TABLE 6.1.4.10: SHOWING SENSITIVITY ANALYSIS USING *SAME MEAN, ALTERNATE MEAN* AND *BOCF* ANALYSES AT WEEK 4 AND WEEK 6 IN STUDY –VOSG-PE-315 (Hand OA)

Table 6.1.4.10(a): Least Squares Means by Treatment Group – Sensitivity Analyses (Week 4)

	Protocol Specified				Same Mean			
	Voltaren	Vehicle	Diff	p-value	Voltaren	Vehicle	Diff	p-value
OA Pain Intensity	43.3	49.3	6.0	0.02	41.6	46.4	4.8	0.048
Total AUSCAN	44.4	50.7	6.3	0.01	43.2	47.6	4.4	0.06
Global Rating of Disease	38.3	43.2	4.9	0.06	37.2	40.8	3.6	0.14

Table 6.1.4.10(b): Least Squares Means by Treatment Group – Sensitivity Analyses (Week 6)

	Protocol Specified				Same Mean			
	Voltaren	Vehicle	Diff	p-value	Voltaren	Vehicle	Diff	p-value
OA Pain Intensity	41.1	47.4	6.3	0.02	38.7	42.6	3.9	0.13
Total AUSCAN	42.5	49.6	7.1	0.006	40.2	45.2	4.9	0.04
Global Rating of Disease	35.5	41.5	6.0	0.02	33.8	37.5	3.7	0.13

Table 6.1.4.10(c): Least Squares Means by Treatment Group – Sensitivity Analyses (Week 4)

	Protocol Specified				Alternate Mean			
	Voltaren	Vehicle	Diff	p-value	Voltaren	Vehicle	Diff	p-value
OA Pain Intensity	43.3	49.3	6.0	0.02	42.1	46.0	3.9	0.11
Total AUSCAN	44.4	50.7	6.3	0.01	43.5	47.3	3.8	0.11
Global Rating of Disease	38.3	43.2	4.9	0.06	37.5	40.5	3.0	0.23

Table 6.1.4.10(d): Least Squares Means by Treatment Group – Sensitivity Analyses (Week 6)

	Protocol Specified				Alternate Mean			
	Voltaren	Vehicle	Diff	p-value	Voltaren	Vehicle	Diff	p-value
OA Pain Intensity	41.1	47.4	6.3	0.02	39.1	42.0	2.9	0.27
Total AUSCAN	42.5	49.6	7.1	0.006	40.7	44.6	3.9	0.11
Global Rating of Disease	35.5	41.5	6.0	0.02	34.1	37.2	3.1	0.21

Table 6.1.4.10(e): Least Squares Means by Treatment Group – Sensitivity Analyses (Week 4)

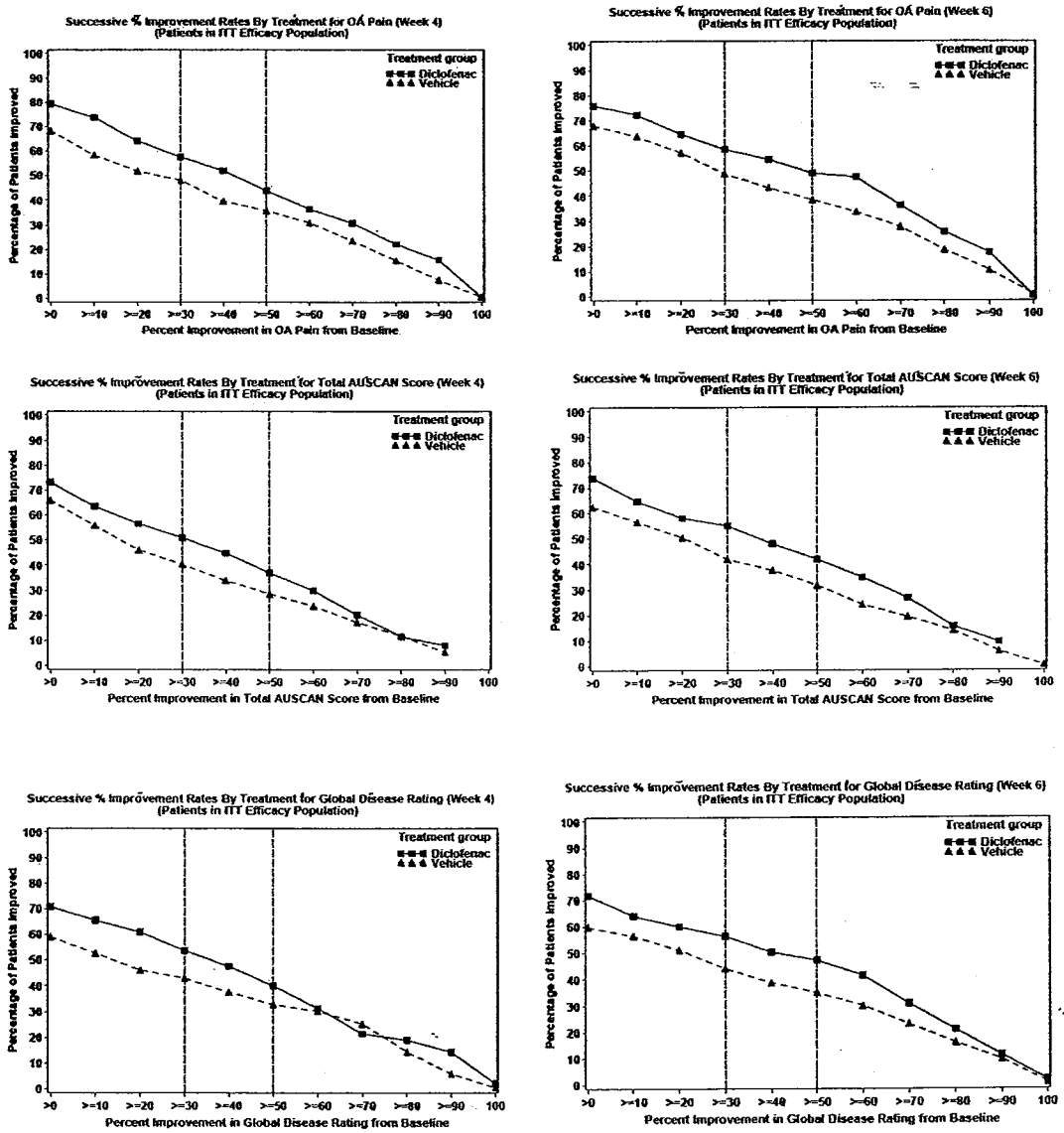
	Protocol Specified				BOCF			
	Voltaren	Vehicle	Diff	p-value	Voltaren	Vehicle	Diff	p-value
OA Pain Intensity	43.3	49.3	6.0	0.02	44.3	49.7	5.5	0.03
Total AUSCAN	44.4	50.7	6.3	0.01	45.2	50.6	5.4	0.03
Global Rating of Disease	38.3	43.2	4.9	0.06	39.3	43.8	4.5	0.08

Table 6.1.4.10(f): Least Squares Means by Treatment Group – Sensitivity Analyses (Week 6)

	Protocol Specified				BOCF			
	Voltaren	Vehicle	Diff	p-value	Voltaren	Vehicle	Diff	p-value
OA Pain Intensity	41.1	47.4	6.3	0.02	42.6	48.1	5.6	0.045
Total AUSCAN	42.5	49.6	7.1	0.006	43.9	49.8	6.0	0.02
Global Rating of Disease	35.5	41.5	6.0	0.02	36.7	42.4	5.7	0.03

Source: FDA's Statistical Reviewer- R. Davi

FIGURE 6.1.4.10: CONTINUOUS RESPONDER ANALYSIS OF PRIMARY EFFICACY ENDPOINTS (Week 4 and Week 6)- STUDY -315



Source: FDA's Statistical Review- R. Davi

- *SECONDARY EFFICACY OUTCOME ANALYSIS*

Secondary outcomes were analyzed only in the ITT efficacy population.

The result of the secondary efficacy outcome measures in the target hand in Study VOSG-PE-315 is shown in Table 10.1.2.5 in the individual study report section of this review. Comparisons of every measurement at all post-baseline visits favored DSG treatment, with statistically significant superiority demonstrated at most weeks for numerous outcomes.

Secondary measures of efficacy showed greater improvement in OA symptoms for the DSG group, and the differences in comparison with the vehicle group were frequently statistically significant. In general, the data demonstrate an improvement in DSG-treated subjects compared to vehicle treated subjects improvements increased over time but did not reach statistical significance except in 2 instances.

6.1.5 Clinical Microbiology

Not applicable to this submission.

6.1.6 Efficacy Conclusions

Study VOSG-PN-310 (knee OA) provide statistically significant treatment effect across primary efficacy endpoints, that topical DSG 1% is effective therapy for mild to moderate pain symptoms of hand and knee OA. These differences were provided in both the MES and ITT analysis populations. The conclusions are robust against concerns regarding multiple sensitivity analyses yielded supportive conclusions.

Study VOSG-PE-315 (hand OA), the efficacy of Voltaren is supported, but the support is not as clear cut. Comparisons of the average outcomes for 2 of the three primary end points (that is OA pain and Total AUSCAN score at both Week 4 and Week 6 resulted in p-values of less than 0.05. Comparison of the mean global rating of disease at Week 4 resulted in a p-value of 0.06 and at Week 6 a p-value less than 0.05. According to the pre-specified multiplicity, comparison of the mean global rating of disease endpoint at week 4 should have precluded any claims of efficacy and testing the primary efficacy endpoints at week 6. However, due to the borderline nature of the result at Week 4, the relative clinical importance of the three endpoints, and the fact that the conclusion would be different if a hieracherial multiple comparison procure were implemented (an approach that would seem reasonable if the protocol were being designed today), this study does provide supportive evidence of efficacy of Voltaren over vehicle despite the failure to satisfy the strict multiple comparison procedure.

7. INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The safety of DSG was evaluated using the following data sources:

1) Pooled data from 4 large Phase 3 controlled trials. This data comprised the major safety population.
2) An open label, uncontrolled, long term study (VOSG-PN-309). This long term safety study affords an assessment of time-dependent AE rates.
3) Three (3) special safety trials performed to obtain special safety data regarding the potential for skin sensitization, irritation and photo-toxicity.
4) Safety data from the PK/PD studies in healthy volunteers.
5) Post marketing safety surveillance data of the marketed European topical formulation of diclofenac DEA.
6) Worldwide literature search that capture any investigator reports of safety aspects not included in the study reports.

7.1.1 Deaths

There was a single death in the course of the clinical trials conducted with DSG 1%. This death occurred in Study VOSG-PN-310. The subject was a 76-year-old male, known to suffer from hypercholesterolemia, muscle spasms, insomnia, and hypothyroidism, who was randomized to the DSG arm, and who died following an episode of ventricular fibrillation, which occurred on Day 5 while driving. The patient subsequently was involved in a motor vehicle accident. He was admitted to the hospital, where he died of cardiac arrest. It is unlikely that the clinical presentation and subsequent death noted above was related to the 5 day topical administration of DSG.

7.1.2 Other Serious Adverse Events

Serious Adverse Events (SAE's) in controlled Phase 3 trials

Table 7.1.2.1 summarizes of the severe adverse events experienced by the subjects in the pooled major controlled clinical studies. A total of 10 SAEs were experienced by subjects assigned to the DSG treatment arm, while a total of 9 SAEs were experienced by subjects in the vehicle arm.

TABLE 7.1.2.1: SEVERE ADVERSE EVENTS (SAEs) and DEATHS EXPERIENCED IN THE CONTROLLED PHASE 3 STUDIES -310, -315, -304 AND -314

STUDY	DSG	VEHICLE
-310	76 y/o ♂ with ventricular fibrillation, with resultant MVA and death on Day 5 of Rx	77 y/o ♀ with Syncope
	49 y/o ♀ with post menopausal bleeding on Day 32	57 y/o ♀ with benign abdominal mass , noted on Day 58; excised surgically
	64 y/o ♀ with AF, hypertension, hyperlipidemia	
-315	50 y/o ♀ w PH depression, Bipolar Disorder, hospitalized for severe depression on Day 54	55 y/o ♀ with Type 2 DM developed diabetic nephropathy on Day 9 of Rx
	82 y/o ♀with severe diarrhea and mild vomiting on Day 43.	
-304	67 y/o ♀ w H/O diverticulitis, s/p colon resection, with mild diarrhea on Day 42. Study med temporarily interrupted with improvement in diarrhea	53 y/o ♀ with type 2 DM/hypertension, CAD, admitted with chest pain. No MI by cardiac enzymes, EKG showed AF.
	80 y/o ♀ with PH hypertension/DM/hypercholesterolemia, with DVT & PE on Day 78	74 y/o ♂ with protrusion of L4-L5 disc
	65 y/o ♀with PH osteoporosis and with H/o fall with forearm Fx. Hospitalized for surgical pinning of fx.	72 y/o ♀ with PH CVA, cerebral aneurysm, and HA. Rx with verapamil and prednisone
-314	65 y/o ♀ with PUO found to be related to segmental colitis. Rx'ed w ciprofloxacin, w complete recovery.	71 y/o ♀ w PH hypertension, s/p STENT placement On Day 52 of Rx required additional STENT placement
	49 y/o perimenopausal ♀ w reactional depressive syndrome.	60 y/o ♀ w fx wrist post fall
		79 y/o ♀ DM, gastritis and osteoporosis, admitted with Idiopathic VIIth N palsy

Soure: FDA compilation based on information submitted by the applicant.

Two SAEs in one patient (# 113/6532) were judged by the sponsor to be related to study medication. The latter events were deep venous thrombosis and a pulmonary embolism in occurred in an obese 80 year old woman with a history of diabetes, hypertension and hypercholesterolemia on day 78 of VOSG-PN-304. The deep venous thrombosis occurred

in the leg of the knee being treated in the study, and was therefore considered to have been related to the application of DSG 1%.
This reviewer however does not believe that the above venous thrombotic events can be attributed to an NSAID product because it is more likely that obesity and inactivity contributed to the venous thrombotic event, than the topical application of DSG.

Severe adverse events in open label clinical trial
Table 7.1.2.2 (below) shows a listing of all treated subjects who developed SAE's during the course of treatment with DSG, and includes the subject numbers, day of onset of SAE, and the action taken. Most of the SAE's listed were incidental, consisting on burn infections, diarrhea and miscellaneous cystic lesions.

The following cardio-thrombotic SAEs were possibly related to treatment with DSG:
1) *Subject # 134/6144* – was a 63 y/o male with a PH of hyperlipidemia, hypertension and DM, who developed a myocardial infarction on Day 296. The study drug was temporarily interrupted for the duration of the event.
2) *Subject # 140/0001* was an 83 y/o woman, with a PH hypertension, hypercholesterolemia, fluid retention and DM, who experienced angina pectoris on Day 267.
3) *Subject # 211/4593* was a 64 y/o woman, with a PH atrial fibrillation (AF), hypertension, hyperlipidemia and sleep apnea, who experienced moderate AF on Day 44 of therapy. Study drug was temporarily discontinued.
4) *Subject # 2324/4144* was a 58 y/o woman with a H/o hypertension, type II DM and sleep apnea, who experienced myocardial infarction on Day 22. Study drug was permanently discontinued.

There was one case of gastro-intestinal hemorrhage that occurred in subject *#118/0000* in the setting of gastritis, acute pancreatitis, and acute renal and respiratory failure. Subject # 107/0003, a 64 y/o woman, with a PH hypercholesterolemia and hypertension developed an intracranial hemorrhage on Day 33.

All serious cases of gastrointestinal bleeding, cardiothrombotic events could be attributed to pre-existing medical conditions or concurrent disease.

Two (2) subjects, *# 220/0002* and *# 228/0004* were reported as having asthma; one case occurred in the setting of pneumonia. It is unclear if there was a prior history of asthma, or whether this may have been evoked by topical NSAID.

Three subjects developed neoplasms during the course of therapy:
Subject *#116/0002* developed colon cancer on Day 184; subject *# 123/6108* developed a sarcoma; subject *# 201/4071* developed colon cancer and subject *# 213/4041* developed a malignant lung neoplasm on Day 188. This reviewer does not believe that the neoplasms were related to the use of topical NSAID.

Overall, the incidence of SAEs in the DSG arm was similar to the incidence of SAEs in the

placebo (vehicle) arm of the controlled studies. These SAEs were not felt to be related to the use of topical DSG 1%.

Seroius adverse events in the combined Phase 3 controlled trials and the open label uncontrolled Trial -309

Overall, all SAE's experienced by subjects treated with DSG in the present study and/or one of the previous double-blind studies are listed in Table 7.1.2.2 shown below. Twenty-nine subjects experienced a total of 36 SAEs. Pneumonia (including bronchopneumonia) was experienced by 3 subjects. Diarrhea, acute pancreatitis, myocardial infarction, and asthma were each experienced by 2 subjects. Five subjects had a diagnosis of cancer / neoplasm (2 colon cancer, 1 breast cancer, 1 sarcoma, 1 malignant lung neoplasm). Twenty-two SAEs were rated as severe.

Treatment with DSG 1% did not appear to be associated with any specific SAE.

TABLE 7.1.2.2: SHOWING ALL SAE'S IN ALL TREATED SUBJECTS IN THE CONTROLLED PHASE 3 STUDIES -310, -315, -304 AND -314 AND THE OPEN LABEL STUDY -309

Subject	Event	Day of Onset	Severity	Study Drug Relation Suspected	Action taken [a]
100/0003	Burn infection	94	severe	no	3, 4, 5
107/0003	Haemorrhage intracranial	33	moderate	no	2, 4, 5
	Syncope vasovagal	39	mild	no	4, 5
113/6265	Diarrhoea	42	mild	no	1, 3, 5
113/6532	Deep vein thrombosis	78	mild	yes	3, 5
	Pulmonary embolism	78	mild	yes	3, 5
116/0002	Colon cancer	184	severe	no	2, 5
116/6101	Oxygen saturation decreased	134	moderate	no	1, 3, 5
118/0009	Gastritis	168	severe	no	3, 4, 5
	Gastrointestinal hemorrhage	168	severe	no	2, 3, 4, 5
	Pancreatitis acute	168	severe	no	2, 3, 4, 5
	Renal failure acute	168	severe	no	3, 4, 5
	Respiratory failure	179	severe	no	4, 5
123/6108	Sarcoma	NK	severe	no	2
128/6300	Cystocele	77	severe	no	4, 5
134/0001	Comminuted fracture	199	severe	no	1, 2, 3, 4
134/6144	Myocardial infarction	296	severe	no	1, 4, 5
139/0001	Pneumonia	18	moderate	no	3, 5
140/0001	Angina pectoris	267	severe	no	3, 5
140/6351	Cholelithiasis	198	severe	no	1, 3, 4, 5
144/0002	Bronchopneumonia	22	severe	no	1, 3, 5
146/6222	Forearm fracture	28	severe	no	3, 4, 5
201/4069	Pancreatitis acute	312	severe	no	5
201/4071	Colon cancer	233	severe	no	4
208/4018	Postmenopausal hemorrhage	32	mild	no	2, 3
209/4274	Cerebral cyst	381	moderate	no	0
211/4593	Atrial fibrillation	44	moderate	no	1, 3, 5
213/4041	Lung neoplasm malignant	188	severe	no	5
219/0003	Diarrhoea	179	moderate	no	3, 5
220/0002	Asthma	12	moderate	no	3, 5
	Pneumonia	106	moderate	no	3, 5
228/0004	Asthma	334	severe	no	1, 3, 5
231/4269	Injury	187	severe	no	1, 3, 5
234/4144	Myocardial infarction	22	severe	no	2, 4, 5
238/0005	Breast cancer	351	moderate	no	0

[a] Action taken: 0 = none, 1 = study drug dosage adjusted / temporarily interrupted, 2 = study drug permanently discontinued, 3 = concomitant medication taken, 4=Non-drug therapy given, 5 = hospitalization / prolonged hospitalization
Source: [Appendix 7], [Listing 10.3]

Source: Applicants Table 5-17; page 74

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

(i) Controlled Phase 3 Studies

Disposition of subjects in the controlled Phase3 trials
Table 7.1.3.1(i) shown below lists the disposition of study subjects, and classifies the reason for drop out as based on analysis of the disposition dataset.

