

Cisplatin/Epinephrine Injectable Gel

Background Document

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NDA 21-236

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TABLE OF CONTENTS

Abbreviations	vi
List of Studies	1
Treatment Plan for Studies 414-94-2 and 514-94-2	3
<u>1 EXECUTIVE SUMMARY</u>	4
<u>1.1 Introduction</u>	4
<u>1.2 Study Design</u>	5
<u>1.3 Dosing and Treatment</u>	6
<u>1.4 Evaluation of Efficacy & Safety</u>	6
<u>1.5 Demographics and Baseline Disease Status</u>	7
<u>1.6 Efficacy Results</u>	8
<u>1.7 Additional Evidence of Benefit</u>	11
<u>1.8 Safety Results</u>	11
<u>1.9 Conclusions</u>	13
<u>2 BACKGROUND INFORMATION</u>	14
<u>2.1 Epidemiology of HNSCC</u>	14
<u>2.2 Natural History</u>	14
<u>2.3 Standard Treatment for Recurrent or Metastatic HNSCC</u>	14
<u>2.4 Limitations of Current Therapy</u>	15
<u>3 PRODUCT DESCRIPTION</u>	18
<u>4 NONCLINICAL STUDIES</u>	20
<u>4.1 Biodistribution</u>	21
<u>4.2 Tumor Pharmacology</u>	22
<u>4.3 Toxicology</u>	23
<u>4.4 Summary of Nonclinical Studies</u>	26
<u>5 CLINICAL PHARMACOKINETICS OF INTRATUMORAL CDDP/EPI GEL</u>	27
<u>5.1 Pharmacokinetic Parameters following Intratumoral CDDP/epi Gel and Intravenous CDDP Solution</u>	29
<u>6 PIVOTAL CLINICAL STUDIES</u>	31
<u>6.1 Study Design</u>	31
6.1.1 <u>Protocol Amendments</u>	32
6.1.2 <u>Entry Criteria</u>	33
6.1.3 <u>Randomization</u>	34
6.1.4 <u>Blinding</u>	34
<u>6.2 Treatment Administration</u>	34
6.2.1 <u>Formulation</u>	34
6.2.2 <u>Schedule and dosing</u>	35
6.2.3 <u>Concomitant Therapy</u>	36
<u>6.3 Endpoints</u>	36
6.3.1 <u>Primary Efficacy Endpoints</u>	36

6.3.2	Secondary Efficacy Endpoints	37
6.3.3	MTT and Selection of Treatment Goals	37
6.3.4	Definition of Response	38
6.3.5	Type and Timing of Assessments	38
6.4	Statistical Analysis	39
6.4.1	Statistical Methods	39
6.4.2	Primary Efficacy Analyses	39
6.4.3	Sample Size Calculations - Based on Tumor Response Rate	39
6.5	Results	40
6.5.1	Patient Disposition	40
6.5.2	Demographics	41
6.5.3	Disease Characteristics	43
6.5.4	Dose Administered	46
6.5.5	Response to Therapy	48
6.5.5.1	MTT Response–Blinded Treatment Phase	48
6.5.5.2	Time to MTT Progression	51
6.5.5.3	MTT Response–Study Overall	52
6.5.5.4	MTT Response in Placebo Crossover Patients	52
6.5.5.5	Response Rate for All Individual Treated Tumors	52
6.5.6	Covariate Analyses of MTT Response	53
6.5.6.1	Multiple Regression Analysis of the MTT Response	54
6.5.7	Inter-Study Differences in Tumor Response	56
6.5.8	Survival	56
6.5.9	Patient Benefit and Attainment of Primary Treatment Goals	58
6.5.9.1	Attainment of Patient Benefit During the Blinded Treatment Phase	58
6.5.9.2	Achievement of Primary Treatment Goals	60
6.5.10	Association of the Primary Efficacy Endpoints, MTT Objective Response and Patient Benefit	61
6.5.11	Additional Evidence of Palliative Benefit	62
6.5.12	Inter-Study Differences in Rate of Patient Benefit Attainment	64
7	SAFETY	65
7.1	Adverse Event Reporting and Coding	65
7.1.1	Local Tissue Conditions	65
7.1.2	Serious Adverse Events (SAEs)	66
7.2	Concomitant Medications	66
7.3	Incidence of Adverse Events	66
7.3.1	Incidence of Immediate Injection Effects	66
7.3.2	Incidence of Local Reactions at the Treatment Site	67
7.3.3	Incidence of Systemic and Other Local Effects	67
7.4	Local Tissue Conditions	69
7.5	Clinically Significant Adverse Reactions	70
7.5.1	Cerebrovascular Events	70
7.5.2	Hemorrhage	71
7.5.3	Cardiovascular Events Other than Cerebrovascular Events	71
7.5.4	Allergy	72

<u>7.6</u>	<u>Serious Adverse Events</u>	72
<u>7.7</u>	<u>Deaths</u>	73
<u>7.8</u>	<u>Drop-outs due to Adverse Events</u>	74
<u>7.9</u>	<u>Systemic Toxicity of Cisplatin</u>	74
8	<u>RISK/BENEFIT ASSESSMENT</u>	77
9	<u>CONCLUSIONS</u>	80
10	<u>BIBLIOGRAPHY</u>	81
11	<u>REFERENCES</u>	83
	Appendix 1: Treatment Goal Questionnaire & Patient Benefit	
	Appendix 2: Individual Outcomes of Therapy	
	Appendix 3: Primary Study Results Before and After Amendment V	
	Appendix 4: Treatment Outcomes: Stratum 3	
	Appendix 5: Supportive Clinical Studies	
	Appendix 6: Draft Package Insert	

Abbreviations

AE	adverse event
BSE	bovine spongiform encephalopathy
CABO	cisplatin, methotrexate, bleomycin, and vincristine
CDDP	cisplatin
CDDP/epi gel	cisplatin/epinephrine injectable gel
CF	cisplatin and fluorouracil
CI	confidence interval
CR	complete response: 100% decrease in baseline tumor volume sustained for ≥ 28 days
CRF	case report form
CVE	cerebrovascular event
EORTC	European Organization of Research and Treatment of Cancer
epi	epinephrine
FACT H&N	Functional Assessment of Cancer Therapy—head and neck version
HNSCC	squamous cell carcinoma of the head and neck
i.d.	intra dermal
i.h.	intrahepatic
i.m.	intramuscular
i.p.	intraperitoneal
i.t.	intratumoral
i.v.	intravenous(ly)
KPS	Karnofsky Performance Status
MTT	most troublesome tumor
NCI	National Cancer Institute
NDA	New Drug Application
PD	progressive disease
PK	pharmacokinetics
PR	partial response: $\geq 50\%$ decrease in baseline tumor volume sustained for ≥ 28 days
RIF	Radiation-induced fibrosarcoma
SAE	serious adverse event
sd	standard deviation
SD	stable disease
Study 414	414-94-2: pivotal efficacy study in patients with HNSCC, North America
Study 514	514-94-2: pivotal efficacy study in patients with HNSCC, Europe
Study 403	403-93-2: supportive efficacy study in patients with solid tumors, North America
Study 503	503-93-2: supportive efficacy study in patients with solid tumors, Europe
TGD	tumor growth delay
TGQ	Treatment Goals Questionnaire
TVQT	tumor volume quadrupling time

List of Studies

Table 1: Placebo-Controlled Studies of CDDP/Epi Gel in Patients with Recurrent or Refractory HNSCC

Study	Location/ Status	Design	Treatments	n
414-94-2	USA, Canada/ Closed 44 sites Study Dates: 15-Jun-95 to 22-Mar-00	Phase III, multi-center, randomized (2:1), double-blind, placebo- controlled Blinded period followed by optional open-label period Patients stratified by tumor volume: Stratum 1: $\leq 5 \text{ cm}^3$ Stratum 2: $>5 - 20 \text{ cm}^3$ Stratum 3: $> 20 \text{ cm}^3$	CDDP/epi gel: 0.25 mL per cm^3 of tumor volume Placebo gel: 0.25 mL per cm^3 of tumor volume Treatments given weekly for ≤ 6 treatments in ≤ 8 weeks then followed for 4 weeks (blinded period) Any patient with disease progression or requiring re-treatment for new or recurrent tumor could receive CDDP/epi gel in the open-label period	Stratum 1: 43 Stratum 2: 43 Stratum 3: 23 (safety only ^a)
514-94-2	Europe, Israel/ Closed 28 sites Study Dates: 21-Jun-95 to 22-Mar-00	Phase III, multicenter, randomized (2:1), double-blind, placebo- controlled Blinded period followed by optional open-label period Patients stratified by tumor volume: Stratum 1: $\leq 5 \text{ cm}^3$ Stratum 2: $>5 - 20 \text{ cm}^3$ Stratum 3: $> 20 \text{ cm}^3$	CDDP/epi gel: 0.25 mL per cm^3 of tumor volume Placebo gel: 0.25 mL per cm^3 of tumor volume Treatments given weekly for ≤ 6 treatments in ≤ 8 weeks then followed for 4 weeks (blinded period) Any patients with disease progression or requiring re-treatment for new or recurrent tumor could receive CDDP/epi gel in the open-label period	Stratum 1: 48 Stratum 2: 44 Stratum 3: 23 (safety only ^a)

^a Stratum 3 not part of original study design; added to the study protocols from Sept. 1995 to May 1997

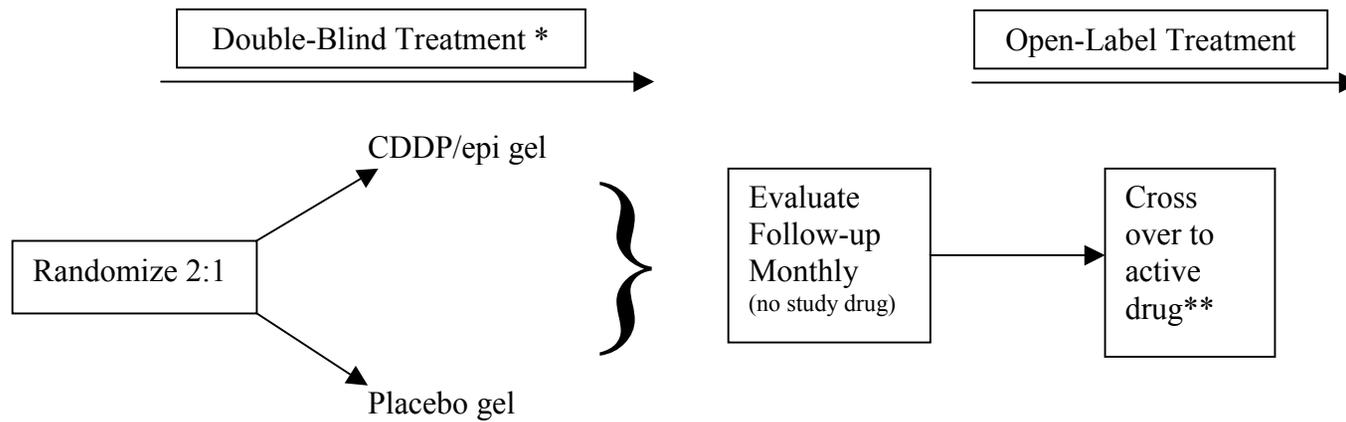
Table 2: Open-Label Studies of CDDP/Epi Gel in Patients with Recurrent or Refractory Solid Tumors

Study	Location/ Status	Design	Treatments	n	Tumor type
39-92-P	USA Closed	Multi-center, open-label, dose escalation/dose-confirmation, Phase I	CDDP/epi gel 0.25, 0.5, 1 and 1.5 mL/ cm ³ of tumor volume weekly for 4 treatments over 3 weeks.	45	Breast (n=13) HNSCC (n=14) Melanoma (n=3) Other (n=14)
403-93-2	USA Closed	Multi-center, open-label, Phase II	CDDP/epi gel 0.5 mL per cm ³ of tumor volume, given weekly for ≤ 6 treatments. Re-treatment was allowed at discretion of investigator.	67	Breast (n=16) Esophageal (n=8) Melanoma (n=13) Other ^a (n=30)
503-93-2	Europe, South Africa/ Closed	Multi-center, open-label, Phase II	CDDP/epi gel 0.5 mL per cm ³ of tumor volume, given weekly for ≤ 6 treatments. Re-treatment was allowed at discretion of investigator.	59	Breast (n=13) Esophageal (n=16) Melanoma (n=15) Other ^a (n=15)
516-99-PK	USA Europe Ongoing	Phase I, open-label, single arm, PK	CDDP/epi gel 0.25 mL per cm ³ of tumor volume, given weekly for ≤ 6 treatments. Re-treatment was allowed at discretion of investigator.	16	HNSCC

^a Includes cervical, colorectal, kidney, lung, ovary, parotid, and rectal cancer.

Figure 1: Treatment Plan for Phase III Trials

Study Schema: Studies 414-94-2 and 514-94-2



* Study remained blinded until last patient completed follow-up phase.

** At progression, any time after three blinded visits

1 Executive Summary

1.1 Introduction

The subject of NDA 21-236 is for the use of cisplatin/epinephrine injectable gel for the treatment of patients with recurrent, advanced local-regional squamous cell carcinoma of the head and neck (HNSCC). Local recurrence of HNSCC is a common and morbid event, since approximately 60–70% of patients experience local tumor recurrences after primary treatment with conventional surgery and radiation.* Recurrent tumors can be painful, invade vital tissues resulting in impaired function, and curtail normal activity. Patients with such tumors are often not candidates for repeat irradiation or resection because the tumors occur in previously irradiated locations and surgical excision is associated with excessive morbidity, slow recovery and cost.* In this difficult setting of locally recurrent disease with or without distant metastases, systemic platinum-based chemotherapy has long been a palliative option.* However, many of these patients are too fragile to tolerate the high-dose systemic cisplatin-based chemotherapy required to achieve substantial rates of local tumor control. Even for those who can tolerate therapy, results have been disappointing with limited responses, poor compliance, and high toxicity levels.⁵⁻⁹ Cisplatin/epinephrine (CDDP/epi) injectable gel, a novel drug system developed by Matrix Pharmaceutical, Inc. is designed to treat local tumors while limiting systemic toxicity. CDDP/epi gel is intended to be injected directly into tumors, with the goal of achieving high, sustained, intratumoral cisplatin concentrations for extended periods of time, but without the toxicities typically seen with systemically administered cisplatin.

CDDP/epi gel is composed of a uniform suspension of cisplatin and epinephrine in an aqueous collagen matrix. The major active component, cisplatin, is an antineoplastic agent with a long history of proven effectiveness that is widely used in the management of head and neck cancer. The gel matrix entraps the cisplatin, providing a uniform suspension of the drug, and is believed to provide enhanced drug retention by inhibiting local interstitial fluid flow and slowing drug clearance.* The second active component, epinephrine, acts as a local vasoconstrictor that further inhibits cisplatin clearance away from the injection site. This localized delivery system also results in slowed and/or reduced entry of drug into the systemic circulation, resulting in minimal exposure of distant tissues to the drug, and a low incidence of systemic side effects. Thus, efficacy can be attained with total cisplatin doses lower than those administered systemically.

Because the pharmacology of both active agents, cisplatin and epinephrine, has been well characterized, the preclinical studies of CDDP/epi gel focused on demonstrations of safety and efficacy of the novel drug system in various tumor models.* These studies showed that intratumoral administration of

* For a selected list of literature references detailing the preclinical and clinical development of this treatment please see the bibliography at the end of this document.

CDDP/epi gel is efficacious and superior to aqueous CDDP solutions administered either intratumorally or systemically. Preclinical studies also documented that epinephrine was essential to optimize antitumor efficacy.

Phase I and II clinical trials demonstrated the safety and efficacy of CDDP/epi gel in various solid tumors, including breast cancer, esophageal cancer, and melanoma, as well as head and neck cancer. The pivotal Phase III trials focused on HNSCC, particularly on patients with advanced disease. The results of these trials demonstrate that treatment with CDDP/epi gel provides not only objective tumor response, but also durable benefits—such as reduced pain and prevention of obstruction—for patients who have few if any options remaining after failure of surgery, radiation, and systemic chemotherapy.

This briefing document describes the Phase III clinical trials and summarizes the data available to support this New Drug Application for the use of CDDP/epi gel in patients with recurrent HNSCC who are not suitable candidates for other standard therapies such as surgery, radiation, or systemic chemotherapy. In May 1999 CDDP/epi gel was granted Fast Track Status by FDA for this indication, and in April 2000 was given orphan drug designation for recurrent or refractory HNSCC.

1.2 Study Design

The two pivotal Phase III studies conducted in support of this NDA were prospective, randomized, double-blind, placebo-controlled trials that compared the safety and efficacy of CDDP/epi gel to placebo gel in the treatment of patients with recurrent or refractory HNSCC (Protocols 414-94-2 and 514-94-2, referred to as Studies 414 and 514). Patients were required to have received at least one course of prior therapy (radiation, chemotherapy, surgery) for their disease, and most patients had undergone treatment with two or three of these modalities.

Patients were stratified by pretreatment volume of the “most troublesome tumor” (MTT) that is, the most symptomatic or threatening tumor, selected by the physician into stratum 1 ($0.5 \text{ to } \leq 5 \text{ cm}^3$) and stratum 2 ($5 \text{ to } > 20 \text{ cm}^3$). A third stratum for tumors $> 20 \text{ cm}^3$ was added later by protocol amendment. Patients with tumors $> 20 \text{ cm}^3$ were designated for inclusion in the safety analysis, but excluded from the efficacy analysis.

The studies were designed and powered to assess objective tumor response as the primary efficacy variable. In this cancer where even small tumors can compromise the structure and function of the oral cavity, pharynx, larynx, and sinuses, control of tumor mass is expected to provide clinical benefit by relieving or preventing a patient’s most life-impacting symptoms. Convincing evidence that control of individual tumors provides a durable clinical benefit to patients is important. Traditional quality-of-life and functionality instruments, such as the Functional Assessment of Cancer Therapy–Head and Neck (FACT–H&N) scale and Karnofsky Performance Status (KPS), provide good general measures of how systemic cancer affects a patient’s quality of life (and were both used in this study). However, patients with problematic individual tumor masses may benefit from local therapy in ways not captured by these

commonly used instruments. For this reason, and in conjunction with the FDA, a new instrument, the Treatment Goals Questionnaire, was developed in which “Patient Benefit” was rigorously defined and based on the patient’s and investigator’s progress toward achieving prospectively selected treatment goals.

In 1997, an amendment to the study protocols was made to exclude tumors directly adjacent to the carotid artery and to close enrollment to patients with tumors $> 20 \text{ cm}^3$. This was done after evaluation of safety reports of six patients who experienced a cerebrovascular adverse event. In the same amendment, the dose was reduced from 0.5 mL/cm^3 tumor volume to 0.25 mL/cm^3 tumor volume. No change in tumor response occurred as a result of the change in dosage and no treatment-related cerebrovascular accidents occurred after this protocol amendment.

1.3 Dosing and Treatment

CDDP/epi gel (containing 4 mg of cisplatin and 0.1 mg of epinephrine per mL of gel) or placebo gel (containing neither active component) was administered in an outpatient setting or during a brief hospital stay. In the blinded treatment phase, patients received weekly treatments until they either had received six treatments within an 8-week period or had achieved a complete objective response (CR) of the MTT, whichever occurred first. Patients achieving a complete response were then evaluated weekly for 4 weeks without treatment. If after three treatments in the blinded phase treated tumors progressed, patients could cross over to open-label phase, during which they received open label active drug. Concomitant therapy with other anti-cancer therapy was not allowed.

1.4 Evaluation of Efficacy & Safety

The original primary efficacy endpoint in both trials was objective response of the most troublesome tumor. Secondary endpoints included evaluation of tumor-related symptoms and other quality of life parameters. The endpoint of Patient Benefit was first requested by the FDA in 1997, and was incorporated into the analysis plan as an endpoint. In May 2000, Patient Benefit was further designated as a primary endpoint.

Objective tumor response was based on reductions in baseline tumor volume of the MTT sustained for at least 28 days: complete response (CR), 100% reduction in tumor volume; or partial response (PR), 50 to $<100\%$ reduction. Non-response was defined as stable disease (SD), $<50\%$ reduction or an increase of $< 25\%$; or progressive disease (PD), $\geq 25\%$ increase in tumor volume.

Patient Benefit was based on the patient’s achievement of prospectively–selected treatment goals selected by patient and investigator associated with the most troublesome tumor (the “primary” treatment goals; other secondary goals could be selected but were not included in the determination of the Patient Benefit). The Treatment Goals Questionnaire listed eight “palliative” goals (improvements in wound care; pain control; ability to see, to hear, or to smell; physical appearance; obstructive

symptoms; or mobility) and three “preventive” goals (prevention of obstruction, tumors breaking through the skin, or invasion of a vital structure). Patients were given the option to select one primary palliative goal for their most troublesome tumor; investigators were to choose at least one primary palliative or one primary preventive goal for the most troublesome tumor. Progress related to the palliative goals was graded on a 4-point scale in which “achievement” was defined as ≥ 1 -point improvement sustained for at least 28 days; in contrast, preventive goals were either “achieved”, i.e., the event was prevented for at least 28 days, or “not achieved”, i.e., the event occurred. Both patient and physician assessments were incorporated into an algorithm such that Patient Benefit was ascribed if either (1) both said that the goal was achieved or (2) one said that the goal was achieved and the other said there was no worsening of symptoms. The association of objective response rate and Patient Benefit was also evaluated.

