Ching Lin for further details on the CMC issues related to this application.

During the course of the review, three impurities were identified. These compounds contain structure alert moieties that exceed the — genotoxic limit for qualification.

Further qualification by genotoxicity tests on impurities was requested of the Applicant, and the results of these tests will be submitted by the end of September 2007. The results were not available at the time of writing of this review.

Chemical Inspections of all sites are acceptable.

3.2 Animal Pharmacology/Toxicology

The current application is for a dermal preparation containing diclofenac sodium (DSG 1%) in a gel formulation.

The biotransformation of diclofenac is species specific.

No animal pharmacokinetic data has been obtained with the proposed DSG 1% formulation, as the clinical pharmacokinetic program has obtained cogent information on absorption from *human skin*, in vivo.

Results of in vitro and bioequivalence clinical PK studies have demonstrated that the absorption of diclofenac from DSG 1% and diclofenac DEA are very similar. The absorption, distribution, metabolism and excretion of diclofenac sodium have been extensively studied in different animal species. Reference is made to NDA 19-201.

Tissue distribution studies in rats and mice with diclofenac DEA indicate relatively high levels of diclofenac sodium in the liver and kidneys, reflecting the main sites of excretion.

Diclofenac is extensively bound to plasma proteins (99.6% in most species).

Diclofenac and/or its metabolites can pass the placental barrier but has no particular affinity for any fetal tissues and is eliminated from the fetus at about the same rate as from the mother.

Please refer to the report of Dr Lawrence Leschin's report for details of the animal Pharmacology/Toxicology Studies.

4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

No specific dose-selection trials were undertaken with DSG. Dose selection was based on the extensive clinical experience available with diclofenac DEA gel and on a PK trial with DSG. Study VOSG-PE-303 is an efficacy and safety trial of diclofenac DEA gel in knee OA; VOSG-PE-107 is a PK trial that compared the bioavailability of DSG 1% and diclofenac DEA gel.

The applicant performed four (4) large, adequate and well controlled trials Phase 3 trials:

1) VOSG-PN-304 - OA of the knee (supportive)
2) VOSG-PN-310 - OA of the knee (pivotal)

3) VOSG-PE-315 - OA of the hand (pivotal)
4) VOSG-PE-314 - OA of the hand (supportive)

Additionally, the applicant performed a fifth trial, Study VOSG-PN-309. This was an uncontrolled study that evaluated up to 12 months of treatment in subsets of the overall study population.

Finally, the applicant performed three trials to specifically evaluate the dermal safety of DSG 1%.

Table 4.1.1 (below) lists the trials that contributed to the data contained in the NDA

TABLE 4.1.1: SHOWING OVERVIEW OF TRIALS OR SOURCES OF DATA

Source of data	Details
Dose-selection trials	No specific dose-selection trials were undertaken with DSG. Dose selection was based on the extensive clinical experience available with topical diclofenac DEA, 1.16%. VOSG-PE-303 (CTD 5.3.5.4.1) is an efficacy and safety trial of topical diclofenac DEA in knee OA. VOSG-PE-107 (CTD 5.3.3.1.1) is a pharmacokinetic trial that compared the bioavailability of DSG and diclofenac DEA.
Controlled trials	(VOSG-PN-310, CTD 5.3.5.1.2); (VOSG-PN-304, CTD 5.3.5.1.1); (VOSG-PE-315, CTD 5.3.5.1.4); (VOSG-PE-314, CTD 5.3.5.1.3) 4 large, controlled phase III trials (4 adequate and well controlled); VOSG-PN-310 and VOSG-PN-304 both in OA of the knee; VOSG-PE-315 and VOSG-PE-314 both in OA of the hand.
Uncontrolled trials	(VOSG-PN-309, CTD 5.3.5.2.1) 1 uncontrolled long-term safety trial with an efficacy component in OA of the knee; no statistical testing of treatment effects was protocol-specified and none was performed.
Long-term data	VOSG-PN-309 (CTD 5.3.5.2.1) was uncontrolled but evaluated 6, 9 and 12 months of treatment in subsets of the overall study population. No specific long-term efficacy trials were conducted.
Other sources of efficacy data	(VOSG-PE-303, CTD 5.3.5.4.1); (VE-OA-1, CTD 5.3.5.4.2) 2 short-term trials of diclofenac DEA 1.1%: VOSG-PE-303 is an adequate and well controlled trial of diclofenac DEA 1.16% in moderate to severe pain due to unilateral OA of the knee; VE-OA-1 is a double-blind, double-dummy non-inferiority trial of diclofenac DEA 1.16% compared to oral ibuprofen in the treatment of hand OA.
Trials used for combined efficacy analysis	No trials were combined for the purposes of any efficacy analyses. In each of the controlled studies for knee and hand OA, descriptive statistics for primary efficacy endpoints were computed for various subgroups (sex, age, race and center) but were not formally analyzed.

4.2 Tables of Clinical Studies

Efficacy Trials:

The efficacy review was based on the review of efficacy data from two (2) Phase 3 placebo controlled studies clinical trials shown in Table 4.2.1A. These two pivotal, 12 week duration, placebo controlled studies (VOSG-PN-310 and VOSG-PE-315) were the primary source of efficacy conclusions in this review.