Altogether, 34 of 913 (3.7%) patients in the active arms discontinued because of unsatisfactory therapeutic effect, while 48/876 (5.5%) subjects in the control (vehicle arm) discontinued for that reason.

Forty five (45) of 913 patients (4.9%) in the DSG arm discontinued because of adverse events, compared to 24/876 discontinued (2.7%) in the control (vehicle arm). In examining the type of AEs, 41.1% (or 23 of 56) of AE terms coded as events in the DSG subjects were skin-related, whereas the corresponding fraction for the vehicle arm was 25.8 % (8/31).

Rates of drop out due to withdrawal of consent were similar between treatment groups; 4.4% of subjects in the DSG arm and 4.8% subjects in the vehicle arm withdrew consent. The case report forms for the patients who discontinued due to withdrawal of consent were reviewed to ascertain whether these patients actually discontinued due to an adverse event. The review found that:

- In Study -310, 6 subjects in the DSG arm and 3 subjects in the vehicle arm discontinued because of lack of efficacy
- In Study -315, one vehicle assigned subject withdrew because of lack of efficacy
- In Study-304, 2 vehicle assigned subjects withdrew because of lack of efficacy, and one DSG assigned subject withdrew because of an AE (skin rash)
- In Study 314, 1 DSG assigned subject withdrew because of lack of efficacy, and one withdrew because of an AE.

Finally, 13/913 (1.4%) in the DSG arm and 20/876 (2.3%) were lost to follow up.

TABLE 7.1.3.1(i): SHOWING SUBJECT DISPOSITION IN THE CONTROLLED PHASE 3 CLINICAL TRIALS –310, -315, -304, and -314

	Knee*		Hand*		Overall Total	
Total number of subjects	**DSG**	**Vehicle**	**DSG**	**Vehicle**	**DSG**	**Vehicle**
Randomized	513 (100)	493 (100)	400 (100)	383 (100)	913 (100)	876 (100)
Treated	512 (99.8)	493 (100)	400 (100)	383 (100)	912 (99.9)	876 (100)
Completed	420 (81.9)	380 (77.1)	354 (88.5)	347 (90.6)	774 (84.8)	727 (83.0)
Discontinued	93 (18.1)	113 (22.9)	47 (11.8)	36 (9.4)	140 (15.3)	149 (17.0)
Main reason for discontinuation						
Death	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse event(s)	25 (4.9)	15 (3.0)	20 (5.0)	9 (2.3)	45 (4.9)	24 (2.7)
Unsatisfactory therapeutic effect	23 (4.5)	31 (6.3)	11 (2.8)	17 (4.4)	34 (3.7)	48 (5.5)
Protocol deviation	1 (0.2)	9 (1.8)	2 (0.5)	1 (0.3)	3 (0.3)	10 (1.1)
Subject withdrew consent	32 (6.2)	35 (7.1)	8 (2.0)	7 (1.8)	40 (4.4)	42 (4.8)
Lost to follow-up	11 (2.1)	19 (3.9)	2 (0.5)	1 (0.3)	13 (1.4)	20 (2.3)

Source: ISS, page 46

ii) Long term, uncontrolled, open-label (OL) safety trial (Study -309)
Study -309 was a 12 month open label evaluation of DSG 1% (≤ 32 mg /day in patients with osteoarthritis of the knee). This long term safety trial provided the only data regarding the effects of dose and duration of DSG therapy on withdrawal rates.. This study allowed dosing of both knees. This study had a higher discontinuation rate (49.6 %) than the observed rate in the shorter duration controlled trials, with subjects dosing both knees having a 61.4 % discontinuation rate, while those dosing one knee having a 42 % discontinuation rate.

A total of 107 subjects discontinued because of a total of 122 adverse events. Skin related AEs accounted for 57.4% (70/122) of all reported AEs associated with discontinuations.

- 88/583 (15.1%) subjects in the study population developed AE's
- 57/583 (9.8 %) subjects in the study population discontinued because of an unsatisfactory therapeutic effect.

Overall, adverse events rates were higher in the open label trial as compared to the controlled trails, and the discontinuation rates were 61% in the subjects dosing two knees, and 42% in the subjects dosing one knee. (These proportions are contrasted with the 15% discontinuation rate of subjects randomized to DSG in the controlled trials).

More subjects withdrew for AEs than the DSG-treated subjects in the controlled trials (15.1%, 88/583 versus 4.9%, 45/913) and of these, a greater proportion of the subjects treating both knees withdrew for AEs (20.2%, 46/228 versus 11.8%, 42/355).

In general the attrition rate in the long term safety population was very high, and overall participation fell over time.

TABLE 7.1.3.1(ii): SHOWING THE DISPOSITION OF SUBJECTS ENROLLED IN THE LONG-TERM SAFETY TRIAL -309. (This table excludes subjects the actively treated subjects in studies -304 and -310 who did not continue in the roll-over study -309).

	One Knee	Two Knees	Overall total
Total number of subjects - n (%)			
Enrolled	355	228	583
Treated	350 (98.6)	228 (100)	578 (99.1)
Completed	206 (58.0)	88 (38.6)	294 (50.4)
Discontinued	149 (42.0)	140 (61.4)	289 (49.6)
Origin of subjects in VOSG-PN-309 - n (%)			
New subjects enrolled	64 (18.0)	228 (100)	292 (50.1)
Continuing subjects from VOSG-PN-304	169 (47.6)	0	169 (29.0)
Continuing subjects from VOSG-PN-310	122 (34.4)	0	122 (20.9)
Main reason for discontinuation - n (%)			
Death	0 (0.0)	0 (0.0)	0 (0.0)
Subject withdrew consent	57 (16.1)	48 (21.1)	105 (18.0)
Adverse events	42 (11.8)	46 (20.2)	88 (15.1)
Unsatisfactory therapeutic effect	25 (7.0)	32 (14.0)	57 (9.8)
Lost to follow-up	13 (3.7)	9 (3.9)	22 (3.8)
Protocol deviation	6 (1.7)	3 (1.3)	9 (1.5)
Administrative problems	6 (1.7)	2 (0.9)	8 (1.4)

The percent basis is the number of subjects enrolled for a given treatment.
Source: VOSG-PN-309 (CTD 5.3.5.2.1); Post-text Table 7-1

In the long term safety studies, AE rates generally increased with increasing duration of exposure. Although the data do not permit a precise quantitative comparison it does appear that the longer duration of treatment (from 2-3 months to 6-12 months) does produce a

relative increase in the rate of AE reporting.

7.1.3.2 Adverse events associated with dropouts

Adverse events associated with dropouts will be considered separately in the controlled Phase 3 studies, and in the open label study:

In the controlled studies, a total of 44 (4.8%) subjects in the DSG arm discontinued the study because of AE's, while 23 (2.6%) subjects in the vehicle discontinued because of AEs. In examining the entire list of AEs, 41% were skin related, whereas the corresponding fraction was 25.8% for the vehicle- treated subjects. The other AEs associated with discontinuations included arthralgia, back pain and nausea, with equal proportions.
In the open label study, Skin-related AE's accounted for 57.4% of all reported AEs associated with discontinuations. The remaining AEs associated with discontinuation included back pain, meniscus lesions, neck pain, arthralgia and 3 reports of elevated AST levels. These AST elevated levels were twice the ULN and resolved with discontinuation of study drug.

While no relationship to dose or duration of therapy can be derived from the available data for discontinuations, it is apparent that skin-related AEs were a significant factor in the overall withdrawal rates.

7.1.3.3 Other significant adverse events

Dermal adverse events and transaminitis will be discussed in greater detail in this section. In both the DSG and the vehicle groups, the most frequently reported skin adverse events were application site dermatitis and rash. Dermal adverse events are therefore considered to be a significant adverse event, and will be discussed in further detail in this section.

The proportion of subjects reporting skin adverse events in the major safety population was 10.1% of all subjects exposed to active drug and 3.8% of all subjects exposed to vehicle (See Table 7.1.7.3.1 below). No serious skin-related adverse event occurred in the major safety population.

TABLE # 7.1.3.3.1: SHOWING ALL SKIN-RELATED ADVERSE EVENTS IN THE POOLED MAJOR SAFETY POPULATION VEHICLE-CONTROLLED STUDIES [VOSG-PN-304, VOSG-PN-310, VOSG-PN-314, AND VOSG-PN-315] - N (%)

	Knee		Hand		Combined	
	DSG 1%	**Vehicle**	**DSG 1%**	**Vehicle**	**DSG 1%**	**Vehicle**
Total # Subjects exposed	513	493	400	383	913	876
Any skin AE	53 (10.3)	16 (3.2)	39 (9.8)	17 (4.4)	92 (10.1)	33 (3.8)
Application site dermatitis	26 (5.1)	4 (0.8)	6 (1.5)	2 (0.5)	32 (3.5)	6 (0.7)
Application site erythema	5 (1.0)	3 (0.6)	1 (0.3)	-	6 (0.7)	3 (0.3)

Source: FDA's compilation of sponsor's submission data

Table 7.1.3.3.2 lists skin-related adverse events occurring in the long-term uncontrolled safety study VOSG-PN-309, stratified in consecutive 3-month intervals in which all subjects were treated with topical DSG 1%. This Table includes all skin adverse events and exposure data from all subjects who were treated with topical DSG 1% in Studies VOSG-PN-304 and VOSG-PN-310, whether or not they continued into VOSG-PN-309. This was done to avoid bias, since subjects with skin adverse events in the double-blind studies would be less likely to continue into VOSG-PN-309. Events were counted once and according to their time of onset following start of treatment.

TABLE 7.1.3.3.2: SHOWING ALL SKIN-RELATED ADVERSE EVENTS IN THE ACTIVE-TREATED SUBJECTS IN THE CONTROLLED CLINICAL TRIALS AND THE LONG-TERM SAFETY STUDY (VOSG-PN-309) BY 3-MONTH INTERVALS FOLLOWING START OF TREATMENT - N (%)

Preferred Term (MedDRA 9.0)	0-3 months	3-6 months	6-9 months	9-12 months	0-12 months
Total subjects exposed	947	473	347	235	947
Any skin AE	112 (11.8)	44 (9.3)	25 (7.2)	4 (1.7)	169 (17.8)
Application site dermatitis	65 (6.9)	27 (5.7)	13 (3.7)		99 (10.5)
Application site erythema	7 (0.7)	1 (0.2)	1 (0.3)		9 (1.0)

Source: FDA's compilation of data supplied by applicant

The frequency of any skin-related adverse event over the first year was 17.8%. The rate declined over successive quarters from 11.8% of exposed subject in the 1st quarter to 1.7% of exposed subjects in the 4th quarter. The most frequent reports were for Application site dermatitis (overall rate 10.5%, 99/947) and Rash (overall rate 2.0%, 19/947). No other single event had an overall reporting frequency exceeding 1%.

The incidence of skin-related adverse events in the long-term safety population was comparable for the different 3-months periods during the first 9 months of exposure, in which the number of exposed subjects allowed for meaningful comparison. The incidence rates in each of these three month periods are also comparable to the overall incidence rates for topical DSG 1% in Table 7.1.3.3.1.

In conclusion, to the extent that the number of cases allowed for meaningful comparison, the nature and distribution of skin adverse events did not change over time. The most frequently observed skin adverse events were *Application site dermatitis* and *Rash.*
No skin-related serious adverse events were reported.

Table 7.1.3.3.3 presents the number of subjects in the pooled major safety population who discontinued participation due to a skin-related AE. Each cell in the table contains the number of subjects who discontinued and the total number of AEs for the given treatment followed in parentheses by the percentage of subjects who discontinued. The percent basis is the total number of subjects exposed for a given treatment.

TABLE 7.1.3.3.3: SHOWING ALL SKIN-RELATED AEs RESULTING IN DISCONTINUATIONS IN THE MAJOR SAFETY POPULATIONS VEHICLE-CONTROLLED STUDIES VOSG-PN-304, VOSG-PN-310, VOSG-PN-314 AND VOSG-PN-315

	Knee		Hand		Combined	
	DSG 1%	**Vehicle**	**DSG 1%**	**Vehicle**	**DSG 1%**	**Vehicle**
Total subjects exposed	513	493	400	383	913	876
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any skin AE	14 (2.7)	3 (0.6)	7 (1.8)	2 (0.5)	21 (2.3)	5 (0.6)
Application site dermatitis	8 (1.6)	2 (0.4)	4 (1.0)	1(0.3)	12 (1.3)	3 ((0.3)

Source: FDA compilation of data supplied by the applicant

The proportion of subjects discontinuing because of *any skin AE* was greater consistently greater in the DSG arm than in the vehicle arm, 2.3% versus 0.6% respectively.

Limitations:

1) Pooled analyses do not account for the source of the data (that is from different studies and location of application) as could be done in a more formal meta-analysis.

2) No specific named skin AE classification system was defined by protocol. The designation of mild, moderate and severe grade assignment ascribed by the field investigators served to characterize the clinical importance of the adverse event, and as a check to enable the field monitors to determine if an adverse event had worsened and if so, it needed to be recorded as a separate event. It was left to the investigator's clinical judgment and discretion to assign a grade. The lack of a severity classification system for dermal adverse events may have produced an inter-investigator variability in the classification of the severity of dermal AEs.

CONCLUSION ON DERMAL ADVERSE EVENT

The incidence of any skin AE in the pooled Phase 3 controlled clinical trial was 10.1 % in the DSG arm and 3.8% in the vehicle arm. The nature of the rash was classified as application site dryness, irritation, pruritus, paraesthesia or rash. Of varying types of application site rash, application site dermatitis and application site erythema were the most outstanding.

In the controlled studies, All skin related AEs resulted in the discontinuation of 2.3% of

subjects in the control group and 0.6% of the vehicle arm.

In the long term studies, the incidence of rash was 17.8%. The most frequent reports were for *application site dermatitis* and *Rash.* The incidence rate did not appear to increase over time. No skin related SAE were reported in the clinical trial population.

TRANSAMINITIS

Controlled Phase 3 safety population

The knee OA trials were of 12 weeks duration and a Week 4 follow-up blood sample was obtained for LFTs only. The post baseline Week 4 results are included in the table noted below. In the hand OA studies post baseline LFT's were performed at Week 8.

Table 7.1.3.3.4 (below) shows the latest post-baseline LFT's as frequencies of multiples of the upper limit of normal (ULN) for the knee and hand and combined OA studies.
In general, the mean values for the LFT determinations for the knee OA or hand OA studies did not suggest any clinically significant systematic shift in values during the course of the trials. The proportion of DSG and vehicle treated subjects with elevated ALT's, AST's, GGT's and bilirubin levels were similar in both treatment arms.

Extreme values noted at Week 4 or in the latest post-baseline determination for certain analytes were generally present at baseline and were observed in both the DSG- and vehicle-treated populations.

TABLE 7.1.3.3.4: SHOWING THE LATEST POST-BASELINE LFT's AS MULTIPLES OF THE ULN FOR THE KNEE AND HAND OA STUDIES SEPARATELY AND COMBINED

	Knee OA		Hand OA		Combined	
	DSG	**Vehicle**	**DSG**	**Vehicle**	**DSG**	**Vehicle**
	513	493	400	383	913	876
ALT –n (%)						
1x ULN	52 (10.1)	61 (12.4)	26 (6.5)	30 (7.8)	78 (8.5)	91 (10.4)
2 x ULN	4 (0.8)	5 (1.0)	4 (1.0)	2 (0.5)	8 (0.9)	7 (0.8)
3 x ULN	0 (0.0)	0 (0.0)	2 (0.5)	1 (0.3)	2 (0.2)	1 (0.1)
5 x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AST –n (%)						
1 x ULN	13 (2.5)	29 (5.9)	17 (4.3)	14 (3.7)	30 (3.3)	43 (4.9)
2 x ULN	2 (0.4)	0 (0.0)	1 (0.3)	2 (0.5)	3 (0.3)	2 (0.3)
3 x ULN	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
5 x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
GGT –n (%)						
1x ULN	105 (20.5)	94 (19.1)	41 (10.3)	40 (10.3)	146 (16.0)	134 (15.3)
2 x ULN	25 (4.9)	22 (4.5)	10 (2.5)	12 (3.1)	35 (3.8)	34 (3.9)
3 x ULN	9 (1.8)	9 (1.8)	5 (1.3)	8 (2.1)	14 (1.5)	17 (1.9)
5 x ULN	3 (0.6)	2 (0.4)	2 (0.5)	3 (0.8)	5 (0.5)	5 (0.6)
Bilirubin –n (%)						
1x ULN	16 (3.1)	12 (2.4)	8 (2.0)	5 (1.3)	24 (2.6)	17 (1.9)
2 x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3 x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
5 x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Post Text Table 10.7, page 105 (ISS)

Long term safety population

In the long term safety population, plasma ALT and AST were measured at baseline, at months 6 and 12, as well as the latest post-baseline determination and the highest post-baseline result. In general, examination of the mean values for the LFT parameters at baseline, and at 6 months, 12 months post baseline in the long term safety population did not reveal any systematic shifts.

Laboratory observation of the major safety population which had a time of exposure and a period of observation that was 8-12 weeks compared to the 3 to 12 month period of exposure and observation in the long-term safety study. No consistent effect on change from baseline when treating one versus both knees was noted in the data. This suggests an absence of a dose response effect over the DSG dose range of 4-8 g QID.

Table 7.1.3.3.5 shown below presents the latest open label LFT's as the number of occurrences for the various multiples of the ULN for the open-label safety population. In general, the frequencies of abnormal results 1 x ULN were approximately 30% higher than those observed in the major safety population.

The cause for the low frequency of higher multiples for the various LFT's is uncertain but it should be noted that the rescue medication was acetaminophen and its use has been associated with transient elevations in LFTs. At the very least, this concomitant use of acetaminophen as a rescue medication complicates interpretation of the data.

Interpretation of the results of the open label study is complicated by the lack of a control population and the effect of increasing time of observation for possibly random events. Within the one-knee and both-knee treatment populations, subjects were treated for variable lengths of time dictated by their willingness to continue in the study with an upper limit of 12 months duration.