1.5 Demographics and Baseline Disease Status

One hundred seventy-eight (178; 119 CDDP/epi gel and 59 placebo gel) patients in studies 414 and 514 had an MTT ≤ 20 cm³ and represent the intent-to-treat efficacy population. An additional 46 treated patients with tumors > 20 cm³ were included in the safety analysis. All patients enrolled in Studies 414 and 514 had advanced HNSCC. There were no substantial differences in demographics or baseline disease characteristics between the CDDP/epi gel and placebo gel treatment groups. In descending order of frequency, the primary cancer site was the oral cavity, larynx, or oropharynx for both CDDP/epi gel and placebo gel groups. This group of patients with advanced recurrent disease had undergone multiple prior treatments: 89% had been treated with at least two modalities (surgery, radiation or chemotherapy). Nearly all target tumors (89%) were located in a previously irradiated field with chronic post-radiation changes such as fibrosis and inflammation.

Table 3: Patient Demographics by Study

	414-94-2 United States and Canada		514-94-2 Europe and Israel	
	CDDP/epi Gel n= 62	Placebo Gel n= 24	CDDP/epi Gel n=57	Placebo Gel n= 35
Male (%)	50 (81%)	17 (71%)	45 (79%)	30 (86%)
Female (%)	12 (19%)	7 (29%)	12 (21%)	5 (14%)
Age	63	61	57	61
Median (range)	(33-87)	(40-82)	(37-82)	(43-84)
Ethnic background				
white	51 (82%)	18 (75%)	57 (100%)	35 (100%)
black	4 (6%)	1 (4%)	0	0
other	7 (12%)	5 (21%)	0	0
Karnofsky Performance Status				
100-90	25 (40%)	12 (50%)	26 (46%)	13 (37%)
80-70	26 (42%)	9 (38%)	24 (42%)	13 (37%)
60-50	11 (18%)	2 (8%)	7 (13%)	8 (23%)
40	0 (0%)	1 (4%)	0 (0%)	1 (3%)
FACT-H&N Baseline Score	98	108	105	103
Median (range)	(64-139)	(60-146)	(65-136)	(62-132)

Baseline MTT vol. (cm ³)	5.3	4.8	4.9	5.3
Median (range)	(0.49–20)	(0.13–19)	(0.75–20)	(0.50–20)

1.6 Efficacy Results

In the intent-to-treat analysis, the response rate for patients treated with CDDP/epi gel in each phase III trial was 34% and 25% (Study 414, p=0.001; Study 514, p=0.007). Complete responses were nearly twice as frequent as partial responses (see Tables 4a and 4b). Only one patient treated with placebo gel had a response (p < 0.001).

For the studies combined, the overall objective response of the MTT was 29% (35/119). For patients responding to CDDP/epi gel, the median time to onset of response was 21 days and the median response duration was 78 days (range, 30⁺ to 554⁺ days). Of the 35 patients who responded to CDDP/epi gel, 33 (94%) of the MTTs were still in remission at the time the patient left the study. Many of the responding patients were not able to extend their participation in the study beyond a few months, due to systemic disease progression, general physical debilitation, death, or loss to follow-up.

Patients randomized to the placebo gel group in the blinded treatment period who crossed over to receive open-label CDDP/epi gel had a response rate of 27% which was similar to the MTT response rate (29%) in the blinded treatment phase. Of note was that for the placebo gel treated patients, the median percent increase in MTT volume during the placebo gel treatment period was 50%. In addition to treating the MTT, the protocol permitted treatment of other tumors in the same patient. For patients treated with CDDP/epi gel in the Phase III controlled studies, the response rate of all individual treated tumors (MTT plus other tumors treated at the discretion of the investigator) was 30% (68/227).

Table 4a: Summary of MTT Efficacy Results, by Study

	414-94-2	
	CDDP/epi Gel n=62	Placebo Gel n=24
Complete response (CR)	14 (23%)	0 (0%)
Partial response (PR)	7 (11%)	0 (0%)
Overall response (CR + PR)	21 (34%)	0 (0%)
(95% Confidence Interval)	(22-47%)	(0-14%)
p value ^a	p=0.001	
Median Time to Onset of Response (days)	17	n/a
Median Duration of Response (days)	85	n/a

^aExact Cochran-Mantel-Haenszel test

Table 4b: Summary of MTT Efficacy Results, by Study

	514-94-2	
	CDDP/epi Gel n=57	Placebo Gel n=35
Complete response (CR)	9 (16%)	1 (3%)
Partial response (PR)	5 (9%)	0 (0%)
Overall response (CR + PR) (95% Confidence Interval)	14 (25%) (14-38%)	1 (3%) (0.072-15%)
p value ^a	p=0.007	
Median Time to Onset of Response (days)	53	56
Median Duration of Response (days)	64	54

^aExact Cochran-Mantel-Haenszel test

Table 5: Summary of MTT Efficacy Results, Studies Combined

	CDDP/epi Gel n=119	Placebo Gel n=59
Complete response (CR)	23 (19%)	1 (2%)
Partial response (PR)	12 (10%)	0
p-value ^a	p<0.001	
Overall response (CR + PR) (95% Confidence Interval)	35 (29%) (21-38%)	1 (2%) (0.043-9.1%)
Median Time to Response, days (range)	21 (7-162)	56
Median Duration of Response, days (range)	78 (30-554+)	54
^a Exact Cochran-Mantel-Haenszel test		

The objective response rate of the MTT was analyzed with regard to a number of covariate effects, including demographics, baseline clinical characteristics, previous cancer therapy, and tumor location. In a multiple regression analysis, tumor response was only affected by baseline KPS, baseline volume of the MTT and location of the MTT. An effect of baseline KPS was observed when the KPS was divided into two categories, 40-80 and 90-100 ($p = 0.018$), with MTT response being more likely to occur in patients with a higher KPS. Baseline volume of the MTT and location of the MTT (cervical, facial, oral, or other) had apparent prognostic value ($p=0.033$ and $p=0.027$, respectively) with regard to the response of the MTT in patients treated with CDDP/epi gel. Smaller MTTs had a higher response rate (37%) than did larger MTTs (21%), and MTTs in facial or oral had higher response rates (44% and 42% respectively) than cervical or “other” locations (20% and 14%, respectively).

Treatment with CDDP/epi gel reduced tumor-related symptoms as measured by the Treatment Goal Questionnaire (TGQ). Results from the TGQ were used in the Patient Benefit Algorithm to determine a prospectively defined outcome, “Patient Benefit.” The primary treatment goals most frequently selected by patients were pain control (34%), relief of obstructive symptoms (22%), and wound care (20%). The primary treatment goals most frequently selected by investigators were pain control (22%), wound care (20%), and prevention of tumor erosion through skin (19%). Relief of obstructive

symptoms and prevention of invasion of vital structures were two other common investigator-chosen goals.

In both studies 414 and 514, Patient Benefit was higher in patients treated with CDDP/epi gel than in patients treated with placebo gel (Table 6). For the combined studies, the difference in Patient Benefit rates between patients treated with CDDP/epi gel and placebo gel was statistically significant (27% versus 12%, exact Cochran-Mantel-Haenszel test, $p = 0.046$). There was a positive trend in each individual Phase III study ($p = 0.18$ and $p = 0.24$, for Studies 414 and 514, respectively). The rate of attainment of Patient Benefit for the CDDP/epi gel group was at least twice that of the placebo gel group in both trials.

Of the 119 patients treated with CDDP/epi gel, 35 (29%) had an objective MTT response and are referred to as “responders.” There were 84 patients treated with CDDP/epi gel in the treatment phase who did not have an objective response of the MTT and are referred to as “non-responders.” There was a significant association between objective tumor response and Patient Benefit ($p = 0.012$); responders were 2.4 times more likely to benefit from treatment than were non-responders.

Table 6: Patient Benefit Rate-Blinded Treatment Phase, by Study

	414-94-2					514-94-2				
	CDDP/epi Gel		Placebo Gel		p-value	CDDP/epi Gel		Placebo Gel		p-value
	Benefit Rate (%)		Benefit Rate (%)			Benefit Rate (%)		Benefit Rate (%)		
Strata 1 and 2	21	(34%)	4	(17%)	0.18 ^a	11	(19%)	3	(9%)	0.24 ^a

^a Cochran-Mantel-Haenszel test

Table 7: Patient Benefit Rate-Blinded Treatment Phase, Studies Combined

	CDDP/epi Gel		Placebo Gel		p-value ^a
	Benefit Rate (%)		Benefit Rate (%)		
Strata 1 and 2	32/119	(27%)	7/59	(12%)	0.046

^a Cochran-Mantel-Haenszel test

Table 8: Association Between Objective Response of MTT and Attainment of Patient Benefit in Patients Treated with CDDP/epi Gel, Studies combined

	Responders			Non-responders			p value ^a
	n	No. with Benefit	Benefit Rate	n	No. with Benefit	Benefit Rate	
Strata 1 & 2	35	16	46%	84	16	19%	0.012

^a Cochran-Mantel-Haenszel test

1.7 Additional Evidence of Benefit

Patients randomized to CDDP/epi gel were also compared to placebo gel patients with regard to attainment of other desirable clinical benefit outcomes in blinded treatment phase. In both studies, patients in the active treatment group were more likely than placebo patients to attain one or more of the prospectively selected goals (primary and secondary goals chosen by patient and investigator). This relationship was statistically significant in Study 414 and for the combined studies. In both studies, patients in the CDDP/epi gel groups also tended to be more likely than placebo gel patients to experience an unforeseen benefit during the blinded phase.

1.8 Safety Results

In the Phase III studies, patients were randomized into one of three strata based on the size of their MTT. In keeping with the original analysis plan, only Strata 1 and 2 patients were evaluated for efficacy; however, patients from all three strata were included in the analysis of safety. The safety results are presented from the 150 patients randomized to the CDDP/epi group and 75 patients who were randomized to the placebo gel group. To better characterize the safety of the product, adverse events are presented using the following categories:

- *Immediate Injection Effects* — Adverse events that occurred either during injection or within a 15- to 20-minute period following an injection.
- *Local Reactions at the Treatment Site* — Adverse events that occurred at the injection site after the 15 to 20 minute period immediately following an injection.
- *Systemic/Other Local Effects* — Any systemic or local adverse event not at the injection site.

A tabular summary of the most common adverse events, regardless of relationship, are presented below by category.

Table 9: Summary of Most Common Adverse Events, Studies Combined

	CDDP/epi Gel n=150		Placebo Gel n=75	
	All	Severe	All	Severe
Immediate Injection Effects				
Pain	41 (27%)	15 (10%)	15 (20%)	3 (4%)
Hypertension	6 (4%)	3 (2%)	3 (4%)	0 (0%)
Tachycardia	6 (4%)	1 (<1%)	2 (3%)	2 (3%)
Local Reaction at Treatment Site				
Pain	45 (30%)	18 (12%)	13 (17%)	5 (7%)
Facial Edema	15 (10%)	5 (3%)	0 (0%)	0 (0%)
Local Infection	12 (8%)	2 (1%)	1 (1%)	0 (0%)
Neck Pain	10 (7%)	5 (3%)	2 (3%)	0 (0%)
Hemorrhage	10 (7%)	6 (4%)	2 (3%)	0 (0%)
Swelling	10 (7%)	2 (1%)	1 (1%)	0 (0%)
Necrosis	8 (5%)	2 (1%)	1 (1%)	1 (1%)
Systemic/Other Local Effects				
Pain	32 (21%)	10 (7%)	11 (15%)	3 (4%)
Nausea	25 (17%)	4 (3%)	6 (8%)	2 (3%)
Vomiting	24 (16%)	3 (2%)	2 (3%)	1 (1%)
Asthenia	22 (15%)	8 (5%)	8 (11%)	3 (4%)
Constipation	20 (13%)	4 (3%)	3 (4%)	0 (0%)
Facial Edema	18 (12%)	7 (5%)	2 (3%)	1 (1%)
Anorexia	16 (11%)	4 (3%)	1 (1%)	0 (0%)
Anemia	16 (11%)	6 (4%)	5 (7%)	1 (1%)
Dyspnea	16 (11%)	8 (5%)	6 (8%)	2 (3%)
Infection	15 (10%)	3 (2%)	7 (9%)	1 (1%)
Dysphagia	15 (10%)	4 (3%)	4 (5%)	1 (1%)

There were a total of six patients who experienced a cerebrovascular event (CVE) shortly after administration of study drug (5 CDDP/epi gel, 1 placebo, all in Study 414). These treatment-related CVEs were probably caused by carotid artery vasospasm precipitated by needle trauma to the artery, chemical irritation, tissue damage, and/or mechanical pressure from gel injected into a tumor adjacent to an artery. These events prompted a protocol amendment that specifically prohibited treating tumors directly adjacent to the carotid artery and with baseline, tumor volume >20 cm³, and also resulted in additional recommendations for administration of the study drug. No treatment-related CVEs occurred in the 38 patients enrolled in Study 514 prior to the amendment or in the 110 patients in either study treated after the protocol amendment.

All deaths that occurred on study or within 30 days of study discontinuation were recorded. Overall, there were 54 deaths (36%) among patients randomized to CDDP/epi gel and 28 deaths (37%) among patients randomized to placebo gel. Three patients died due to hemorrhage; a relationship to study treatment could not be excluded.

1.9 Conclusions

The two randomized, placebo-controlled phase III trials, 414 and 514, provide evidence that intratumoral injections of CDDP/epi gel result in objective tumor response. The overall objective response of the primary target tumor (MTT) was 29% in the CDDP/epi gel group and 2% in the placebo gel group ($p < 0.001$) in the blinded treatment period.

Tumor response in patients with advanced disease was clinically meaningful, as indicated by a significant association between tumor response and the attainment of Patient Benefit ($p = 0.012$). Patients with tumor response were 2.4 times more likely to benefit from treatment than were nonresponders.

Intratumoral therapy with CDDP/epi gel is an effective treatment for patients with locally advanced HNSCC who otherwise have few, if any, remaining treatment options.

2 Background Information

2.1 Epidemiology of HNSCC

Between 40,000 and 50,000 patients are diagnosed with non-cutaneous head and neck cancer^{1,2,3} each year in the United States, and estimates of the worldwide incidence reach as high as 500,000 annually. More than 80% of cases are primary squamous cell carcinomas. The most common primary sites are the larynx, the oral cavity, and the pharynx, in descending order of frequency. Head and neck cancers occur more often in males than females (3:1 ratio) and incidence increases with age (median age 50 years) and with the use of alcohol and tobacco. More than 60% of patients present with locally advanced disease (Stages III-IV), and thus are at high risk for failure following primary treatment.

2.2 Natural History

Head and neck cancers tend to invade locally and spread via lymphatic channels early. Their natural history is characterized by a remarkable propensity for local recurrence, even following apparently adequate primary management. Initial surgery^{4,5} may be limited or avoided because of important functional concerns arising from the critical anatomic relations in this region. The occurrence of multiple primaries in such patients may further narrow treatment options. Experts have commented on the rarity of distant relapse in the absence of local or nodal recurrence.⁶ Even with aggressive, modern combined-modality approaches, local or regional failure is a significant problem, which frequently occurs in the absence of clinically detectable distant metastatic disease.⁷ In these settings patients may become candidates for salvage surgery or irradiation. It is not unusual for patients to have multiple local recurrences over time, which may be managed by multiple surgical attempts at control, or more recently, re-irradiation. Such recurrences and treatments often have important functional sequelae. Several specific patterns or syndromes of recurrence have been described, such as recurrence at tracheostomy sites,⁸ which threaten airway access and secretion management. These recurrences can ultimately become unmanageable by current therapies, and can be the predominant clinical problem for patients even in the presence of distant metastatic disease.

2.3 Standard Treatment for Recurrent or Metastatic HNSCC

The majority of patients with recurrent disease^{9,10} have already undergone prior surgery, typically involving complete or radical resection of their primary cancer and/or cervical lymph nodes, followed by reconstructive surgery. Most patients have had prior treatment with ionizing radiation and may not be eligible for further radiation because of the potential for local complications such as soft tissue necrosis, osteoradionecrosis, or radiation myelitis. Although many patients may be helped by “salvage” surgery or re-irradiation, this is not always feasible and patients so treated remain at risk for future recurrence.

There are two therapies currently approved for this patient population: 1) hydroxyurea used concomitantly with radiation therapy is intended for use in the local control of primary HNSCC, and 2) bleomycin.

For patients with recurrent, unresectable disease the primary goal of therapy is palliation. Methotrexate, bleomycin, fluorouracil, cisplatin, carboplatin, and doxorubicin have been studied extensively as individual agents for HNSCC. More recently, ifosfamide, the taxanes, and vinorelbine have been shown to have activity. Most combination regimens derive from these agents.

Treatments with single agents have shown typical partial response rates of 10-30% and median response durations of 2 to 6 months. Combination regimens including CDDP have produced higher response rates.¹⁰ Cisplatin/fluorouracil is a widely used regimen which has been frequently studied in clinical trials.^{7,9,10} The European Organization of Research and Treatment of Cancer (EORTC) conducted a Phase III randomized, parallel group trial of 382 chemotherapy-naïve patients with recurrent or metastatic head and neck cancer.¹¹ The three treatment arms included two combination regimens and one single-agent regimen. The combination regimens were: 1) CABO (cisplatin, methotrexate, bleomycin, and vincristine) and 2) CF (cisplatin and 5-FU) and resulted in response rates of 34% and 31%, respectively. The regimen of cisplatin alone had a lower response rate (15%). The difference between each combination regimen and the cisplatin-only regimen was statistically significant ($p < 0.001$ and $p = 0.003$, respectively). However, because of increased toxicity and mortality associated with the combination regimens used in this study, the EORTC recommended less toxic single-agent therapies as standard treatment for patients with recurrent or metastatic disease, although the benefit of any chemotherapy was deemed questionable.¹¹

Because of the poor prognosis for patients with recurrent and metastatic HNSCC, various types of therapy are under investigation, including gene transfer, photosensitization, biologic response modifiers, and new chemotherapeutic agents.^{5,10,11,12} Some of the newer chemotherapeutic agents under investigation for HNSCC are docetaxel, paclitaxel, gemcitabine, thymetaq, topotecan, and amonafide. These agents have not demonstrated any significant improvements in response rates, with the exception of the taxanes (docetaxel and paclitaxel).¹⁰ Many phase II trials have reported encouraging response rates with taxane-based regimens but no survival benefit has yet been demonstrated. Some of the most impressive results have been in highly selected populations with primary locally advanced, unresectable cancer. As discussed below, toxicity is still a limitation.

2.4 Limitations of Current Therapy

Patients with HNSCC often lack adequate support systems. Gradual, progressive weight loss and inanition are common. Many patients have problems with mouth care due to the disease or therapy. Radiation therapy is typically associated with mucositis, xerostomia, and hypothyroidism. Systemic chemotherapy may be associated with mucositis, nausea, vomiting, peripheral neuropathy, renal

toxicity, and thrombocytopenia. Many patients with advanced HNSCC are elderly, undernourished, and suffer from co-morbid respiratory or cardiac illnesses. These factors increase the risks associated with systemic chemotherapy, especially if the regimen is aggressive.

In the Phase III trial conducted by EORTC,¹¹ toxicity and mortality were higher with combination therapies (CF and CABO) than with CDDP alone. Survival rates were not different among the three treatment arms. Grade 3 to 4 leukopenia was more common with the combination regimens (12-13%) as compared to single-agent cisplatin (3%). Likewise, infection, alopecia, diarrhea, stomatitis, peripheral neuropathy, fever and chills, ototoxicity, bleeding, and skin reactions were more common in the combination regimens, compared to the single-agent regimen.