TABLE 4.2.1A: SHOWING A SUMMARY OF THE PLACEBO-CONTROLLED KEY PIVOTAL PHASE 3 EFFICACY STUDIES

STUDY Country	STUDY DESIGN ENDPOINTS	TOTAL # STUDIED AGE RANGE (MEAN) GENDER (M,F)	DOSAGE Rx DURATION	RESULTS & RELEVANCE TO EFFICACY AND SAFETY
KEY STUDIES				
VOSG-PN-310 USA	Randomized, double-blind, efficacy/safety in *knee OA* Week 12: 1. WOMAC pain 2. WOMACK function 3. Global disease rating	492	DSG 4 gm qid vs vehicle 12 weeks	Efficacy defined as superiority of active compared to vehicle to all 3 1ry endpoints (MES population)
VOSG-PE-315 USA	Randomized, double-blind, efficacy/safety in *hand OA* Weeks 4 & 6: 1. OA pain 2. Total AUSCAN 3. Global disease rating	385	DSG 2 gm qid vs vehicle 8 weeks	Efficacy defined as superiority of active compared to vehicle to all 3 1ry endpoints (ITT population)

Source: FDA compilation of data submitted by the applicant

The table below lists the two failed efficacy studies that contributed to the safety data for the NDA:

TABLE 4.2.1B: SHOWING A SUMMARY OF THE PLACEBO-CONTROLLED SUPPORTIVE PHASE 3 STUDIES

SUPPORTIVE STUDIES				
STUDY **Country**	**STUDY DESIGN** **ENDPOINTS**	**TOTAL # STUDIED** **AGE RANGE (MEAN)** **GENDER (M,F)**	**DOSAGE** **Rx DURATION**	**RESULTS & RELEVANCE TO EFFICACY AND SAFETY**
VOSG-PN-304 USA	Randomized, double-blind, efficacy/safety in *knee OA* Week 12: 1. WOMAC pain 2. WOMACK function 3. Global disease rating	514	DSG 4 gm qid vs vehicle 12 weeks	The efficacy analysis of this study provided the means for identification and selection of the modified efficacy population (MES)
VOSG-PE-314 Germany & France	Randomized, double-blind, efficacy/safety in *hand OA* Weeks 4 & 6: 1. OA pain 2. Total AUSCAN 3. Global disease rating	398	DSG 2 gm qid vs vehicle 8 weeks	

Source: FDA compilation of data submitted by the applicant

1 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Safety trials:
The safety review was based on the analysis of the pooled safety data from the four Phase 3 clinical trials (shown in Tables 4.2.1A and B, above), as well as data from the long term study VOSG-PN-309. (Table 4.2.2, below)

TABLE 4.2.2: SHOWING CONTROLLED ROLL-OVER STUDY –VOSG-PN-309

STUDY	STUDY DESIGN STUDY POPULATION ENDPOINTS	TOTAL # STUDIED AGE RANGE (MEAN) GENDER (M,F)	DOSAGE Rx DURATION	RESULTS & RELEVANCE TO SAFETY/ EFFICACY
VOSG-PN-309	Multicenter, OL, single arm, long term safety in OA knee. To evaluate daily topical applications of typical and maximum doses of DSG 1% in long term use	35-88 (62.3 years)	DSG 1% - 4gm /knee qid on one or both knees - Up to 12 months	DSG tolerated at doses of up to 32 g/day. The nature & distribution of AE's were not influenced by dose or duration of exposure.
USA		578 , all DSG; 210 M 368 F		

Source: FDA compilation of data submitted by the applicant

Dermal safety trials:
The three Phase 1 clinical studies evaluating skin irritation and sensitization (VOSG-PN-108, VOSG-PE-111 and VOSG-112) were reviewed by the Dermatology Consultants Dr. Brenda Vaughn and Dr Markham Luke, and are summarized in Section 7.1.12.

Other trials:
The sponsor also submitted studies evaluating the efficacy and systemic availability of the Diclofenac DEA product. These studies were not considered for the efficacy review of DSG 1%. The studies are shown in schematic tabular form in the Appendix, Section 10.4.

Clinical Pharmacology (Bioavailability) studies (VOSG-PN-107, VOSG-PE-113, were reviewed by Dr. David Lee and are summarized in section 5. These PK/PD studies conducted in healthy volunteers are shown in schematic tabular form in the Appendix, Section 10.3

4.3 Review Strategy

No trials were combined for the purposes of any efficacy analyses. In each of the controlled studies for knee and hand OA, inferential statistics were computed for the primary and secondary endpoints. For efficacy analyses of various subgroups, descriptive subgroups were computed for sex, age and center.

For this application, efficacy reviews of the key controlled studies VOSG-PN-310, VOSG-PE-315 and VOSG-PN-304 and VOSG-PE-314 were jointly conducted by the Statistician Dr Ruthianna Davi and me. A detailed description of all analyses (including responder analysis and findings can be found in Section 6 and in Dr Davis' review.

Analysis of safety based on data from the four pooled placebo-controlled studies and the uncontrolled safety study (VOSG-PN-309), was performed by me (See Section 7).

4.4 Data Quality and Integrity

In general, the data quality and integrity were adequate. The integrity of analyses shown in the Integrated Summary of Safety and Integrated Summary of Efficacy was adequate and corresponded to the attached source tables. Random datasets were audited with their corresponding tables and the integrity of data was found to be satisfactory.

The Division of Scientific Investigation (DSI) inspected five study sites.

The inspections covered studies performed under Protocol VOSG-PN-310, VOSG-PE-315, and VOSG-PN-309.

The following Clinical Investigator/Site #'s were inspected by DSI:
1) Dr. Selwyn Cohen, Site # 309 in Stratford, Connecticut.
2) Dr. Walter Chase, Site # 211 in Austin, Texas.
3) Dr. John Champlin, Site # 209 in Carmichael, California.
4) Dr. H. Richard Barthel, Site # 224 in Santa Barbara, California.
5) Dr. P. Lauren Savage, Site # 233 in Birmingham, Alabama.

Selection of study sites for inspection was based on the selection of the study sites with the largest number of study subjects enrolled. The inspection of the study sites did not identify any significant observations that would compromise the integrity of the data. The medical records reviewed disclosed no findings that would reflect negatively on the reliability of the data. Overall the data appeared acceptable in support of the pending application.

4.5 Compliance with Good Clinical Practices

Each of the clinical trials appeared to be conducted under acceptable ethical standards in accordance with the Declaration of Helsinki and with approval of the appropriate Ethics Committee. Patients were appropriately informed and written consent was obtained prior to study enrollment.

4.6 Financial Disclosures

All the principal clinical investigators of Studies VOSG-PN-304, VOSG-PE-309 and VOSG-PN-310, VOSG-PE-314 and VOSG-PE-315 have certified that they did not have any financial arrangements with the sponsor, nor have they received any compensation that could have affected the outcome of the study as defined in 21 CFR 54,2(a). All the principal investigators have also certified that they did not have any proprietary interest in the product as defined in 21 CFR 54.2(b). The sponsor has further certified that none of the listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(fj.

5. CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Absolute bioavailability was not examined in the course of the DSG 1% development program. Maximum daily doses of 48 g over 1200 cm^2 of topical DSG produced less than 20% of the systemic exposure of the recommended oral dose for the signs and symptoms of OA of the knee, after 7 days of administration.

The Applicant purports that Diclofenac is more than 99% bound to human serum proteins. Serum protein binding is constant over the concentration range (0.15-105 µg/mL) achieved with the recommended [oral] doses.

Maximal topical dosing (12 g four times daily over 1200 cm^2) in Study VOSG-PE-113 produced mean plasma concentrations after 7 days of dosing of 40 ng/mL (0.04 µg/mL).

At maximal recommended dosing of 32 g over 800 cm^2, the systemic exposure to the active moiety is less than 13% of an oral diclofenac dose of 50 mg tid.

Table 5.1. Pharmacokinetic Parameters and Comparison of Voltaren® AT to Oral Diclofenac Sodium Tablets After Repeated Administration

Treatment	C_{max} (ng/mL) Mean ± SD % of Oral (CI)	T_{max} (hr) Median (range)	AUC_{0-24} (ng•h/mL) Mean ± SD % of Oral (CI)
Voltaren® AT 4 x 4 g per day (=160 mg diclofenac sodium per day)	15.0 ± 7.33 0.633% (0.548-0.733)	14 (0-24)	233 ± 128 5.79% (5.00-6.70)
Voltaren® AT 4 x 12 g per day (=480 mg diclofenac sodium per day)	53.8 ± 32.0 2.21% (1.91-2.56)	10 (0-24)	807 ± 478 19.7% (17.00-22.8)
Diclofenac sodium tablets, p.o. 3 x 50 mg per day (=150 mg diclofenac sodium per day)	2270 ± 778 100%	6.5 (1-14)	3890 ± 1710 100%

C_{max} = maximum plasma concentration; t_{max} = time of C_{max}; AUC_{0-24} = area under the concentration-time curve; SD = standard deviation; CI = confidence interval.

Systemic exposure (area under the concentration-time curve) and maximum plasma concentrations of diclofenac are significantly lower with Voltaren® than with comparable oral treatment of diclofenac sodium. Systemic exposure with normal use of Voltaren® AT (4 x 4 g per day applied to 1 knee) is on average 17 times lower than with oral treatment. (Basis: treatment with Voltaren® AT of 1 knee, 4 times a day versus 50 mg, 3 times a day of oral diclofenac tablets). The systemic exposure with Voltaren® is proportional to the amount that is applied. The part of diclofenac sodium that is systemically absorbed from Voltaren® AT is on average 6% to 7% of the part that is systemically absorbed from an oral form of diclofenac sodium. The average peak plasma concentration with normal use of Voltaren® AT (4 x 4 g per day applied to 1 knee) is 158 times lower than with the oral

treatment.

The pharmacokinetics of Voltaren® AT has been tested under conditions of moderate heat (application of a heat patch for 15 minutes prior to gel application) and of moderate exercise (first gel application followed by a 20-minute treadmill exercise). No clinically relevant differences of systemic absorption and of tolerability were found between applications of Voltaren® AT (4 x 4 g per day on 1 knee) with and without heat or exercise.

5.2 Pharmacodynamics

The mechanism of action of DSG, like that of other NSAIDs, is not completely understood but the Applicant theorizes that it may be related to prostaglandin synthetase inhibition.

5.3 Exposure-Response Relationships

The Applicant did not submit any studies evaluating the effect of volume of gel application or concentration on efficacy or safety. A dose of 2 gm qid for the studies of OA of the hand and 4 gm for studies on the knee was selected by the applicant.

The selection of the dose DSG 1% gel concentration was based primarily on overseas clinical experience using diclofenac DEA 1.16%, and results of the controlled clinical study VOSG-PE-303, which compared the efficacy of daily topical applications of DEA 1.16% with vehicle, and VE-OA-1, which compared the efficacy of daily topical applications of DEA 1.16 % with oral ibuprofen.

6. INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The applicant seeks an indication for "joints amenable to treatment, such as the hands and knees".

6.1.1 Methods

The applicant submitted the results of two placebo-controlled studies, VOSG-PN-310 (knee OA) and VOSG-PE-315 (hand OA) to support the joints amenable to treatment, such as the hands and knees. This Reviewer also evaluated the data from VOSG-PE-314 (hand OA) and VOSG-PN-304 (knee OA; a failed

efficacy study whose post hoc analysis provided information on the subjects who were most likely to respond to topical NSAID's. This information was used to prospectively amend the efficacy analysis population of the identically designed study VOSG-PN-310).

6.1.2 General Discussion of Endpoints

For the knee OA studies conducted in support of this application, eligible subjects discontinued their normal pain medication for $\geq$ 7 days and had at least moderate pain at baseline, [defined as a score of $\geq$ 50 mm on the 100 mm Visual Analog Scale (VAS) for pain on movement (POM) and a Western Ontario McMaster Osteoarthritis Index (WOMAC) pain score of > 9 (out of 20)]. DSG was tested versus vehicle using the pain and physical function scores from the established and validated WOMAC assessment tool, in a study of 12 weeks duration. The examination of the knee was standardized and subjects also provided a Global Rating of Disease on a 100 mm VAS.

Primary efficacy variables in the knee OA studies were the following:

- WOMAC Pain Subindex
- WOMAC Function Subindex
- Global Rating of Disease Activity by the subject.

These were measured at Week 12 at the study site.

Secondary efficacy variables in the knee OA study were the following at all post-baseline visits (excluding those outcomes assessed at Week 12 that were designated as primary):

- WOMAC Pain Subindex
- WOMAC Stiffness Subindex
- WOMAC Function Subindex
- Global Rating of Disease Activity
- Global Rating of Benefit
- Pain on movement (POM)
- Spontaneous OA Pain Intensity
- Global Evaluation of Treatment (at the final visit)
- Difference between target knee and contralateral knee on a subset of four WOMAC questions
- Osteoarthritis Research Society International (OARSI) response
- Pain/rescue response
- POM (diary) – daily and averaged by week
- Use of rescue medication.