TABLE 7.1.3.3.5: SHOWING LATEST POST-BASELINE LFT'S AS MULTIPLES OF THE ULN FOR THE LONG TERM SAFETY POPULATION

	One Knee	Two Knees	Total
N	692	223	915
ALT			
1x ULN	66 (9.5)	47 (21.1)	113 (12.3)
2x ULN	8 (1.2)	8 (3.6)	16 (1.7)
3x ULN	2 (0.3)	2 (0.9)	4 (0.4)
5x ULN	1 (0.1)	0 (0.0)	1 (0.1)
AST			
1x ULN	32 (4.6)	17 (7.6)	49 (5.4)
2x ULN	5 (0.7)	3 (1.3)	8 (0.9)
3x ULN	3 (0.4)	1 (0.4)	4 (0.4)
5x ULN	1 (0.1)	0 (0.0)	1 (0.1)
Alkaline phosphatase			
1x ULN	27 (3.9)	15 (6.7)	42 (4.6)
2x ULN	2 (0.3)	1 (0.4)	3 (0.3)
3x ULN	1 (0.1)	0 (0.0)	1 (0.1)
5x ULN	0 (0.0)	0 (0.0)	0 (0.0)
GGT			
1x ULN	122 (17.6)	68 (30.5)	190 (20.8)
2x ULN	32 (4.6)	21 (9.4)	53 (5.8)
3x ULN	13 (1.9)	7 (3.1)	20 (2.2)
5x ULN	6 (0.9)	4 (1.8)	10 (1.1)
Total bilirubin			
1x ULN	19 (2.7)	5 (2.2)	24 (2.6)
2x ULN	0 (0.0)	1 (0.4)	1 (0.1)
3x ULN	0 (0.0)	0 (0.0)	0 (0.0)
5x ULN	0 (0.0)	0 (0.0)	0 (0.0)

Source: VOSG-PN-309 (CTD 5.3.5.2.1) Post-text Table 10.7

Source: Post-Text Table 10.7, page 107 (ISS)

CONCLUSIONS ON ELEVATED LFTs

The proportion of subjects in the controlled studies with elevated ALTs was of equal proportions in the active and the controlled arms. Elevated ALT's resolved while on therapy, without discontinuing study medications. None of the reported cases exhibited concomitant elevation of serum bilirubin, clinical jaundice, or liver failure.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

The adverse events were recorded by the investigator, on a case report form (CRF). Patients also reported events in a patient diary, which was included in the overall assessment of adverse events. Daily diaries were maintained by study subjects and they were asked to record any unusual events that they felt may be related to use of study medication. At each visit, the investigator asked an open-ended question about any adverse events. At each clinic visit, the site of skin application of gel was inspected, and any abnormality was graded by the investigator according to severity of skin reaction, and recorded on the CRF.

No explicit instructions were provided to investigators regarding the severity grading of adverse events and it was left to the investigator's clinical judgment to assign a grade. The applicant states that grade assignment served primarily as a check to enable the field monitors to determine if an adverse event had worsened and if so, it needed to be recorded as a separate event.

The lack of collection of AE severity data according to a standardized system and limits the ability to determine whether most AEs were mild, moderate or severe in intensity.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were coded using modified MedDRA 9.1 system for the major safety population. The appropriateness of the Applicant's coding was assessed by comparing the preferred to the verbatim terms as listed in the ISS AE data set. The assessment focused on the events that led to discontinuation of study participation. The Applicant's coding was found to be reasonably accurate.

7.1.5.3 Incidence of common adverse events

7.1.5.4 Common adverse event tables

Common AEs in the controlled Phase 3 trials

Table 7.1.5.4.1 shows the most frequently observed AE's in the 8-12 week controlled studies by treatment group. The events are in descending order, based on the overall rate observed for all DSG treated subjects. The incidences are by-patient rates for each event. The majority of AE's appeared to be unrelated to the study treatment.

Based on data from the controlled phase 3 trials, the most common adverse events in order of decreasing frequency were as follows:

- headache (17.6%)
- arthralgia (13.9%)
- back pain (11.7%)
- application site dermatitis (10.5%)

The vast majority of AE's occurred with approximately equal frequency in DSG and control arms and is considered to be incidental in nature. Of these, arthralgia and application site dermatitis were more frequent in DSG-treated patients compared to vehicle-treated patients, (7.0% vs 5.95% for arthralgia, and application site dermatitis 3.4% vs 0.77%).

The incidence of application site dermatitis is discussed in Section 7.1.3.3.

The following table 7.1.5.4.1 shows the most frequently occurring AEs (> 1%) in the major safety population. The data are in descending order of the overall rate observed for the DSG-treated subjects. The incidences are by-patient rates for each event (a patient could not be counted twice for the same event). The large majority of the AEs appeared to be incidental to the study treatment.

TABLE 7.1.5.4.1: SHOWING MOST FREQUENT AE'S OCCURRING IN 1% OR MORE OF SUBJECTS IN ANY TREATMENT GROUP FOR THE MAJOR SAFETY POPULATION

		Knee		Hand		Overall	
		DSG	Vehicle	DSG	Vehicle	DSG	Vehicle
	Number studied	513	493	400	383	913	876
	Number of subjects with any AE(s) - n (%)	292 (56.9)	248 (50.3)	163 (40.8)	139 (36.3)	455 (49.8)	387 (44.2)
	Total number of AEs	632	519	299	224	931	743
SOC	**MedDRA Preferred Term - n (%)**						
Nerv	Headache	78 (15.2)	76 (15.4)	36 (9.0)	38 (9.9)	114 (12.5)	114 (13.0)
Musc	Arthralgia	52 (10.1)	36 (7.3)	12 (3.0)	16 (4.2)	64 (7.0)	52 (5.9)
Musc	Back pain	41 (8.0)	35 (7.1)	17 (4.3)	19 (5.0)	58 (6.4)	54 (6.2)
Infec	Nasopharyngitis	25 (4.9)	20 (4.1)	8 (2.0)	13 (3.4)	33 (3.6)	33 (3.8)
Genrl	Application site dermatitis	25 (4.9)	4 (0.8)	6 (1.5)	2 (0.5)	31 (3.4)	6 (0.7)
Musc	Pain in extremity	23 (4.5)	18 (3.7)	8 (2.0)	7 (1.8)	31 (3.4)	25 (2.9)
Infec	Upper respiratory tract infection	20 (3.9)	23 (4.7)	4 (1.0)	1 (0.3)	24 (2.6)	24 (2.7)
Infec	Sinusitis	15 (2.9)	17 (3.4)	6 (1.5)	2 (0.5)	21 (2.3)	19 (2.2)
Genrl	Pain	15 (2.9)	13 (2.6)	3 (0.8)	3 (0.8)	18 (2.0)	16 (1.8)
Musc	Neck pain	8 (1.6)	4 (0.8)	8 (2.0)	1 (0.3)	16 (1.8)	5 (0.6)
Musc	Myalgia	12 (2.3)	9 (1.8)	1 (0.3)	2 (0.5)	13 (1.4)	11 (1.3)
Infec	Influenza	9 (1.8)	13 (2.6)	2 (0.5)	1 (0.3)	11 (1.2)	14 (1.6)
Resp	Pharyngolaryngeal pain	6 (1.2)	4 (0.8)	5 (1.3)		11 (1.2)	4 (0.5)
Gastr	Toothache	9 (1.8)	4 (0.8)	2 (0.5)	7 (1.8)	11 (1.2)	11 (1.3)
Inj&P	Joint sprain	7 (1.4)	6 (1.2)	3 (0.8)	2 (0.5)	10 (1.1)	8 (0.9)
Resp	Sinus congestion	9 (1.8)	1 (0.2)	1 (0.3)		10 (1.1)	1 (0.1)
Nerv	Sinus headache	8 (1.6)	2 (0.4)	2 (0.5)		10 (1.1)	2 (0.2)
Gastr	Diarrhea	4 (0.8)	5 (1.0)	5 (1.3)	5 (1.3)	9 (1.0)	10 (1.1)
Inj&P	Contusion	8 (1.6)	3 (0.6)		2 (0.5)	8 (0.9)	5 (0.6)
Resp	Cough	2 (0.4)	12 (2.4)	6 (1.5)	2 (0.5)	8 (0.9)	14 (1.6)
Infec	Bronchitis	6 (1.2)	8 (1.6)	1 (0.3)		7 (0.8)	8 (0.9)
Vasc	Hypertension	6 (1.2)	5 (1.0)	1 (0.3)	2 (0.5)	7 (0.8)	7 (0.8)
Genrl	Application site erythema	5 (1.0)	3 (0.6)	1 (0.3)		6 (0.7)	3 (0.3)
Inj&P	Muscle strain	5 (1.0)	3 (0.6)	1 (0.3)		6 (0.7)	3 (0.3)
Skin	Pruritus	5 (1.0)	2 (0.4)	1 (0.3)	1 (0.3)	6 (0.7)	3 (0.3)
Gastr	Abdominal pain upper	1 (0.2)		4 (1.0)	2 (0.5)	5 (0.5)	2 (0.2)
Genrl	Application site paraesthesia			5 (1.3)	3 (0.8)	5 (0.5)	3 (0.3)
Inj&P	Back injury	3 (0.6)	5 (1.0)	1 (0.3)	2 (0.5)	4 (0.4)	7 (0.8)
Musc	Joint swelling	3 (0.6)	7 (1.4)			3 (0.3)	7 (0.8)
Genrl	Pyrexia	2 (0.4)	5 (1.0)			2 (0.2)	5 (0.6)
Infec	Gastroenteritis				4 (1.0)	0 (0.0)	4 (0.5)

Source: ISS, page 53

The subjects with hand OA had lower overall rates of AEs compared to those with knee OA. This might be attributable to the duration of exposure or observation since the hand OA studies were of 8 weeks duration and the knee OA studies were of 12 weeks duration.

Although the absolute frequencies are small, four other events had higher relative frequencies in the DSG group than in the vehicle-treated subjects.
They were: Neck pain (1.8%, 16/913 versus 0.6%, 5/876),
Pharyngolaryngeal pain (1.2%, 11/913 versus 0.5%, 4/876),
Sinus congestion (1.1%, 10/913 versus 0.1%, 1/876)
Sinus headache (1.1%, 10/913 versus 0.2%, 2/876).

Among the 10 most frequently reported AEs, all 10 had higher reporting rates in the population treating both knees. This may be attributable to a longer average duration of observation and exposure for the population treating both knees compared to the subjects treating one knee (213.3 days versus 160.4 days). Similarly, the average total exposure was greater in the subjects treating both knees compared to those treating one knee (761.1 total doses versus 588.0 total doses).

Apart from these events, the data showed comparable incidence rates across treatments and did not indicate any event clustering.

COMMON ADVERSE EVENTS OCCURRING IN LONG TERM SAFETY POPULATION IN STUDY -309

In the uncontrolled Study -309, subjects had a mean drug exposure of 235 days compared to the subjects in the controlled trials who had 8 weeks (hand OA) and 12 weeks (knee OA) of drug exposure.

Of the 947 subjects treated in the safety trial, 67.8% experienced at least one treatment-emergent AE. The most common treatment-emergent AE was headache, which occurred in 17.6% of the total population, 16.6% of the one-knee population, and 21.1% of the two-knee population. Other common treatment-emergent AEs were arthralgia (13.9%), back pain (11.7%) and application site dermatitis (10.5%). Application site dermatitis was reported in a larger proportion of subjects in the two-knee population (14.9%) than in the one-knee population (9.0%).

Table 7.1.5.4.2 provides a summary of the most frequently occurring AEs in the entire treated population. The only gastrointestinal AE among the most frequently occurring AEs (frequency $\geq$ 2%) was toothache (2.3%).

The proportion of the all treated subject population who experienced at least one treatment-emergent AE was larger in the two-knee population (75.0%) than in the one-knee population (65.5%).

TABLE 7.1.5.4.2: SHOWING NUMBER (%) OF SUBJECTS WITH MOST FREQUENT AE's (>2% IN TOTAL ONE KNEE OR TWO KNEES) IN UNCONTROLLED SAFETY STUDY-309

	Total N = 947 n (%)	One Knee N = 719 n (%)	Two Knees N = 228 n (%)
Any AE	642 (67.8)	471 (65.5)	171 (75.0)
Headache	167 (17.6)	119 (16.6)	48 (21.1)
Arthralgia	132 (13.9)	99 (13.8)	33 (14.5)
Back pain	111 (11.7)	76 (10.6)	35 (15.4)
Application site dermatitis	99 (10.5)	65 (9.0)	34 (14.9)
Nasopharyngitis	67 (7.1)	44 (6.1)	23 (10.1)
Pain in extremity	59 (6.2)	38 (5.3)	21 (9.2)
Upper respiratory tract infection	54 (5.7)	36 (5.0)	18 (7.9)
Pain	35 (3.7)	26 (3.6)	9 (3.9)
Sinusitis	35 (3.7)	26 (3.6)	9 (3.9)
Influenza	34 (3.6)	21 (2.9)	13 (5.7)
Myalgia	26 (2.7)	22 (3.1)	4 (1.8)
Neck pain	23 (2.4)	15 (2.1)	8 (3.5)
Toothache	22 (2.3)	15 (2.1)	7 (3.1)
Bronchitis	20 (2.1)	13 (1.8)	7 (3.1)
Contusion	19 (2.0)	18 (2.5)	1 (0.4)
Sinus congestion	19 (2.0)	15 (2.1)	4 (1.8)
Rash	19 (2.0)	12 (1.7)	7 (3.1)
Pharyngolaryngeal pain	18 (1.9)	12 (1.7)	6 (2.6)
Pyrexia	13 (1.4)	6 (0.8)	7 (3.1)
Cough	12 (1.3)	6 (0.8)	6 (2.6)
Post-procedural pain	11 (1.2)	5 (0.7)	6 (2.6)
Alanine aminotransferase (ALT) increased	9 (1.0)	4 (0.6)	5 (2.2)

Source: Post-text Table 10.1, Listing 10.2, Appendix 7

However, because subjects were not randomized to the one-knee or two-knee groups, and because the trial was open-label and uncontrolled, it cannot be concluded the increased AE rate in the 2 knee group is due to the greater drug exposure. The population suffering from pain in both knees might be disposed differently to experience AE's over the course of the study, for reasons unrelated to the amount of study drug applied.

Comparison of AE's incidence rates across trials: Comparison of AE incidence rates open label safety results with incidence rates in controlled Phase 3 trials

For the most frequent AEs, incidence rates in Study-309 were typically 2-3 times the incidence in DSG-treated subjects or in vehicle-treated subjects each pooled over the

controlled major safety studies.

This finding may be attributable to the much longer duration of exposure in the current study. Furthermore, 144 subjects treated with DSG in the double-blind knee OA studies continued into VOSG-PN-309 and all of the AEs they experienced in the double-blind studies appear in both in the "VOSG-PN-309" column and the "All studies - DSG" column of Table 7.1.5.4.3 shown below.

The absolute frequencies for a given AE were generally higher in Study -309, reflecting the fact that the uncontrolled study was longer than the other studies. Also, application site disorders tended to be more frequent in the DSG-treated subjects as compared to those treated with vehicle. However, the ordering of AE's by frequency of AEs associated with DSG 1% differed only minimally between DSG-treated subjects in the shorter double-blind studies and the long-term study VOSG-PN-309.

TABLE 7.1.5.4.3: SHOWING NUMBER AND PERCENTAGE (%) OF SUBJECTS WITH MOST FREQUENT AE'S VS COMPILED AE FREQUENCIES FROM DSG 1% - AND VEHICLE –TREATED PATIENTS IN THE CONTROLLED OA STUDIES - IN DESCENDING ORDER OF FREQUENCY

	Study VOSG-PN-309 DSG N = 947 n (%)	All double-blind studies DSG N = 913 n (%)	All double-blind studies Vehicle N = 876 n (%)
Any AE	642 (67.8)	454 (49.7)	387 (44.2)
Headache	167 (17.6)	114 (12.5)	114 (13.0)
Arthralgia	132 (13.9)	64 (7.0)	52 (5.9)
Back pain	111 (11.7)	58 (6.4)	54 (6.2)
Application site dermatitis	99 (10.5)	31 (3.4)	6 (0.7)
Nasopharyngitis	67 (7.1)	33 (3.6)	33 (3.8)
Pain in extremity	59 (6.2)	31 (3.4)	25 (2.9)
Upper respiratory tract infection	54 (5.7)	24 (2.6)	24 (2.7)
Pain	35 (3.7)	17 (1.9)	16 (1.8)
Sinusitis	35 (3.7)	21 (2.3)	19 (2.2)
Influenza	34 (3.6)	11 (1.2)	14 (1.6)
Myalgia	26 (2.7)	13 (1.4)	11 (1.3)
Neck pain	23 (2.4)	16 (1.8)	5 (0.6)
Toothache	22 (2.3)	11 (1.2)	11 (1.3)
Bronchitis	20 (2.1)	7 (0.8)	8 (0.9)
Contusion	19 (2.0)	8 (0.9)	5 (0.6)
Sinus congestion	19 (2.0)	10 (1.1)	1 (0.1)
Rash	19 (2.0)	7 (0.8)	5 (0.6)

Source: [VOSG-PN-309 Post-text Table 10.1], [VOSG-PN-304 Post-text Table 10.1], [VOSG-PN-310 Post-text Table 10.1], [VOSG-PE-314 Post-text Table 10.1], [VOSG-PE-315 Post-text Table 10.1]

7.1.5.5 Identifying common and drug-related adverse events

In order to more precisely enumerate the skin-related AE's which occurred with the use of topical DSG, the skin-related AE's were consolidated from the two SOC's, namely General disorders/administration site conditions and skin and subcutaneous tissue disorders).

Overall, the DSG subjects had a reported rate of skin-related AE's of 10.1% compared to 3.8% for the vehicle-treated subjects. Application site dermatitis was the single AE with the highest overall reporting rate for both treatment groups (DSG 3.4% versus Vehicle 0.7%).

There was a consistent difference in the proportion of subjects reporting *any skin AE*, *application site dermatitis* and *application site erythema*, between active drug and control vehicle arm in the pooled major safety population. These proportions were statistically significant.

In the long term safety population (Study -309), the frequency of *all skin AE's* in the population applying DSG 1% to one knee was 108/719 (15%), while the frequency of *all skin AE's* applying DSG 1% to both knees was 75%.

Dermal related adverse events are discussed in greater detail in Section 7.1.3.3 (Special Assessment Section).

7.1.5.6 Additional analyses and explorations

None performed

7.1.6 Less Common Adverse Events

DSG 1% as with all non-steroidal anti-inflammatory drugs (NSAIDs) poses serious cardiovascular and gastrointestinal risks. These risks are described in a boxed warning of the product label for oral diclofenac.

Cardiovascular Risk
NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction and stroke which can be fatal. This risk may increase with duration of use. Use is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft surgery.

Gastrointestinal Risk
NSAIDs cause an increased risk of serious gastrointestinal adverse events including

bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

Other known effects of NSAIDS include fluid retention, edema, renal toxicity, hepatic enzyme elevation and bronchospasm in patients with aspirin-sensitive asthma.

The systemic risks associated with oral diclofenac are thought to be less likely to occur in patients using DSG 1% since plasma concentrations are negligible (6%) compared to orally administered agent.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

This Reviewer evaluated the baseline and the latest post baseline laboratory parameters:
1) Hematology- hemoglobin, hematocrit, RBC count, WBC count and differential, platelet count.
2) Clinical chemistry- fasting glucose, serum creatinine, BUN, electrolytes, total protein, albumin, calcium and phosphate and uric acid.
In general, the mean values for the various baseline and post baseline clinical chemistry and hematology determinations for the controlled Phase 3 studies and the long-term safety population do not suggest any significant systematic shift in values during the course of the studies.

3) LFT's (LDH, ALT, AST, alkaline phosphatase, GGT, and total bilirubin).
The frequencies of abnormal LFT results were similar across the studies and between the treatments. There is nothing in the data to suggest a consistent significant effect on LFT results attributable to topical therapy with DSG in the controlled trials. In particular, the frequency of GGT elevations was similar in the two treatment groups.

In the long-term safety study (Study-309), the frequencies of abnormal results 1x ULN were approximately 30% higher than those observed in the Phase 3 controlled trials which had a time of exposure and observation that was 8-12 weeks compared to the 3 to 12 month period of exposure and observation in the long-term safety study.

The cause for the low frequency of higher multiples for the various LFTs is uncertain but it should be noted that the rescue medication was acetaminophen and its use has been associated with transient elevations in LFTs.

Further details on the evaluation of subjects with elevated transaminase levels are to be found in Section 7.1.3.3, "other significant adverse events."