Combination regimens with newer agents such as paclitaxel, have been studied, and although response rates are better, toxicity is still an issue. For example, in the ECOG phase III trial of cisplatin in combination with paclitaxel at low or high dose, there was a 32% incidence of study discontinuation due to toxicities, and no significant difference in results of high versus low dose groups.^{12,13} In the Phase II trial of paclitaxel plus cisplatin and ifosfamide,¹⁴ toxicities included hematologic, gastrointestinal, neurologic, infectious, and other adverse effects, which led to hospitalization in 17% of patients. Of the 53 patients, grade 3 or 4 neutropenia occurred in 90% of patients, with neutropenic fever in 27%. Blood transfusions were required in 11% of patients. Non-hematologic toxicity included peripheral sensory neuropathy (50%), mucositis (17%); fatigue (15%); pneumonia requiring hospitalization (15%); renal toxicity (9%); grade 3 nausea and vomiting (6%); and orthostatic hypotension (6%), requiring hospitalization in one patient. A more recent trial utilizing docetaxel, cisplatin and fluorouracil reported an overall response rate of 53% in a highly selected primary cancer population.⁵ Despite the fact that all patients were relatively favorable in performance status (ECOG 0 or 1) toxicity was considerable with 95% grade 3 or 4 neutropenia and a 19% incidence of febrile neutropenia. Another recent trial utilizing paclitaxel and carboplatin reported a 15% incidence of febrile neutropenia in a similar frontline population.¹⁵

The results reported using systemic chemotherapy for advanced disease reflect overall response, most of which are usually partial, and include a mixture of patients who may have either distant metastases, or local-regional recurrent masses or both. Response rates of distant and local-regional disease to systemic therapy are rarely reported separately but when available have shown response of local-regional disease to systemic therapy to be inferior to that of distant metastases.⁴ Although distant metastases are certainly critical in determining overall survival, local disease manifestations frequently dominate symptoms and patient care objectives. From the experience with primary induction chemotherapy for locally advanced HNSCC,^{15,16} it is known that regional lymph node metastases, which are often the precursors of regional recurrences, are actually less likely to respond to systemic chemotherapy than are the primary tumors. Recurrences of cancer within irradiated fields can

furthermore be relatively resistant to systemic chemotherapy. For these reasons alternative methods to manage locally recurrent HNSCC are clearly needed.

3 Product Description

Cisplatin/epinephrine injectable gel (CDDP/epi gel) is a novel drug system developed by Matrix Pharmaceutical, Inc. for intratumoral administration in the treatment of solid tumors, including squamous cell carcinoma of the head and neck (HNSCC). The product contains a fixed combination of cisplatin at 4 mg/mL and epinephrine at 0.1 mg/mL in a biocompatible collagen gel. The product is intended to be injected directly into the tumor tissue. Administration is via a syringe with narrow gauge needle so that any accessible lesion or solid tumor that can be seen, palpated, or visualized with established imaging techniques can be treated. Because of the local nature of the therapy, dosing of the product is based on tumor volume (0.25 mL gel per cm³ tumor volume, or approximately 1 mg CDDP per gram of tumor tissue).

The local retention afforded by the delivery system results in slowed and/or reduced entry of drug into the systemic circulation, minimizing exposure of distant tissues to the drug, resulting in a lower incidence of systemic side effects. This provides high local drug concentrations that are maintained in the tumor (i.e., at or near the site of administration) over an extended time period. Such high tumoral concentrations are unachievable by systemic administration of drug.

The major active species in CDDP/epi gel is cisplatin (CDDP), a cytotoxic drug with an extensive history of use as a cancer therapeutic in humans. The drug is widely used in the treatment of various cancers via intravenous administration. Cisplatin is believed to act primarily via its interaction with DNA, forming inter- and intra-strand crosslinked adducts which interfere with DNA replication and repair, inducing cell death through the apoptotic cascade. Cisplatin also forms DNA-protein crosslinks and interacts with other components of the cell, such as glutathione, but the contribution of these processes to its antitumor activity has not been well characterized. The major dose-limiting toxicity of this drug when administered systemically is nephrotoxicity. Additionally, ototoxicity, myelotoxicity, and peripheral neuropathy can occur with long-term use. Severe nausea, vomiting, and dehydration are other adverse effects of systemic cisplatin treatment that are managed to some degree with hydration and antiemetics.

Epinephrine (epi), or adrenaline, is a well-known catecholamine with alpha- and beta-adrenergic activities. It has a long history of use as a vasoconstrictor, providing enhanced localization and retention of local anesthetics. In the CDDP/epi gel formulation, this activity as a local vasoconstrictor is also exploited, to inhibit cisplatin clearance by restricting blood flow, thereby enhancing local drug retention.

The gel formulation is comprised of highly purified bovine collagen dispersed in an aqueous buffer system and is similar to that used for cosmetic correction of skin deformities and improvement of bladder sphincter function. The viscous collagen gel matrix entraps the cisplatin, providing a physically stable suspension of the drug, allowing accurate dosing and placement of the drug at the

tumor site. Another key feature is that the gel is shear-thinning, allowing ease of injection through a needle, then resuming its high viscosity and retention properties once placed in the tumor. Subsequent to release of drug, the collagen gel matrix is biodegraded locally and/or incorporated into local tissues.

The CDDP/epi gel is prepared immediately prior to use from sterile, nonpyrogenic components supplied in kit form. The kit includes a vial containing a lyophilized cisplatin formulation, a vial containing a specially formulated epinephrine solution, and a prefilled syringe containing collagen gel. The preparation process involves reconstituting the lyophilized cisplatin to a suspension with the epinephrine solution, then mixing an aliquot of the resultant cisplatin suspension with the collagen gel via syringe-to-syringe transfer back and forth, through a Luer-lock connector. The finished gel preparation nominally contains CDDP at 4.0 mg/mL and epinephrine at 0.1 mg/mL. Other ingredients include purified bovine collagen as gellant, sodium phosphates and acetic acid / sodium acetate (as buffering agents), sodium chloride (as a tonicifier), mannitol (as a tonicifier and lyophilization aid) edetate disodium (as a metal chelator for stabilization of epinephrine), sodium metabisulfite (as an antioxidant stabilizer for epinephrine), polysorbate 80 (to aid in producing a uniform suspension upon reconstitution) and water for injection, with sodium hydroxide/hydrochloric acid used to adjust pH.

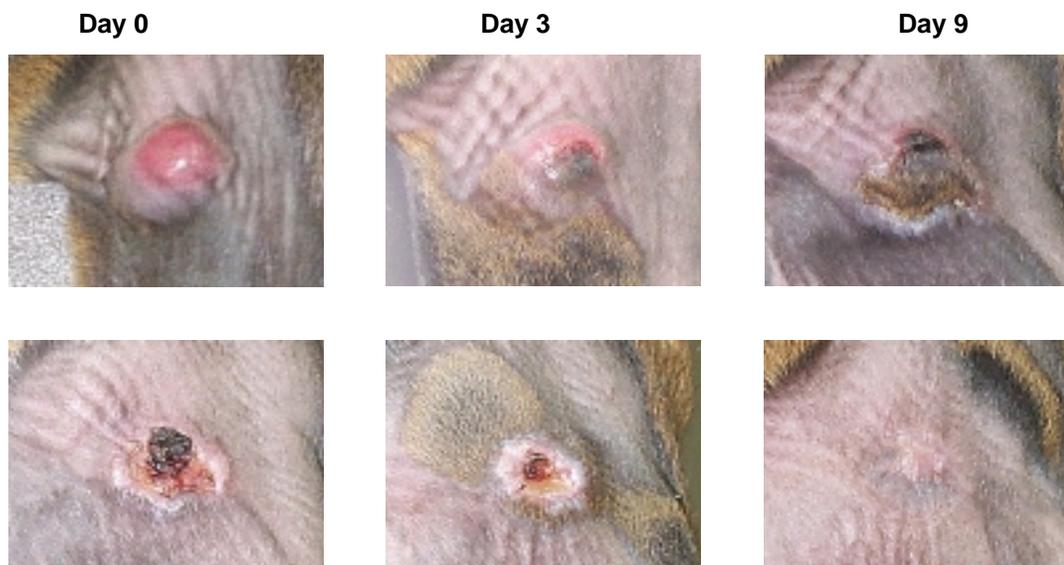
Contamination of cattle-derived products, such as collagen, has been a concern following the discovery of bovine spongiform encephalopathy (BSE; “mad cow disease”) in some herds in Europe. The risk of contamination of the Matrix collagen with the BSE-causing agent is negligible. Matrix derives its collagen from calf skins of US origin, and BSE has never been found in the US. European authorities have concluded that bovine skin is a tissue with no detectable BSE infectivity. Also, in March 2001, the European directorate for the Quality of Medicines issued a Certification of Suitability for the bovine-derived collagen used by Matrix for the manufacture of collagen gel.

4 Nonclinical Studies

Nonclinical studies evaluated the pharmacology (tumor biology), biodistribution, and toxicology of CDDP/epi gel. These studies demonstrated the product concept of enhanced and focused activity of cisplatin at the site of injection with reduced systemic exposure to the drug. The majority of the tumor biology and biodistribution studies were carried out in four syngeneic murine tumor models: the SCCVII squamous cell carcinoma, the RIF-1 radiation-induced fibrosarcoma, the KHT murine fibrosarcoma, and the metastatic MBT-2 bladder tumor model. Toxicology studies were carried out primarily in healthy mice and rats.

As would be expected with local administration of high concentrations of a cytotoxic agent, the CDDP/epi gel produces an intense, localized reaction which is readily observed in cutaneously grown tumors in murine models. Figure 2 depicts the typical response pattern observed in the dermally grown RIF-1 murine fibrosarcoma tumor model. 100 mm³ tumors were treated with CDDP/epi gel on days 0, 2, 4, and 6. Redness and swelling of the tumor become evident within a few days after injection, often followed by erosion and ulceration. Eschar formation and tumor shrinkage are evident six to 14 days after drug administration and the rapid growth (tumor doubling times of two to three days) of these tumors stops. In cases of complete tumor regression, healing of the lesion is well underway 2 weeks after treatment and is complete, sometimes with minor scarring, by three to five weeks. These observations substantiate the antitumor activity of CDDP/epi gel and demonstrate that over time, normal wound resolution at the site of treatment occurs with no significant chronic wound complications. Typically no significant systemic toxicity was observed at CDDP/epi gel doses that were efficacious.

Figure 2: Effect of CDDP/epi Gel on RIF-1 Tumor Growth

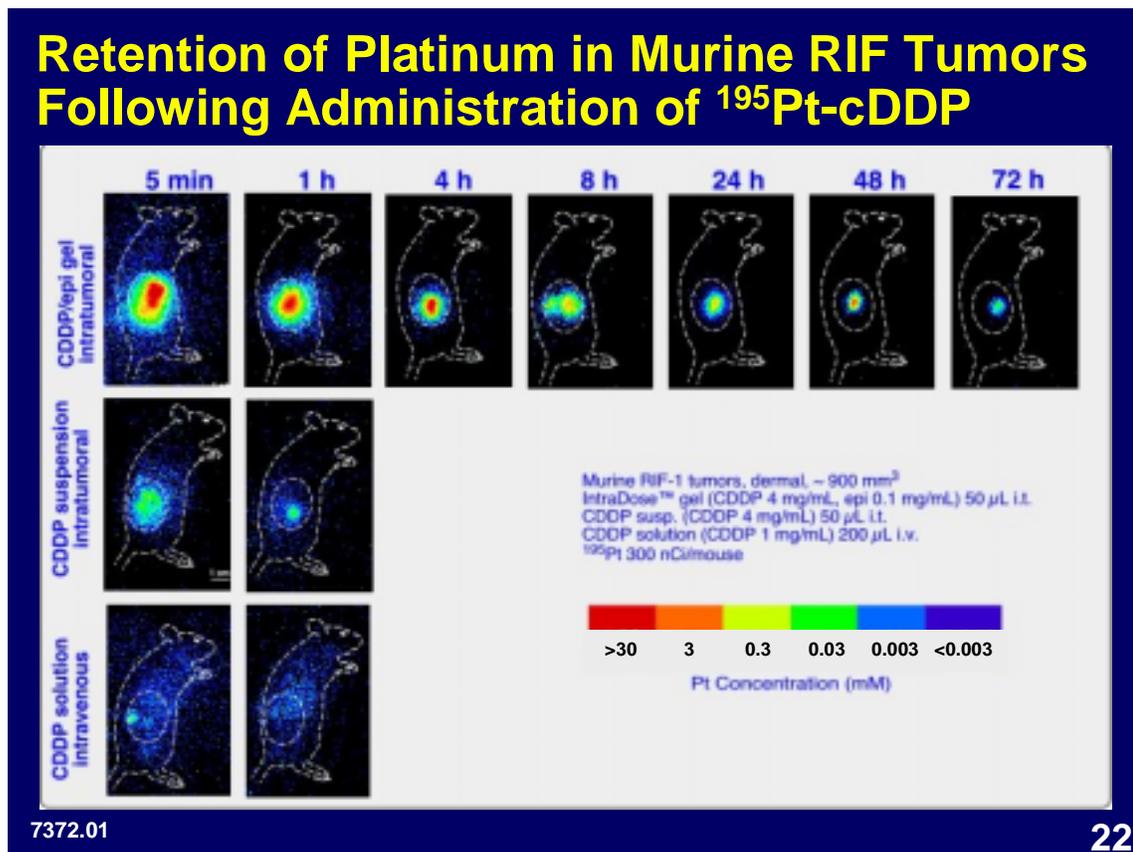


4.1 Biodistribution

Animal pharmacokinetics and biodistribution studies have consistently demonstrated enhanced local retention of CDDP at the site of administration, both in tumors and in various healthy tissues, as well as slowed and/or diminished systemic availability. These studies used many of the same murine tumor models used in the pharmacology studies.

Studies in mice bearing cutaneously grown SCCVII and RIF-1 intradermal tumors have shown that labeled platinum is highly concentrated in the tumor as indicated by the intensity and duration of the signal for up to 72 hours after i.t. injection of CDDP/epi gel. The high concentrations appear to be limited to and highly focused in the area immediately surrounding the injected gel mass (within several millimeters of the gel margin). The appearance of radiolabel platinum in the liver and kidneys was much less than that with systemic administration of CDDP. These results can be observed in the autoradiograms presented in Figure 3.

Figure 3



Inclusion of epinephrine in the CDDP gel (yielding the CDDP/epi gel) resulted in significantly greater retention than either CDDP solution or CDDP gel. Intratumorally administered aqueous CDDP preparation provided little local retention, while increased retention was observed with CDDP gel. The collagen gel, with or without CDDP, also provided enhanced local retention of epinephrine (³H label) in SCCVII tumors after intratumoral injection, as compared to epinephrine solution similarly administered.

Intratumoral administration of CDDP/epi gel provided tumor platinum levels in the first two hours after administration that were 40 to 80 times higher than those achieved with intravenous administration of an equal dose of CDDP. Peak plasma levels of free (unbound) platinum, on the other hand, were eightfold lower. Three to six days after administration of the gel, total platinum levels in the tumors were still in the range of 15 to 60 µg/g, approximately 20 to 40 times higher than those observed after the systemic administration of drug.

Platinum content in the liver and kidney over the first four hours after administration (the time when "free" cisplatin would be available) was approximately two to four times lower with the i.t. administered CDDP/epi gel compared to systemically administered CDDP at the same dose. Total platinum levels in the tumor were 15 to 100-fold greater than those in the kidney with i.t. CDDP/epi gel. In contrast, i.v. dosing of CDDP gave platinum levels in the kidney that were three to six-fold higher than those in the tumor over the same time period (five minutes to six days post-treatment).

4.2 Tumor Pharmacology

Efficacy studies conducted in a variety of cutaneously grown syngeneic murine tumor models compared the activity of intratumorally administered CDDP/epi gel versus systemically (i.p.) administered CDDP. The murine tumor models used were the SCCVII squamous cell carcinoma, the fibrosarcomas RIF-1 and KHT, the MM45T.Li liver tumor model, and the metastatic MBT-2 bladder tumor model. These single-dose studies demonstrated that CDDP/epi gel i.t. was efficacious against these histologically distinct tumor types, and generally had significantly greater antitumor activity (three- to eightfold greater growth delay effects) than treatment with equal doses of systemic CDDP.

Another series of single-dose studies in tumor models (SCCVII, KHT) assessed the antitumor activity of i.t. CDDP/epi gel compared to that of its various formulation congeners (e.g., CDDP/epi suspension, CDDP gel, and CDDP suspension), and demonstrated that the epinephrine was a key contributor to the enhancement of antitumor activity.

In one study, using the SCCVII squamous cell carcinoma model, the histopathology of treated tumors was examined after intratumoral administration of CDDP/epi gel. Histopathologic evidence of tumor necrosis and cytotoxicity was observed up to several millimeters away from the gel margin.

Another key example of the improved antitumor efficacy and diminished systemic toxicity provided by i.t. CDDP/epi gel was seen in a multiple-dose study in SCCVII tumors, where the comparator was an intratumorally administered aqueous solution of CDDP. CDDP solution or CDDP/epi gel at CDDP doses of 2, 4, 6, or 8 mg/kg per treatment were administered i.t. on days 0, 2, 4, and 7 after tumors had reached an average volume of 100 to 150 mm³. Tumor growth delay (TGD) was assessed. Tumor growth delay was defined as the difference between the mean tumor volume quadrupling time of treated versus untreated animals, where tumor volume quadrupling time is defined as the time required for a tumor to grow to four times its volume at the start of treatment. The greater the TGD, the greater is the antitumor activity of the test material.

Table 9 presents the study results. At the 8 mg/kg dose all ten animals treated with the i.t. CDDP solution died; six animals died in the 6 mg/kg group with (TGD 28.4 days); and one animal died in the 2 mg/kg treatment group (TGD 5.8 days). Animals in the CDDP solution group also exhibited significant morbidity as reflected in weight loss, appearance, and behavior (ruffled fur, huddling, etc.). Five of ten mice treated at 6 mg/kg (TGD 43.2 days) and seven of ten mice treated at 8 mg/kg (TGD 53.0 days) in the CDDP/epi gel i.t. group experienced complete tumor regression, observed on by both visual and histological examination on day 60 post treatment initiation. There were no deaths and markedly lower morbidity in the CDDP/epi gel i.t. group.

Table 10: Tumor Growth Delay after Intratumorally Administered CDDP

	Dose			
	2 mg/kg	4 mg/kg	6 mg/kg	8 mg/kg
CDDP Solution	5.8 days ^a	14.1 days	28.4 days ^b	- ^c
CDDP/Epi Gel	9.1 days	24.5 days	43.2 days	53.0 days

^a 1/10 animals died, ^b 6/10 animals died, ^c 10/10 animals died

Other exploratory animal studies in a metastasizing tumor model indicate that a combination of intratumorally administered CDDP/epi gel plus systemically administered CDDP provides local tumor control and suppression of metastasis unachievable with either agent alone.

4.3 Toxicology

Formal toxicology studies and supportive evidence from pharmacology studies demonstrated that the systemic toxicity of CDDP is attenuated when administered as CDDP/epi gel as compared to a systemic (i.v. or i.p.) solution. The LD₅₀ for CDDP/epi gel administered intratumorally in several different mouse tumor models (34 to 39 mg/kg) was approximately twofold higher than that of systemically administered CDDP (19 to 21 mg/kg), consistent with the two- to four-fold lower levels of platinum in liver and kidney seen in the biodistribution study described above. The reduction of systemic toxicity with CDDP/epi gel was also evident with several other injection routes, although the attenuation

appeared to be greater with intratumoral administration than with CDDP/epi gel injected into healthy tissues.

The local toxicity of a single dose of CDDP/epi gel and its various formulation congeners was assessed after injection into the skin of healthy mice. Results were consistent with the cytotoxic properties of CDDP and the sustained retention afforded by epinephrine, and the relative immobilization afforded by the gel vehicle. Local effects included hyperemia, edema, ulceration and focal necrosis of the skin at the injection site. By day 15, reparative changes were in progress; and the injured area appeared to be completely healed by day 63. Administration of an equal dose of CDDP suspension or CDDP gel resulted in similar qualitative observations, in general, but the intensity, extent, and duration of local injury was less severe. Administration of epinephrine gel (without cisplatin) resulted in very mild ulceration. Administration of placebo gel or normal saline resulted in no detectable local gross tissue injury or ulceration. The local effects of CDDP were enhanced in intensity, extent, and duration by the presence of epinephrine and the collagen gel vehicle. The contribution of epinephrine to enhancement of local tissue cytotoxicity was markedly more than that of the collagen gel. The effects on healthy tissue in all cases were reversible.

The local toxicity (gross and histopathological findings) of CDDP/epi gel and placebo gel following perivascular administration of a single dose in the neck of normal rats was also examined. The doses were administered in injection volumes of 500 μ L or 1 mL (a cisplatin dose of 4.5 or 11.1 mg/kg). Gross observations following administration of the CDDP/epi gel included edema, hyperemia and discoloration of the skin and muscles on the treated side of the neck. None of the treatments resulted in sudden mortality suggestive of an embolus-induced stroke. No obvious signs of nerve paralysis (such as changes in gait or neck posture) were apparent with any of the treatments. There was no detectable impairment of normal bodily functions post-injection in any of the rats studied.

After treatment administration histopathological evaluation showed that there was a generalized intense inflammatory response around the injection site and surrounding structures. This was followed by a fibrotic response observed as a palpable hardening of the injected site. Despite some edema, the walls of the carotid artery and jugular vein and minor vessels in the vicinity of the injection site were intact. The infiltrating cells consisted primarily of polymorphs (neutrophils), macrophages and monocytes. A mild inflammatory response was detectable with the placebo gel, but there was no significant injury or discoloration, nor was there fibrosis of the surrounding tissue.