The applicant utilized the Western Ontario MacMaster function, pain and stiffness score **(WOMAC)** and as the outcome measure for the study of knee OA.

The **WOMAC** is a validated instrument designed specifically for the assessment of lower extremity pain and function in Osteoarthritis (OA) of the knee or hip. However, WOMAC

captures more than just knee pain or knee dysfunction, and is influenced by the presence of fatigue, symptom counts, depression and low back pain. WOMAC scores also appear to reflect psychological and constitutional status, suggesting the need to exercise care in interpreting WOMAC scores as just a measure of function, pain or stiffness, and indicate the considerable importance of psychological factors in rheumatic disease and rheumatic disease assessments. (Rheumatology 1999; 38:355-361).

The post hoc analysis of Study VOSG-PN-304 provided the basis for the prospective amendment in the efficacy analysis population of the similarly designed and Study VOSG-PN-310, by identifying the four groups of patients who were less likely to report improvement in topical treatment, and was therefore excluded from the efficacy analysis population. These included:
1) Patients who reported particularly high levels of pain on movement (POM) at the screening visit (while they were still using their usual OA pain medication).
2) Patients whose POM decreased over the period in which they washed out from previous medication; these patients are presumed to be non-responsive to treatment with NSAIDS and analgesics.
3) Patients with significant pain in the untreated contralateral knee at baseline.
4) Patients who entered the studies with pre-existing painful conditions of the back and/or hip.
This modified efficacy analysis population became known as the ***modified efficacy subpopulation (MES)***, and was the efficacy analysis population of Study -310.

At the Pre NDA meeting of 7/26/2006, the applicant presented the argument that modifications in the ITT population were scientifically valid, in that restrictions in the level of pain in the contralateral knee were justified, in that:
1) Not treating pain in the contralateral painful knee was a departure from the real world behavior and distorted the assessment of efficacy in the target knee.
2) Using the MES (instead of the ITT population) did not change the patient demographics.
3) The MES is fully representational of the larger population for whom the product is intended.

The Post Meeting comments reflect that the Agency accepted the argument that demonstration of the efficacy in one knee would be generalizable to the population of OA patients with pain in both knees, and the modified efficacy population was representative of the larger OA population, and that use of the flare design was also acceptable. In summary, the Division concluded that the results of Study VOSG-PN-310 could be used to demonstrate efficacy in OA patients.

The Division stated that the statistical methods for the determination of safety and efficacy were generally acceptable, but required that sensitivity analyses should include baseline observation carried forward (BOCF) imputation as one strategy for the handling of missing data. A responder analysis and a rigorous assessment of rescue medication use were also recommended by the Division.

The analysis of Study VOSG-PE-315 (hand OA) utilized the originally proposed ITT efficacy population. Efficacy was evaluated on three co-primary outcomes:

- Pain (measured by VAS)
- Function (measured by AUSCAN total score)
- Subject's global rating of disease activity.

The primary efficacy end points at Week 4 and Week 6 in the hand OA study was selected by the applicant in view of:

- Knowledge of the natural history of hand OA with its characteristic remissions and flares
- The evaluation of time points beyond 4 weeks may distort the Type I and Type II error rates, due to spontaneous remissions and renewed flares (*Scott-Lennox et al 2001)*
- Recommendations of the task force of the OA Research Society for Phase 3 trials *(Altman et al 2000)*
- The fact that 2-4 weeks are sufficient to demonstrate efficacy of NSAID treatment in hand OA.

The Australian/Canadian Osteoarthritis Hand Index **(AUSCAN)** was used for the primary evaluation of function, since it has been evaluated in patients with hand OA in an international environment (Bellamy et al. 2002a, Bellamy et al. 2002b). The Functional Index for Hand Osteoarthritis (FIHOA) was evaluated as a secondary outcome variable.

The **AUSCAN** Index is a self-administered questionnaire that assesses the three dimensions of pain, disability and joint stiffness in hand osteoarthritis using a battery of 15 questions. This questionnaire-based measurement tool is scaled on 5-point Likert scales and 100mm Visual Analog Scales. The AUSCAN 3.1 is considered to be a valid, reliable and responsive measure of outcome. The index has been subject to validation studies which have addressed the following clinimetric issues of reliability, including stability and internal consistency, validity and responsiveness.

Pain intensity and pain relief are the fundamental parameters that define an analgesic product, and are measured based on patients' subjective report. Pain can be measured on numerical rating scales, visual analog scales or categorical scales that have been validated. The Division prefers measures of pain intensity since, unlike pain relief, pain intensity does not rely on additional internal processing by the patient. Additionally, pain intensity is less impacted by other psychosocial factors that affect other outcome measures such as Patient Global Assessment.

Global assessment variables were utilized as primary efficacy parameters in both the hand and knee OA studies. Global assessment variables assess the subject's state or change in state and thus, inevitably have a subjective component. Despite its subjectivity, the advantage of global assessment is that it is a *summary measure* that does not require multivariate analysis, and is regarded as a surrogate marker of quality of life since it takes the overall condition of the subjects into account, can adapt to nonlinear clinical responses,

and it considers the time profile, initial condition of illness and various personal aspects of the subject's life.

In summary, the WOMAC and AUSCAN instruments are self reporting instruments that are sensitive to pain, in addition to conditions such as fatigue, symptom count and depression, and these variables may contribute to the pain and dysfunction that patients' report.

The endpoints chosen for the pivotal studies VOSG-PN-310 and VOSG-PN-315 were adequate and consistent with recommendations by the Division.

6.1.3 Study Design

Study VOSG-PE-310 (knee OA) was a 12-week, prospective, randomized, double-blind, multi-center, parallel group study that compared DSG, 1% with vehicle in subjects with OA of the knee.