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were obtained at baseline and at the final study visit for all subjects who completed the study in which they participated. Across the controlled studies, there was no significant difference between groups in baseline and end of study vital sign values.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Vital sign data for each of the clinical studies comprising the pooled Phase 3 trials and long-term safety populations were examined.

In the pooled Phase 3 trials mean systolic BP of subjects assigned to DSG group at baseline was 128.4 +/- 14.4 mm Hg and 128 +/- 15 mm Hg post study, while similar measurements in the subjects assigned to vehicle arm was 128.2 +/- 14.5 mm Hg and 127.4 +/- 14.6 mm Hg at baseline and post baseline respectively for the knee OA study. No changes in mean diastolic blood pressure values or pulse measurements were observed for diastolic blood pressure and pulse measurements in the hand OA studies. Similarly, no differences in mean baseline systolic or diastolic blood pressure or pulse measurements were observed in the hand OA studies.

In the long term safety studies, comparisons of the mean baseline and post-study vital sign data revealed no important differences between the groups.

Overall, there were no clinically important differences in the mean systolic or diastolic blood pressure or heart rate between baseline and post-treatment study values for either treatment group or overall.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECG's were obtained only at screening in clinical pharmacology study VOSG-PN-107 because the study had an exercise component in one of the treatment arms. Follow-up ECG's were not obtained in the study.

No other ECGs were obtained in the Phase 3 clinical studies conducted in support of this application.

Refer to NDA 19-201 (Voltaren tablets) and current the current product labeling for

Voltaren® for additional information on vital sign and ECG findings in patients administered diclofenac.

7.1.10 Immunogenicity

Not applicable.

7.1.11 Human Carcinogenicity

Oral administration carcinogenic studies were performed for Voltaren (NDA 19-201) which was approved in 1988 and dermal administration carcinogenicity studies for Solaraze (NDA 21-005) which was approved in the year 2000.

Please refer to the report of Dr Lawrence Leschin's report for further details on the pharmacology toxicology review of this product.

7.1.12 Special Safety Studies

A summary of 3 special dermal safety trials were performed to evaluate the potential of DSG gel for cumulative skin irritation, sensitization, and phototoxicity and is presented in Tables 7.1.12.1 to 7.1.12.3 shown below.

The cumulative skin irritation potential of DSG 1%, was studied using the Lanman method (Lanman et al., 1968). The study was an evaluator-blind, randomized, single-center trial which used 15 occlusive applications of the same 4 treatments to all participating subjects. The treatment groups were as follows:

- DSG, 1% - 200 µL/application
- Gel (vehicle) -200 µL/application
- Sodium lauryl sulfate (SLS) 200 µL/application.
- Blank patch (negative control)

Treatments were applied to assigned patch sites on each subject's back in accordance with a randomization schedule supplied by the Sponsor. There were 15 consecutive patch applications with subsequent removal and evaluation over 21 days. Irritation was assessed 24 hours after each weekday patch application except for Friday when the patch was removed and irritation was evaluated on the following Monday, 72 hours after application.

Enrolled subjects were to be healthy males or females. A total of 42 subjects were enrolled and 36 completed all aspects of the study. Reactions to the test products and effects on superficial layers of the skin were scored on a scale from 0 (no evidence of irritation) to 7 (strong reaction spreading beyond test site) with annotations for superficial effects that included glazing, fissures, exudates, and petechial erosions. Patch applications were terminated if a score of 3 or greater was observed, or at the discretion of the Investigator. Overall safety was assessed by monitoring any treatment emergent AEs.

A total of 42 subjects were randomized and all received treatment. Six subjects

discontinued the study prematurely: 3 withdrew consent, 1 was lost to follow-up, 1 missed an evaluation visit and 1 was withdrawn at the Investigator's discretion following severe tape reaction. Thirty-six (36) subjects completed all aspects of the study and represent the population whose results are presented in the following paragraphs. A second population was composed of all 42 subjects and was the population evaluated for safety. In the final study report, all the irritation analyses were performed on both populations and no important differences in the outcomes were observed between them.

The demographic characteristics of the 36 subjects who completed all aspects of the study were as follows. Their mean age was 44 years (range: 28-66); the sex distribution was 14% (5/36) male and 86% (31/36) female. With respect to ethnicity, 58% were White, 17% were Black and 25% (9/36) were Other.

The results of the trial are shown in the table below:

TABLE 7.1.12.1: SHOWING SCHEMATIC TABLE OF STUDY VOSG-PN-108 with RESULTS

STUDY Country	STUDY DESIGN STUDY POPULATION ENDPOINTS	TOTAL # STUDIED AGE RANGE (MEAN) GENDER (M:F)	DOSAGE Rx DURATION	RESULTS
VOSG-PN-108 **Cumulative, irritation potential (Lanman Method)**	Evaluator blinded, Randomized, Multiple application - DSG 1% - Sodium lauryl sulfate (SLS) - blank patch	36 subjects completed. Range 28-66 years 14% (M) 86% (F)	200 µg per application x 15 consec. applications x 24 hours; 72 hours on w/e	Cumulative irritation effect of DSG 1% was minimal when compared to that of the positive irritant control, and only slightly higher than that of the blank patch.
USA	Healthy volunteers -Irritation score -Mean irritation score - Cumulative irrit score -freq indices -time irritation score		21days	

Source: FDA compilation from information supplied by applicant

Conclusion on Study VOSG-PE-108: the study revealed that the cumulative irritation effect of DSG, 1%, applied occlusively on the skin over 21 days, as assessed by irritation rate, mean irritation score, cumulative irritation score, frequency indices and time to irritation

was reported by the sponsor as showing being minimal when compared to that of SLS (positive irritant control) and only slightly higher than that of the blank patch (negative control). Independent review by FDA's Dermatology Consultation confirmed this conclusion.

Study VOSG-PN-111 was a study of the potential of DSG, 1% to cause cutaneous sensitization by repeated occlusive topical application to the skin of healthy volunteers. A secondary objective was to evaluate the potential of the drug to cause cutaneous irritation under the test conditions. The study was an evaluator-blind, randomized, two-center trial (repeated insult patch test) which used 9 applications of the same 3 test materials over 3 weeks in 260 healthy volunteer subjects. (See Table 7.1.12.2)

The treatments were: DSG, 1% (200 µL/application)
Gel (vehicle) (200 µL/application)
Blank patch (negative irritant control)

Treatments were applied to assigned patch sites on each subject's back in accordance with a randomization schedule supplied by the Sponsor. All 3 test materials were applied at each visit. There were 3 visits per week for 3 weeks (9 applications) with patch removal, evaluation and reapplication at each visit subsequent to the first and without reapplication at the final visit (Days 1-22). Following a rest period (Days 23-35), a challenge patch was applied on Day 36 and evaluations for sensitization were made at 48, 72 and 96 hours (Days 36-40). A re-challenge was scheduled if any challenge resulted in a "+" grade at any site at 72 or 96 hours. Irritation was assessed after each patch removal during the treatment phase of the study.

Enrolled subjects were to have been healthy males or females, 18 to 50 years of age.

During the challenge phase (sensitization potential evaluation), one subject demonstrated a possible positive response that required a rechallenge. This subject exhibited erythema and edema (+) for the vehicle gel at the time of the 48 hour challenge evaluation.

TABLE 7.1.12.2: SHOWING SCHEMATIC TABLE OF STUDY VOSG-PN-111

STUDY Country	STUDY DESIGN STUDY POPULATION ENDPOINTS	TOTAL # STUDIED AGE RANGE (MEAN) GENDER (M/F)	DOSAGE DURATION	RESULTS
VOSG-PN-111 **- Sensitizing potential** **- Cutaneous irritation potential**	Evaluator blinded, randomized, multiple applications -DSG 1% - Vehicle Healthy volunteers Sensitization potential with ICDRG scale @- 48 hours - 72 hours - 96 hours Irritation potential during the induction phase	233 44(M) 189 (F)	9 x 200 µL per application 3 weeks	DSG 1% said comparable to that of vehicle. Evidence of weak sensitization potential in one subject. The conditions of the repeated insult patch test exaggerates the conditions of normal use

Source: FDA compilation from information supplied by applicant

The results of the trial are shown in the table above.

Conclusion on Study VOSG-PN-111 revealed that DSG 1% exhibited a weak sensitization potential.

Study VOSG-PE-112 was conducted to assess the photo-toxicity potential of DSG, 1%, following a single application and ultraviolet light exposure in 30 healthy male and female volunteers. The trial was a single-center, single-application, randomized, double-blind, within-subject comparison study of active and vehicle vs. blank controls (area treated but not irradiated and area not treated but irradiated) in 35 healthy male and female volunteers.

Following determination of individual minimal erythema dose (MED), three sets of 3 areas were delineated on the skin of the subjects' backs. For each set, one area was treated with DSG, 1% (200 µL), another one with vehicle gel (200 µL), and the third remained untreated. A pre-established randomization table determined the order of the treatments. All drugs were directly applied into Finn Chambers that were fixed on the skin with medical paper tape (empty Finn Chambers were used for untreated control areas).

After 24 hours, the Finn chambers were removed and two of the three sets of applications were irradiated: one with 20 J/cm2 UV A (320-400 nm) and the second with 0.75 MED UV B (280-320 nm) and the third set was not irradiated. Cutaneous readings by two independent assessors were performed before the treatment application, 15-30 min after Finn chamber removal and at 10 min, 24 h and 48 h after UV exposure.

An erythema reaction score (ERS) was assigned based on the following scale: 0 = no erythema, 0.5 = barely visible, 1 = mild, 2 = moderate, 3 = severe. Any ERS score of greater than zero was considered to reflect an erythema reaction.

The results of the trial are shown in the table that follows.

Conclusion VOSG-PE-112 demonstrated the absence of clinically relevant photo-toxicity potential of DSG 1% in healthy volunteers after a single dose applied for 24 hours (under occlusion and followed by single UVA or UVB irradiation.

TABLE 7.1.12.3: SHOWING SCHEMATIC TABLE OF STUDY VOSG-PN-112 with RESULTS

STUDY	STUDY DESIGN	TOTAL # STUDIED	DOSAGE	RESULTS
Country	STUDY POPULATION	AGE RANGE (MEAN)		
	ENDPOINTS	GENDER (M/F)	R. DURATION	
VOSG-PE-112 **UVA and UVB phototoxicity**	Single application, randomized, double blind, within subject evaluation - DSG 1% - vehicle gel - Blank patch	35 healthy volunteers 6% (M) 94% (F)	3 x 200 µL 24 hour application x 1 day	No evidence clinical relevant phototoxic potential of DSG 1% gel.
UK	Healthy volunteers	38.9 +/- 10.3 years		
	Cutaneous reading by 2 independent assessors @ - 10 mins - 24 hours - 48 hours after UV exposure			

Source: FDA compilation from information supplied by applicant

Overall, all three Dermal Safety Studies did not identify a potential to produce irritation, sensitization or photo-toxicity.

Dermatology Consultation concluded that under conditions of the dermal safety studies, clinically significant potential for irritation, sensitization or phototoxicity were not identified. However, they recommended that labeling should reflect that adequate precautions should be taken to minimize sunlight exposure while using this product.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Specific clinical trials or systematic analyses evaluating the potential withdrawal and rebound effects of DSG 1% have not been conducted.

However, post hoc assessment of withdrawal emergent signs and symptoms showed that the overall safety/tolerability profile of DSG 1% was not negatively impacted by interruption or discontinuation of treatment.

7.1.14 Human Reproduction and Pregnancy Data

Not performed for this topical reformulation of diclofenac.

7.1.15 Assessment of Effect on Growth

Not performed for this topical reformulation of diclofenac.

7.1.16 Overdose Experience

There has been no experience of overdose with DSG 1%.

The systemic exposure from topical DSG is less than 6% of the comparable oral dose (diclofenac sodium 50 mg TID) for one knee and less than 13% for the recommended maximum daily dose of 32 g over 800 cm^2 . Due to the low systemic absorption of topically applied DSG 1%, overdosage would appear to be unlikely. This topical product would require an application of drug at least 8 x higher than the recommended maximum dose of 32 g per day and surface to achieve the same plasma levels observed with standard oral doses of diclofenac.

Reference is made to NDA 19-201 (Voltaren® sodium tablets) and current product labeling for Voltaren® for additional background information on overdosage
No events of accidental ingestion have been reported with DSG. Effects similar to those observed after an overdose of diclofenac tablets can be expected if substantial amounts of DSG are ingested.

Symptoms following acute oral NSAID overdoses are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression, and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur after an overdose.

In the event of oral ingestion resulting in significant systemic side effects, it is recommended that the stomach be emptied by vomiting or lavage. Forced diuresis may theoretically be beneficial because the drug is excreted in the urine. The effect of dialysis or hemoperfusion in the elimination of diclofenac (99% protein-bound) remains unproven.

In addition to supportive measures, the use of oral activated charcoal may help to reduce the absorption of diclofenac. Supportive and symptomatic treatment should be given for complications such as renal failure, convulsions, gastrointestinal irritation, and respiratory depression.

7.1.17 Postmarketing Experience

DSG 1% has not been approved for marketing in any country. Novartis provided post marketing data for the European diclofenac DEA product. However, due to the differences in excipients and the presence of diethylamine in the DEA formulation, these data are not considered to be greatly relevant to the safety of DSG.

The Novartis Worldwide Safety Database was queried for all spontaneous and literature case reports related to diclofenac DEA gel since its launch in October 1985 through 30 April 2006. During this period, diclofenac DEA gel is estimated to have been used by over [redacted] patients. The search identified 1,423 cases with 2,711 associated AE terms. 232 cases (16.3%, 232/1,423) were considered serious. Seven cases of death were reported.

Table 10-6 summarizes the seven death cases of patients using diclofenac DEA gel. For all but one of these cases, use of other concomitant medication is documented. The use of concomitant medication confounds making a causative association between diclofenac DEA and the clinical conditions surrounding death.

Table 10-6 Spontaneous cases: Deaths

Case number (publication)	Year	Age, Sex	Cause of Death	Concomitant or historical condition	Concomitant medications
PHNU1988DE00259	—	78y M	Sudden death from pulmonary embolism before hospital discharge	Perforated ulcer after 3 days of treatment; History of varicose veins	Diclofenac oral and IM
PHNU1993DE01142	—	87y M	Toxic epidermal necrolysis (Lyell's syndrome), treatment duration unknown	Pruritus had begun a month prior, patient died on 6th day of hospitalization. Details sparse	Tenoxicam, oxaceprol, antihistamines, corticosteroids, Euphytose®
PHNU1995DE00183	—	81y F	Septic shock following Circulatory disorder with massive metabolic acidosis after fasciotomy for necrotizing fasciitis	Coronary artery disease and old myocardial infarction. Patient had fallen, was treated for 2 days with Diclofenac DEA gel for arm pain, developed necrotizing fasciitis	Not reported
PHRM2001FR02549	—	68y F	Death following convulsions, cardiac arrest (resolved), and coma with convulsive status	Advanced diabetes mellitus, renal failure (dialysis), hypothyroidism and heart failure. Treatment duration 8 days.	18 other medications. French Health Authorities considered causality as unlikely for all drugs.
PHFR2002GB00524	—	89y F	Renal failure one month after onset of treatment	Anemia	Aspirine, acetaminophen, dextropropoxy-phene
PHRM2003FR00575	—	93y F	Cardiorespiratory decompensation	Toxic epidermal necrolysis, after treatment for 28 days. Flu syndrome. History of acute/ subacute ischemic cardiomyopathy, angina pectoris, bronchitis	12 concomitant medications, including ketoprofen, acetylsalicylate and acetaminophen
PHNU2005DE03060	—	86y M	Pneumonia, 4 months after increased GGT	Increased GGT (400-600 U/l), no information on transaminases	Acetaminophen, oxaceprol, ramipril, insulin

Source: Novartis worldwide safety database to 30 April 2006

Source: ISS; page 150

Table 5-10 shown below shows reports of most frequent SAE's- Post Marketing safety

Table 5-10 Spontaneously reported cases: Most frequent SAEs (≥ 6 terms)

		Total AE terms: 2,711 (100%)	Total cases: 1,423 (100%)
SOC	MedDRA Preferred Term	n (% of terms)	n (% of cases)
Gastr	Gastrointestinal hemorrhage	16 (0.6)	16 (1.1)
Skin	Pruritus	16 (0.6)	16 (1.1)
Skin	Dermatitis bullous	14 (0.5)	14 (1.0)
Gastr	Melena	13 (0.5)	13 (0.9)
Skin	Erythema	12 (0.4)	12 (0.8)
Skin	Dermatitis contact	11 (0.4)	11 (0.8)
Immun	Hypersensitivity	10 (0.4)	10 (0.7)
Skin	Blister	10 (0.4)	10 (0.7)
Skin	Eczema	10 (0.4)	10 (0.7)
Gastr	Gastric ulcer	8 (0.3)	8 (0.6)
Skin	Purpura	8 (0.3)	8 (0.6)
Genrl	Drug interaction	7 (0.3)	7 (0.5)
Genrl	Edema peripheral	7 (0.3)	7 (0.5)
Renal	Renal failure acute	7 (0.3)	7 (0.5)
Skin	Angioneurotic edema	7 (0.3)	7 (0.5)
Skin	Toxic epidermal necrolysis	7 (0.3)	7 (0.5)
Blood	Anemia	6 (0.2)	6 (0.4)
Genrl	Pyrexia	6 (0.2)	6 (0.4)
Resp	Dyspnea	6 (0.2)	6 (0.4)
Skin	Photosensitivity reaction	6 (0.2)	6 (0.4)
Skin	Rash	6 (0.2)	6 (0.4)
Skin	Rash vesicular	6 (0.2)	6 (0.4)
Skin	Skin necrosis	6 (0.2)	6 (0.4)

The full text of the abbreviations follows the Table of Abbreviations at the beginning of this document. Percent basis is the total number of subjects in a category.

Source: ISS; Table 10-4; page 148

Five post marketing surveillance studies of diclorfenac DEA gel were conducted in 4 non-US countries in which a total of 30,566 patients with a variety of soft tissue inflammatory disorders, arthritis, spinal disorders, sports injuries, and musculoskeletal injuries participated. No SAEs or deaths were reported in these studies and diclofenac DEA gel.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

All reasonably applicable tests were conducted to assess the safety of DSG 1%. A detailed description of the safety analysis is discussed in Section 7 of this report.

The doses of diclofenac in DSG 1% that were used in the Phase 3 trials were equivalent to the doses used with the diclofenac DEA (European formulation). The dose of gel used in the hand OA and knee OA trials appeared to be efficacious in the population treated.

The 12 week duration of treatment in the knee OA controlled studies was also appropriate. The 8 week duration of exposure in the hand OA controlled studies although of shorter than

the optimal duration of exposure.

A total of 1860 patient with OA were exposed to DSG 1%. Additionally, the long term uncontrolled roll-over study provided a mean duration of exposure of 235 days. The number and duration of subject exposure far exceeded that which is required by the ICH.

The demographic and baseline characteristics of the patient population exposed to DSG 1%, were similar to those likely to be exposed to the drug in the non-clinical trial/real world setting.

All appropriate pre-clinical tests were observed in this submission, and via reference to the reference products in this 505(b) (2) application.

7.2.1.1 Study type and patient enumeration

Refer to the tables in Section 4.2

7.2.1.2 Demographics

A summary of the overall baseline demographics for the major safety population of patients is provided for each of the treatment groups in Table 7.2.1.2. These were patients with knee or hand OA, who received, respectively, 12 and 8 weeks of exposure to DSG in the 4 controlled trials comprising the major safety population.

Approximately 70% of the major safety population was female and 85% was Caucasian; 8% was Black and approximately 1% was Asian. With respect to individual studies and OA site, the treatment groups were generally well matched for demographic and disease characteristics at baseline.