The results suggest that perivascular administration of CDDP/epi gel in the carotid artery-jugular vein region in the neck is unlikely to injure the vascular walls or affect the patency of normal healthy major blood vessels in this anatomic region.

Another time course study investigated the persistence of collagen and any associated histopathologic effects after administration of CDDP/epi gel in normal mice by the intradermal (i.d.), intrahepatic (i.h.),

intramuscular (i.m.), or intraperitoneal (i.p.) routes. The gel dose for the first three routes was 0.1 ml (400 µg CDDP, or 13.3 mg/kg); for intrahepatic injections, the dose was 0.05 mL of gel (200 µg CDDP).

A rapid loss of the injected mass of CDDP/epi gel (to about 50% of its original wet weight) occurred within the first day after administration by all routes. Thirty days after intradermal administration, approximately 20% of the gel mass remained, and by 6 months the injected mass was no longer dissectable from the surrounding tissue. Nor was it detectable by gross observation at any of the injection sites. Histological examination of tissue sections obtained 90–180 days after dosing showed clear evidence of digestion and/or incorporation of the injected material into the surrounding tissue.

Local effects at earlier time points were similar to those seen in other studies. Gross pathology observations in the intradermally treated group included erythema, ulceration, necrosis, and scabbing at the injection site the first week after injection. The dermal wounds resolved and complete healing was observed by 60 days. With intrahepatic administration, an area of the lobe in the immediate vicinity of the injected gel mass was affected with a 1- to 3-mm zone of liquefactive necrosis at day 1–4 after injection that resolved in 30–60 days. The hepatic capsule remained intact, with no leakage of gel from the injected lobe. Normal hepatic histology was regained at the injection site as early as day 30. Following intramuscular administration the tissue effects were milder than with intradermal or intrahepatic injection: a mild inflammatory response was apparent at the injection site within a few days after injection, but the characteristic cytotoxic injury was delayed and less severe than observed at other sites of injection. Reparative changes were evident by day 30, and full recovery of the tissue was essentially complete by day 60.

The results demonstrate that collagen from CDDP/epi gel persists at the injection site for several months after a single injection in various sites in mice. The gel is digested and/or incorporated with no long-term adverse sequelae. The absence of adverse histopathological responses after recovery from the cytotoxic effects of the CDDP after administration into different tissues, along with regaining normal tissue histology, demonstrates the safety and biocompatibility of the CDDP/epi gel formulation.

Thirteen-week multiple-dose toxicology studies were conducted in mice examining local and systemic toxic effects associated with weekly intradermal administration of CDDP/epi gel or placebo gel compared to systemically administered (via intraperitoneal injection) CDDP. Cumulative CDDP dose levels of 3, 16, and 35 mg/kg were used for both CDDP formulations.

Dermal observations following intradermal injection of CDDP/epi gel were discoloration, blanching, scab, and scar formation. In addition, edema and ulceration with necrosis were evident 10 to 20 days after injection. Histologically, dermal fibrosis with or without acanthosis at the injection sites and a mild renal tubular basophilia were evident. Lesions began to heal four to eight weeks after final

administration in all CDDP/epi gel treatment groups, typically attaining complete resolution with some scarring.

Systemic toxicity was seen with intraperitoneally administered CDDP at the higher cumulative doses (16 and 35 mg/kg). Clinical observations in these animals included hunched posture, organ or extremity swelling, and wasting. In contrast, little apparent systemic toxicity with intradermal CDDP/epi gel or placebo gel was observed.

4.4 Summary of Nonclinical Studies

Results from these studies demonstrated that:

- Local concentrations of CDDP (as monitored by total platinum levels) in tumors after intratumoral administration of CDDP/epi gel were up to two orders of magnitude higher than those achieved after systemic administration (i.p., i.v.) of CDDP.
- Platinum levels in tumor tissue were localized to the immediate area surrounding the gel mass (within several mm to a cm from the gel margin).
- Platinum levels in the blood, kidney, and liver were substantially lower with local administration of CDDP/epi gel as compared to CDDP systemically (i.p., i.v.) administered at the same dose.
- Local administration of CDDP/epi gel produces focused cytotoxic effects including tumor growth inhibition and/or complete regression. Typically complete wound resolution was observed at the site of injection in conjunction with tumor regression.
- Epinephrine was a key contributor to the increased efficacy and localization observed.
- When administered into healthy tissue, there was a tissue dependent cytotoxic response, that readily healed and a return to normal histology.
- At CDDP doses known to produce systemic toxicity, intratumoral administration of CDDP/epi gel resulted in minimal systemic toxicities.

5 Clinical Pharmacokinetics of Intratumoral CDDP/epi Gel

Clinical pharmacokinetic studies were conducted to determine the systemic availability of CDDP after i.t. administration of CDDP/epi gel. Studies were conducted in patients with SCCHN (516-99-PK) and in patients with hepatocellular carcinoma.¹⁷ Circulating levels of platinum in whole plasma (total Pt) and platinum present after ultrafiltration (free Pt) were measured. Free Pt levels, which include intact cisplatin, closely related reactive species and metabolites, are generally associated with drug activity and toxicity.¹⁸ Total Pt includes free Pt as well as cisplatin bound to proteins such as serum albumin.

In the HNSCC study presented here,¹⁹ the dosing regimen was the same as that used in the pivotal trials. Patients received a series of intratumoral (i.t.) injections, one each week until up to 6 treatments of CDDP/epi gel had been administered. The dose was 0.25 mL CDDP/epi gel per cm³ of tumor volume (equivalent to 1 mg CDDP/cm³). Blood samples for plasma platinum measurements were to be obtained pre-dosing at Treatments 1 through 6, and at 5, 20, 40 minutes, 1, 2, 4 to 6, 24, and 48 hours following initiation of dosing for Treatments 1 and 3. Platinum concentrations in plasma and plasma ultrafiltrate were measured using atomic absorption spectroscopy.

Sixteen patients had plasma samples available for analysis. The total administered dose of CDDP/epi gel ranged from 2.6 to 6.4 mL, corresponding to 10.5 to 25.6 mg of cisplatin, with an average of 16.3 ± 0.8 mg (mean \pm SE), approximately 10 mg/m² of body surface area).

Platinum concentrations in plasma following i.t. administration of CDDP/epi gel were generally quite low. Maximum total Pt concentration, C_{\max} , ranged from 132 to 419 ng/mL, and generally increased with dose over the limited dose range used in this study. The time to attain maximum plasma concentration, t_{\max} , of total Pt varied among patients, ranging from 5 minutes to 24 hours with a mean \pm SE of 9.8 ± 2.9 hours. After C_{\max} , total plasma levels declined slowly, consistent with the slow clearance of platinated proteins observed following systemic administration of the drug.^{18,20,21,22} Concentration-time curves (median values for Dose 1, n=14) are shown in Figure 4.

There was little increase or accumulation in total Pt levels with multiple dosing as indicated by the total Pt concentration measured prior to each dose administration (7 days after the last treatment). Similarly, comparison of total Pt C_{\max} for Dose 1 and 3, in the four patients for whom data were available for both doses, revealed no apparent trend of change in peak concentrations with multiple dosing.

Plasma concentrations of free Pt increased after the start of injection of CDDP/epi gel and reached a maximum concentration, C_{\max} , of 95 ± 12 ng/mL at an average t_{\max} of 0.75 ± 0.12 hours. There was a rapid decrease in free Pt concentration thereafter with average values falling below the quantitation limit (12 ng/mL) after 4 hours. The C_{\max} and AUC of free Pt varied between treatments, but generally increased with dose. The $AUC_{0 \rightarrow \infty}$ value averaged about 0.85 $\mu\text{g}\cdot\text{h}/\text{mL}$ and ranged from 0.204 to 4.310

$\mu\text{g}\cdot\text{h}/\text{mL}$, similar to the $\text{AUC}_{0 \rightarrow \infty}$ seen in previous studies of CDDP/epi gel administered into liver tumors.¹⁷ Pharmacokinetic parameters are summarized in Table 10.

Figure 4. Plasma Platinum Concentrations following Intratumoral Administration of CDDP/epi Gel in HNSCC Tumors (average CDDP dose $10 \text{ mg}/\text{m}^2$)

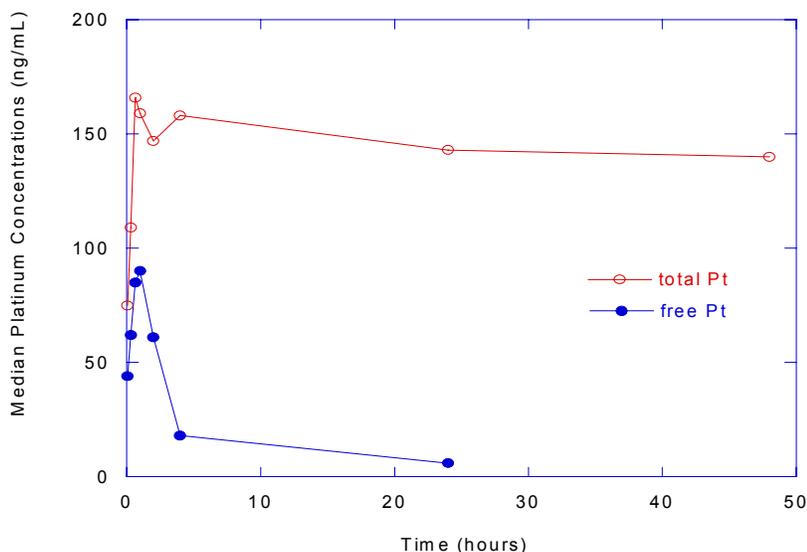


Table 11: Pharmacokinetics Parameters following Intratumoral Administration of CDDP/epi Gel (average CDDP dose $10 \text{ mg}/\text{m}^2$) in Patients with HNSCC (516-99-PK)

Number of patients	16
Number of treatments	20
CDDP dose (mg) per treatment	16.3 ± 0.8 (range 11–26)
Parameter	
Total plasma platinum	
C_{\max} ($\mu\text{g}/\text{mL}$)	0.25 ± 0.02
t_{\max} (h)	9.8 ± 2.9
$\text{AUC}_{0 \text{ to } \infty}$ ($\mu\text{g}\cdot\text{h}/\text{mL}$)	87 ± 18
Clearance ($\text{mL}/\text{h}/\text{kg}$)	5.0 ± 1.2
Volume of Distribution (L/kg)	0.83 ± 0.10
Initial $t_{1/2}$ (h)	-
Terminal $t_{1/2}$ (h)	299 ± 56
Free platinum in plasma	
C_{\max} ($\mu\text{g}/\text{mL}$)	0.095 ± 0.012
t_{\max} (h)	0.75 ± 0.12
$\text{AUC}_{0 \text{ to } \infty}$ ($\mu\text{g}\cdot\text{h}/\text{mL}$)	0.85 ± 0.23
Clearance ($\text{mL}/\text{h}/\text{kg}$)	573 ± 155
Volume of Distribution (L/kg)	3.5 ± 0.4
Initial $t_{1/2}$ (h)	—
Terminal $t_{1/2}$ (h)	11.5 ± 3.2

Values are provided as mean \pm SE

5.1 Pharmacokinetic Parameters following Intratumoral CDDP/epi Gel and Intravenous CDDP Solution

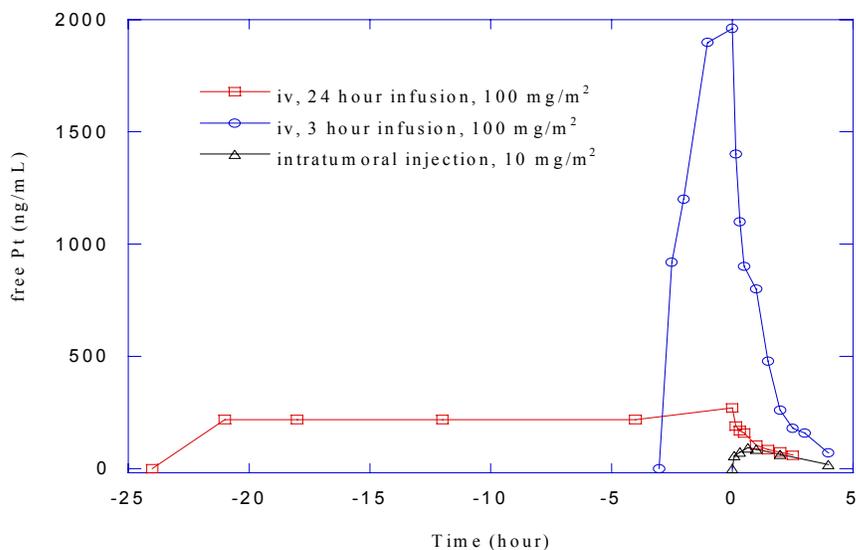
When used as a systemic chemotherapy, CDDP is typically given as an intravenous infusion of 100 mg/m² administered over several hours. Information from the literature are presented in Table 12 and Figure 5. These data suggest that the free Pt in plasma can reach high levels that are sustained through the majority of the infusion. Plasma levels of 1.5 to 2.0 µg/mL have been associated with nephrotoxicity.²⁰ Longer infusions or continuous infusion regimens reportedly show no reduction in nephrotoxicity, suggesting that lower but sustained levels of free Pt are also quite toxic. In contrast, free platinum C_{max} of only 0.1 µg/mL was observed after intratumoral administration of CDDP/epi gel at the recommended therapeutic dose (average total dose of 10 mg/m²). It is estimated that, when treating multiple tumors, at a maximum recommended total daily dose of 10 mL of CDDP/epi gel (40 mg CDDP), the peak free Pt level would be only 0.25 µg/mL or less.

Table 12: Plasma Pt C_{max} Values Following IV Infusion of CDDP and IT Injection of CDDP/epi Gel

Intravenous			
Dose (mg/m ²)	Infusion Duration	Total Pt (µg/mL)	Free Pt (µg/mL)
100	Bolus ¹⁶	11	10
100	3 h ¹⁶	4.7	3.3
100	24 h ¹⁶	2.0	0.7
125	5 d ¹⁷		
Intratumoral			
Dose (mg/m ²) ^a		Total Pt (µg/mL)	Free Pt (µg/mL)
10	Injection ¹⁸	0.25	0.10
17	Injection ¹⁶	0.44	0.38

^aPatients were dosed based on tumor volume. Dose presented is an equivalent per body surface area

Figure 5. Free Platinum Plasma Levels for a 24 Hour and 3 Hour Intravenous Infusion of Cisplatin (100 mg/m^2)¹⁸ and Intratumoral Injection of CDDP/epi Gel (10 mg/m^2) (intratumoral administration at time 0).



The present data indicate that after an i.t. injection of CDDP/epi gel, CDDP is retained at or near the site of injection and the availability of CDDP to the systemic circulation was delayed compared to iv. administration. With intravenous or intraarterial infusions, maximum plasma concentrations occur during the infusion or immediately after cessation of administration, while after intratumoral injection, the peak free Pt concentration was not reached until about 45 min.

Cisplatin/epinephrine gel (CDDP/epi gel) is designed to deliver extremely high concentrations of drug to tumor tissue over an extended period. The recommended dose of CDDP/epi gel is considerably lower than the typical systemic dose reported in the literature (170 mg CDDP , equivalent to 100 mg/m^2). This low dose and the retention of drug at the site of administration limits the amount of CDDP that enters the systemic circulation. Thus, drug exposure and related toxicities are much lower than those associated with systemically administered cisplatin.

Summary of clinical pharmacokinetics studies:

- After the i.t. administration of CDDP/epi gel, free platinum levels typically reached a maximum of approximately $0.1 \mu\text{g/mL}$ at 45 min., and fell below quantitation limits after 4 hours.
- Free Pt levels in plasma following administration of i.t. CDDP/epi gel, even at maximum doses, will be considerably lower and/or less sustained than those associated with systemic toxicity
- Multiple dosing resulted in minimal accumulation of platinum in the plasma
- Pharmacokinetic behavior is consistent with retention of CDDP at the site of injection, with slowed availability into the systemic circulation.

6 Pivotal Clinical Studies

6.1 Study Design

The two Phase III trials were multicenter, randomized, double blind, and placebo controlled. Study 414-94-2 was conducted in the United States and Canada, and Study 514-94-2 in Europe and Israel. The studies' primary objectives were to demonstrate an effect of CDDP/epi gel on treated tumor volume and an accompanying clinical benefit of CDDP/epi gel treatment to patients with late-stage HNSCC, who had already undergone treatment with one or more anticancer therapies.

The two trials were identical in design, each consisting of three distinct phases, through which the patients moved in sequence. The three phases are described below.

Study Phase	Patients Participating in Phase	Activities
Blinded Treatment Phase (up to 8 weeks)	All patients	Blinded weekly treatment with CDDP/epi gel or placebo gel for up to 6 treatments
Follow-Up Phase (up to 4 weeks)	Patients with MTT response	Follow patients weekly to track response duration
Extended Follow-up Phase	<ul style="list-style-type: none"> • Patients without MTT response in Blinded Treatment Phase • Patients with recurrence after response • Patients with new tumors requiring treatment • Patients with continuing response who have completed Follow-Up Phase 	<ul style="list-style-type: none"> • Re-treatment of recurrent tumors with open-label CDDP/epi gel • Treatment of other or new tumors with open-label CDDP/epi gel • Continuing follow-up of responders to track response duration

All patients were treated with blinded study drug (CDDP/epi gel or placebo) in the Blinded Treatment Phase. Patients with MTT response (CR or PR) entered the follow-up phase after completing blinded treatment, and were evaluated weekly for duration of response. Alternatively, these patients could enter extended follow-Up for open-label treatment of partial responses and/or new tumors. Patients with stable disease in blinded treatment phase moved directly into extended follow-up phase for treatment with open-label CDDP/epi gel. Patients with MTT progression were permitted to move directly from blinded treatment phase to extended follow-up phase at the fourth treatment visit or later, for treatment with open-label CDDP/epi gel.

Prior to beginning treatment, the investigator was required to identify as the "most troublesome tumor" (MTT) the tumor that was either the most symptomatic, most clinically dominant, or the most likely to cause an undesirable event. For the duration of the study, this tumor was identified as the investigator-selected MTT. Based on baseline volume of the MTT, patient randomization was stratified into two

groups: patients with an MTT of volume 0.5 cm³ to 5.0 cm³ (Stratum 1) and patients with an MTT of volume >5.0 cm³ to 20 cm³(Stratum 2).

At the time the studies were conducted there was no standard therapy available to serve as a comparator, although a variety of salvage chemotherapy regimens or re-irradiation regimens were under investigation. Therefore, placebo gel containing no active ingredients was selected for use as a comparator group in these studies. This choice was discussed with and agreed upon by the FDA.

Advantages of a placebo control group are that it allows measurement of the absolute effectiveness of treatment, and provides maximum ability to distinguish adverse effects due to drug from those due to underlying disease or intercurrent illness.

6.1.1 Protocol Amendments

The protocol was amended during the conduct of the study to clarify treatment and data collection instructions and to incorporate safety information as needed. Two major amendments were made that modified the patient entry criteria and dosage instructions. In 1995, shortly after initiating the studies, an additional stratum (Stratum 3) was added at the request of the investigators to enable enrollment of patients with MTT volumes > 20 cm³. Data from this stratum were specifically excluded from the core efficacy analysis, and patients in Stratum 3 were not counted in the 90-patient sample size required for each study. Safety data from patients enrolled in Stratum 3 are included in the safety analysis.

The most clinically important amendment was Amendment V, adopted in May 1997. Amendment V excluded patients with tumors that directly involved or threatened to invade the carotid artery and closed Stratum 3 after the enrollment of 46 Stratum 3 patients (23 in each of the studies). The amendment further excluded patients with a known history of clinically significant extracranial carotid vascular disease due either to atherosclerosis, radiation therapy, or previous carotid artery surgery. This action was prompted by the receipt of six reports of cerebrovascular events, two of which occurred in Stratum 3 patients. Assessment of the data by the Data Safety Monitoring Board indicated that the overall MTT response rate in Stratum 3 was lower than the other two strata (available study results for Stratum 3 patients are provided in Appendix 4). After consideration of these events with the DSMB and a consultant neurologist, enrollment of patients with tumors larger than 20 cm³ (Stratum 3) was discontinued by protocol Amendment V for precautionary reasons.

Amendment V also reduced the dose from 0.5 mL/cm³ of baseline tumor volume (fixed-dose) to 0.25 mL/cm³ of tumor volume at each treatment (adjusted-dose) during the blinded treatment phase and, if tolerated, allowed escalation of the dose to 0.5 mL/cm³ beginning with the second open-label CDDP/epi gel treatment in extended follow-up phase. Prior to Amendment V, the dose calculation was fixed for each visit and was based on tumor volume at the first treatment visit; blinded evaluation of the data suggested that many tumors were unable to accommodate this dose volume, especially tumors that were responding and decreasing in size. Amendment V therefore required that the volume of study

drug for each treated tumor be recalculated at each treatment visit, in order to provide a more consistent ratio of dose per unit of tumor volume across all treatment visits.