Study subjects were male and female subjects ≥ 35 years of age with OA of one or both knees, but with a history of clinically symptomatic OA in one knee only, diagnosed at least 6 months previously and verified by X-ray (Kellgren-Lawrence Grade 1-3). Subjects had OA-related knee pain for at least 15 days of the month preceding screening and the pain in the target knee had required the use of NSAIDs or acetaminophen.

After washing out any prior analgesics for one week or at least 5 elimination half-lives, eligible subjects were to have a baseline score of ≥ 50 mm on a 100 mm VAS when rating POM and a baseline WOMAC pain score ≥ 9 (out of 20) immediately prior to randomization. Subjects with a POM score of ≥ 20 in the contralateral knee at the baseline visit were excluded.

The knee OA study utilized a dose of 4 gm DSG or vehicle qid for duration of 12 weeks, while the hand OA studies utilized a dose of 2 gm DSG or vehicle qid for 8 weeks.

The twelve (12) week duration of placebo controlled study for knee OA is considered an appropriate duration for the assessment of efficacy of a drug to be used in the treatment of chronic knee OA pain.

Study VOSG- PN-315 (hand OA) was an 8-week, prospective, randomized, double-blind, multi-center, placebo- controlled, parallel group study in subjects with OA of the hand.

The trial population comprised symptomatic subjects aged 40 years or more, with a diagnosis of primary OA in their dominant hand as defined by The American College of Rheumatology (ACR) criteria. An X-ray of the dominant hand was required to show signs of OA in the painful joints with Kellgren-Lawrence grade 1, 2, or 3 disease. Subjects had to use the same hand preferentially for certain key activities assessed by the AUSCAN index. When subjects had primary OA in their non-dominant hand, the symptoms in the non-

dominant hand had to be of lower intensity. Subjects with a history of other inflammatory diseases or with secondary arthritis or other forms of arthritis were excluded as were subjects requiring treatment for OA in locations besides the hands.

Prior to randomization, pain in the target hand during the previous 24 hours had to be rated ≥ 40 mm on a 100 mm VAS. Subjects being washed out from non-steroidal anti-inflammatory drugs (NSAIDs) after screening, had to have an increase of pain over the past 24 hours in the target hand of ≥ 15 mm (on a 100 mm VAS) between the screening and the baseline visits.

DSG or placebo/vehicle was applied four times daily for 8 weeks (2 gm to the dominant hand, and 2 gm to the non-dominant hand. The use of acetaminophen (up to doses of 4 gm per day) as rescue medication was allowed.

TABLE 6.1.3: SCHEMATIC FIGURE OF STUDY DESIGN FOR STUDY VOSG-PN-310 (knee OA) and STUDYVOSG- PE-315 (hand OA)

	Screening	Washout	Baseline	Treatment				End of Study
Knee OA	Visit 1		Visit 2	Visit 3	Visit 4	Visit 5		Visit 6
	Screening Day -14 to -7	Approx. 7 days	Day 1	Week 1	Week 4	Week 8		Week 12
Hand OA	Visit 1		Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	Screening Day -7 to -5	Approx. 7 days	Day 1	Week 1 Day 8	Week 2 Day 15	Week 4 Day 29	Week 6 Day 43	Week 8 Day 57

Study duration was 12 weeks for VOSG-PN-310 and VOSG-PN-304 and 8 weeks for VOSG-PE-315 and VOSG-PE-314.

Reference: VOSG-PN-310 (CTD 5.3.5.1.2), VOSG-PN-304 (CTD 5.3.5.1.1), VOSG-PE-315 (CTD 5.3.5.1.4), VOSG-PE-314 (CTD 5.3.5.1.3), Module 5.2

In general, trials of eight (8) week duration are shorter than what is preferred for chronic pain studies. However this duration was considered to be adequate for the evaluation of efficacy of drugs used in the treatment of pain of hand OA. The Applicant justified the design of the hand OA study by stating that the highly variable cyclic course of hand OA may confound the assessment of efficacy. The initial time point for testing efficacy was therefore set at 4 weeks, based on the recommendations of a task force of the Osteoarthritis Research Society for Phase 3 trials [Altman et al. 1996] and the observation that 2-4 weeks are sufficient to demonstrate efficacy of NSAID treatment in hand OA [Hochberg et al. 2000, Lequesne and Maheu 2000, Chevalier et al. 2000].

The three possible outcomes of the study were: (1) efficacy at 4 and 6 weeks, (2) efficacy at 4 weeks only, (3) no efficacy. With this sequential testing, no adjustment of the criteria

for statistical significance was required despite the multiple comparison for the evaluation of efficacy at both Weeks 4 and 6. At the request of Division, the duration of the study was extended to allow a determination of safety and efficacy at Week 8.

Efficacy was evaluated on three co-primary outcomes, *pain, function,* and *global rating of disease activity.* The AUSCAN index has been evaluated in patients with hand OA in an international environment [Bellamy et al. 2002a, Bellamy et al. 2002b] and was agreed to by the Agency in discussions with the Applicant.

The secondary outcome global rating of benefit was also included at the request of FDA. This was a modification of the global rating of disease, whereby subjects assessed their status considering all effects of study medication.

Although most patients with hand OA have both hands affected to some extent, the disease is usually most severe in the dominant hand. The dominant hand is also better suited for the assessment of function. It was therefore chosen as the target hand for this study. In order to better evaluate the (dominant) target hand and to limit confounding factors to acceptable levels for a clinical trial, pain at baseline was required to be clearly prevailing in the dominant hand. To limit interference from pain in the non-dominant hand, and in particular to prevent all subjects treated both hands.

The placebo-controlled, randomized, double-blind study design is the "gold standard" in the evaluation of efficacy in a clinical trial. In such a trial design, the risk of bias is reduced, as treatment effects and outcomes are reported without knowledge of the treatment allocation.

The inclusion and exclusion factors selected by the applicant were inclusive, and the broad eligibility criteria helped to ensure that the results and inferences from the clinical trial population are generalizable to the external population of subjects with knee and hand OA.

6.1.4 Efficacy Findings

DEMOGRAPHICS

Across the studies, there were no major differences in the treatment arms of the subject populations with regard to baseline demographics and disease characteristics. In these trials, age and sex distributions were typical for patients with painful osteoarthritis of the knee and hands; that is elderly subjects with a predominance of women.