A summary of the baseline disease characteristics was as follows:

- Tenderness on pressure
- X-Ray evaluations
  - joint space narrowing (occurred in 82 – 84 % subjects),
  - subchondral sclerosis (occurred in 33-39%)
  - osteophyte (occurred in 71-75%)
- Kellgren-Lawrence Grade
  - Mean Grade 2 is 2.2 or 2.1 in DSG and vehicle population respectively in Study PN-310 and 2.4 and 2.2 in DSG and vehicle respectively.

Other features that may have differed between treatments in the major population are not known and potential differences caused by geographical location or medical practice in certain countries or certain centers were not apparent except in Study VOSG-PE-314 (hand OA) which was the only trial conducted in Europe.
In VOSG-PE-314, the use of medication for the treatment of the subjects' OA at screening was less compared to the study population in VOSG-PE-315. Although not a baseline

characteristic, generally fewer AEs were reported in both the DSG-and vehicle-treatment groups in VOSG-PE-314 compared to VOSG-PE-315. The use of rescue medication was also lower in the European subjects compared to those in the US (52.1% versus 82.4%). These differences are not thought to have an important impact on the safety findings in the major population.

TABLE 7.2.1.2: SHOWING THE DEMOGRAPHIC CHARACTERISTICS OF THE POOLED PHASE 3 SAFETY POPULATION

	Knee studies		Hand studies		Overall total	
	DSG	Vehicle	DSG	Vehicle	DSG	Vehicle
Total subjects *	**N = 513**	**N = 493**	**N = 400**	**N = 383**	**N = 913**	**N = 876**
Sex - n (%)						
Female	335 (65.3)	312 (63.3)	317 (79.3)	311 (81.2)	652 (71.4)	623 (71.1)
Male	178 (34.7)	181 (36.7)	83 (20.8)	72 (18.8)	261 (28.6)	253 (28.9)
Race - n (%)						
Caucasian	407 (79.3)	402 (81.5)	372 (93.0)	361 (94.3)	779 (85.3)	763 (87.1)
Black	66 (12.9)	58 (11.8)	12 (3.0)	7 (1.8)	78 (8.5)	65 (7.4)
Other	33 (6.4)	29 (5.9)	11 (2.8)	13 (3.4)	44 (4.8)	42 (4.8)
Asian	7 (1.4)	4 (0.8)	5 (1.3)	2 (0.5)	12 (1.3)	6 (0.7)
Age (yr) - n (%)						
≤ 40	14 (2.7)	11 (2.2)	3 (0.8)	2 (0.5)	17 (1.9)	13 (1.5)
> 40 - 50	66 (12.9)	68 (13.8)	32 (8.0)	29 (7.6)	98 (10.7)	97 (11.1)
> 50 - 60	160 (31.2)	159 (32.3)	121 (30.3)	111 (29.0)	281 (30.8)	270 (30.8)
> 60 - 70	180 (35.1)	156 (31.6)	138 (34.5)	134 (35.0)	318 (34.8)	290 (33.1)
> 70 - 80	85 (16.6)	87 (17.6)	86 (21.5)	90 (23.5)	171 (18.7)	177 (20.2)
> 80	8 (1.6)	12 (2.4)	20 (5.0)	17 (4.4)	28 (3.1)	29 (3.3)
N	513	493	400	383	913	876
Mean ± SD	61.0 ± 10.1	61.1 ± 10.5	63.8 ± 10.0	64.1 ± 9.7	62.2 ± 10.1	62.4 ± 1.02
Range	25-90	35-92	40-92	40-87	25-92	35-92
Height (cm)						
N	510	490	398	383	908	873
Mean ± SD	167.9 ± 10.4	168.3 ± 10.9	164.6 ± 9.5	164.5 ± 8.9	166.5 ± 10.1	166.6 ± 10.3
Range	132 - 198	123 - 198	132 - 193	132 - 193	132-198	123-198
Weight (kg)						
N	507	489	400	382	907	871
Mean ± SD	88.5 ± 20.4	89.8 ± 20.0	74.6 ± 15.9	74.5 ± 17.3	82.3 ± 19.8	83.1 ± 20.3
Range	49.0 - 190.5	49.9 - 190.5	42.2 - 138.3	30.5 - 166.4	42.2-190.5	30.5-190.5
BMI (kg/m^2)						
N	507	489	398	382	905	871
Mean ± SD	31.3 ± 6.6	31.7 ± 6.7	27.5 ± 5.4	27.5 ± 5.6	29.6 ± 6.4	29.9 ± 6.6
Range	18.4 - 62.0	18.5 - 57.7	17.4 - 55.0	14.3 - 49.8	17.4 - 62.0	14.3 - 57.7

* Unless otherwise indicated, the number of subjects used to calculate the mean values is given at the top of the table as "N".
SD = standard deviation; BMI = body mass index

Source: Post-Text Table 7.6, ISS, page 34

7.2.1.3 Extent of exposure (dose/duration)

The overall extent of exposure to study medication in the target treatment population in the clinical trials undertaken for the DSG development program was 2223 subjects; 1347 subjects were treated with DSG and 876 were treated with vehicle.
These totals include all subjects from the controlled clinical trials as well as the long term uncontrolled safety trial. A total of 142 subjects originally treated with vehicle in Study - 304 and Study -310, rolled over into the long term safety study and were treated with DSG.

A total of 76 healthy volunteers were exposed to DSG in the course of the 2 clinical pharmacology trials.

TABLE 7.2.1.3: SHOWING THE OVERALL EXPOSURE FOR THE MAJOR SAFETY POPULATION

	KNEE STUDIES *		**HAND STUDIES ****		**COMBINED TOTAL**	
Total doses - n (%)	**DSG**	**VEHICLE**	**DSG**	**VEHICLE**	**DSG**	**VEHICLE**
<101	27 (5.5)	29 (6.3)	24 (6.1)	25 (6.6)	51 (5.8)	54 (6.4)
101-150	18 (3.7)	28 (6.1)	21(5.4)	22 (5.8)	39 (4.4)	50 (6.0)
151-200	18(3.7)	11 (2.4)	95 (24.2)	76 (20.2)	113 (12.8)	87 (10.4)
201-250	29 (5.9)	31 (6.7)	252 (64.3)	257 (67.6)	281 (31.9)	288 (34.3)
251-300	82 (16.8)	85(18.5)	-	-	82 (9.3)	85 (10.1)
> 300	315 (64.4)	276 (60.0)	-	-	315 (35.8)	276 (32.9)
N	**489**	**460**	**392**	**380**	**881**	**840**
MEAN	**286.4**	**279.7**	**196.0**	**194**	**246.1**	**240.9**
RANGE	**4- 411**	**1-386**	**16-483**	**1- 287**	**4-483**	**1-386**

*The duration of the knee OA studies was 12 weeks
**The duration of the hand OA studies was 8 weeks

In the ***placebo controlled trials***, 913 subjects were exposed to at least one application of DSG. Using the mean total doses and the total number of subjects, the total number of doses of DSG administered to the major safety population across all the trials and all the subjects was 216,814. For the vehicle, the total number of doses was 202,356. Considered overall, 881 subjects received an average of 246 doses of DSG in the 4 controlled trials.

In the ***long-term safety study- 309***, 947 subjects were exposed to topical DSG, including those actively treated patients from VOSG-PN-310 and VOSG-PN-304 who are included in the all treated population. Using the mean total doses and the number of subjects for the treatments, the total number of applied doses in VOSG-PN-309 is estimated to be 622,269. This count assumes two doses for each treatment of the subjects applying drug to both knees.

Analysis of the long term exposure study showed the following:
- 112 subjects were exposed to DSG for 6-9 months
- 150 subjects were exposed to DSG for 9-12 months
- 85 subjects were exposed for more than 12 months

The total number of applied doses in -309 is estimated to be 622,269. This counts two doses for each treatment of the subject applying drug to both knees.

The long term safety subjects had a mean drug exposure of 235 days compared to the subjects in the controlled trials with 8 weeks exposure in the hand OA study, and 12 weeks in the knee OA studies.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

There are no other sources of data for DSG 1%.

Novartis referred to the available safety data for the approved dosage forms of diclofenac sodium. The use of the parenteral diclofenac salt has been associated with toxic skin manifestations such as rashes, erythema multiforme, Stevens-Johnson syndrome and even Toxic Epidermal Necrolysis. (Refer to diclofenac label).

Novartis also provided information on the European formulation of topical diclofenac or diclofenac DEA. Although the active drug component of both the European formulation and the DSG formulation is diclofenac, these two formulations are different, in that the European formulation utilizes an excipient called diethylamine (DEA) which is not allowed by the FDA, as it is suspected to possess immunotoxicant, neurotoxicant, respiratory toxicant, and skin and/or sense organs toxicant properties.

Nevertheless, this source of data could provideimportant information for review, in that because of the larger data set, and the greater patient exposure with the DEA formulation, many of the less common and more serious adverse events become apparent. For example, in this application, examination of the DEA data revealed confounded cases of severe, life-threatening, dermal AEs, such as Stevens Johnson Syndrome and Toxic Epidermal Necrolysis, or even rare systemic effects, such interstitial nephritis, eosinphillia with pulmonary infiltrates and cases of gastrointestinal bleeding with diclofenac DEA. These less common AE's were not revealed in the DSG clinical trial population of less than 2000 subjects.

However, based on the fact that DSG 1% is systemically absorbed, and if DSG is approved in the USA, and if the number of patients exposed to DSG increases, there is the possibility of greater likelihood of the occurrence of the above described AEs.

7.2.2.1 Other studies

None.

7.2.2.2 Postmarketing experience

DSG 1% is not marketed in any country. The Applicant provided post-marketing data for diclofenac DEA gel to address, in part, the safety of DSG.

The topical gel formulation of the diethylamine salt of diclofenac DEA (Voltaren® Emulgel™) has been marketed for over 20 years in over 115 countries. In the majority of these countries the product is available over-the-counter (OTC). The sponsor estimates exposure for topical diclofenac DEA is over — patients. Present US regulations do not allow the marketing of the diethylamine salt of diclofenac, and hence the development of the DSG compound for the USA market.

The Table 7.2.2.2 shown below shows the results of 5 post marketing studies conducted outside the USA in a total of 30,566 patients with a variety of soft tissue inflammatory disorders, sports injuries and musculoskeletal injuries. In summary, a total of 641 (2.1%) patients reported AEs. There were an estimated 530 (1.7%) patients with local cutaneous reactions. Ninety-seven or (0.5%) patients discontinued from the studies because of AEs. Studies lasted 7 to 15 days, and subjects received a total of 2-4 gm qid. No SAEs or deaths were reported.

TABLE 7.2.2.2 SHOWING A SUMMARY OF POSTMARKETING SURVEILLANCE STUDIES CONDUCTED USING DICLOFENAC DEA GEL IN NON-US COUNTRIES

	Germany 1990	Germany 1987	Brazil 1990	India 1992	France 1995	TOTALS (%)
Total patients	13,113	6,101	8,957	349	2,046	30,566 (100%)
Dosing Duration of treatment	BID-QID 4-24 days	2-4 g TID/QID 14 days	2-4 g TID/QID 1-14 days	2-4 g QID 7 days	Unknown 7 days	
Total patients with AEs - n (%)	178 (1.4%)	147 (2.4%)	286 (3.2%)	19 (5.4%)	11 (0.53%)	641 (2.1%)[2]
Patients with local AEs - n (%)	164 (1.2%)[1]	141 (2.3%)	195 (2.2%)	19 (5.4%)	11 (0.53%)	530 (1.7%)
Patients with systemic AEs - n (%)	14 (0.11%)[3]	6 (0.098%)	91 (1.01%)	0 (0%)	0 (0%)	111 (0.36%)[3]
Patients withdrawn due to AEs - n (%)	48 (0.36%)	37 (0.61%)	unknown	11 (3.2%)	1 (0.049%)	97 (0.45%)[4]

[1]Since 221 of 240 AE reports were local cutaneous reactions, the fraction of patients reporting such events is approximated at 164/178 (or 92%)

[2]Approximated using the calculated value of 164 for Germany 1990

[3]Estimated using the calculated value of 14 for Germany 1990

[4]Calculated using denominator 21,609 after the exclusion of Brazilian population, for which information about study withdrawal was not provided.

Source: Investigators' Brochure, Diclofenac Sodium Gel, 1%, 24 May 2005, and original references.

Intensive monitoring project - Germany

Three reports of serious skin reactions that occurred in patients treated with diclofenac DEA were received from a non-Novartis project which intensively monitored serious skin reactions in German hospitals. Each reported Stevens-Johnson syndrome in a patients using diclofenac DEA, during the period from 1996 to 2000. In all cases, the patients were using a number of concomitant medications for other medical conditions, which confounded a causative association with DEA.

These three cases are summarized in the narrative noted below:

PHNU1997DE00163: A 76-year-old female patient with a past history of diabetes mellitus and bronchitis, was treated with several drugs for pain and myalgia. The patient developed first symptoms of Stevens-Johnson syndrome (with skin and mouth lesions), 3 days after discontinuation of (ibuprofen), Muskel Trancopal® (chlormezanon) and Voltaren® Emulgel™ (diclofenac DEA gel). Other concomitant medications included Maninil® (glibenclamide), Complamin® tablets, Venoplant® tablets, Cephoral® tablets and Bromhexin® syrup. Two days later plantar vesicles appeared and after three days patient was hospitalized due to erosions of the oral and genital mucosa. Outcome of this SAE is unknown.

PHNU1997DE00163: A 71-year-old female patient was treated for an attack of gout with diclofenac gel and allopurinol. Eighteen days later she developed maculae and typical lesions of Stevens Johnson syndrome. She was hospitalized 4 days later. Vesicles, conjunctivitis and erosions of oral mucosa occurred 5 days later. Concomitant medication consisted of Briserin (clopamid, reserpine) for hypertension. Megacillin® (phenoxymethylpenicillin) was started on the day of hospitalization because of suspected scarlet fever. Allopurinol and diclofenac gel were discontinued. The patient recovered completely.

PHNU2001DE02749: A 44 year-old male patient with history of malignant lymphoma, radiation therapy and atrial fibrillation was admitted to hospital for hypercalcaemia, weakness, hallucinations and slurred speech. Three days later he developed gastroenteritis with diarrhea and fever and within a few weeks, developed renal failure and sepsis, and then pneumonia and oral candidiasis. During these weeks he used diclofenac DEA gel for 2 days, for back pain. Erythema was noted about 8 days later. Generalized exanthema followed with mouth blisters and erosions, and by a month after admission, conjunctivitis and genital erosions appeared. Stevens Johnson syndrome was diagnosed. The patient died of multiorgan failure about 5 weeks after hospital admission. During the hospital admission the patient was treated with 42 different drugs. The reporter suspected a relationship between Stevens Johnson syndrome and 33 of these drugs. Other possible contributing factors included gastroenteritis, pneumonia, malignant lymphoma and hypercalcaemia.

The above three cases from Germany have demonstrated the occurrence of Stevens Johnson syndrome in association with the use of diclofenac DEA gel; all three cases were

confounded by the concomitant use of other medications which may have caused this exfoliating skin condition.

7.2.2.3 Literature

The Applicant conducted a search of the US National Library of Medicine database for citations related to topical diclofenac.

The search identified a total of 156 citations. The literature covered a wide range of formulations, including gels, patches and liquids. Topical diclofenac was used to treat a range of conditions including osteoarthritis, traumatic injuries associated with inflammation, solar keratoses and mastitis.

The predominant form of AE associated with the use of topical diclofenac was an application site reaction or dermatitis of varying severity; dermatitis generally resolved following withdrawal of the drug.

The incidence of the application site skin effects ranged from less than 3% to over 40%. [The 40% incidence of application site reactions was reported in association with Pennsaid, a formulation which included a substantial concentration of dimethyl sulphur oxide (DMSO)].

Other rarer more serious adverse events include interstitial nephritis, pulmonary infiltrates with eosinophilia and 5 case reports of gastrointestinal bleeding.

CONCLUSIONS FROM SECONDARY SOURCES OF SAFETY DATA:
The secondary sources of safety data primarily originates from the extensive experience from post marketing surveillance, intensive monitoring programs in Germany, and a worldwide literature search on the use of the DEA formulation of diclofenac in Europe and over 115 countries in other parts of the world. The sponsor estimates that over —— persons have been exposed to this agent.

The data obtained from the literature search was confounded by the varied forms and concentrations of active agent and the varying topical drug delivery systems eg gels, patches and liquids.

The various topical applications stated above were used to treat a variety of clinical conditions including solar keratoses, mastitis, traumatic soft tissue injuries and osteoarthritis.

With the European diclofenac DEA formulation, the most frequently reported AE was an application site reaction or dermatitis, which was similar to that which was observed with the DSG formulation, manufactured for approval in the US market. However, because of

the wider and more extensive exposure of the European product, one was able to confirm the occurrence of rarer and more severe systemic adverse events such as angioneurotic edema or hypersensitivity reactions, in addition to more serious local dermal events such as Stevens-Johnson syndrome. In fact, the label of the European diclofenac formulation includes cautionary words of warning on the occurrence of the above mentioned more serious, systemic and dermal events.

Historically, the use of the parenteral diclofenac salt has been associated with toxic skin manifestations such as rashes, erythema multiforme and TENS. Despite the low systemic exposure of DSG 1%, and despite the foreign experience with topical diclofenac DEA, it is conceivable that the incidence of these rarer, more life-threatening AEs underscores the need for full NSAID labeling of this topical DSG 1% agent.

7.2.3 Adequacy of Overall Clinical Experience

The overall development program for DSG 1% has provided adequate clinical experience to assess the safety and efficacy of DSG 1% for the —— of joints amenable to —— treatment, such as the hands and knees.

The doses and durations of exposure were adequate to assess safety for the intended use; in fact the amount of exposure surpasses the amount of exposure required by the current requirements of the International Committee of Harmonization guidance on extent and duration of exposure needed to assess safety.

The potential class effects of NSAIDs were appropriately addressed in the review.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

An extensive series of preclinical safety tests has been performed with diclofenac sodium in many species. Acute toxicity, mid-term and long-term toxicity, in vitro and in vivo mutagenicity, teratogenicity, fertility, peri-and post-natal toxicity, carcinogenicity and special safety pharmacology studies were performed in rats, mice, rabbits, dogs and monkeys. Reference is made to studies that have been submitted and reviewed in NDA 19-201, approved on July 28, 1988.

As with all topical products, issues of local tolerance and phototoxicity were considered. Safety studies performed with DSG 1% confirmed that the formulation was not irritating to the eye, was not sensitizing and did not have phototoxic nor photosensitizing potential. Results from photogenotoxicity studies indicated that diclofenac sodium was not genotoxic following exposure to UV irradiation.

Three life-span carcinogenic studies with orally administered diclofenac sodium of up to 2 mg/kg have been performed in rats and mice (Reference is made to NDA 19-201). Mortality, mainly resulting from gastrointestinal ulceration was observed at high doses (1mg/kg and 2 mg/kg). None of these studies suggest that diclofenac sodium has any

potential to induce tumors.

Carcinogenicity studies- The carcinogenic and photocarcinogenic potential of diclofenac have been evaluated following topical application of a diclofenac gel (Solaraze™ formulation). (Reference is made to the review of NDA 21-005- Solaraze™). The dermal carcinogenic potential of Solaraze™ was determined following topical administration of 0.09%, 0.018% and 0.035% (maximum tolerated dose) diclofenac gel during the lifetime of the animals. The photocarcinogenicity studies were performed during a period of 52 weeks when mice were exposed to 600 RBU/week simulated solar UV and 0.0045%, 0.009%, 0.018% and 0.035% (maximum tolerated dose) diclofenac gel. There were 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.