6.1.2 Entry Criteria

Adult patients who had histologically confirmed recurrent or refractory HNSCC were eligible for study entry. The main inclusion criteria for the phase III trials were:

- Histologic confirmation of recurrent or refractory HNSCC.
- Treatment site(s) that were readily measurable, accessible for direct intratumoral injection, and that, in the investigator's opinion, did not pose an immediate risk of hemorrhage or embolization.
- Full recovery from the side effects of any previous treatment.
- Presence of a primary or metastatic tumor located in the skin, lymph nodes, subcutaneous tissue, or muscle. Any tumor selected for treatment (referred to in the protocol as a "target" tumor) was to be biopsied before the beginning of treatment (added by Amendment III). Tumors located in lymph nodes had to be palpable.
- A total tumor volume that required no more than 10 mL CDDP/epi gel per treatment. Patients did not need to have all tumors present at baseline selected for treatment (added by Amendment III). An investigator-identified MTT must have measured 0.5 cm³ or larger.
- Previous treatment of the head and neck cancer with at least one course of therapy (e.g., chemotherapy, radiation, surgery, biologic response modifier). Patients receiving systemic chemotherapy, radiation, major surgery or other cancer therapy in the previous 28 days could not enter the study without documented evidence of stable disease or disease progression (clarification of allowed cancer therapies and patient population were added in Amendment III).
- A Karnofsky Performance Status (KPS) of between 60 and 100 and an anticipated survival of at least 6 months (revised from 40 or higher by Amendment V).

The following patients were to have been excluded from study participation:

- Patients with head and neck cancer histology other than squamous cell carcinoma.
- Patients with New York Heart Association Class III or greater cardiovascular symptoms.
- Patients with a history of cardiac arrhythmias who, in the opinion of the investigator, might have an increased risk of arrhythmia from the study treatment.
- Patients with a known hypersensitivity to cisplatin, bovine collagen, epinephrine, or sulfites.
- Patients with systemic disease in tissues such as the liver, lung, or pancreas (excluded by Amendment II).
- Patients with a history of clinically significant extracranial carotid vascular disease from either atherosclerosis, radiation therapy, or previous carotid artery surgery (excluded by Amendment V).
- Fibrotic tumors
- Tumors that were complicated by uncontrolled local infection at the treatment site(s).
- Tumors larger than 20 cm³ (excluded by Amendment V)
- Tumors that directly involved or threatened to invade the carotid artery; also, any tumor in close proximity to a major vessel of the extracranial vascular system including the common, internal, and external carotid artery or the vertebral artery (excluded by Amendment V).

6.1.3 Randomization

At screening, eligible patients were placed in one of three strata according to the pretreatment volume of the MTT prospectively identified by the investigator. Within each stratum, patients were randomized in a 2:1 ratio to receive treatment with CDDP/epi gel or placebo gel. The randomization scheme was blocked such that each sequential group of three patient identification numbers included, in random sequence, two CDDP/epi gel patients and one placebo patient.

Table 13: Stratification of Patients by MTT Volume

Stratum	MTT Volume
1	$\leq 5 \text{ cm}^3$
2	$> 5 \text{ but } \leq 20 \text{ cm}^3$
3	$> 20 \text{ cm}^3$

6.1.4 Blinding

The studies were conducted in double-blind fashion to conceal treatment assignments from Matrix, investigators, and patients. The central randomization lists were generated by Matrix and kept by an individual in the Quality Control department, which was geographically and organizationally distant from the Clinical and Biostatistics departments.

CDDP/epi gel and placebo were packaged in identical cartons ("kits"), and study kits were assigned to investigational sites in blocks of three. Each study kit was identified by a randomization number and affixed with a two-part tear-off occluded label. At the study site, syringes for administering study drug were prepared by a pharmacist who was not to administer treatment or perform patient evaluations. Because of the slight difference in color between CDDP/epi gel and placebo gel, syringe barrels were covered with a yellow film that rendered the two drugs indistinguishable. Blinding was maintained for all patients until the last patient completed the follow-up phase. Both studies were unblinded on the same day: 18 April 2000.

6.2 Treatment Administration

6.2.1 Formulation

The test product was cisplatin/epinephrine injectable gel (CDDP/epi gel), which consists of cisplatin and epinephrine in an aqueous, purified bovine collagen gel. One mL of CDDP/epi gel contains 4 mg cisplatin and 0.1 mg epinephrine. In addition to bovine collagen, the gel contains sodium phosphates and sodium chloride, and water for injection, with sodium hydroxide or hydrochloric acid to adjust pH.

The placebo gel contained purified bovine collagen, sodium phosphates and sodium chloride, and water for injection, with sodium hydroxide or hydrochloric acid to adjust pH.

6.2.2 Schedule and dosing

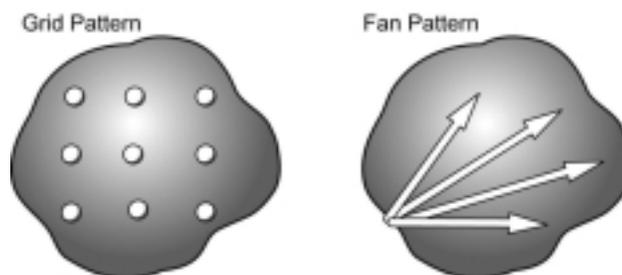
In the blinded treatment phase, patients were to receive weekly treatments of CDDP/epi gel or placebo gel until treated tumors either had received up to six treatments within an 8-week period or had achieved a CR of the MTT, whichever occurred first. Patients who achieved a CR were then evaluated weekly for four weeks without treatment. These patients were subsequently followed for recurrence on a monthly schedule.

Patients attaining a PR in blinded treatment phase were not required to enter follow-up phase, but could proceed directly to extended follow-up to receive open-label CDDP/epi gel. Patients with PD in blinded treatment phase had the option of moving to open-label CDDP/epi gel after receiving at least three treatments with blinded drug. In the extended follow-up (open-label period), patients could receive up to six open-label CDDP/epi gel treatments in 8 weeks, followed by four consecutive weekly evaluations. This cycle could be repeated at the investigator's discretion.

The volume of gel administered was calculated by multiplying the assigned dose by the volume of the tumor (estimated as length x width x height x 0.5). The formula used to calculate tumor volume provides a good approximation of the volume of a prolate ellipsoid with ratio of major to minor axes no greater than 3:1. At the time the protocol was initiated, the assigned dose was 0.5 mL of CDDP/epi gel or placebo gel per cm^3 of baseline tumor volume per treatment. The protocol was later amended to reduce the assigned dose to 0.25 mL/ cm^3 of tumor volume at each treatment. Tumors smaller than 0.5 cm^3 received a fixed dose of 0.1 mL per treatment.

Injection technique was standardized across study centers by the use of training sessions and an instructional video. Investigators were trained in two injection techniques, the "grid" pattern and the "fan" pattern (Figure 6). Injection technique was permitted to vary, depending on the size, shape and location of the tumor and the technique most suited to ensuring adequate intratumoral drug distribution. Treatment was administered by direct intratumoral injection in increments of 2.5 mL, and vital signs were monitored between increments. On any given treatment day, the maximum total dose of gel administered to all treated tumors combined was limited to 10 mL.

Figure 6: Grid and Fan Patterns of Injecting CDDP/epi gel



6.2.3 Concomitant Therapy

Concurrent systemic chemotherapy, other local cancer therapy, or any other cytotoxic or biologic agents were prohibited during the treatment phase of the studies. Other cancer therapies were permitted in extended follow-up phase, including radiation therapy to distant, untreated metastases. Other therapies initiated in the extended follow-up phase were to be recorded in the Case Report Form (CRF). Patients whose tumors were responding following therapy with blinded study drug who received other cancer therapies in extended follow-up had their duration of response censored on the day of first treatment with other therapy. Other cancer therapies were never permitted to be given concurrently with open-label CDDP/epi gel in extended follow-up.

Patients were permitted to enter the studies on established maintenance doses of hormonal therapy such as megestrol acetate (e.g., Megace[®]) or tamoxifen if their tumors were progressing or stable.

Investigators were to identify a comprehensive pain management program to control treatment-related pain for each patient, consulting, if necessary, an anesthesiologist or other pain management specialists. Investigators were instructed to assess the patient's pain prior to injection, anticipate increased pain during and after injection, and administer appropriate anesthesia or analgesia, taking into account the time needed for the anesthetic or analgesic to take effect.

Topical and other local anesthetics, local-regional nerve blocks, and systemic agents were permitted and encouraged, as appropriate (e.g., opioid analgesics and sedatives). If a local anesthetic was used, injection around the tumor margins was suggested. Anesthetics containing epinephrine/adrenaline were prohibited, as was bupivacaine HCl.

6.3 Endpoints

The two Phase III studies were designed to evaluate a number of primary and secondary efficacy endpoints as well as analyze the safety profile of CDDP/epi gel.

6.3.1 Primary Efficacy Endpoints

The original primary efficacy endpoint in both trials was objective response of the most troublesome tumor. The initial and subsequent protocols specified this as the primary endpoint, and sample sizes were calculated based on the 40% objective per-tumor response to CDDP/epi gel observed in an earlier Phase I-II trial. Secondary endpoints included evaluation of tumor-related symptoms and other quality of life parameters. A specific endpoint of "Patient Benefit" was first requested by the FDA in 1997, and was incorporated into the analysis plan as a secondary endpoint that year. Patient Benefit was further defined by FDA as a primary endpoint (with MTT response remaining the other primary endpoint) in May 2000. Thus, the two primary endpoints were:

- Objective response rate of the most troublesome tumor (MTT) determined by the change in volume from baseline.
- “Patient Benefit”, a composite endpoint based on the attainment of primary treatment goals prospectively selected by the patient and investigator. The Patient Benefit endpoint was added midway through the studies and was derived from data collected on all patients, including those enrolled before the Patient Benefit endpoint was added. Hence, all patients could be evaluated for this parameter. Patient Benefit was required to be strongly associated with objective response of the MTT but was not required to reach statistical significance.

6.3.2 Secondary Efficacy Endpoints

A number of secondary endpoints were evaluated in the two Phase III studies. The key secondary endpoints are identified below:

- Association between objective response rate of the MTT and Patient Benefit
- Time to MTT response and time to MTT progression
- Response rate of all individually treated tumors (MTT and other treated tumors)
- Quality of life as assessed by the Functional Assessment of Cancer Therapy (FACT-H&N) Scale

6.3.3 MTT and Selection of Treatment Goals

In addition to response rate of the MTT, the sponsor deemed it essential to quantify the benefit afforded to the patient by successful control of the local tumor. At the time of MTT selection, the investigator identified one improvable Primary Treatment Goal for the MTT that was either palliative (wound care, pain control, ability to see, ability to hear, ability to smell, physical appearance, obstructive symptom, or mobility) or preventive (prevention of subcutaneous tumors breaking through the skin, prevention of invasion of vital structure(s) and/or blood vessels(s), or prevention of obstruction) in nature. Patients were encouraged, but not required, to choose a primary palliative treatment goal. The respective goals of the investigator and patient did not have to be the same, although they often were the same.

Achievement of a prospectively identified Primary Treatment Goal was determined by (i) improvement from baseline of the investigator- or patient-selected primary palliative treatment goal by at least one full category (one “scale” point or more), that was sustained for at least 28 days, or (ii) absence of failure of the investigator-defined primary preventive treatment goal sustained for at least 28 days. For each palliative treatment goal the investigator and patient could choose one of four progressive categories that best described the patient’s current condition relative to the treatment goal. These four categories constituted the 4-point scale used to determine goal achievement. For example, if the treatment goal was pain control, one of the following responses could be selected to describe the

patient's condition:

1. Patient has no pain, or has minor pain that does not require medicine.
2. Patient has pain that goes away when taking medicine purchased at a drugstore without a doctor's prescription.
3. Patient has pain that only goes away when taking medicine prescribed by a doctor.
4. Patient has pain that does not go away even when taking medicine prescribed by a doctor.

Appendix 1 describes each palliative goal and the corresponding descriptive categories. "Patient Benefit" is a dichotomous composite outcome ("benefit"/"no benefit") based on the patient's progress toward achievement of investigator- and/or patient-selected "Primary Treatment Goals", and agreement between the patient and investigator with regard to goal achievement. More specific information on Primary Treatment Goals and Patient Benefit are included in Appendix 1.

6.3.4 Definition of Response

Objective tumor response was defined as a 50% or greater decrease in tumor volume lasting for 28 days or more, not confounded by systemic or other local-regional cancer therapy. All treated tumors (the MTT and any other treated tumors) were evaluated for objective response.

6.3.5 Type and Timing of Assessments

The treatment phase consisted of a series of injections—one each week until up to six treatments had been administered within an 8-week period—followed by a weekly evaluation for four weeks. Tumors were not required to receive six injections; the number of injections given was determined by tumor response or progression, extent of local cytotoxic effects at the treated site, the patient's general state of health (including presence of systemic disease progression at distant, untreated sites) and other factors.

Tumors were measured at every study visit. For each patient, the method selected for measuring tumors was to remain the same throughout the study (e.g., clinical/physical examination, CT, ultrasound, or endoscopy, as applicable). Disease-free areas, areas of necrotic tissue, and adjacent areas of erythema and swelling were not included in the measured tumor volume.

Biopsy to document response was optional in this study and rarely done. In general, investigators reserved the use of biopsy to investigate or document local progression of cancer. Investigators were often reluctant to perform biopsies to document response, and some investigators voiced concern that the clinical benefit gained from local tumor regression would be diminished if the patient experienced delayed healing because the biopsy site was located in an area previously treated with surgery or radiation.

6.4 Statistical Analysis

6.4.1 Statistical Methods

All computations were performed using base SAS software and SAS/STAT procedures. Exact Clopper-Pearson confidence intervals for binomial rates were computed.²³ Binomial proportions were compared using Fisher's exact test. Fisher's exact test was also used to compare CDDP/epi gel rates across patient subgroups. For stratified comparisons, the hypothesis that CDDP/epi gel and placebo gel rates are equal within each stratum was tested using exact Cochran-Mantel-Haenszel tests. Three types of time-to-event summaries were computed: where possible, time-to-event distributions were estimated by the Kaplan-Meier method.²⁴ Time-to-event summaries were also computed for exact times only; for instance, time to target tumor response was summarized for target tumors with CR or PR. Because nearly all response durations were censored, "duration of observed response" was summarized, treating censored intervals of response as if they had ended on the date of the censoring event. This method produces an estimate of median duration that is conservatively biased.

6.4.2 Primary Efficacy Analyses

Patients who received at least one treatment with CDDP/epi gel or placebo gel were considered evaluable for intent-to-treat efficacy analysis. All treated MTTs were included in the efficacy analysis, including two patients who had MTTs that were under 0.5 cm³ at baseline.

Key analyses of the studies include comparison of the two treatment groups, CDDP/epi gel and placebo, on the primary endpoints, objective MTT response rate and Patient Benefit in the treatment phase. It was also important to demonstrate that there was an association between tumor response and attainment of Patient Benefit.

The goals of treatment were identified and tracked using the Treatment Goals Questionnaire (TGQ), an independent, validated instrument (see Appendix 1). Achievement of a prospectively identified Primary Treatment Goal was determined by (i) improvement from baseline of the investigator- or patient-selected primary palliative treatment goal by at least one full category (one "scale" point or more), that was sustained for at least 28 days, or (ii) absence of failure of the investigator-defined primary preventive treatment goal sustained for at least 28 days. Patient progress in achievement of preventive treatment goals was assessed at the Week 4 evaluation visit (treatment phase), at the end of the follow-up Phase, and at the last study visit. Patient progress in achievement of palliative treatment goals was assessed at each study visit.

6.4.3 Sample Size Calculations - Based on Tumor Response Rate

The sample size for each of the phase III studies was calculated based on the outcome variable of MTT response. A sample size of 90 evaluable patients with MTT volume ≤ 20 cm³, 60 assigned to CDDP/epi gel and 30 assigned to placebo gel, was planned. A total sample size of 90 patients provides a power of

0.80 or greater to detect a difference in response rates of at least 20% depending on stratum, using a two-sided test at an alpha level of 0.05.

The total sample size was also influenced by the anticipated size of the total CDDP/epi gel safety patient database; using the combined database from all relevant studies allows detection of events with a population incidence of 1% with a probability of 0.90.

6.5 Results

Results obtained from the two phase III studies (414-94-2 and 514-94-2) are presented in the following section by study, studies combined, and where appropriate by stratum (i.e., baseline MTT volume). In addition to the categories described, the dosing section also presents results prior to, and after modifying the dose in Amendment V. An analysis was also conducted on the effect of Amendment V with regard to MTT response and Patient Benefit. There were no differences in the rate of objective tumor response before and after Amendment V. Summaries of this analysis are located in Appendix 3.

6.5.1 Patient Disposition

A total of 178 patients (119 CDDP/epi gel and 59 placebo gel) from Strata 1 and 2 comprise the intent-to-treat efficacy sample for the two Phase III trials, 414-94-2 (62 CDDP/epi gel and 24 placebo gel) and 514-94-2 (57 CDDP/epi gel and 35 placebo gel). Two additional patients were enrolled but did not receive study drug. One of these patients died before the first treatment visit and is excluded from the analysis of efficacy and safety. The other had the needle inserted for injection at the first treatment visit, but the procedure was aborted due to pain before any drug was injected; this patient is excluded from efficacy analysis but included in the safety analysis. A total of 44 and 27 sites participated in the conduct of the two studies (subsequently referred to as 414 and 514 respectively). In study 414, 17 sites (46%) treated three or more patients and in study 514, 16 (64%) sites treated three or more patients. An additional 46 patients (23 in each study) with tumors $>20 \text{ cm}^3$ (stratum 3) are included in the safety analysis for a total of 225 patients.

There were a total of 121 protocol violations or deviations in the two studies during the five years of enrollment and treatment. The most frequent types of deviations were minor scheduling changes that were approved in advance by Matrix, and eligibility exceptions also approved by Matrix before the patient was enrolled. More significant deviations included errors in dose calculation (three patients from study 414 and 19 patients from study 514), inappropriate administration of open-label CDDP/epi gel during the blinded treatment phase (two patients from each study, all of whom had been randomized to blinded CDDP/epi gel) or mistaken use of blinded drug during the open-label period (one patient from study 414 and three patients from study 514), failure of the investigator to select a treatment goal (two patients from study 514), and the enrollment of a patient (study 514) whose primary cancer was esophageal (although the metastasis treated was in the neck). None of the protocol deviations resulted

in harm to a patient, and no patients were excluded from the intent-to-treat analysis because of protocol deviations.

In the blinded treatment phase, 42% of the 119 patients treated with CDDP/epi gel in the intent-to-treat efficacy analysis completed the prescribed treatment of the MTT, either by completing the six treatments or by demonstrating a response before receiving all of the six treatments. In both studies, the primary reason for early termination of prescribed treatment was disease progression. For placebo gel-treated patients, a lower percentage of patients completed the prescribed treatment, and a greater percentage experienced disease progression.

Table 14: Treatment Termination Status by Study-Blinded Phase

	414-94-2				514-94-2			
	CDDP/epi Gel		Placebo Gel		CDDP/epi Gel		Placebo Gel	
	n=62 (%)		n=24 (%)		n=57 (%)		n=35 (%)	
Completed six treatments	14	(22%)	0		25	(44%)	6	(17%)
Early response with less than six treatments	8	(13%)	0		3	(5%)	1	(3%)
Disease progression, local	15	(24%)	14	(58%)	15	(26%)	18	(51%)
Disease progression, systemic	8	(13%)	1	(4%)	3	(5%)	4	(11%)
Adverse event	3	(5%)	3	(13%)	5	(9%)	0	(0%)
Other	14	(22%)	6	(25%)	6	(11%)	6	(17%)
TOTAL	62		24		57		35	

Table 15: Treatment Termination Status, Studies Combined- Blinded Phase

	CDDP/epi Gel		Placebo Gel	
	n = 119 (%)		n = 59 (%)	
Completed six treatments	39	(33%)	6	(10%)
Early response with less than six treatments	11	(9%)	1	(2%)
Disease progression, local	30	(25%)	32	(54%)
Disease progression, systemic	11	(9%)	5	(8%)
Adverse event	8	(7%)	3	(5%)
Other ^a	20	(17%)	12	(20%)
TOTAL	119		59	

^a Delay in scheduled dosing for >2 weeks (3 CDDP/epi gel patients); need for confounding therapy (1 placebo patient); patient decision (4 CDDP/epi gel patients, 2 placebo); other (13 CDDP/epi gel patients; 9 placebo patients).