Relevant demographic and disease characteristics combined for each study are shown in Table 6.1.4.1 and Table 6.1.4.2

TABLE 6.1.4.1: SHOWING THE DEMOGRAPHIC CHARACTERISTICS OF STUDY IN MES population -310 (knee OA)

CATEGORY	DSG (N=127)	VEHICLE (N=119)
Sex – n (%)		
Male	44 (34.6)	40 (33.6)
Female	83 (65.4)	79 (66.4)
Race – n (%)		
Caucasian	101 (79.5)	99 (83.2)
Black	9 (7.1)	10 (8.4)
Asian	4 (3.1)	0
Other	13 (10.2)	10 (8.4)
Age (yr) – n (%)		
Mean +/- SD	59.7 (+/-) 10.8	58.4 (+/-) 10.4
Range	36-90	35-82
BMI		
Mean +/- SD	30.1 +/- 6.4	32.2 +/- 7.1
Range	20.0-53.2	18.5 -54.9

Source: ISE; VOSG-PN-310, Post-text Table 7.1

TABLE 6.1.4.2: SHOWING THE DEMOGRAPHIC CHARACTERISTICS OF STUDY IN ITT Population -315 (hand OA)

CATEGORY	DSG (N=198)	VEHICLE (N=187)
Sex – n (%)		
Male	46 (23.2)	43 (23.0)
Female	152 (76.8)	144 (77.0)
Race – n (%)		
Caucasian	173 (87.4)	170 (90.9)
Black	11 (5.6)	13 (7.0)
Asian	11 (5.6)	4 (2.1)
Other	3 (1.5)	0
Age (yr) – n (%)		
Mean +/- SD	63.6 +/- 10.3	64.7 +/- 9.6
Range	40- 92	40-87
BMI		
Mean +/- SD	28.0 +/- 6.3	28.6 +/- 6.5
Range	17.6- 55	17.5 - 49.8

Source: ISE; VOSG-PE- 315; CTD 5.3.3.1.4

BASELINE DISEASE CHARACTERISTICS

The ensuing table shows the baseline knee examination characteristics for the MES population in Study -310. There was no important difference between the treatment groups in Study -310.

Further discussion of the details on the baseline osteoarthritis baseline assessments are noted in Section 10.1.1 (Individual Study Report).

TABLE 6.1.4.3: [redacted] THE BASELINE DISEASE CHARACTERISTICS EXAMINATION OF THE AFFECTED KNEE IN STUDY -310 (MES SUBJECTS)

	VOSG-PN-310	
Category*	**DSG N = 127**	**Vehicle N = 119**
Affected knee – n (%)		
Left	59 (46.5)	55 (46.2)
Right	68 (53.5)	64 (53.8)
Receiving physical therapy at Visit 1 – n (%)		
No	123 (96.9)	117 (98.3)
Yes	4 (3.1)	2 (1.7)
Subjects with periarticular pain – n (%)		
No	38 (29.9)	30 (25.2)
Yes – caused by OA	89 (70.1)	89 (74.8)
Range of motion		
Extension (degree)		
N	123	116
Mean ± SD	1.0 ± 4.7	1.6 ± 16.0
Range	-10 - 35	-10 - 170
Neutral (degree)		
N	123	116
Mean ± SD	3.7 ± 8.9	5.9 ± 8.9
Range	0 - 77	0 - 40
Flexion (degree)		
N	123	114
Mean ± SD	114.8 ± 20.3	110.2 ± 19.6
Range	60 - 150	56 - 150
Tenderness on pressure - n (%)		
Joint space medially		
0 = None	40 (31.7)	27 (22.7)
1 = mild	47 (37.3)	43 (36.1)
2 = moderate	36 (28.6)	41 (34.5)
3 = severe	3 (2.4)	8 (6.7)
N	126	119
Mean ± SD	1.0 ± 0.8	1.3 ± 0.9

	VOSG-PN-310	
Category*	**DSG N = 127**	**Vehicle N = 119**
Joint space laterally		
0 = none	62 (49.2)	46 (38.7)
1 = mild	46 (36.5)	41 (34.5)
2 = moderate	17 (13.5)	32 (26.9)
3 = severe	1 (0.8)	0 (0.0)
N	126	119
Mean ± SD	0.7 ± 0.7	0.9 ± 0.8
Patella medially		
0 = none	65 (51.6)	54 (45.4)
1 = mild	37 (29.4)	34 (28.6)
2 = moderate	24 (19.0)	27 (22.7)
3 = severe	0 (0.0)	4 (3.4)
N	126	119
Mean ± SD	0.7 ± 0.8	0.8 ± 0.9
Patella laterally		
0 = none	79 (62.7)	71 (59.7)
1 = mild	31 (24.6)	28 (23.5)
2 = moderate	16 (12.7)	18 (15.1)
3 = severe	0 (0.0)	2 (1.7)
N	126	119
Mean ± SD	0.5 ± 0.7	0.6 ± 0.8
Swelling of joint capsule- n (%)		
0 = none	59 (46.5)	54 (45.4)
1 = slight	47 (37.0)	48 (40.3)
2 = moderate	20 (15.7)	16 (13.4)
3 = severe	1 (0.8)	1 (0.8)
N	127	119
Mean ± SD	0.7 ± 0.8	0.7 ± 0.7
Joint effusion – n (%)		
No	99 (78.0)	95 (79.8)
Yes	28 (22.0)	24 (20.2)

Source: Post Text table 7.7.a

DISPOSITION

In Study -310, 25 % of the vehicle population and 17.7 % of the DSG group failed to complete the study. The proportion of patients who discontinued due to adverse events was

slightly greater in the DSG group (5%) than in the 3.8% in the vehicle group. Approximately 7% of vehicle assigned subjects vs 4% DSG subjects failed to complete the study because of lack of efficacy (See Table 6.1.4.3 below).