Reproductive toxicology studies- (Reference to NDA 19-201). In both the segment I and segment III rat studies, treatment with diclofenac sodium was associated with an increased duration of gestation and dystocia with consequent effects on perinatal survival. Again in both of these studies there was an apparent increase in the sensitivity of the rats to the ulcerogenic effects of diclofenac sodium leading to increased mortality at 4 mg/kg/day and, in the peri-natal and post-natal study, at 2mg/kg/day. This contrasts with the lack of any deaths among rats treated at 4mg/kg/day in the oral gavage, repeat dose toxicity studies of up to 26 weeks duration.

On both of these studies there were additional effects at 2 and 4 mg/kg/day on fetal development and survival including increased fetal losses, reduced live births and reduced fetal weight. Although there was little evidence of significant maternal toxicity at 2 mg/kg/day on the segment I study, the increased mortality associated with peritonitis in the segment III study clearly indicates that this is a maternally toxic dosage when given peri-natally. The fetal changes at 2 mg/kg/day are therefore considered to be associated with maternal toxicity.

The lowest dosage investigated on the segment I and III studies was 2 mg/kg/day and therefore a NOAEL was not established for either fetal or maternal toxicity.
Oral treatment at up to 4 mg/kg/day in segment II studies in mice, rats and rabbits was without any consistent effect on fetal survival or development. Changes identified at higher dosages including reduced survival or viability and reduced ossification clearly associated with maternal toxicity. There was no indication of any effect on organogenesis. The results of two parenteral segment II rat studies were consistent with this although retarded ossification was identified in one of these studies at a dosage of 1.2mg/kg/day, which did not appear to be a maternally toxic dosage. In contrast, the fetal NOAEL in the other parenteral segment II study was 10 mg/kg/day.

Mutagenicity studies- In vitro and in vivo mutagenicity studies showed that diclofenac sodium was neither mutagenic nor photogenotoxic.

Summary of findings from animal data- An extensive series of preclinical safety tests has been performed with diclofenac sodium in many species. Diclofenac sodium was not found to be carcinogenic in rodent life time carcinogenicity studies and in a dermal carcinogenicity study. In vitro and in vivo mutagenicity studies showed that diclofenac sodium was neither mutagenic nor photogenotoxic. Reproduction toxicity was apparent only at maternally toxic dosages.

The topical formulation DSG was well tolerated in a variety of local toxicity studies. The sensitization potential of DSG which was observed in the first maximization test was not reproducible in two subsequent tests.

Bioequivalence animal studies showed that the plasma concentrations measured in rats treated topically with Voltaren Emulgel™, a product similar to DSG and containing 1.16 % diclofenac diethylamine, indicate significant absorption of diclofenac. Approximately 30% of the topically applied dose of 10 mg/rat was absorped systemically. Results from an in vitro skin penetration study comparing Voltaren® Emulgel™ with the current DSG 1% formulation showed similar same skin penetration rates.

7.2.5 Adequacy of Routine Clinical Testing

The types of routine clinical and laboratory testing of subjects during the pivotal and supportive trials were adequate. The appropriate laboratory tests and dermal evaluations were performed on clinical subjects at an appropriate frequency throughout the clinical development program. The frequency of clinical tests was also adequate. The method of eliciting adverse events was also adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The applicant performed adequate vivo testing for DSG 1%. Refer to Section 5 for details.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

DSG 1% contains an NSAID, diclofenac. Therefore, there is a risk that DSG 1% may be associated with NSAID-related AE's. The clinical trials incorporated laboratory and AE assessments that did not demonstrate greater cardiovascular, renal, hepatic or gastrointestinal risks for DSG compared to placebo.

7.2.8 Assessment of Quality and Completeness of Data

The applicant included adequate numbers of subjects who were exposed to study drug for adequate durations of time, which are in keeping with the ICH document on safety. The overall quality and completeness of the data submitted for the safety review is adequate.

7.2.9 Additional Submissions, Including Safety Update

The 120 day safety update required under 21 CFR 314.50(d)(vi)(b) or 21 CFR 314.50 iv(b) was submitted by the applicant on April 18th 2007. This submission was reviewed with respect to serious adverse events and deaths. Results of this review are reported here and not integrated into the Safety review. No new safety signals were identified between the time of the original database lock and dates.

This reviewer evaluated the safety results under the following headings:
1) The results of the [redacted] No serious adverse events have been identified, and to date, no new safety issues have been identified with the use of DSG 1%.

2) Post marketing safety. Since the end of the previous post marketing safety review for diclofenac DEA gel, 465 AE's among 194 patient cases were reported among the estimated — of subjects using diclofenac DEA product. Most of the AEs were cutaneous-type reactions, and the vast majority of these were non-serious. No cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, or angioneurotic edema, were reported. There were no reported cases of anaphylactic shock or anaphylactic shock reaction. No cardiac disorder adverse events were reported, and no cases with adverse events suggestions underlying thrombotic conditions were identified.

All serious cases of gastrointestinal bleeding, hepatic and renal disorders could be attributed to pre-existing medical conditions, concurrent disease and/or use of concomitant oral medications which contributed to a high likelihood of alternate etiologies.

3) Review of the medical literature identified a case of premature closure of the ductus arteriosus, associated with third trimester use of topical diclofenac DEA, and oral tramadol. This condition reversed with discontinuation of the medications.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The following issues were identified during the review:

- Statistically significant difference in the cutaneous application site reactions (See Section 7.1.3.3)
- Relatively low representative percentage of Blacks and males within the clinical trial population, as compared to the number of subjects with the disease of OA in the general population. See Section 7.2.1.2)

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Patients in 4 randomized, blinded, controlled phase 3 trials and a single long-term safety study comprised the major safety population. Trials were similar in design and studied comparable patient populations were pooled to improve the precision of estimates and sensitivity to any differences in incidence rates. The analysis focused on the affected body system, the type of AE's, their severity and suspected drug relatedness

The patients in all other trials or sources of data were not subjected to pooled data analysis, as the study designs, populations studied and collection of AE data were not comparable. The data from these trials were evaluated singly, by comparing the overall rate and type of AEs with those of other studies and with the data in the pooled safety population.

The rationale for merging the data from the hand and knee OA studies is that although the trials lasted 8 weeks and 12 weeks respectively, the studies were similar in design and the study populations represent the target population intended for treatment. The two knee OA studies were of virtually identical design as were the two hand studies.

With respect to the AE data from the knee and hand OA studies, it is worth noting that the studies were of different durations; the knee OA studies were of 12 weeks duration and the hand OA studies were of 8 weeks duration.

It is also important to keep in mind that the data from VOSG-PN-309 overlap that from the pooled knee and hand studies because the AEs from subjects treated with DSG in the knee studies are counted in both datasets.

7.4.1.1 Pooled data vs. individual study data

(See Section 7.4.1)

7.4.1.2 Combining data

(See Section 7.4.1)

7.4.2 Explorations for Predictive Factors

Refer to Sections 7.1.3.3 and 7.1.5

Explorations for drug-drug interactions

No formal studies of drug-drug interactions with topical DSG have been conducted as part of its development program to date. At maximal recommended dosing, the systemic exposure to the active moiety is less than 20% of an oral diclofenac dose of 50 mg TID and it would be expected that the drug-drug interactions observed with the oral form of diclofenac would be applicable, taking into consideration the reduced plasma levels and systemic exposure of the topical formulation.(See Section 8.2).

7.4.3 Causality Determination

Refer to Sections 7.1.2, 7.1.2.3 and 7.1.5)

8. ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The recommended adult dose is 4 grams DSG 1% applied to the affected areas four times a day (for knee OA) and 2 grams DSG 1% applied to affected areas four times a day (for hand OA). This dosage was derived from extensive experience with topical diclofenac DEA in the European population and bioequivalence studies performed with that formulation and DSG 1%. Total usage should not exceed 32 grams per day (the dose studied in the efficacy trials), over all affected joints. The systemic exposure obtained with the maximal daily dosage produces a diclofenac systemic exposure that is 8 times less than the exposure obtained with the approved 50 mg tid oral dosage of the reference product. Each application is measured using a disposable dosing card.

8.2 Drug-Drug Interactions

No formal drug-drug interaction studies were performed as part of the development program of this topical drug thus far. The systemic exposure achieved at even the maximal recommended daily dose of 32 g DSG 1% per day, is 8 times less than the systemic exposure with the approved oral dose of diclofenac sodium 50 mg po tid.

The following information is taken from the current oral Voltaren label:

"***Aspirin:*** When Voltaren® is administered with aspirin, its protein binding is reduced. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of diclofenac and aspirin is not generally recommended because of the potential of increased adverse effects.

Methotrexate: NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

Cyclosporine: Voltaren®, like other NSAIDs, may affect renal prostaglandins and increase the toxicity of certain drugs. Therefore, concomitant therapy with Voltaren® may increase cyclosporine's nephrotoxicity. Caution should be used when Voltaren® is administered concomitantly with cyclosporine.

ACE-inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE inhibitors.

Diuretics: Clinical studies, as well as post-marketing observations, have shown that Voltaren® can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure, as well as to assure diuretic efficacy.

Lithium: NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Warfarin: The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

No diclofenac-specific risk associated with the use of a particular concomitant medication is recognized and no specific analysis of AEs stratified by concomitant medication was conducted in the safety analysis of topical DSG 1%.

8.3 Special Populations

Special population studies were not performed as part of this 505(b)(2) application. Explorations based on race, gender and age of adults did not affect the safety of this topically applied product. Dosage adjustment is not indicated for older patients or those with renal or hepatic impairment. Dosing in pediatric patients has not been studied.

8.4 Pediatrics

The Applicant requested a full waiver from the requirements of 21 CFR 314.55 for data on the efficacy and safety of DSG 1% in a pediatric subpopulation with OA. The Applicant maintains that there is no reported incidence of OA of the superficial joints in subjects below the age of 18 years, [redacted] Additionally, the Applicant has requested a waiver for the conduct of pediatric studies in subjects less than 10 years of age. At the time of this review, the Applicant's proposal is under consideration.

8.5 Advisory Committee Meeting

An Advisory Committee was not required for this submission.

8.6 Literature Review

Please refer to Section 7.2.2.3 for results of literature review.

8.7 Postmarketing Risk Management Plan

A risk management plan is not indicated for this product.

8.8 Other Relevant Materials

The Division of Medication Errors and Technical Support (DMETS) found that the proprietary name of Voltaren Gel to be an acceptable name for this product.

A Dermatology Consult was obtained as part of the evaluation of DSG 1%.
The Consultant concluded the following:
1) The three dermal safety studies Cumulative Irritation Potential Study (VOSG-PN-108) Skin Sensitizing Potential Study (VOSG-PN-111) and the UVA and UVB Phototoxicity Potential Study (VOSG-PE-112) were adequate in design and study duration. Each clinical

trial provided data derived from sufficient numbers of evaluable subjects. Clinically significant potential for irritation, sensitization or phototoxicity were not identified.
2) The presence of an acceptable named graded dermatologic adverse event grading scale would have been useful in order to reduce inter-investigator variability in the classification of the severity of AEs.
3) Recommendations that labeling should include a statement that adequate precautions should be taken to minimize sunlight while using DSG 1% topical product.

9. OVERALL ASSESSMENT

9.1 Conclusions

This reviewer has concluded that the randomized, controlled, blinded studies in patients with osteoarthritis of the hand and knees demonstrate that topical diclofenac gel (DSG 1%) was safe and effective , of joints amenable to treatment, such as the hands and knees. The data collection, study population, selection of primary and secondary endpoints, and primary and secondary efficacy analyses were adequate and appropriate to make the conclusion that topical DSG 1% was superior to vehicle through 8 weeks of dosing in hand OA, and 12 weeks of dosing in knee OA.

Independent FDA statistical analysis confirmed the applicant's analysis of the primary efficacy endpoint for both Phase 3 trials. Multiple secondary end point analyses also supported the conclusion of efficacy over 8 and 12 weeks of dosing in hand OA and knee OA respectively.

A total of 1347 subjects have been treated with DSG in the course of the clinical work conducted in support of this submission. The data demonstrate that the drug is tolerated in the target treatment population and that no special safety concerns have been identified in the clinical trials, except for varying forms of application site reactions.

In general, topical DSG was well tolerated by the subjects in the controlled Phase 3 clinical trials and in the single uncontrolled long-term safety study. There was a single report of a death due to ventricular fibrillation in an elderly patient with a history of heart disease on Day 5 of DSG 1% administration that was not attributable to DSG 1%. SAEs were balanced between active and vehicle (control) arms and were not felt to relate to administration of DSG 1 %. The incidence of skin irritation of various types (eg dermatitis) was reported in 10.1 % of subjects treated with DSG compared to 3.8% in the vehicle-treated subjects.

Three special safety studies related to the potential for skin irritation, sensitization, and photo-toxicity were conducted during the development program. Under the conditions of dermal safety studies, clinically significant potential for irritation, sensitization or phototoxicity were not identified. Photoallergic studies were not done and it is

recommended that they be conducted as part of a Phase 4 commitment.

Long-term exposure did not identify any special concerns regarding safety nor did a review of safety within subgroups reveal any concerns based on age, sex or race.

Safety data pooled from the population with knee OA (those that received long-term exposure to DSG in controlled trials and the uncontrolled continuation trial), showed that 16-32 g/day DSG over one or two knees is safe and that the systemic effects occasionally observed with the oral formulation of the drug are less evident at these doses of DSG.

Subgroup analyses showed no differences in safety profile with age, sex or race, and dose adjustment was not required in long-term studies. Long-term safety data from patients with up to 12 months of exposure did not reveal any new safety concerns with increasing duration of exposure.

Oral diclofenac has been the subject of a previously approved NDA (NDA 19-201) submitted by the Sponsor Corporation. 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. The safety profile for oral diclofenac is well characterized. Apart from the statistically significant cutaneous sensitivity described, the topical formulation presented here did not produce any unexpected AEs compared to oral diclofenac. Similarly, the proposed product has the same active moiety in the same concentration as Voltaren® Emulgel™ a product that 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 benign safety profile.

Overall, the safety of DSG was demonstrated in the major safety population, also in the pooled knee OA population, as well as in all data from all other sources. All showed that the incidence and type of rare or serious events resembled those of vehicle. The data indicate that the drug is well tolerated in the target population at the target dose, as required for registration. The primary AEs associated with DSG were non-serious application site reactions (for example dermatitis).

9.2 Recommendation on Regulatory Action

Based on the review of the efficacy and safety review of Voltaren, in NDA submission 22-122, this reviewer recommends the approval under 21 CFR 314. 54.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Although Novartis did not submit a formal risk management plan there are risk management activities planned for topical diclofenac gel
- The label contains a number of usage statements to assist healthcare providers in how, when and in whom to use this product
- The Office of Drug Safety has been involved with this NDA submission, and if warranted will be consulted formally to evaluate any new or increased post marketing safety signals.

9.3.2 Required Phase 4 Commitments

1) Photocontact Allergic Potential Study is required as part of a Phase 4 commitment.

9.4 Labeling Review

Recommendations for the label are described here in general terms:
1) Due to systemic absorption of diclofenac from DSG 1%, the label should contain language from the NSAID template.
2) The indication should
3) should be deleted from the label.

9.5 Comments to Applicant

The following comments will be relayed to the Applicant:

- A photocontact allergic potential study should be conducted as a Phase 4 commitment.
- Due to the lack of information regarding photoallergic potential of diclofenac gel, 1%, product labeling should include the following precautionary language: "

TABLE OF CONTENTS (APPENDIX)

10.1 Review of Individual Study Reports

SECTION 10

10.1.1 INDIVIDUAL STUDY REPORT- VOSG-PN-310

Title of study: A 12-week, randomized, double-blind, multi-center, vehicle-controlled, parallel group study to assess the efficacy and safety of diclofenac sodium gel 1% for the relief of signs and symptoms in subjects with osteoarthritis of the knee.

Primary objective: To compare the efficacy of daily topical applications of diclofenac sodium gel (DSG) 1% with vehicle when 4 g were applied four times a day to one knee for 12 weeks by subjects with mild to moderate knee osteoarthritis (OA).

Secondary objective: The secondary objective was designed to evaluate and compare the safety of DSG 1% with vehicle.

Study Design:
This was to have been a 12-week, prospective, randomized, double-blind, multi-center, placebo-controlled, parallel group study in subjects with OA of the knee.

A total enrollment of 480 subjects (240 in each group) with OA symptoms in one knee was planned. Subjects were to have been treated with DSG 1% or vehicle. DSG 1% or vehicle was to have been applied topically, 4 g four times daily for 12 weeks.

The protocol specified that subjects have a 1-week washout of analgesics (or at least 5 half-lives, whichever was longer). Following screening, were to visit the study site four times for assessments of efficacy, safety, and compliance. Subjects would also complete daily diaries throughout the washout and treatment periods in which efficacy and study medication compliance information were recorded.

The duration of therapy was to have been 12 weeks. Safety was to have been assessed by monitoring adverse events (AE's), clinical laboratory evaluations, vital sign measurements and physical examinations.

Evaluation was to have been performed at Week 12 with regard to reducing pain (Western Ontario McMaster Osteoarthritis Index (WOMAC) pain index), improving functional capacity (WOMAC function index), and improving global disease rating Visual Analog Scale, (VAS).

Inclusion criteria:
Subjects included were to have been men and women ≥ 35 years of age who met the following criteria:

1. Had a clinical diagnosis of OA of the knee according to ACR criteria with symptoms at least 6 months prior to screening, defined as:
   -Knee (not referred) pain for 15 days of the preceding month (periarticular knee pain had to be due to OA and not due to other conditions like bursitis, tendonitis, chondropathia patellae, meniscopathia).
   AND
   -The pain in the target knee required the use of NSAIDs or acetaminophen (topical or oral treatments).
2. Had an X-ray of the target knee, no more than one year old, showing evidence of OA with Kellgren-Lawrence grade 1-3 disease.
3. Able to tolerate rescue medication with only 500 mg acetaminophen taken as 1-2 tablets up to a maximum of 8 tablets (4 g) per day for the duration of the study.
4. Had a baseline score of ≥ 50 mm on a 0-100 mm VAS when rating POM and a baseline WOMAC pain score of at least 9 immediately prior to randomization.

Exclusion criteria:
Subjects were to have been excluded if they met any of the following criteria:

1. Had an X-ray showing grade 4 Kellgren-Lawrence disease.
2. Had a baseline contralateral knee score of more than 20 mm on a 100 mm VAS when rating POM.
3. Had a history of OA pain in the contralateral knee within the previous year.
4. Had secondary OA, i.e., history or present evidence of an inflammatory joint condition, such as septic arthritis, inflammatory joint disease, and gout, recurrent episodes of pseudogout, Paget's disease, articular fracture, ochronosis, acromegaly, hemochromatosis, Wilson's disease, primary osteochondromatosis, heritable disorders (e.g. hypermobility) or collagen gene mutations.
5. Had a history of rheumatoid arthritis or laboratory values indicative of rheumatoid arthritis with subsequent diagnosis by a physician.
6. Had a history of any other chronic inflammatory disease, such as colitis within the previous year.
7. Had a history of fibromyalgia within the previous year.

Treatment:
DSG 1% or vehicle 4 gm was to have been applied to the knee four times per day for 12 weeks.

Permitted Concomitant medication:
Generally patients were to have been allowed to continue taking stable (non-analgesic) medications that would not interfere with the metabolism of DSG.

Rescue medication:
Restricted use of rescue medication (acetaminophen) was to have been allowed up to a maximum of 4 g per day.