6.5.2 Demographics

Patient demographics were balanced between the two treatment groups and were representative of those reported for patients diagnosed with HNSCC, except that there were fewer black patients.

Table 16: Patient Demographics by Study

Characteristic	414-94-2		514-94-2	
	CDDP/epi Gel	Placebo Gel	CDDP/epi Gel	Placebo Gel
Age (years), n	62	24	57	35
Mean	62	61	60	62
Median	63	61	57	61
Range	33-87	40-82	37-82	43-84
Gender, n	62	24	57	35
Male	50 (81%)	17 (71%)	45 (79%)	30 (86%)
Female	12 (19%)	7 (29%)	12 (21%)	5 (14%)
Ethnicity, n	62	24	57	35
White	51 (82%)	18 (75%)	57 (100%)	35 (100%)
Black	4 (6%)	1 (4%)		
Hispanic	6 (10%)	1 (4%)		
American Indian	1 (2%)	2 (8%)		
Asian	0 (0%)	2 (8%)		
Weight (kg), n	58	20	56	35
Mean	64	64	64	67
Median	64	62	65	66
Range	39-107	34-103	36-103	45-103
Karnofsky Performance Status, n	62	24	57	35
100-90	25 (40%)	12 (50%)	26 (46%)	13 (37%)
80-70	26 (42%)	9 (38%)	24 (42%)	13 (37%)
60-50	11 (18%)	2 (8%)	7 (13%)	8 (23%)
40	0 (0%)	1 (4%)	0 (0%)	1 (3%)

Table 17: Patient Demographics, Studies Combined

Characteristic	CDDP/epi Gel		Placebo Gel		All Patients	
Age (years), n	119		59		178	
Mean (sd)	61	(11.7)	61	(11.2)	61	(11.5)
Median	61		61		61	
Range	33–87		40–84		33–87	
Gender, n	119		59		178	
Male	95	(80%)	47	(80%)	142	(80%)
Female	24	(20%)	12	(20%)	36	(20%)
Ethnicity, n	119		59		178	
White	108	(91%)	53	(90%)	161	(90%)
Black	4	(3%)	1	(2%)	5	(3%)
Hispanic	6	(5%)	1	(2%)	7	(4%)
American Indian	1	(1%)	2	(3%)	3	(2%)
Asian	0	(0%)	2	(3%)	2	(1%)
Weight (kg), n	114		55		169	
Mean (sd)	64	(14.1)	66	(16.8)	65	(15.0)
Median	64		63		64	
Range	36–107		34–103		34–107	
Karnofsky Performance Status, n	119		59		178	
100-90	51	(43%)	25	(42%)	76	(43%)
80-70	50	(42%)	22	(37%)	72	(40%)
60-50	18	(15%)	10	(17%)	28	(16%)
40	0		2	(3%)	2	(1%)

6.5.3 Disease Characteristics

There were no substantial differences in baseline disease characteristics between the two studies or treatment groups.

Table 18: Location of Original Primary Disease by Study

	414-94-2		514-94-2	
	CDDP/epi Gel n=62 (%)	Placebo Gel n=24 (%)	CDDP/epi Gel n=57 (%)	Placebo Gel n=35 (%)
Oral Cavity	21 (34%)	7 (29%)	17 (30%)	12 (34%)
Larynx	9 (15%)	5 (21%)	12 (21%)	3 (9%)
Oropharynx	5 (8%)	1 (4%)	8 (14%)	5 (14%)
Hypopharynx	5 (8%)	1 (4%)	4 (7%)	4 (11%)
Nasal Cavity	3 (5%)	3 (13%)	0	0
Salivary Glands	4 (6%)	1 (4%)	0	1 (3%)
Other	2 (3%)	1 (4%)	1 (2%)	3 (9%)
Not available	13 (21%)	5 (21%)	15 (26%)	7 (20%)

Table 19: Location of Original Primary Disease, Studies Combined

	CDDP/epi Gel n=119 (%)		Placebo Gel n=59 (%)		All Patients n=178 (%)	
Oral Cavity	38	(32%)	19	(32%)	57	(32%)
Larynx	21	(18%)	8	(14%)	29	(16%)
Oropharynx	13	(11%)	6	(10%)	19	(11%)
Hypopharynx	9	(8%)	5	(8%)	14	(8%)
Nasal Cavity	3	(3%)	3	(5%)	6	(3%)
Salivary Glands	4	(3%)	2	(3%)	6	(3%)
Other	3	(3%)	4	(7%)	7	(4%)
Not available	28	(24%)	3	(20%)	40	(22%)

Table 20: Location of MTT and of All Tumors Treated in Blinded Treatment Phase by Study

Location	414-94-2				514-94-2			
	CDDP/epi Gel		Placebo Gel		CDDP/epi Gel		Placebo Gel	
Tumor(s) Treated	MTT	All	MTT	All	MTT	All	MTT	All
Total n (tumors)	n=62	n=160	n=24	n=36	n=57	n=67	n=35	n=44
Cervical	33%	99%	9%	16%	21%	25%	20%	25%
Oral cavity	8%	11%	2%	2%	24%	25%	8%	8%
Facial	13%	29%	7%	11%	6%	10%	6%	10%
Laryngopharyngeal	3%	3%	4%	4%	4%	4%	1%	1%
Nasopharyngeal	2%	2%	2%	2%	0%	0%	0%	0%
Cranial	2%	11%	0%	0%	2%	3%	0%	0%
Chest wall	1%	5%	0%	0%	0%	0%	0%	0%

Table 21: Location of MTT and of All Tumors Treated in Blinded Treatment Phase, Studies Combined

Location	CDDP/epi Gel n=119		Placebo Gel n=59		All Patients n=178	
	MTT	All	MTT	All	MTT	All
Tumor(s) Treated	MTT	All	MTT	All	MTT	All
Total n (tumors)	119	227	59	80	178	307
Cervical	45%	55%	49%	52%	47%	54%
Oral cavity	27%	16%	17%	13%	24%	15%
Facial	16%	17%	22%	27%	18%	20%
Laryngopharyngeal	6%	3%	8%	6%	7%	4%
Nasopharyngeal	2%	1%	3%	3%	2%	1%
Cranial	3%	6%	0%	0%	2%	5%
Chest wall	1%	2%	0%	0%	1%	2%

Table 22: Volume (cm³) of MTT at Treatment Visit 1 (Baseline) by Study

	414-94-2		514-94-2	
	CDDP/epi Gel n=62	Placebo Gel n=24	CDDP/epi Gel n=57	Placebo Gel n=35
Median	5.3	4.8	4.9	5.3
Range	0.49-20	0.13-19	0.75-20	0.50-20

Table 23: Volume (cm³) of MTT at Treatment Visit 1 (Baseline), Studies Combined

	CDDP/epi Gel n=119	Placebo Gel n=59	All Patients n=178
Mean	7.1	6.9	7.0
sd	5.9	5.9	5.9
Median	4.9	5.3	5.0
Range	0.49-20	0.13-20	0.13-20

It is important to note that the patients included in these trials had advanced, incurable disease and few therapeutic options remaining. The advanced state of disease in these patients is illustrated by their extensive prior cancer therapy, as well as by the period of time between initial diagnosis and the start of study treatment.

Table 24: Cancer Treatment History, by Study

	414-94-2		514-94-2	
	CDDP/epi Gel n=62 (%)	Placebo Gel n =24(%)	CDDP/epi Gel n=57 (%)	Placebo Gel n=35 (%)
Months from Diagnosis to 1 st Treatment visit on study				
Median	23	19	17	13
Range	2-206	7-236	3-386	4-88
Any Previous Therapy	62	24	56 ^a	35
Single modality only				
Surgery	2 (3%)	1 (4%)	2 (4%)	1 (3%)
Radiation	1 (2%)	2 (8%)	3 (5%)	5 (14%)
Systemic chemotherapy	0	0	2 (4%)	0
Multiple modalities				
Surgery and radiation	26 (42%)	12 (50%)	28 (50%)	12 (34%)
Surgery, radiation, and systemic chemotherapy	31 (50%)	8 (33%)	17 (30%)	14 (40%)
Radiation and systemic chemotherapy	1 (2%)	1 (4%)	4 (7%)	3 (9%)
Surgery and systemic chemotherapy	1 (2%)	0	0	0
Post-relapse chemotherapy	31 (50%)	8 (33%)	12 (21%)	9 (26%)

^a One patient had refused previous therapy

Table 25: Cancer Treatment History, Studies Combined

	CDDP/epi Gel n=119 (%)	Placebo Gel n=59 (%)	All Patients n=178 (%)
Months from Diagnosis to 1 st Treatment visit on study			
Mean (sd)	33 (47.5)	28 (36.6)	32 (44.1)
Median (range)	19 (2-386)	18 (4-236)	19 (2-386)
Any Previous Therapy	118 (99%)	59 (100%)	177 (99%)
Single modality only	10 (8%)	9 (15%)	19 (11%)
Surgery	4 (3%)	2 (3%)	6 (3%)
Radiation	4 (3%)	7 (12%)	11 (6%)
Systemic chemotherapy	2 (2%)	0 (0%)	2 (1%)
Multiple modalities	108 (91%)	50 (85%)	158 (89%)
Surgery and radiation	54 (45%)	24 (41%)	78 (44%)
Surgery, radiation, and systemic chemotherapy	48 (40%)	22 (37%)	70 (39%)
Radiation and systemic chemotherapy	5 (4%)	4 (7%)	9 (5%)
Surgery and systemic chemotherapy	1 (1%)	0 (0%)	1 (1%)
Post-relapse chemotherapy	43 (36%)	17 (29%)	60 (34%)

Table 26: Previous Platinum-Based Treatment by Study

Previous Platinum Therapy	414-94-2		514-94-2	
	CDDP/epi Gel n=62 (%)	Placebo Gel n=24 (%)	CDDP/epi Gel n=57 (%)	Placebo Gel n=35 (%)
None	33 (53%)	15 (63%)	38 (67%)	20 (57%)
Any platinum-based therapy	29 (47%)	9 (38%)	19 (33%)	15 (43%)
Cisplatin only	12 (19%)	7 (29%)	5 (9%)	8 (23%)
Carboplatin only	9 (15%)	1 (4%)	12 (21%)	6 (17%)
Both cisplatin and carboplatin	8 (13%)	1 (4%)	2 (4%)	1 (3%)

Table 27: Previous Platinum-Based Treatment, Studies Combined

Previous Platinum Therapy	CDDP/epi Gel n=119 (%)	Placebo Gel n=59 (%)	All Patients n=178 (%)
None	71 (60%)	35 (59%)	106 (60%)
Any platinum-based therapy	48 (40%)	24 (41%)	72 (40%)
Carboplatin only	21 (18%)	7 (12%)	28 (16%)
Cisplatin only	17 (14%)	15 (25%)	32 (18%)
Both cisplatin and carboplatin	10 (8%)	2 (3%)	12 (7%)

6.5.4 Dose Administered

At the time of study initiation the assigned dose was 0.5 mL of drug per cm³ of baseline tumor volume. Amendment V changed the dose to 0.25 mL/cm³ tumor volume, calculated at each study visit. A total of seventy-two (40%) of the 178 patients enrolled in both studies were treated at the higher assigned

dose. Prior to the protocol amendment, the median cumulative dose administered to the MTT was 10 mL in each treatment group, when considering both studies together. Following the amendment, the median cumulative dose was 5.0 mL for the CDDP/epi gel group and 4.4 mL for placebo gel group when combining both studies. Further details of the effects of the amendment are presented in Appendix 3.

Table 28: Cumulative Dose (mL) Administered Before and After Amendment V, Studies Combined

	Stratum 1		Stratum 2		Strata 1 and 2	
	CDDP/epi Gel	Placebo Gel	CDDP/epi Gel	Placebo Gel	CDDP/epi Gel	Placebo Gel
Before Amendment V	n=22	n=11	n=23	n=16	n=45	n=27
Median	3.8	4.0	17	12	10	10
Range	1.1 – 21	1.3 – 38	2.3 – 46	6.0 – 29	1.1 – 46	1.3 - 38
After Amendment V	n=40	n=18	n=34	n=14	n=74	n=32
Median	3.0	2.2	8.2	7.3	5.0	4.4
Range	0.36 – 9.9	0.4 – 9.2	2.3 – 32	1.4 – 29	0.36 – 32	0.4 - 29

Tables 29 and 30 summarize the dosing by study, and strata for the studies combined, for all patients in the intent-to-treat analysis.

Table 29: Summary of Dosing by Study

	414-94-2		514-94-2	
	CDDP/epi Gel (n=62)	Placebo Gel (n=24)	CDDP/epi Gel (n=57)	Placebo Gel (n=35)
No. of treatments				
Median	3	3	4	3
Range	1-6	1-5	1-6	1-6
Dose (mL) per treatment				
Median	1.0	2.1	1.6	1.7
Range	0.1- 5.4	0.1- 7.1	0.2-8.5	0.50-10
Cumulative dose (mL)				
Median	4.4	4.9	5.4	5.3
Range	0.2 - 24	0.3 - 29	1.0 - 46	0.8 - 29
% of assigned dose delivered per treatment				
Median	80	98	100	100
Range	17-556	42-280	41-213	58-693
% of assigned dose delivered, cumulative				
Median	75	97	100	100
Range	17-243	32-141	37-213	54-666
No. (%) of visits where $\geq 80\%$ of assigned dose delivered	29 (47%)	16 (67%)	48 (84%)	32 (91%)

Table 30: Summary of Dosing, Studies Combined, by Strata

	Stratum 1		Stratum 2		Strata 1 and 2	
	CDDP/epi Gel (n=62)	Placebo Gel (n=29)	CDDP/epi Gel (n=57)	Placebo Gel (n=30)	CDDP/epi Gel (n=119)	Placebo Gel (n=59)
No. of treatments						
Median	4.0	3.0	3.0	3.0	4.0	3.0
Range	1-6	1-6	1-6	1-6	1-6	1-6
Dose (mL) per treatment						
Median	0.5	0.8	2.5	3.6	1.2	1.7
Range	0.1–2.5	0.1–3.1	0.5–8.5	1.0–10	0.1–8.5	0.1–10
Cumulative dose (mL)						
Median	2.4	2.3	10	10	5.0	5.0
Range	0.2–12	0.3–9.2	2.3–46	1.4–29	0.2–46	0.3–29
% of assigned dose delivered per treatment						
Median	100	100	82	100	94	100
Range	20 - 556	50 - 693	17 - 101	42 - 100	17 - 556	42 - 693
% of assigned dose delivered, cumulative						
Median	100	100	83	100	94	100
Range	20 - 243	49 - 666	17 -101	32 - 100	17 - 243	32 - 666
No. (%) of visits where $\geq 80\%$ of assigned dose delivered	44 (71%)	26 (90%)	33 (58%)	44 (71%)	26 (90%)	33 (58%)

Various factors affected the volume of study drug that was injected per treatment visit and cumulative. The most common reason in the blinded period was the tumor's inability to accommodate the entire volume of gel. Other factors were tumor size (since assigned dose is calculated on the basis of tumor volume), and number of treatments, which is affected by the response to treatment (e.g., early response could curtail treatments, as could local progression of disease and early discontinuation from the study).

6.5.5 Response to Therapy

6.5.5.1 MTT Response–Blinded Treatment Phase

Results are presented for Strata 1 and 2 for the individual studies and for the studies combined (Tables 31 and 32). The difference in MTT response between the two treatment groups was highly significant in both studies 414 (US and Canada) and 514 (Europe and Israel) and when results are combined. The response rates in the 2 studies were similar, although somewhat higher in the US/Canada study. Responses were high grade with complete response nearly twice as frequent as partial responses. In both studies patients with smaller MTT (stratum 1) had higher response rate than larger MTT (stratum 2).

Table 31a: Response Rate of MTT by Study

	414-94-2 (n=86)					p-value	
	n	CR		PR			CR+PR
Stratum 1							
CDDP/epi Gel	31	10	(32%)	3	(10%)	13 (42%)	0.008 ^b
Placebo Gel	12	0		0		0	
Stratum 2							
CDDP/epi Gel	31	4	(13%)	4	(13%)	8 (26%)	0.082 ^b
Placebo Gel	12	0		0		0	
All Patients							
CDDP/epi Gel	62	14	(23%)	7	(11%)	21 (34%)	0.001 ^a
Placebo Gel	24	0		0		0	

^a Exact Cochran-Mantel-Haenzel Test^b Fisher's Exact Test**Table 31b:** Response Rate of MTT by Study

	514-94-2 (n=92)					p-value	
	n	CR		PR			CR+PR
Stratum 1							
CDDP/epi Gel	31	6	(19%)	4	(13%)	10 (32%)	0.070 ^b
Placebo Gel	17	1	(6%)			1 (6%)	
Stratum 2							
CDDP/epi Gel	36	3	(12%)	1	(4%)	4 (15%)	0.13 ^b
Placebo Gel	18	0		0		0	
All Patients							
CDDP/epi Gel	57	9	(16%)	5	(9%)	14 (25%)	0.007 ^a
Placebo Gel	35	1	(3%)	0		1 (3%)	

^a Exact Cochran-Mantel-Haenzel Test^b Fisher's Exact Test**Table 32:** Response Rate of MTT, Studies Combined

	n	CR		PR		CR+PR		p-value
Stratum 1								
CDDP/epi Gel	62	16	26%	7	11%	23	37%	< 0.001 ^b
Placebo Gel	29	1	3%	0		1	3%	
Stratum 2								
CDDP/epi Gel	57	7	12%	5	9%	12	21%	0.015 ^b
Placebo Gel	30	0		0		0		
All Patients								
CDDP/epi Gel	119	23	19%	12	10%	35	29%	< 0.001 ^a
Placebo Gel	59	1	2%	0	0%	1	2%	

^a Exact Cochran-Mantel-Haenzel Test^b Fisher's Exact Test

Time to response and number of treatments to response are summarized for responders treated with CDDP/epi gel. Figure 7 presents the Kaplan-Meier plot for time to response for Studies 414 and 514. Duration of observed response, exact or censored, is summarized in the tables below for individual and

combined studies. In the combined studies (Table 34), responses occurred promptly (median 21 days) and were durable (median 78 days) (studies combined, stratum 1 and 2). In responding patients, the onset of response occurred after a median of 2 treatments; patients received a median of 5 treatments. Response characteristics were similar in the two individual studies (Tables 33a and 33b). Thirty-three of 35 tumors were still responding when the patient discontinued the study or began confounding therapy.

Table 33a: Response Characteristics for Patients Randomized to CDDP/epi Gel Who Responded, by Study

	414-94-2		
	Stratum 1 n=13	Stratum 2 n=8	Strata 1 & 2 n=21
Median No. of Treatments to MTT Response	2	2.5	2
Median No. of Treatments	3	5.5	4
Time to Onset of MTT Response (days)			
Median	14	21	17
Range	7 - 35	7 - 50	7 - 50
Duration of Observed MTT Response (days)			
Median	78	90	85
Range	34 - 168 ⁺	36 ⁺ - 124 ⁺	34 - 168 ⁺

Plus sign (⁺) indicates response ongoing when patient discontinued the study or was censored

Table 33b: Response Characteristics for Patients Randomized to CDDP/epi Gel by Study Who Responded

	514-94-2		
	Stratum 1 n=10	Stratum 2 n=4	Strata 1 & 2 n=14
Median No. of Treatments to MTT Response	5	3.5	4.5
Median No. of Treatments	6	4.5	6
Time to Onset of MTT Response (days)			
Median	62	30	53
Range	14 - 162	10 - 104	10 - 162
Duration of Observed MTT Response (days)			
Median	61	228	64
Range	30 ⁺ - 136 ⁺	46 ⁺ - 554 ⁺	30 ⁺ - 554 ⁺

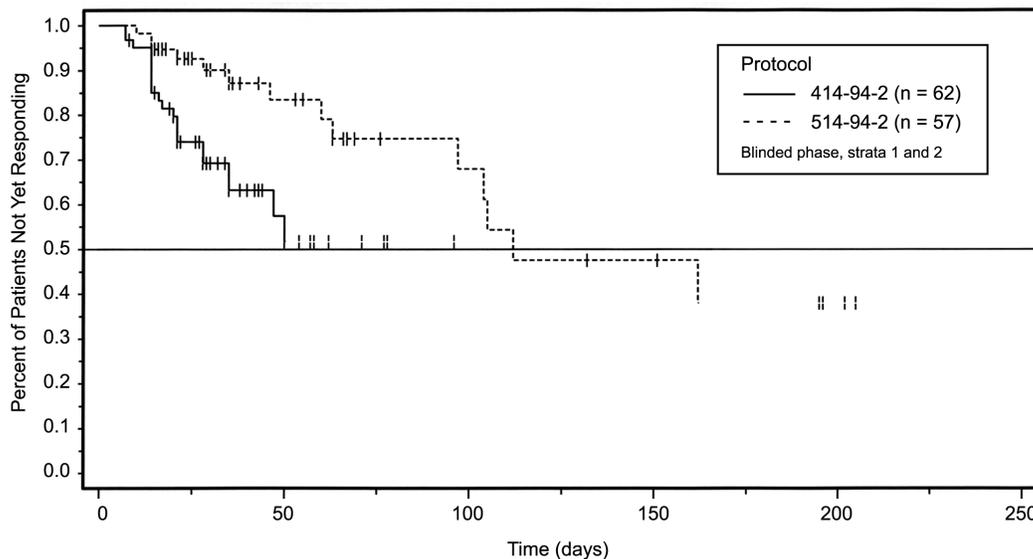
Plus sign (⁺) indicates response ongoing when patient discontinued the study or was censored

Table 34: Response Characteristics for Patients Randomized to CDDP/epi Gel, Studies Combined

	Stratum 1 n=23	Stratum 2 n=12	Strata 1 & 2 n=35
Median No. of Treatments to Response in Responding Patients	2	2.5	2
Median No. of Treatments in Responding Patients	5	5.5	5
Time to Response (days) in Responding Patients ^a			
Median	21	21	21
Range	7-162	7-104	7-162
Duration of Observed Response (days)			
Median	77	90	78
Range	30-168 ⁺	36-554 ⁺	30-554 ⁺

Plus sign (⁺) indicates response ongoing when patient discontinued the study or was censored

Figure 7: Time to Response, Studies 414 and 514



6.5.5.2 Time to MTT Progression

For all patients randomized to CDDP/epi gel (both responders and non-responders in both studies combined), the median time from the start of study treatment to MTT progression was 149 days (range 5 to 564⁺ days). For patients randomized to placebo gel, the median time from treatment at first study visit to MTT progression was 35 days (range 5 to 263⁺ days). Times to progression varied by stratum and study, as shown in Table 33, below.