TABLE 6.1.4.3: SHOWING SUBJECT DISPOSITION FOR STUDY- 310 (Knee OA)

TOTAL # OF SUBJECTS	DSG	VEHICLE
Randomized	254	238
Intent-to-treat population	253 (99.6)	238 (100)
MES population	127 (50%)	119 (50%)
Completed – n (%)	209 (82.3%)	178 (74.8%)
DISCONTINUATIONS n (%)		
Total	45(17.7)	60 (25.2)
AE's	13 (5.1)	9 (3.8)
Lack of efficacy	10 (3.9)	16 (6.7)
Protocol deviation	1 (0.4)	5 (2.1)
Subject withdrew consent	15 (5.9)	16 (6.7)
Lost to follow up	5 (2.0)	12 (5.0)
Administrative	1 (0.4)	2 (0.8)

In Study -315, discontinuations for AE's were higher in the DSG- treated group, 13.1% versus 2.1% in the vehicle arm. Unsatisfactory therapeutic effect accounted for a higher proportion of withdrawals in the vehicle group (7%) compared to the 4% in the DSG group.

TABLE 6.1.4.4: SHOWING SUBJECT DISPOSITION IN STUDY -315 (Hand OA)

TOTAL # OF SUBJECTS	DSG	VEHICLE
Randomized	198	187
Intent-to-treat population	198 (100%)	187 (100%)
Completed – n (%)	173 (87.4%)	161 (86.1%)
DISCONTINUATIONS n (%)		
Total	26 (13.1%)	26 (13.9%)
AE's	11 (5.6%)	4 (2.1%)
Lack of efficacy	8 (4.0%)	13 (7.0%)
Protocol deviation	1 (0.5%)	1 (0.5%)
Subject withdrew consent	2 (1.0%)	6 (3.2%)
Lost to follow up	2 (1.0%)	1 (0.5%)
Administrative	0	1 (0.5%)

EFFICACY ANALYSIS: Study -310 (knee OA)

- PRIMARY EFFICACY OUTCOME ANALYSIS

Table 6.1.4.5 shows the results of the primary efficacy analysis for study-310. With respect to each co-primary endpoint, the DSG group was statistically significant superior to vehicle.

TABLE 6.1.4.5: SHOWING PRIMARY EFFICACY OUTCOME FOR STUDY VOSG-PN-310 (Knee OA) @ WEEK 12 (MES POPULATION)

	VOSG-PN-310	
Efficacy outcome	**DSG N = 127**	**Vehicle N = 119**
WOMAC Pain Score (Scale: 0-20)		
Mean ± SD	5.62 ± 4.50	7.38 ± 5.22
Mean change from baseline ± SD	5.85 ± 4.23	4.68 ± 4.89
LS mean (LS SE)	5.95 (0.42)	7.29 (0.44)
LS mean difference, Veh-DSG (LS SE)	1.34 (0.59)	
95% CI	(0.18, 2.49)	
p-value	0.023	
WOMAC Physical Function Score (Scale: 0 to 68)		
Mean ± SD	19.7 ± 15.1	25.7 ± 17.6
Mean change from baseline ± SD	17.5 ± 15.4	11.8 ± 15.5
LS mean (LS SE)	20.2 (1.4)	25.9 (1.4)
LS mean difference, Veh-DSG (LS SE)	5.7 (1.9)	
95% CI	(2.0, 9.4)	
p-value	0.003	
Global Rating of Disease 100 mm VAS		
Mean ± SD	31.6 ± 29.0	41.5 ± 30.4
Mean change from baseline ± SD	30.0 ± 31.2	22.4 ± 29.4
LS mean (LS SE)	34.1 (2.6)	42.6 (2.7)
LS mean difference, Veh-DSG (LS SE)	8.5 (3.6)	
95% CI	(1.5, 15.6)	
p-value	0.018	

- *SENSITVITY ANALYSIS AND CUMULATIVE RESPONDER ANALYSIS*

Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used. The applicant performed several sensitivity analyses of the primary endpoint.

The FDA Statistical Reviewer also performed the sensitivity analyses to confirm the robustness of the primary analysis by utilizing a variation in the output of the model using baseline observation carried forward (BOCF) method imputation, analysis with same mean imputation and analysis with the alternative mean imputation. These analyses are shown in Tables 6.1.4.6, 6.1.4.7 and 6.1.4.8 shown below.

TABLE 6.1.4.6: SHOWING ***BOCF*** SENSITIVITY ANALYSIS OF STUDY -310

	PROTOCOL SPECIFIED PRIMARY ANALYSIS				**ANALYSIS WITH BOCF IMPUTATION**			
	DSG 1%	**Vehicle**	**Diff**	**p-value**	**DSG 1%**	**Vehicle**	**Diff**	**p-value**
WOMAC Pain	5.9	7.3	1.3	0.02	6.4	7.9	1.5	0.02
WOMAC Function	20.2	25.9	5.7	0.003	21.2	27.4	6.2	0.001
Global rating of Disease	34.1	42.6	8.5	0.02	35.4	44.1	8.6	0.02

Source: FDA Statistician –R. Davi

The BOCF sensitivity analysis revealed that the difference in mean pain, function and global scores, the active and vehicle arms remained statistically significant even when the BOCF was substituted for the LOCF imputation, and sensitivity analysis achieved statistical significance for WOMAC pain, WOMAC function and global pain.

TABLE 6.1.4.7: SHOWING RESULTS OF ***SAME MEAN*** ANALYSIS SENSITIVITY ANALYSIS OF STUDY -310

	PROTOCOL SPECIFIED PRIMARY ANALYSIS				**ANALYSIS WITH SAME MEAN IMPUTATION**			
	DSG 1%	**Vehicle**	**Diff**	**p-value**	**DSG 1%**	**Vehicle**	**Diff**	**p-value**
WOMAC Pain	5.9	7.3	1.3	0.02	5.5	5.9	0.5	0.37
WOMAC Function	20.2	25.9	5.7	0.003	18.8	22.2	3.4	0.04
Global rating of Disease	34.1	42.6	8.5	0.02	30.2	35.7	5.6	0.07

Source: FDA Statistician –R. Davi

In the "same mean" analysis, statistically significant lower function WOMAC function and global rating of disease values were found for the DSG group compared to the vehicle group (Table 6.1.4.7).