Outcome measures:
Primary efficacy Outcome
There were to have been three primary efficacy outcomes. Statistical significance was required on all 3 measures. The outcomes that were to have been evaluated at the final visit were:
1. WOMAC pain score
2. WOMAC physical function score
3. Patient's global disease rating

Secondary Efficacy Endpoints:
The secondary efficacy variables were designed to have been collected at all post-baseline visits, excluding those outcomes assessed at Visit 6 (Week 12) that were to have been designated as primary.
The secondary efficacy variables were to have been designated as follows:
1) WOMAC pain score
2) WOMAC stiffness score
3) WOMAC Physical function score
4) Global rating of disease
5) Global rating of benefit
6) Pain on movement (POM), spontaneous pain
7) Global evaluation of treatment (at the final visit)
8) Difference between target knee and contralateral knee on subset of four WOMAC questions
9) Osteoarthritis Research Society International (OARSI) response
10) Use of pain/rescue response
11) Pain on movement [POM] (by diary) – daily and averaged by week
12) Use of rescue medication.

Study visit Schedule:

TABLE # 10.1.1.1 : SHOWING EVALUATION AND VISIT SCHEDULE FOR STUDY VOSG-PN-310

Procedure	Screening / washout	Random-ization	Treatment phase				Termination
Visit	1	2	3	Phone contact	4	5	6
Week			1	mid break[5]	4	8	12
Day	-7 (-5 to -14)	1	8 (+3)		29 (± 7)	57 (± 7)	85 (± 7)
Written informed consent	X						
Background information	X	X					
Assessment of osteoarthritis	X						
X-ray evaluated/ordered	X	X					
Safety laboratory	X				X[3]		X
Physical examination		X					X
Vital signs		X					X
Urine pregnancy test		X					X
Inclusion/exclusion criteria	X	X					
Randomization		X					
Efficacy assessments[1]	X	X	X		X	X	X
Dispense drug		X[4]	X		X	X	
Collect drug			X		X	X	X
Dispense diary[2]	X	X	X		X	X	
Collect and check diary		X	X		X	X	X
Dispense rescue medication	X	X	X		X	X	
Collect rescue medication		X	X		X	X	X
Concomitant medication	X	X	X		X	X	X
Adverse event reporting		X	X		X	X	X
Global Evaluation of Treatment							X

[1] **Efficacy assessments:** Spontaneous pain, POM, global rating of disease, global rating of benefit (Visit 3-Visit 6 only), and WOMAC at the study site.
[2] **Diary efficacy assessment**: POM assessed daily from Visit 1 through Day 14.
[3] **Laboratory**: only measure liver function tests (LFTs).
[4] **Treatment:** To standardize application, the investigator or designee applied the first dose.
[5] **Telephone contact:** Principal Investigator or designee contacted subject approximately midway between Visits 3-4, 4-5, and 5-6.

Statistical Analysis Plan and Definition of Analyzed Study Populations:
Information from a completed companion study of identical design (VOSG-PN-304) was to have been used to define a subset of the intent-to-treat (ITT) efficacy population, referred to as the modified efficacy subpopulation (MES), which was used as the primary population for efficacy analyses. This MES population was defined as study subjects with 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 at baseline. (Prior to protocol amendment the initial analysis population was to have been the ITT population).

Treatment groups were to have been compared on each primary efficacy outcome in the MES with an analysis of covariance (ANCOVA) model including main effects of treatment and center, and the baseline as covariate. Two-sided 95% confidence intervals (CIs) on the difference between normally distributed means were supplied. Continuous secondary efficacy outcomes were analyzed in parallel fashion to the primary outcomes. All dichotomous secondary efficacy outcomes were to have been tested for differences between treatments with the Cochran-Mantel-Haenszel (CMH) test of general association stratified by center.

The global evaluation of treatment was to have been recorded once at the end of the study and the difference between treatment groups was tested with the CMH test of mean stratified by center. Differences between knees on the subset of abridged WOMAC pain and function indices were to have been summarized with simple summary statistics by knee (target, contralateral and difference) within treatment group. Differences between knees and between treatment groups were not formally tested.

A secondary efficacy analysis was to have been performed in the ITT population.

Imputation of missing data

The protocol provided was to have the following conventions for imputation of missing data relevant to the primary efficacy comparisons.

I. For the case where the entire post-baseline visit(s) were missing:

- Missing data resulting from a visit or consecutive visits being skipped by a subject in the middle of the study were to have been replaced by the average of the outcome for the latest non-missed visit before the missed visit(s) and the earliest non-missed visit after the missed visit.
- Missing data resulting from a visit or consecutive visits being skipped by a subject when no earliest non-missed visit after the missed visit was available (i.e., early termination) would be replaced by the outcome for the latest non-missed visit before the missed visit(s), i.e. last-observation carried forward.
    - Exception: If a subject discontinues because of lack of efficacy, the imputed value would be the maximum of the value from the last non-missed visit and the baseline value.

II. For the case where only a subset of the questions needed to compute a WOMAC index were missing:

- A value for each missing question were to have been imputed as described in the preceding case with the additional stipulation that if a subset of questions in a WOMAC index was not answered at the **baseline** visit, the score for that patient on the index would be computed and analyzed at all visits as if the question(s) did not exist.

III. For cases where a subject is determined to be a "treatment failure"

Treatment failures were to have been defined as cases where there is a series of four or more consecutive days (after day 7) in which a subject takes either (a) all eight

tablets of rescue medication or (b) the maximum daily OTC dose of a NSAID or (c) one or more single prescription strength doses of a nonselective or COX-2 selective NSAID, specifically to treat osteoarthritis in the target knee)

- Efficacy data beginning at the first of the four days leading to designation of a subject as a treatment failure would be ignored and would be replaced as if the subject had prematurely discontinued for lack of efficacy (i.e., the imputed value would be the maximum of the value from the last non-missed visit and the baseline value).

IV. For cases where a subject is determined to be a "treatment confounder"
Treatment confounders were to have been defined as cases where there is a series of four or more consecutive days in which a subject takes either (a) any rescue medication or (b) any other analgesic, including nonselective or COX-2 selective NSAIDs at any dose, specifically to treat osteoarthritis pain in the contralateral knee or (c) applies study medication to the contralateral knee)

- Efficacy data recorded at the visit immediately following the episode leading to designation of a subject as a treatment confounder would be replaced with the corresponding efficacy data from the immediately preceding visit. This would be applied to every immediately following visit for as long (and only if or as long) as the subject continued to satisfy the definition of a treatment confounder.
    - In addition, a sensitivity analysis will be conducted in which the criteria of the treatment confounder with respect to NSAID and APAP use are modified to match those of treatment failure.

The protocol also specified the following sensitivity analyses for the primary efficacy outcomes:
(1) An analysis substituting the mean of all non-missing values in the *active group* at visit X for any missing values in the *active group* at visit X and correspondingly, substituting the mean of all non-missing values in the *placebo group* at visit X for any missing values at visit X in the *placebo group*.
(2) An analysis substituting the mean of all non-missing values in the *active group* at visit X for any missing values in the *placebo group* at visit X and correspondingly, substituting the mean of all non-missing values in the *placebo group* at visit X for any missing values at visit X in the active *group*.

Protocol Amendments:

Amendment 1 (October 20th 2004)

Amendment 1 changed the study entrance criteria as follows:

- Inclusion criteria were to have been revised to state that:
    - Subjects had to have a clinical diagnosis of OA of the knee per ACR criteria for at least the previous 6 months with symptoms. The stipulation that pain in the target

knee for >25 days preceding screening that required the use of NSAID's or acetaminophen was removed.
- The minimum age for enrollment in the study was changed from 45 years to 35 years.

• Exclusion criteria were to have been revised to exclude:
- Subjects who had a history of pain in the contralateral knee were further defined to exclude subjects who had a history of pain in the contralateral knee within the last year.
- "History of rheumatoid arthritis or laboratory values indicative of rheumatoid arthritis with subsequent diagnosis by a physician." Originally stated "History of rheumatoid arthritis or positive laboratory values for Rheumatoid Factor (RF), C-Reactive Protein (CRP) and Sedimentation Rate (BSR) at screening",
- Subjects who had a history of chronic inflammatory disease or fibromyalgia.
- Subjects who had received anticoagulants such as warfarin or heparin in the preceding week or antiaggregants other than aspirin (such as Plavix®) in the preceding month.

The subpart of this criterion that addressed subjects taking concomitant psychoactive drugs was to have been modified to permit anxiolytics, stipulating that only stable, low doses present at entry and maintained throughout the study were permitted.

• Exclusion criterion #13: The part of this criterion that concerned the amount of aspirin a subject was to have been modified to allow subjects to receive (under the specified circumstances) was changed from 160 mg/day to 162 mg/day.

Amendment 2 (Nov 12th, 2004)
Amendment 2 changed a study entrance criterion as follows:
• Exclusion criterion #2: The criterion that excluded subjects who had a baseline contralateral POM VAS score of more than 10 mm was changed to exclude subjects who had a score of more than 20 mm.

Amendment 3 (03-May-2005)
Amendment 3 was to have been generated to accommodate a request by the EU health authority for the addition of a fourth primary outcome. The added primary outcome was already listed among the secondary outcomes. The analysis of the new primary outcome was unchanged. Thus, this amendment only modified the implications of the result of the analysis of an existing outcome and only for the EU.

Information Amendment 1 (19-Jan-2006)
Information from a completed companion study of identical design (VOSG-PN-304) was used to define a subset of the intent-to-treat (ITT) efficacy population, referred to as the ***modified efficacy subpopulation (MES)***, which was used as the primary population for efficacy analyses. Subjects in the MES were required to have ***no decline*** in POM score

between the screening and baseline visits and to have a score of 0 or 1 on the WOMAC abridged pain index for the contralateral knee.

The sponsor implemented a formal modification of the efficacy population prior to unblinding of the study. This change was filed to the FDA in the form of an Information Amendment after completion of the study and was implemented in the Statistical Analysis Plan.

Safety was to have been assessed mainly as the frequency of AEs that were treatment-emergent and on the number of laboratory values at post-baseline visits that fell outside of pre-determined ranges. A pooled safety analysis of controlled Studies VOSG-PN-304, VOSG-PN-310, VOSG-PN-314 and VOSG-PN-315 is discussed in Section 7 of this report.

RESULTS:

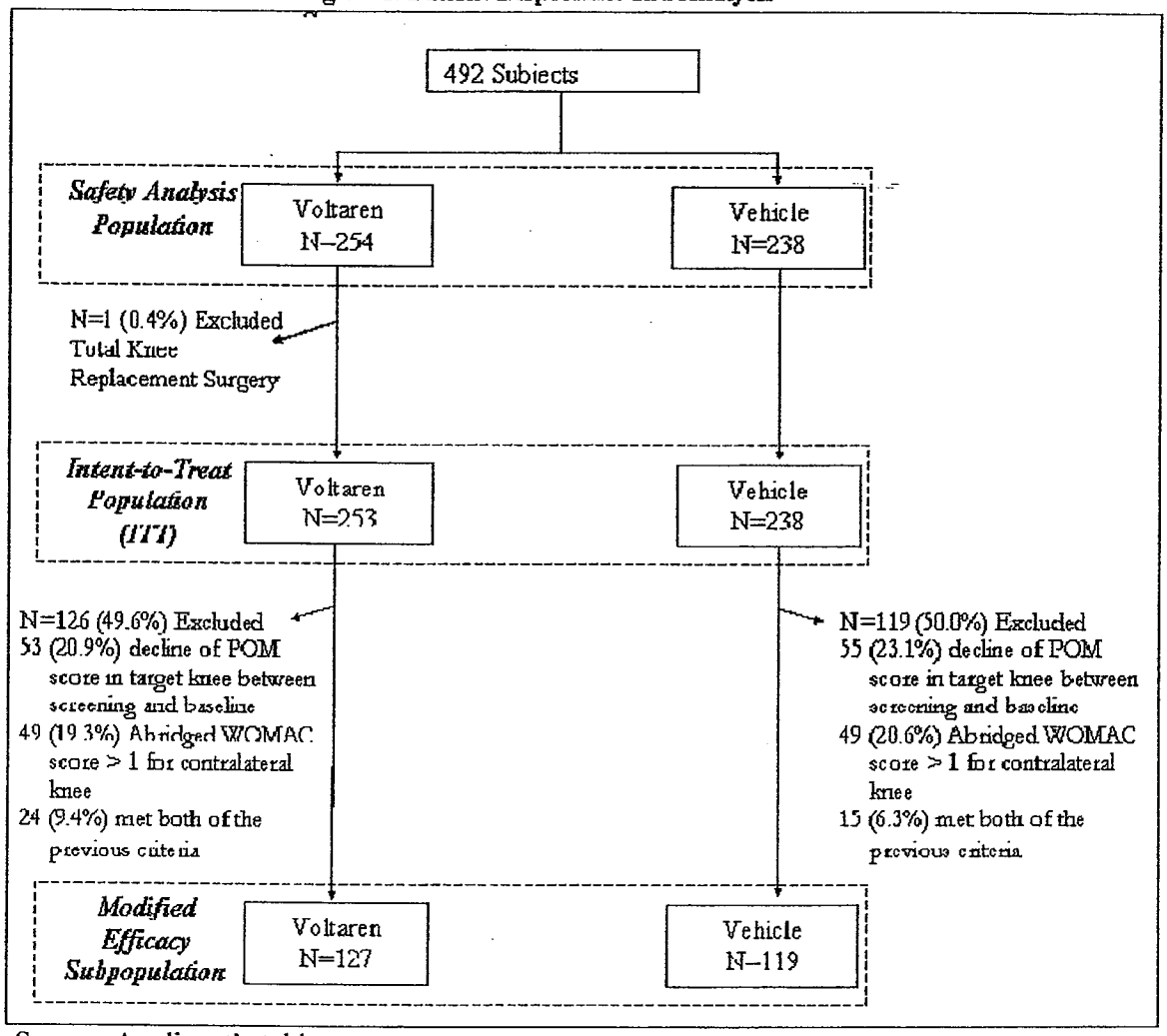
- **Disposition**

A total of 918 subjects were screened in this study were not randomized.
The most common reasons why screened subjects were not randomized were:
1) Clinically significant laboratory abnormalities - 73 subjects
2) Maintaining effective birth control in women of childbearing potential – 51 subjects
3) Withdrawal of consent – 34 subjects.

The total number of randomized subjects was 492, with 254 subjects in the DSG and 238 in the vehicle group.

After the result of Study -304 was available, and the profile of the subject most likely to respond to topical DSG was determined, and the MES population was defined for the purpose of determination of efficacy. The MES population was approximately 50% of the ITT population. (See Figure 1 noted below).

Figure 1: Patient Disposition and Analysis



Source: Applicant's table ___ , report , page

- **Drop outs**

The proportions of subjects in the DSG and vehicle groups who completed the study were 82.3% and 74.8%, respectively.
The most common reasons for discontinuing the study were:
1) Withdrawal of consent (DSG: 5.9%; vehicle: 6.7%),
2) Unsatisfactory therapeutic effect (DSG: 3.9%; vehicle: 6.7%)
3) AE's (DSG: 5.1%; vehicle: 3.8%).

Overall, a total of 45 (17.7%) subjects in the DSG group and 60 (25.2%) subjects discontinued the study prior to its termination. Of these, 10 (3.9%) subjects in the DSG arm

and 16 (6.7%) subjects in the vehicle arm discontinued because of an unsatisfactory therapeutic effect.
A total of 22 subjects, 13 (5.1%) in the DSG group and 9 (3.8%) in the vehicle group experienced AE's that led to discontinuation of the study drug.

TABLE 10.1.1.2: SHOWING THE DISPOSITION OF SUBJECTS IN STUDY VOSG-PN-310

Reported Term for the Disposition Event	DSG Gel	VEHICLE
Randomized	254 (100.00%)	238 (100.00%)
Completed	209 (82.3)	178 (74.8)
Discontinuations - Total	45 (17.7)	60 (25.2)
Patient withdrew Consent	15 (5.9%)	16 (6.7)
Adverse Event	13 (5.1%)	9 (3.8%)
Unsatisfactorty Therapeutic Effect	10 (3.9%)	16 (6.7%)
Lost to follow up	5 (2.0)	12 (5.04%)
Administrative Problems	1 (0.4)	2 (0.8%)
Protocol Deviations	1 (0.4%)	5 (2.1%)
Total Subjects	254 (100.00%)	238 (100.00%)

Source: FDA's analysis of disposition dataset

Approximately equal proportions of subjects 15 (5.9%) in the DSG arm and 16 (6.7%) vehicle withdrew consent. The case report forms for the patients who discontinued due to withdrawal of consent were reviewed to ascertain whether these patients actually discontinued due to an adverse event or lack of efficacy. This review found that two subjects in the DSG arm, and zero subjects in the vehicle arm actually discontinued because of AE, while 3 subjects in the DSG arm withdrew because of lack of efficacy, and 6 subjects in the vehicle arm withdrew because of efficacy.

Subjects who discontinued due to AE's are discussed in further detail in Section 7 of this report.

- **Protocol Deviations**

The proportion of subjects who had at least one protocol violation was 20.1% in the DSG arm, compared with 22.3% in the vehicle arm.
The most common protocol violations were as follows:
- Dosing violations, 6.3% in the DSG arm and 3.8% in the dosing arm
- Visit violations, 5.5% in the DSG arm and 8.4% in the vehicle arm

Most of the dosing violations involved study subjects not applying study medication on

the day of the last efficacy visit and at least the 2 days immediately preceding the last study visit, while most of the visit violations occurred in early terminators within 2 weeks after randomization.

These protocol violations as described are not likely to interfere with the integrity of the data.

DEMOGRAPHICS and BASELINE CHARACTERISTICS:
The proportions of subjects in the DSG and vehicle groups who completed the study were 82.3% and 74.8%, respectively. About two thirds of subjects in each treatment group were female and over 75% were Caucasian. The mean age was approximately 60 years, with almost two-thirds of subjects in the range of 50-70 years. The distribution of demographic factors in the MES was very similar to the population of all randomized subjects. There was a statistical significant difference in BMI between treatment groups of the MES population (DSG- 30.1kg/m^2 versus vehicle 32.2 kg/m^2 (p=0.019). Given that this product is a topically (and not systemically) administered, BMI baseline differences in treatment groups would not be expected to affect the final outcome. Please refer to Table 10.1.2.