Table 35: Time to MTT Progression (days)

	Study 414		Study 514		Combined studies	
	CDDP/epi gel n=62	Placebo n=24	CDDP/epi gel n=57	Placebo n=35	CDDP/epi gel n=119	Placebo n=59
Stratum 1						
Time to MTT progression (days)						
Median	*	21	223	35	223	29
Range	7-216 ⁺	5-212 ⁺	8-223	7-210 ⁺	7-223	5-212 ⁺
Stratum 2						
Time to MTT progression (days)						
Median	*	*	54	43	149	49
Range	6-154 ⁺	7-263 ⁺	5-564 ⁺	6-170 ⁺	5-564 ⁺	6-263 ⁺
Stratum 1 and Stratum 2						
Time to MTT progression (days)						
Median	*	35	149	35	149	35
Range	6-216 ⁺	5-263 ⁺	5-564 ⁺	6-210 ⁺	5-564 ⁺	5-263 ⁺

Plus sign (*) indicates patient discontinued the study or was censored from follow-up before progressing

*could not be calculated due to censoring

Time to MTT progression is affected by several factors. First, although most patients who crossed over to open-label drug did so only after being classified as "PD" in blinded treatment phase, there are a few who did not and therefore received open-label CDDP/epi before progressing; this makes comparison of patients randomized to placebo vs. patients randomized to CDDP/epi gel more difficult to interpret by prolonging the time to progression in placebo patients who received open-label CDDP/epi gel. Second, patients in open-label phase (extended follow-up) were permitted to receive other cancer therapies; when this occurred, patients who had not yet progressed were censored for progression. Finally, some patients (particularly those who had received CDDP/epi gel in blinded phase, and placebo patients who did not progress in blinded phase and received open-label CDDP/epi gel) discontinued study without experiencing MTT progression.

6.5.5.3 MTT Response—Study Overall

A total of 160 of the 178 patients (84 in Stratum 1 and 76 in Stratum 2) went on to receive open label treatment with CDDP/epi gel after initial treatment in the blinded treatment phase. The MTT response rate for patients ever treated with CDDP/epi gel was 32% (95% CI: 25-40%) which was comparable to the MTT response of CDDP/epi gel-treated patients in the blinded treatment phase (29%, 95% CI: 21-38%).

6.5.5.4 MTT Response in Placebo Crossover Patients

Further support for the effect of CDDP/epi gel on MTT response rate comes from examining patients initially treated with placebo but then crossed over to CDDP/epi gel. Of the 59 patients who received placebo gel during the blinded treatment phase, 41 patients received CDDP/epi gel in the open-label period. An objective response of the MTT was observed in 11 (27%) placebo crossover patients. Complete response was noted in 7 (17%) of these patients and partial response in 4 (10%) patients. It is important to note that their MTT volume had a median increase of 50% from baseline during blinded placebo treatment.

6.5.5.5 Response Rate for All Individual Treated Tumors

In addition to treating the MTT, additional tumors were treated at the discretion of the investigator. The group of all treated tumors, both MTTs and other treated tumors combined, was referred to as "Individual Treated Tumors". In the blinded treatment phase, there were a total of 307 tumors treated, 178 tumors designated as the MTT and 129 additional tumors. Thirty-six patients had at least one tumor in addition to the MTT treated. This occurred in 23 of the patients randomized to CDDP/epi gel and 13 patients randomized to placebo gel.

The combined response rates of all individual treated tumors are provided in the following tables by study and original randomization stratum. For all tumors treated with CDDP/epi gel versus those

treated with placebo gel, the response rates were 30% versus 1%, respectively. The response rate considering all tumors treated with CDDP/epi gel (30%) was nearly identical to the MTT response rate in the blinded treatment phase (29%).

Table 36a: Objective Response Rate of All Individual Treated Tumors, by Treatment Group, Stratum, and Study

Patient Strata	414-94-2					
	CDDP/epi Gel			Placebo Gel		
	Tumors (n)	No. of Responses (%)		Tumors (n)	No. of Responses (%)	
Stratum 1	118	42	35%	20	0	0%
Stratum 2	42	9	22%	16	0	0%
Strata 1& 2	160	51	32%	36	0	0%

Table 36b: Objective Response Rate of All Individual Treated Tumors, by Treatment Group, Stratum, and Study

Patient Strata	514-94-2					
	CDDP/epi Gel			Placebo Gel		
	Tumors (n)	No. of Responses (%)		Tumors (n)	No. of Responses (%)	
Stratum 1	35	13	37%	23	1	4%
Stratum 2	32	4	12%	21	0	0%
Strata 1& 2	67	17	25%	44	1	2%

Table 37: Objective Response Rate of All Individual Treated Tumors, by Treatment Group and Stratum, Studies Combined

Patient Strata	CDDP/epi Gel			Placebo Gel		
	Tumors (n)	Number of Responses (%)		Tumors (n)	Number of Responses (%)	
Stratum 1	153	55	(36%)	43	1	(2%)
Stratum 2	74	13	(18%)	37	0	(0%)
Strata 1& 2	227	68	(30%)	80	1	(1%)

6.5.6 Covariate Analyses of MTT Response

The objective response rate of the MTT during the blinded treatment phase was analyzed conditional on a number of covariates, including demographics, baseline clinical status, previous cancer therapy, and tumor location. The covariate of baseline tumor size was defined by stratum as part of the study design. The covariates analyzed that related to baseline clinical and treatment status included previous cancer treatment history, time from diagnosis to first study visit, baseline KPS, and tumor location. Only

baseline tumor volume, baseline KPS and location of MTT were found to influence the probability of tumor response.

Table 38: Response Rate of MTT by Baseline Clinical and Disease Covariates in Patients Treated with CDDP/epi Gel

Covariate	n	Number of Responses (%)		95% CI for Response Rate
Previous Treatment ^a				
Previous surgery	107	31	(29%)	21-39%
No surgery	12	4	(33%)	10-65%
Previous chemotherapy	56	16	(29%)	17-42%
No chemotherapy	63	19	(30%)	19-43%
Previous Systemic Platinum Therapy				
Cisplatin or carboplatin	48	14	(29%)	17-44%
None	71	21	(30%)	19-42%
Time from Diagnosis to 1 st Treatment Visit ^b				
<12 months	35	9	(26%)	12-43%
12-24 months	36	9	(25%)	12-42%
>24 months	47	17	(36%)	23-51%
Baseline Karnofsky Performance Status				
40-60	18	4	(22%)	6-48%
70-80	50	10	(20%)	10-34%
90	42	18	(43%)	28-59%
100	9	3	(33%)	8-70%

^a 86% of MTTs in CDDP/epi gel group and 95% of MTTs in placebo gel group were located in fields with prior radiation

^b One patient was missing diagnosis date; hence, total n = 118 instead of 119.

The response rates of MTTs in facial and oral locations were observed to be higher than the response rate of MTTs in cervical or other locations. The subgroup of “other” locations included such locations as chest wall, nasopharyngeal, laryngopharyngeal, and cranial.

Table 39: Response by Tumor Location in Patients Treated with CDDP/epi Gel, Studies Combined

Location of MTT	n	No. of Responses (%)		95% CI for Response Rate
Oral	32	14	(44%)	(26-62%)
Facial	19	8	(42%)	(20-67%)
Cervical	54	11	(20%)	(11-34%)
Other	14	2	(14%)	(2-43%)

6.5.6.1 Multiple Regression Analysis of the MTT Response

A logistic regression analysis was conducted to explore the effects of selected covariates on MTT response in patients treated with CDDP/epi gel. A “study” factor (414, 514) was also included in the logistic regression analysis. Candidate predictors included the categorical variables age group, gender, MTT location, baseline KPS group, time from original diagnosis to treatment visit 1, previous chemotherapy (yes/no) and the intervally scaled variable MTT baseline volume.

Certain covariates were not included in the analysis. Ethnic category was eliminated since only 11 patients were nonwhite and all of these were Study 414 patients. Because almost all patients who had received previous chemotherapy had received previous platinum-based treatment, “previous platinum-based treatment” was excluded.

For all prognostic variables except previous chemotherapy, essentially no differences in baseline parameters between studies were observed. For previous chemotherapy, North American patients were more likely to have received previous chemotherapy than were European patients ($p = 0.052$), consistent with clinical practice differences in the two geographic areas.

Baseline volume of the MTT and location of the MTT (cervical, facial, oral, or other) had apparent prognostic value with regard to the response of the MTT in patients treated with CDDP/epi gel. Smaller MTTs had a higher response rate (37%) than did larger MTTs (21%), and MTTs in facial or oral locations had a higher response rate (42% and 44% respectively) than did MTTs in cervical or “other” locations (20% and 14%).

The MTT response rates in patients with a baseline KPS of 40-60, and 70-80, were 22%, and 20%, respectively. In contrast, the MTT response rates in those with higher baseline KPS scores of 90 and 100 were 43% and 33%, respectively. Because patients with higher baseline KPS scores may have had higher response rates due to being able to remain on treatment longer, the association of baseline KPS with time on study (treatment phase) was evaluated by examining the association of the number of blinded treatments (1-6) with categories of baseline KPS score (100, 90, 70-80, 40-60) using a test for trend. Results showed that patients with higher KPS scores at entry received more treatments ($p = 0.026$), which implies that patients with good functional status were more likely to remain on study. A significant effect of baseline KPS was observed when the KPS was divided into two categories, 40-80 and 90-100 ($p = 0.018$), with MTT response being more likely to occur in those with a higher KPS. In contrast, age group, gender, time from original diagnosis to study entry, and previous chemotherapy had no apparent influence on the response of MTT.

Table 40: Contribution of Covariates to MTT Response, Patients Treated with CDDP/epi Gel

Covariate	Favorable Clinical Condition	p-value^a
Baseline KPS	KPS 90-100	0.018
MTT location	Facial or oral	0.027
Baseline MTT volume	Smaller tumors	0.033
Time since diagnosis	-	0.27
Gender	-	0.35
Age group	-	0.83
Previous chemotherapy	-	0.83

^a Type 3 likelihood ratio test.

6.5.7 Inter-Study Differences in Tumor Response

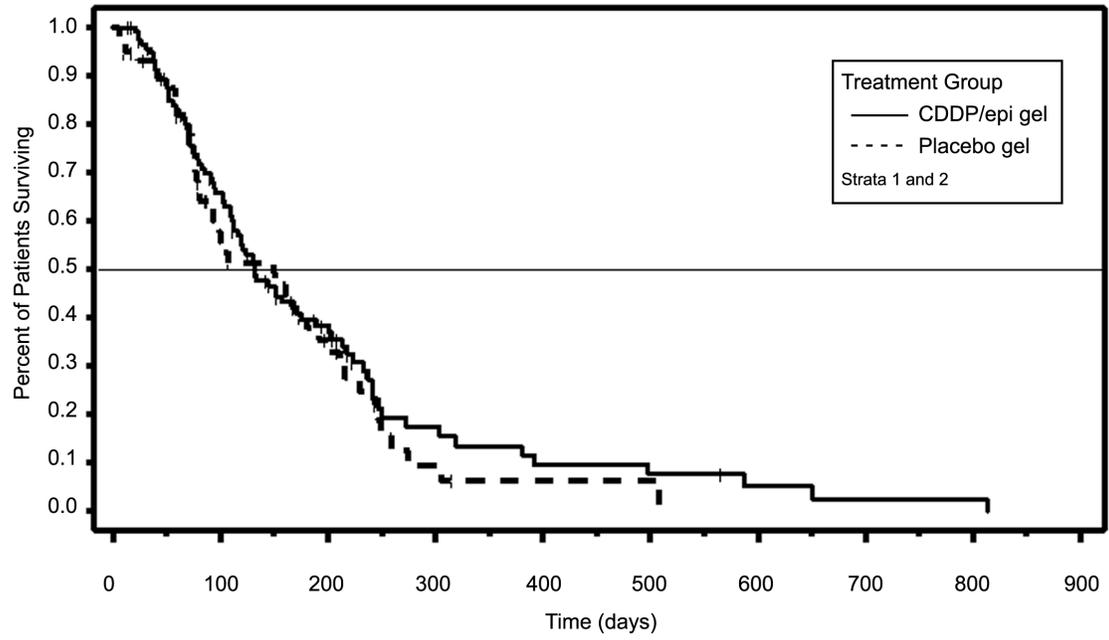
There are a number of differences in MTT response outcomes between Study 414 and Study 514. These differences, while not statistically significant, are consistent enough to suggest a real geographic effect. Differences in the two studies can be seen in the endpoints MTT response (34% in Study 414 and 25% in Study 514), median number of treatments to response (2 vs.4.5), time to response (see Figure 7), and response rate of individual treated tumors (32% vs 25%). These differences are not explainable on the basis of demographics, previous treatment, dose, or tumor characteristics. It is likely that they reflect clinical practice and/or reporting differences in the geographic locals sampled for the two studies.

6.5.8 Survival

The Phase III controlled studies 414 and 514 were not designed to evaluate survival. CDDP/epi gel was developed to control tumor growth and palliate symptoms of local disease, and no impact on overall survival was anticipated. Furthermore, any impact on survival would have been difficult to detect because of the ability of patients in the placebo group to cross over to CDDP/epi gel therapy in the open-label phase.

For patients in Strata 1 and 2 randomized to CDDP/epi gel, the median time from first dose to death was 133 days (95% CI 116 to 201). For patients in Strata 1 and 2 randomized to placebo gel, the median time from first dose to death was 151 days (95% CI 93 to 200). Time to death in the two treatment groups was estimated by the Kaplan-Meier method (see Figure 8). For the two treatment groups, the estimated survival curves were similar. The stratified log rank test p-value is 0.65.

Figure 8 Patient Survival



6.5.9 Patient Benefit and Attainment of Primary Treatment Goals

The difficulty of conducting quality-of-life studies in cancer patients is well known, and no standard has been established that provides a reliable and accurate method for determining quality of life. Appropriate methods to document improvements in patient function or quality of life must be adopted within each clinical setting, and for each study design.

Achievement of Patient Benefit was determined from the patients' and investigators' assessments of Primary Treatment Goals from the Treatment Goal Questionnaire. The Primary Treatment Goals could be either palliative (selected by the investigator and/or the patient) or preventive (investigator-selected only). According to the Patient Benefit Algorithm, Patient Benefit was ascribed if either the patient's or the investigator's goal was met *and* neither person's goal had worsened. (See Appendix 1 for detailed information on the Treatment Goal Questionnaire.) Provided below is 1) an analysis of attainment of Patient Benefit for studies 414 and 514, and as combined data; and 2) the attainment of the Primary Treatment Goals selected by the investigators (preventive or palliative) and by the patient (palliative), from which the Patient Benefit outcome is derived.

6.5.9.1 Attainment of Patient Benefit During the Blinded Treatment Phase

Table 41a shows Patient Benefit attainment rates by MTT stratum in study 414. In both strata, more patients in the CDDP/epi gel group attained Patient Benefit than patients treated with placebo, although this effect was not statistically significant (p=0.18).

Table 41a: Patient Benefit Rate-Blinded Treatment Phase, Study 414

	414-94-2				
	CDDP/epi Gel		Placebo Gel		p-value
	Benefit Rate (%)		Benefit Rate (%)		
Stratum 1	13/31	(42%)	3/12	(25%)	0.48 ^b
Stratum 2	8/31	(26%)	1/12	(8%)	0.40 ^b
Strata 1 and 2	21/62	(34%)	4/24	(17%)	0.18 ^a

^a Exact Cochran-Mantel-Haenszel test

^b Fisher's exact test

Patient Benefit is further evaluated in the following two sections: The association between objective response of the MTT and Patient Benefit is included in 6.5.10; discussion of additional evidence of palliative benefit is in 6.5.11.

As shown in Table 41b, Patient Benefit rates in study 514 were lower than those seen in study 414, but the same trend to greater Patient Benefit attainment rates in patients treated with CDDP/epi gel was observed.

Table 41b: Patient Benefit Rate-Blinded Treatment Phase, Study 514

	514-94-2				
	CDDP/epi Gel		Placebo Gel		
	Benefit Rate (%)		Benefit Rate (%)		p-value
Stratum 1	7/31	(23%)	2/17	(12%)	0.46 ^b
Stratum 2	4/26	(15%)	1/18	(6%)	0.63 ^b
Strata 1 and 2	11/57	(19%)	3/35	(9%)	0.24 ^a

^a Exact Cochran-Mantel-Haenszel test

^b Fisher's exact test

When the two studies were combined (Table 42), 27% of CDDP/epi gel-treated patients attained Patient Benefit in the blinded treatment phase, compared to 12% of placebo gel-treated patients (exact Cochran-Mantel-Haenszel test $p = 0.046$). For CDDP/epi gel-treated patients, the rate of Patient Benefit attainment was higher than for placebo gel-treated patients in each of the two strata.

Table 42: Patient Benefit Rate-Blinded Treatment Phase, Studies Combined

	CDDP/epi Gel			Placebo Gel		
	Benefit Rate (%)	95% CI ^a		Benefit Rate (%)	95% CI ^a	p-value ⁶
Stratum 1	20/62 (32%)	(21-45%)		5/29 (17%)	(6-36%)	0.20
Stratum 2	12/57 (21%)	(11-34%)		2/30 (7%)	(1-22%)	0.13
Strata 1 and 2	32/119 (27%)	(19-36%)		7/59 (12%)	(5-23%)	0.046

^a Clopper-Pearson exact 95% confidence interval

⁶ Exact Cochran-Mantel-Haenszel test

Of the 59 patients treated with placebo gel in blinded treatment phase, 41 had their MTT subsequently treated with open-label CDDP/epi gel in extended follow-up. Combining these patients' open-label experience with the experience of patients randomized to CDDP/epi gel in blinded treatment phase allows calculation of the Patient Benefit rate for patients *ever* treated with CDDP/epi gel. These rates are shown in Table 43 for the individual studies, and in Table 44 for the combined studies.

Table 43: Patient Benefit Rate for Patients Ever Treated with CDDP/epi Gel, by Study

	414-94-2		514-94-2	
	Benefit Rate (%)		Benefit Rate (%)	
Stratum 1	15/41	37%	10/43	23%
Stratum 2	11/38	29%	7/38	18%
Strata 1 and 2	26/79	33%	17/81	21%

Table 44: Patient Benefit Rate - Patients Ever Treated with CDDP/epi Gel, Studies Combined

	Benefit Rate (%)		95% CI ^a
Stratum 1	25/84	(30%)	(20-41%)
Stratum 2	18/76	(24%)	(15-35%)
Strata 1 and 2	43/160	(27%)	(20-34%)

^aClopper-Pearson exact 95% confidence interval

6.5.9.2 Achievement of Primary Treatment Goals

The attainment rate and duration of achievement of preventive goals selected by the investigator are presented below for studies 414 and 514 combined. The rate of attainment and duration of achievement of preventive goals were higher in the group treated with CDDP/epi gel. For all three investigator-selected preventive goals, patients receiving CDDP/epi gel achieved the goal at a higher rate than patients treated with placebo gel.