The "alternative mean" sensitivity analysis showed no statistically significant difference between the treatment arms (Table 6.1.4.8).

TABLE 6.1.4.8: SHOWING RESULTS OF *ALTERNATE MEAN* ANALYSIS SENSITIVITY ANALYSIS

	PROTOCOL SPECIFIED PRIMARY ANALYSIS				ANALYSIS WITH ALTERNATIVE MEAN IMPUTATION			
	DSG 1%	**Vehicle**	**Diff**	**p-value**	**DSG 1%**	**Vehicle**	**Diff**	**p-value**
WOMAC Pain	5.9	7.3	1.3	0.02	5.6	5.6	0.0	>0.99
WOMAC Function	20.2	25.9	5.7	0.003	19.4	20.9	1.5	0.37
Global rating of Disease	34.1	42.6	8.5	0.02	31.2	33.5	2.3	0.46

Source: FDA Statistician –R. Davi

The BOCF sensitivity analysis is particularly reassuring due to the relatively low and balanced adverse event dropout rate of 5.1% for active arm, and 3.9 % for vehicle arm.

- *SECONDARY EFFICACY OUTCOME ANALYSIS*

There was a greater response favoring active treatment in secondary efficacy assessments in subjects who received DSG, in comparison with subjects who received vehicle. The differences in response between the treatment groups were statistically significant at most time points. Ten (10) of the twelve (12) protocol-defined secondary endpoints was met. Table 10.1.1.5 shown in Section 10 of this report (individual study report section) lists the results of the secondary efficacy outcome analysis.

EFFICACY ANALYSIS: STUDY-315 (Hand OA)

- *PRIMARY EFFICACY OUTCOME ANALYSIS*

In study VOSG-PE-315 at Week 4, OA pain intensity and the AUSCAN index showed statistically significant improvement of the DSG-treated subjects compared to vehicle

treated subjects. The Global Rating of Disease just missed achieving statistical significance (p = 0.06) at Week 4. In spite of this, evaluation of the Week 6 primary endpoints was undertaken and all showed statistically significant improvement favoring active treatment for all of the primary efficacy outcomes. (See Table 6.1.4.9).

TABLE 6.1.4.9: SHOWING PRIMARY EFFICACY OUTCOME FOR STUDY VOSG-PE-315 (Hand OA) @ WEEK 4 and WEEK 6 (ITT POPULATION)

PRIMARY EFFICACY OUTCOMES	WEEK 4		WEEK 6	
	DSG 1% N= 198	VEHICLE N= 187	DSG 1% N= 198	VEHICLE N= 187
OA pain intensity (100 mm VAS)				
Mean +/- SD	42.6+/-30.5	49.7+/-28.8	39.9 +/-31.6	46.9+/-29.9
Mean change from baseline +/- SD	31.1+/- 25.8	23.9+/- 27	33.7 +/- 27.8	26.7+/-28
LS mean (LS SE)	43.3 +/- 1.9	49.3 +/-2.1	41.1+/- 2.1	47.4+/- 2.2
LS mean difference, Vehicle-DSG (LS SE)	6.0 +/-2.5		6.3 +/-2.8	
95% CI	(1.1,11.0)		(0.9,11.7)	
p-value	0.018		0.023	
AUSCAN Index (Scale 0-100)				
Mean +/- SD	43.7+/- 28.2	50.2+/-27.3	41.4 +/- 28.8	48.5 +/-28.1
Mean change from baseline +/- SD	23.5+/- 24.4	16.8+/-25.2	25.9 +/-25.1	18.6+/-26.2
LS mean (LS SE)	44.4+/- 1.9	50.7 +/-2.0	42.5 +/- 2.0	49.6+/- 2.1
LS mean diff, Vehicle-DSG (LS SE)	6.3 +/- 2.5		7.1 +/-2.6	
95% CI	(1.5,11.2)		(2.1,12.2)	
p-value	0.011		0.006	
SUBJECT GLOBAL RATING OF DISEASE				
Mean +/- SD	37.5 +/- 26.8	41.9 +/-25.8	35.2+/- 27.3	40.4 +/-26.3
Mean change from baseline +/- SD	20.8 +/-27.1	14.8 +/-28.1	23.1+/-27	16.3 +/-28
LS mean (LS SE)	38.3 +/- 2	43.2 +/- 2.1	35.5 +/- 2	41.5 +/- 2.1
LS mean diff, Vehicle-DSG (LS SE)	4.9 +/- 2.6		6 +/-2.6	
95% CI	(-0.2,9.9)		(0.8, 11.2)	
p-value	0.06		0.023	

o *SENSITIVITY ANALYSES and CONTINUOUS RESPONDER ANALYSES*

The analyses incorporating the "same mean" imputation scheme are somewhat supportive of the conclusions from the protocol-specified primary efficacy analyses. As expected, the least squares mean for each endpoint and each treatment group is numerically higher in the primary efficacy analysis; however, the numerical differences between treatment groups continue to favor the Voltaren group.

Statistically significant by-treatment group differences are not achieved in the analyses incorporating the "alternate mean" imputation scheme. However, as highlighted by the Applicant, this analysis is conservative and biased in favor of the vehicle group in this case since more favorable results are imputed for the missing data in the vehicle group than in the Voltaren group. The lack of statistically significant findings in this analysis is not unexpected.

The results of the analyses when imputing according to the BOCF approach yield similar conclusions to the primary efficacy analyses and therefore, provide support for the primary efficacy analyses and minimize the concern regarding the possible impact of the missing data.

In summary, the qualitative conclusions from the missing data sensitivity analyses are largely supportive of the protocol-specified primary efficacy analysis. Several instances with p-values greater than 0.05 do occur but the numerical by-treatment group differences continue to favor Voltaren.

At the request of the division, the sponsor provided cumulative distribution plots (i.e., a continuous responder analyses) for the primary efficacy endpoints for weeks 4 and 6. The descriptive conclusions from these plots are supportive of the efficacy of Voltaren over vehicle for the primary efficacy endpoints and are provided. (See Figure 6.1.4.10).