TABLE 10.1.1.2: SHOWING DEMOGRAPHIC SUMMARY BY TREATMENT GROUP- ALL RANDOMIZED AND MES SUBJECTS

	All randomized subjects		MES subjects	
Category*	**DSG N = 254**	**Vehicle N = 238**	**DSG N = 127**	**Vehicle N = 119**
Sex – n (%)				
Male	83 (32.7)	82 (34.5)	44 (34.6)	40 (33.6)
Female	171 (67.3)	156 (65.5)	83 (65.4)	79 (66.4)
Race – n (%)				
Caucasian	191 (75.2)	191 (80.3)	101 (79.5)	99 (83.2)
Black	34 (13.4)	31 (13.0)	9 (7.1)	10 (8.4)
Asian	6 (2.4)	1 (0.4)	4 (3.1)	0
Other	23 (9.1)	15 (6.3)	13 (10.2)	10 (8.4)
Age (yr) – n (%)				
≤ 40	9 (3.5)	6 (2.5)	5 (3.9)	2 (1.7)
> 40-50	42 (16.4)	47 (19.7)	20 (15.7)	29 (24.4)
> 50-60	86 (33.9)	76 (31.9)	45 (35.4)	39 (32.8)
> 60-70	76 (29.9)	73 (30.7)	34 (26.8)	31 (26.1)
> 70-80	34 (13.4)	31 (13.0)	20 (15.7)	16 (13.4)
> 80	7 (2.8)	5 (2.1)	3 (2.4)	2 (1.7)
Mean ± SD	59.7 ± 10.5	59.2 ± 10.6	59.7 ± 10.8	58.4 ± 10.4
Range	36 – 90	35 – 92	36 – 90	35 – 82
Height (cm)				
N	252	236	127	117
Mean ± SD	168.2 ± 10.6	168.3 ± 11.6	168.0 ± 10.3	167.5 ± 12.2
Range	132 – 198	123 – 196	132 – 198	123 – 193
Weight (kg)				
N	250	235	127	116
Mean ± SD	87.5 ± 18.8	90.0 ± 20.6	85.2 ± 19.6	89.9 ± 20.9
Range	49 – 159	50 – 159	49 – 159	54 – 159
BMI (kg/m^2)				
N	250	235	127	116
Mean ± SD	30.9 ± 6.2	31.8 ± 7.0	30.1 ± 6.4	32.2 ± 7.1
Range	18.4 – 53.2	18.5 – 57.7	20.0 – 53.2	18.5 – 54.9

*Sample sizes for summary statistic calculation are given at the top of the table unless otherwise indicated.
Source: Post-text Table 7.6 and Post-text Table 7.6a; Appendix 7, Listing 7.7

The baseline OA assessments in the all randomized subjects and MES populations were similar. The baseline OA assessments of the two treatment groups of study subjects were similar, when quantified in terms of global rating of disease, spontaneous pain, pain intensity of movement in the target and in the contralateral knee.

TABLE 10.1.1.3: SHOWING A SUMMARY OF BASELINE VISIT OSTEOARTHRITIS ASSESSMENTS- ALL RANDOMIZED SUBJECTS AND MES SUBJECTS

	All randomized subjects		MES subjects	
Category*	**DSG N = 254**	**Vehicle N = 238**	**DSG N = 127**	**Vehicle N = 119**
Global rating of disease[1]				
Mean ± SD	62.3 ± 19.4	61.9 ± 19.5	61.6 ± 20.2	63.9 ± 21.0
Range	9 – 100	1 – 100	9 – 98	1 – 100
Spontaneous pain[2]				
Mean ± SD	59.2 ± 22.7	59.2 ± 24.4	58.9 ± 23.6	60.9 ± 26.7
Range	0 – 100	1 – 100	0 – 98	1 – 100
Pain on movement[2]				
Target knee				
Mean ± SD	71.3 ± 11.8	71.4 ± 12.7	72.9 ± 11.5	74.3 ± 13.0
Range	47 – 99	40 – 101	50 – 99	50 – 100
Contralateral knee				
N	253	238	127	119
Mean ± SD	6.2 ± 5.9	6.2 ± 5.7	4.7 ± 5.7	4.4 ± 4.5
Range	0 – 24	0 – 21	0 – 20	0 – 20
WOMAC pain index[3]				
Mean ± SD	11.67 ± 2.43	11.72 ± 2.45	11.47 ± 2.51	12.06 ± 2.71
Range	5 – 18	5 – 18	5 – 18	5 – 18
WOMAC stiffness index[3]				
Mean ± SD	4.77 ± 1.47	4.91 ± 1.46	4.67 ± 1.58	4.87 ± 1.62
Range	0 – 8	0 – 8	0 – 8	0 – 8
WOMAC physical function index[3]				
Mean ± SD	38.0 ± 10.0	37.9 ± 10.7	37.2 ± 10.9	37.5 ± 12.0
Range	4 – 65	9 – 64	4 – 61	9 – 64

*Sample sizes for summary statistic calculation are given at the top of the table unless otherwise indicated.
[1] 0 = very good, 100 = very poor
[2] 0 = no pain, 100 = unbearable pain
[3] Pain: 0-20; stiffness: 0–8; physical function: 0-68
Source: Post-text Table 7.10 and Post-text Table 7.10a; Appendix 7, Listing 9.1 and Appendix 7, Listing 9.2

Source: Applicant's submission; VOSG-PN-310; Post-Text Supplement 3; Table 7.6
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- PRIMARY EFFICACY

- The primary efficacy endpoints were the *WOMAC pain score* and *physical function score* and *the global rating of disease* measured at Visit 6 (Week 12) at the study site.

The primary population for the analysis of efficacy was the MES. The mean WOMAC pain index scores (scale: 0 to 20) at Week 12 in the DSG and vehicle groups were 5.6 and 7.4, respectively. These scores reflect mean decreases from baseline of 5.9 in the DSG group and 4.7 in the vehicle group and a least squares mean difference of 1.3 (p = 0.023; 95% CI [0.2, 2.5]).

The mean WOMAC Physical function scores (scale: 0 to 68) at Week 12 in the DSG and vehicle groups were 19.7 and 25.7, respectively. These scores reflect mean decreases from baseline of 17.5 in the DSG group and 11.8 in the vehicle group and a least squares mean difference of 5.7 (p = 0.003; 95% CI [2.02, 9.41]).

The mean global rating of disease VAS scores (scale: 0= very good to 100 = very poor) at Week 12 in the DSG and vehicle groups were 31.6 mm and 41.5 mm, respectively. These scores reflect mean decreases (indicating improvement in rating) from baseline of 30.0 mm in the DSG group and 22.4 mm in the vehicle group and a least squares mean difference of 8.5 mm (p = 0.018; 95% CI [1.5, 15.6]).

(See Table 10.1.1.4 shown below).

TABLE 10.1.1.4: SHOWING THE APPLICANT'S RESULTS FOR THE WOMAC PAIN AND PHYSICAL FUNCTION AND GLOBAL RATING OF DISEASE AT WEEK 12 – MES POPULATION

	DSG N = 127	Vehicle N = 119	Difference (V-D)
WOMAC pain score (Scale = 0 to 20)			
Mean ± SD	5.62 ± 4.50	7.38 ± 5.22	
Range	0 – 20	0 – 19	
LS mean ± SE	5.95 ± 0.42	7.29 ± 0.44	1.34 ± 0.59
Change from baseline			
Mean ± SD	5.85 ± 4.23	4.68 ± 4.89	95% CI: (0.18, 2.49)
Range	-3 – 15	-4 – 16	p-value: 0.023
WOMAC physical function score (Scale = 0 to 68)			
Mean ± SD	19.7 ± 15.1	25.7 ± 17.6	
Range	0 – 63	0 – 64	
LS mean ± SE	20.2 ± 1.4	25.9 ± 1.4	5.7 ± 1.9
Change from baseline			
Mean ± SD	17.5 ± 15.4	11.8 ± 15.5	95% CI: (2.0, 9.4)
Range	-14 – 60	-22 – 49	p-value: 0.003
Global rating of disease (100 mm VAS)			
Mean ± SD	31.6 ± 29.0	41.5 ± 30.4	
Range	0 – 98	0 – 100	
LS mean ± SE	34.1 ± 2.6	42.6 ± 2.7	8.5 ± 3.6
Change from baseline			
Mean ± SD	30.0 ± 31.2	22.4 ± 29.4	95% CI: (1.5, 15.6)
Range	-29 – 90	-68 – 93	p-value: 0.018

Change from baseline was calculated as baseline minus post-baseline score.
Analysis was analysis of covariance (ANCOVA) with main effects of treatment and center and baseline covariate.
Source: Post-text Table 9.2 and Post-text Table 9.4; Appendix 7, Listing 9.1 and Appendix 7, Listing 9.2

- *Secondary Efficacy Endpoints:*

There was a greater response favoring active treatment in secondary efficacy assessments in subjects who received DSG, in comparison with subjects who received vehicle, and 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 below lists the results of the secondary efficacy outcome analysis.

TABLE 10.1.1.5 : SHOWING SUMMARY TABLE OF SECONDARY EFFICACY OUTCOME ANALYSIS – MES (STUDY -310)

SECONDARY ENDPOINT	Least Mean Squares difference between DSG & vehicle		p-value @ Week 4	p-value @ Week 8
	Week 4	Week 8	(95% CI)	(95% CI)
WOMAC Functional Disability Index:				
o **Pain**	1.45	1.46	0.008 (0.39, 2.51)	0.010 (0.35, 2.57)
o **Physical function**	6.0	6.5	< 0.001 (2.7, 9.3)	< 0.001 (2.9, 10.1)
o **Stiffness**	0.58	0.74	0.009 (0.15, 1.02)	0.002 (0.27, 1.20)
Global rating of disease	8.7	8.3	0.009 (2.2, 15.2)	0.018 (1.4, 15.1)
Global rating of benefit	8.7	9.7	0.014	0.009
Pain on movement assessed at site	13.6	11.3	0.001	0.002
Pain on movement assessed in the subject diary *	*	*	0.025 **	
Spontaneous pain	10.1 mm	11.6 mm	0.001	0.046
Subject global evaluation of treatment				0.005
OARSI response			0.043	0.013
Time-weighed WOMAC pain index				0.009 (0.30, 2.06)
Pain/Rescue response			0.002	< 0.001
Incidence of use of rescue medication (entire study)				<0.010 #

* Assessment of Pain on movement assessed in subject diary Averaged over Days 8 to 14
** p-value averaged over Days 8 to Day 14
# p-value of difference in rescue medication use between treatment groups over entire study.

INCIDENCE OF USE OF RESCUE MEDICATIONS (MES POPULATION):
Use of acetaminophen was slightly lower in the diclofenac sodium group. Over 90% of subjects in each group used rescue medication at some point after randomization.

The mean number of acetaminophen tablets taken per day was 1.4 in the DSG group and

1.7 in the vehicle group. The mean number of days subjects used rescue medication was 29.1 in the DSG group and 34.9 in the vehicle group.

The incidence of rescue medication use was highest at Week 1 (approximately 80% of subjects in both groups), declined over the first 4 weeks and then remained roughly stable thereafter (55-60% in the diclofenac sodium group, 60-70% in the vehicle group).

The use of rescue medication in the MES during the study as a whole is summarized in Table 10.1.1.6 (shown below). The proportions of subjects in the DSG and vehicle groups who used any rescue medication during the study were 90.6% and 90.8%, respectively.

The incidence of rescue medication use was higher in the vehicle group than in the DSG group at each weekly assessment and the differences between the treatment groups were statistically significant at Weeks 2-8, 11 and 12 ($p = 0.007$ to $p = 0.036$).
Statistically significant differences were observed in the number of weeks without rescue medication use and in the average number of tablets taken per day.

The mean number of weeks with no use of rescue medication was 4.74 in the DSG group and 3.14 in the vehicle group ($p = 0.004$), while the average number of rescue medication tablets taken per day was 1.16 in the DSG group and 1.73 in the vehicle group ($p = 0.010$). (See Table 10.1.1.6).

TABLE 10.1.1.6: SHOWING RESCUE MEDICATION USE OVER THE ENTIRE STUDY VOSG-PN-310- MES POPULATION

	DSG N = 127	Vehicle N = 119	p-value
Patients using any rescue medication			
n (%)	115 (90.6)	108 (90.8)	0.72 [1]
Weeks with no rescue medication			
Mean ± SD	4.74 ± 4.41	3.14 ± 4.13	0.004 [2]
Average tablets taken per day			
N	124	104	
Mean ± SD	1.16 ± 1.71	1.73 ± 1.85	0.010 [2]

[1] p-value from Cochran-Mantel-Haenszel (CMH) Chi-squared test of association, stratified by center
[2] p-value from Cochran-Mantel-Haenszel (CMH) Chi-squared test of treatment means, stratified by center
Source: Post-text Table 9.11

Continuous Responder analysis

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.

SAFETY
A pooled safety analysis of controlled Studies VOSG-PN-304, VOSG-PN-310, VOSG-PN-314 and VOSG-PN-315 is discussed in Section 7 of this report.

Deaths, serious adverse events, and adverse events leading to discontinuation are discussed in Section 7 (Safety) of this review in the pooled major safety population.

CONCLUSIONS:
The differences between the DSG and vehicle groups in the primary efficacy endpoints were all statistically significant and favored treatment with topical DSG, 1%.
Primary efficacy comparisons reached statistical significance in both the modified efficacy (MES) and the intent-to-treat (ITT) population.

There was a greater response favoring DSG treatment on all secondary assessments of efficacy in subjects who received DSG vs. those who received vehicle and the differences between the treatment groups were statistically significant at most time points.

Sensitivity analyses and continuous responder analyses confirmed the robustness of the above findings.

10.1.2 INDIVIDUAL STUDY REPORT- VOSG-PE-315 (Hand OA)

Title of Study: An 8-week, randomized, double-blind, multi-center, vehicle-controlled, parallel group study to assess the efficacy and safety of diclofenac sodium gel 1% for the relief of signs and symptoms in subjects with osteoarthritis of the hand

Primary Objective: The primary objective of this 8-week study was to have been to compare the efficacy of diclofenac sodium gel 1% (DSG), applied four times a day versus vehicle in osteoarthritis (OA) of the hand.

Secondary objectives of this study were to have been to evaluate:

- Onset of efficacy of DSG in the dominant hand by assessment of above efficacy outcomes at the study site during the visits at Weeks 1 and 2
- Daily OA pain intensity in the diary over Days 1-14.
- Durability of efficacy, by assessment of above efficacy outcomes at the study site visit at Week 8.
- Effect of DSG on the non-dominant hand by assessment of OA pain intensity as well as the pain and function subscales of the AUSCAN index at the study site during all visits and in the diary.
- Safety profile and tolerability of DSG versus vehicle over 8 weeks.

Study Design: This was to have been an 8-week, prospective, randomized, double-blind, multi-center, placebo- controlled, parallel group study in subjects with OA of the hand. A total of 385 subjects were to have been randomized to treatment, 198 to DSG and 187 to placebo. All randomized subjects were to have been included in the intent-to-treat (ITT analysis).

The protocol specified that subjects were to have used 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 was to have been of lower intensity.

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

DSG or placebo/vehicle was to have been 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 4gm per day) as rescue medication was to have been allowed.

Inclusion Criteria:
Subjects included were to have been men and women ≥40 years of age who met the following criteria:

At Screening:

- Ability to indicate right- or left-handedness (the dominant hand was the target hand for the primary efficacy analysis and both right and left-handed subjects were included).
- A diagnosis of primary hand OA according to ACR criteria with symptoms including pain for at least 12 months, with at least two painful episodes in at least one finger joint during this period and reporting use of a NSAID or salicylate whether oral or topical, during at least one of these episodes, and reporting pain > 15 days during the preceding 30 day period.
- Had reported that pain was usually greater in the dominant hand.
- Expected need to treat the target hand for at least 7 weeks.

At Baseline:

- Pain in the target hand during previous 24 hours rated ≥ 40 mm on a 100 mm VAS.
- If washed out from NSAIDs between screening and baseline visit, 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 visit.
- If there was pain in the non-dominant hand, the rating of pain over the past 24 hours must have been at least 20 mm lower (on a 100 mm VAS) than the corresponding rating in the target hand.
- A posterior-anterior X-ray of the dominant hand, no more than one year old, showing signs of OA in the same painful joints with Kellgren-Lawrence grade 1, 2, or 3 in the dominant hand [Kellgren and Lawrence 1957.
- Confirmed willingness to avoid the use of other topical or systemic (prescription or over-the-counter) analgesic or anti-inflammatory treatments other than the study medications during the course of the study, including other topical anti-arthritic medications such as capsaicin or salicylate.

Exclusion Criteria:
Subjects were to have been excluded if they met any of the following criteria:

- Secondary post-traumatic OA, history and/or evidence of any other rheumatic disease involving the potential target hand or the arm: algodystrophy, septic arthritis, inflammatory joint disease (e.g. psoriatic arthritis), rapidly destructive osteoarthropathy, chondrocalcinosis, gout, recurrent episodes of pseudogout, Paget's disease of bone, articular fracture, ochronosis, acromegaly, hemochromatosis, primary osteochondromatosis, heritable disorders (e.g. hypermobility), collagen gene mutations, carpal tunnel syndrome, Dupuytren's disease and neurological diseases of the hand or arm.

- Symptomatic OA at additional locations besides the hand(s), requiring any symptomatic or disease-modifying treatment at present or the subject is expected to

require such treatment.
- Radiological signs of Kellgren-Lawrence grade 4 OA in the dominant hand.
- Adult juvenile chronic arthritis (i.e. juvenile chronic arthritis with continued activity in adulthood).
- History of rheumatoid arthritis or laboratory values indicative of rheumatoid arthritis with subsequent diagnosis by a physician.
- History of other inflammatory diseases such as colitis within the previous year.
- History of fibromyalgia within the previous year.
- Failure to indicate a dominant hand, i.e. truly ambidextrous.

Treatment: DSG or placebo/vehicle was to have been applied four times daily for 8 weeks (2 gm to the dominant hand, and 2 gm to the non-dominant hand.

Rescue medication:
The use of acetaminophen (up to doses of 4gm per day) as rescue medication was to have been allowed.

Statistical Analysis:
The ***primary efficacy outcome measures*** were to have been:
- OA pain intensity in the dominant target hand over the previous 24 hours.
- Total Australian/Canadian Hand Index (AUSCAN) score for the dominant hand
- Global rating of disease activity

Statistical significance was required to all three co-primary outcomes, analyzed at Week 4 (Visit 5) and Week 6 (Visit 5).

Function was to have been measured by the AUSCAN total score standardized to a 0-100 scale. Pain was to have been measured as OA pain intensity in the target hand in the previous 24 hours on the 100 mm VAS scale.

The ***secondary efficacy outcome measures*** were to have been measured after 1, 2 and 8 weeks of treatment.
These measures were to have been as follows:
- OA pain intensity in the target hand (in the previous 24 hours)
- Global rating of disease activity
- Total AUSCAN score in the target hand (unweighed sum of the scores on 15 questions)

Secondary endpoints that were to have been derived from the above assessment were:
- Time to resolution of pain (OA pain intensity $\leq$ 10 mm in the target hand
- Time to OA pain intensity $\leq$ 20 mm in the target hand
- Osteoarthritis Research Society International response at each visit defined as either of the following:
  - improvement in pain $\geq$ 50% and absolute change $\geq$ 20
  or *at least 2* of the following

- improvement in pain ≥ 20% and absolute change ≥ 10
- improvement in function ≥ 20% and absolute change ≥ 10
- improvement in global rating of disease ≥ 20% and absolute change ≥ 10

- Pain/ rescue response at each visit defined as not taking any rescue medication in the 3 days prior to the day of the study visit and showing a reduction from baseline of at least 20 mm on the VAS assessment of pain intensity in the target hand in the previous 24 hours
- Weekly averages of the diary assessment of daily OA pain intensity

Pain intensity outcomes:
OA pain intensity in the target and in the non-dominant hand was to have been assessed at each visit in the CRF and daily in the diary over Days 1 to 14. The treatment groups were to have been compared on the assessments by day over Days 1-14 and averaged by week (week 1: study days 1-7, week 2: study days 8-14).

Time to pain events:
Time to resolution of pain and time to OA pain intensity ≤20 mm in the target hand, were to have been both determined based on the VAS assessments from the CRF and from the diary. If for one day there was more than one assessment, the higher VAS value was to have been used. The treatments were to have been compared with the Cox proportional hazards model. A patient whose OA pain intensity in the target hand never achieved the target level of pain (whether 10 mm or 20 mm) contributed a censored observation, where the time to event was to have been taken as the number of days between baseline and the day of the last completed VAS assessment.

If there were no statistically significant treatment-by-center interactions among the three primary efficacy outcomes, then a stratified Cox model with the centers chosen as strata was to have been applied.

Safety:
Safety assessments were to have consisted of monitoring and recording of all AE's, SAE's and their severity, monitoring of hematology and blood chemistry, and assessments of vital signs and physical condition.