Table 45: Achievement of Investigator-Selected Primary Preventive Treatment Goals, Studies Combined

Primary Goals	CDDP/epi Gel (n = 119)			Placebo Gel (n = 59)		
	Selected	Met (%)	Duration ^a (Range in Days)	Selected	Met (%)	Duration ^a (Range in Days)
Prevention of tumor breaking the skin	20	11 (55%)	78 (50 ⁺ -156 ⁺)	13	4 (31%)	30 (26 ⁺ -50 ⁺ ^a)
Prevention of invasion	14	10 (71%)	65 (29 ⁺ -189 ⁺)	6	1 (17%)	44 (44 ⁺)
Prevention of obstruction	8	5 (62%)	44 (36 ⁺ -154 ⁺)	4	1 (25%)	35 (35 ⁺)

^a Median; a plus sign (+) indicates that the response was ongoing when the patient discontinued the study

The attainment rate and duration of achievement of primary palliative goals selected by the investigator and patient are presented in Tables 46 and 47, respectively. In the blinded treatment phase, the attainment rate and duration of achievement of palliative goals were higher in the group treated with

CDDP/epi gel than in patients treated with placebo gel.

Table 46: Achievement of Investigator-Selected Primary Palliative Treatment Goals, Studies Combined

Primary Goals	CDDP/epi Gel (n = 119)			Placebo Gel (n = 59)		
	Selected	Met (%)	Duration ^a (Range in Days)	Selected	Met (%)	Duration ^a (Range in Days)
Wound care	23	3 (13%)	114 (69 ⁺ -162 ⁺)	13	0	n/a
Pain control	26	3 (12%)	57 (29 ⁺ -536 ⁺)	14	0	n/a
Obstructive symptom	24	2 (8%)	91 (91 ⁺)	5	0	n/a
Physical appearance	3	0	n/a	3	1 (33%)	39 (39)

^a Median; a plus sign (+) indicates that the response was ongoing when the patient discontinued the study

Table 47: Achievement of Patient-Selected Primary Palliative Treatment Goals, Studies Combined

Primary Goals	CDDP/epi Gel (n = 119)			Placebo Gel (n = 59)		
	Selected	Met (%)	Duration ^a (Range in Days)	Selected	Met (%)	Duration ^a (Range in Days)
Pain control	38	4 (11%)	41 (27 ⁺ -56 ⁺)	22	1 (5%)	38 (38 ⁺)
Wound care	26	3 (12%)	114 (69 ⁺ - 170 ⁺)	9	0	n/a
Obstructive symptom	27	3 (11%)	91 (63 ⁺ - 91 ⁺)	11	0	n/a
Physical appearance	8	1 (13%)	213 (213 ⁺)	4	1 (25%)	39 (39)

^a Median; a plus sign (+) indicates that the response was ongoing when the patient discontinued the study

6.5.10 Association of the Primary Efficacy Endpoints, MTT Objective Response and Patient Benefit

Of the 119 total patients treated with CDDP/epi gel in the blinded treatment phase, 35 (29%) had an objective MTT response and are referred to as “responders.” Those 84 patients treated with CDDP/epi gel in the blinded treatment phase who did not have an objective response of the MTT are referred to as “non-responders.” Data on the association of Patient Benefit and objective MTT response are provided in Tables 38 – 40 for studies 414, 514, and combined. Of the patients who responded, 46% attained Patient Benefit, compared to 19% of non-responders (p = 0.012). Responders were 2.4 times more likely to benefit from treatment as measured by the Patient Benefit Algorithm than were non-responders.

Both Patient Benefit and objective MTT response were rigorously defined outcome measures, and independently determined. Therefore 100% concurrence of these two measurements was not expected and did not occur. Sixteen patients (19%) achieved Patient Benefit without objective tumor response. Conversely, 19 (54%) of the patients with objective MTT response did not achieve Patient Benefit,

although in some of these cases secondary goals specified by either the patient or the investigator were attained. In a few instances patients selected a goal that was unimprovable (i.e., had the best baseline score of “1”). Patient Benefit rates did not differ significantly by age group, gender, ethnic category, MTT location, previous treatment history, or study center. This supports the interpretation that the Patient Benefit outcome was dependent upon treatment and response, rather than favorable patient characteristics.

Table 48: Association Between Objective Response of MTT and Attainment of Patient Benefit in Patients Treated with CDDP/epi Gel

	Responders			Non-responders			p value ^a
	n	No. with Benefit	Benefit Rate	n	No. with Benefit	Benefit Rate	
Stratum 1	23	13	57%	39	7	18%	0.004
Stratum 2	12	3	25%	45	9	20%	1
Strata 1 & 2	35	16	46%	84	16	19%	0.012

^a Chi-squared test

In the placebo gel group, 7 of 59 patients (12%) achieved Patient Benefit. Only one patient in the placebo gel group achieved a response during the blinded treatment phase. This patient also achieved Patient Benefit. Appendix 2 contains tabular summaries of those patients who achieved an objective response and those patients who achieved Patient Benefit.

6.5.11 Additional Evidence of Palliative Benefit

Palliative goal outcomes were further examined to evaluate the importance of symptom palliation in this disease population. The analysis of Patient Benefit described above was based solely on the single, prospectively-defined, primary treatment goals separately selected by the patient and investigator. The analysis represents a conservative approach as it excludes other benefits that were reported by patients and investigators during the study. In addition to the primary treatment goal, both patients and investigators were encouraged to prospectively select secondary goals from the TGQ. Patients and investigators could also record “unforeseen benefits” on the case report forms.

The analyses presented below were carried out to further explore the palliative benefit attributable to intratumoral treatment with CDDP/epi gel when palliative goals other than the primary treatment goal are considered. Although the analyses were specified in the analysis plans for the individual studies, the plans did not provide for a combined analysis of these data. Included below, for Studies 414 and 514 combined, are tables showing the rate of attainment of *any* palliative goal (primary or secondary, selected by the investigator or patient), the percent of patients with an unforeseen benefit, as reported by patient or investigator, and the percent of patients who attained any palliative goal and/or had an unforeseen benefit. In each case, results are compared for CDDP/epi gel and placebo gel patients in blinded treatment phase.

Table 49 compares the attainment rate of any palliative treatment goal (primary or secondary) selected from the TGQ by either patient or investigator. When all palliative goals selected were considered, patients treated with CDDP/epi gel in blinded phase were more likely to attain one or more of these goals than patients treated with placebo gel.

Table 49. Rate of Attainment of Any Palliative Treatment Goal (Primary or Secondary) Selected from the TGQ By Patient or Investigator

	CDDP/epi Gel	Placebo Gel
Study		
414 and 514 Combined	20/111 (18%)	3/54 (6%)

^a Exact Cochran-Mantel-Haenszel test p=0.032. Chi-squared p-value = 0.007 for association of this outcome with MTT response.

Patients and investigators also reported unforeseen benefits; space was provided to record verbatim descriptions of unforeseen benefits on the CRF. Unforeseen benefits reported included the ability of one patient to sleep on his side and another to attend her daughter's wedding without wound problems. Others reported the ability to enjoy favorite seasonal foods, wear eyeglasses, or eat meals with the family. Table 50 shows an analysis of any unforeseen benefit recorded. Patients treated with CDDP/epi gel were more likely to experience an unforeseen benefit than were patients treated with placebo gel.

Table 50. Rate of Unforeseen Benefit Reported by Patient or Investigator

	CDDP/epi Gel	Placebo Gel
	Any unforeseen benefit reported	Any unforeseen benefit reported
Study		
414 and 514 Combined		
By patient	19/119 (16%)	4/59 (7%)
By investigator	16/119 (13%)	0/59 (0%)
By either	24/119 (20%)	4/59 (7%)

When the above two benefits, Attainment of any Palliative Goal and/or Attainment of an Unforeseen Benefit were combined, patients treated with CDDP/epi gel in blinded phase were more likely to experience a beneficial effect than patients treated with placebo gel. This is shown in the following table.

Table 51. Attainment of any Palliative Goal and/or Attainment of an Unforeseen Benefit

	CDDP/epi Gel	Placebo Gel	p-value^a
	Any goal attained, and/or unforeseen benefit reported	Any goal attained, and/or unforeseen benefit reported	
Study			
414 and 514 Combined	40/119 (34%)	57/59 (8%)	<0.001

^a Exact Cochran-Mantel-Haenzel test; chi-squared p-value <0.005 for association of this outcome with MTT response.

The availability of detailed goal attainment data from the two studies provides a more thorough opportunity to evaluate palliative benefit. While these analyses were not pre-specified and must be viewed as exploratory rather than confirmatory, there are clear trends in nearly all assessments of clinical benefit favoring the CDDP/epi gel arm of the studies. While patients randomized to CDDP/epi gel tended to remain slightly longer in blinded treatment phase, this difference is not sufficient to account for the differences in clinical improvement between the two groups. Examination of the CDDP/epi gel and placebo groups on a patient-by-patient basis indicates that patients in both groups who had progressive disease tended to move into open-label treatment; these patients were unlikely to attain treatment goals or report unforeseen benefit in the blinded treatment phase. Treatment with CDDP/epi gel, on the other hand, often resulted in clinical benefit that could be measured in a variety of ways and was internally consistent in both studies.

6.5.12 Inter-Study Differences in Rate of Patient Benefit Attainment

In Study 414, rates of desirable outcomes were consistently higher than those seen in Study 514 – for example, MTT response rates (34% vs 25%), patient benefit rates (34% vs 19%), and rate of attainment of any treatment goal (61% vs 32%), while not statistically significant, are different enough to suggest a real geographic effect. These differences are not explainable on the basis of demographics, previous treatment, dose, tumor characteristics, or any other covariate; we conclude that they reflect clinical practice and/or reporting difference in the geographic locales sampled for the 2 studies.

As was seen for tumor response outcome (Section 6.5.7), Patient Benefit Rate was higher in Study 414 than in Study 514, however the difference was not significant. As with tumor response, this difference may be attributable to practice patterns in the two geographic areas in which the studies were conducted.

7 Safety

In keeping with the original analysis plan, patients from all three strata (Stratum 1: $\leq 5 \text{ cm}^3$, 91 patients, Stratum 2: > 5 and $\leq 20 \text{ cm}^3$, 87 patients, and Stratum 3: $> 20 \text{ cm}^3$, 46 patients) are included in the analyses of safety for a total of 225 patients. All patients who received at least one treatment were considered evaluable for the safety analysis. One patient is included who did not receive study medication (placebo gel), the needle of the injection syringe was inserted but no material was administered due to pain.

7.1 Adverse Event Reporting and Coding

Because tumors treated in these studies could be located in a variety of body systems under standard adverse event coding systems, it was necessary to create special categories to avoid a confusing and misleading adverse event listing. The following adverse event categories (AE categories) were developed to provide information useful in understanding the etiology and characteristics of adverse events reported in trials of CDDP/epi gel given as an intratumoral injection:

- *Immediate Injection Effects* — Adverse events that occurred either during injection or within a 15- to 20-minute period after injection
- *Local Reactions at the Treatment Site* — Adverse events that occurred at the injection site more than 15 to 20 minutes following an injection.
- *Systemic/Other Local Effects* — Any systemic or local adverse event not at the injection site.

Adverse events were mapped to COSTART terminology, counting an adverse event only once, with the highest severity, for any patient. Adverse events were rated on a three-point scale: mild, moderate, or severe.

7.1.1 Local Tissue Conditions

A Case Report Form (CRF) titled “Local Tissue Conditions” was used to elicit information on tissue conditions present at baseline and at each treatment visit. The specific conditions were selected to be representative of possible clinical observations at local tumor sites and included erythema, swelling, bleeding/hemorrhage, necrosis, ulceration, eschar/scabbing, and erosion. Local tissue conditions were evaluated at baseline and at each study visit and rated by severity on a four-point scale (none, mild, moderate, severe). If a baseline condition became worse after an injection, it was considered a “local cytotoxic effect.” Investigators also reported certain of these conditions on the adverse event log, under “Local reactions at the treatment site”. Time to worsening and resolution of worsened conditions were also recorded.

7.1.2 Serious Adverse Events (SAEs)

Serious adverse events (SAEs) were defined as events that were fatal, life-threatening, permanently disabling, requiring or prolonging hospitalization, or a congenital abnormality, or any event that suggested a significant hazard, contraindication, side effect, or precaution that occurred during the study. Patients who died on study or within 30 days of study termination were tabulated.

7.2 Concomitant Medications

The most common indication for a concomitant medication was pain. This is consistent considering the advanced stage of the patients enrolled in the two trials and the palliative treatment goals of therapy. The most common medications were prescribed for pain including local anesthetics, opiates/opioids, acetaminophen products, and non-steroidal anti-inflammatory agents. These were either limited to the time of the procedure or administered chronically. Several gastrointestinal agents were used to alleviate nausea or constipation when needed. Antibiotic usage was not notable in either study, nor were hypnotic or sedative agents used extensively.

7.3 Incidence of Adverse Events

Adverse events are presented below combining results from both the 414 and 514 studies, in order to provide a more comprehensive overview. In general, the rates of adverse events reported tended to be higher in Study 414 than 514. Except as noted the pattern was similar or identical. The overall differences in adverse event rates may have been related to differences in patients entering the two studies. Patients entering 514 had shorter median time from diagnosis to first study visit and a lower incidence of post-relapse chemotherapy (Table 24). There may have also been differences in ascertainment of adverse events, perhaps due to geographically based cultural differences.

7.3.1 Incidence of Immediate Injection Effects

The most common adverse event associated with injection (within 20 minutes) was pain. The frequency of pain was moderately higher in the group randomized to CDDP/epi gel than the group randomized to placebo. The incidence of pain in the placebo group presumably reflects pain from placement of a needle or injection into tumor. Blood pressure increases and tachycardia were reported in a few patients after study drug administration. Some degree of hypertension and tachycardia were expected in the CDDP/epi gel-treated patients, as the formulation contains epinephrine, but no difference between the two treatment groups was observed.

Table 52: Incidence of Immediate Injection Effects ($\geq 3\%$), Regardless of Relationship–Blinded Treatment

Adverse Event	CDDP/epi Gel (n = 150)		Placebo Gel (n = 75)	
	All	Severe	All	Severe

Pain	41	(27%)	15	(10%)	15	(20%)	3	(4%)
Hypertension	6	(4%)	3	(2%)	3	(4%)	0	(0%)
Tachycardia	6	(4%)	1	(<1%)	2	(3%)	2	(3%)
Hemorrhage	5	(3%)	0	(0%)	2	(3%)	0	(0%)
Tremor	5	(3%)	1	(<1%)	0	(0%)	0	(0%)

7.3.2 Incidence of Local Reactions at the Treatment Site

The incidence of local reactions (i.e., at the injection site but > 20 minutes after injection) was higher in the CDDP/epi gel group than in the placebo gel group. As in the immediate injection effects, the most common event was pain. Other events that were more common in the group randomized to CDDP/epi gel may have been related to CDDP and may be a result of successful tumor cell killing. The extent to which these were truly adverse events or signs of tumor regression are examined further in section 7.4, “Local Cytotoxic Effects”.

Table 53: Incidence of Local Reactions at the Treatment Site Occurring in ≥ 5% of Patients, Regardless of Relationship–Blinded Treatment Phase

Adverse Event	CDDP/epi Gel (n = 150)				Placebo Gel (n = 75)			
	All		Severe		All		Severe	
Pain	45	(30%)	18	(12%)	13	(17%)	5	(7%)
Facial Edema	15	(10%)	5	(3%)	0	(0%)	0	(0%)
Infection	12	(8%)	2	(1%)	1	(1%)	0	(0%)
Neck Pain	10	(7%)	5	(3%)	2	(3%)	0	(0%)
Hemorrhage ^a (local)	10	(7%)	6	(4%)	2	(3%)	0	(0%)
Swelling	10	(7%)	2	(1%)	1	(1%)	0	(0%)
Necrosis	8	(5%)	2	(1%)	1	(1%)	1	(1%)

^a COSTART term for events ranging from blood-tinged saliva, bleeding from injection, to hemorrhage of an innominate artery

7.3.3 Incidence of Systemic and Other Local Effects

The overall incidence of systemic adverse events was higher in the CDDP/epi gel group than the placebo gel group. Notable among these were facial edema, hypertension, nausea, vomiting, constipation, anorexia, dehydration, and hypomagnesemia. The difference between the randomized groups in the incidence of pain at sites other than the treatment site was modest.

Table 54: Incidence of Systemic/Other Local Effects Occurring in $\geq 5\%$ of Patients, Regardless of Relationship–Blinded Treatment Phase

Adverse Event	CDDP/epi Gel (n = 150)				Placebo Gel (n = 75)			
	All		Severe		All		Severe	
Body as a Whole								
Pain	32	(21%)	10	(7%)	11	(15%)	3	(4%)
Asthenia	22	(15%)	8	(5%)	8	(11%)	3	(4%)
Facial Edema	18	(12%)	7	(5%)	2	(3%)	1	(1%)
Infection	15	(10%)	3	(2%)	7	(9%)	1	(1%)
Fever	14	(9%)	1	(<1%)	5	(7%)	0	(0%)
Headache	13	(9%)	1	(<1%)	5	(7%)	2	(3%)
Cardiovascular System								
Hypertension	10	(7%)	3	(2%)	2	(3%)	1	(1%)
Hemorrhage ^a	9	(6%)	5	(3%)	2	(3%)	1	(1%)
Digestive System								
Nausea	25	(17%)	4	(3%)	6	(8%)	2	(3%)
Vomiting	24	(16%)	3	(2%)	2	(3%)	1	(1%)
Constipation	20	(13%)	4	(3%)	3	(4%)	0	
Anorexia	16	(11%)	4	(3%)	1	(1%)	0	
Dysphagia	15	(10%)	4	(3%)	4	(5%)	1	(1%)
Hemic and Lymphatic System								
Anemia	16	(11%)	6	(4%)	5	(7%)	1	(1%)
Metabolic and Nutritional								
Dehydration	13	(9%)	9	(6%)	3	(4%)	0	
Weight Loss	10	(7%)	3	(2%)	4	(5%)	0	
Hypomagnesemia	9	(6%)	3	(2%)	1	(1%)	0	
Edema	8	(5%)	4	(3%)	0		0	
Hypokalemia	8	(5%)	1	(<1%)	1	(1%)	0	
Nervous System								
Dizziness	9	(6%)	0		5	(7%)	0	
Insomnia	9	(6%)	0		3	(4%)	0	
Respiratory System								
Dyspnea	16	(11%)	8	(5%)	6	(8%)	2	(3%)
Pneumonia	8	(5%)	3	(2%)	1	(1%)	0	

^a COSTART term for events ranging from blood-tinged saliva, bleeding from injection, to hemorrhage of the innominate artery

7.4 Local Tissue Conditions

Injection of CDDP/epi gel into tumors results in a high intratumoral concentration of CDDP for an extended period of time. Expected local cytotoxic effects in the tumor and adjacent tissue may include erythema, swelling, erosion, ulceration, necrosis, eschar formation, and/or bleeding. As such, these specific conditions were monitored throughout therapy. The randomized groups were comparable with respect to the condition of the injection site tissues at baseline. As shown in Table 55, the most common finding was erythema, of which very few cases were severe. Patients treated with CDDP/epi gel were more likely to experience local cytotoxic effects than patients treated with placebo gel (Table 56). During the blinded phase of the study treatment, the most significant local cytotoxic effect was necrosis (65% incidence, 30% severe). Among the patients randomized to placebo gel, erythema was the most common local cytotoxic effect (35% incidence, 8% severe).

Necrosis had a positive association with MTT response. Of the 76 patients with worsening necrosis, 27 (36%) experienced a complete or partial MTT response, whereas of 43 patients who had no necrosis or on-study increase of necrosis, only 8 (19%) had a complete or partial response of the MTT.

Table 55: Local Tissue Conditions at Baseline

Tissue Condition	CDDP/epi Gel (n= 150)		Placebo Gel (n=75)	
	Total Incidence	Severe	Total Incidence	Severe
Necrosis	27%	2%	32%	3%
Erosion	38%	3%	41%	4%
Eschar	17%	3%	19%	0%
Ulceration	43%	7%	48%	9%
Erythema	55%	3%	52%	7%
Swelling	51%	5%	44%	5%
Bleeding	17%	0%	17%	0%

Table 56: Local Cytotoxic Effects (worsened local tissue conditions) Occurring During Treatment

Tissue Condition	CDDP/epi Gel (n=150)				Placebo Gel (n=75)			
	Treatment Phase		Highest Incidence, Any Phase		Treatment Phase		Highest Incidence, Any Phase ^a	
	Total Incidence	Severe	Total Incidence	Severe	Total Incidence	Severe	Total Incidence	Severe
Necrosis	65%	30%	74%	36%	32%	13%	63%	29%
Erosion	52%	15%	57%	18%	28%	3%	56%	17%
Eschar	50%	19%	57%	21%	12%	3%	48%	15%
Ulceration	49%	13%	54%	16%	28%	7%	54%	21%
Erythema	49%	11%	53%	13%	35%	8%	54%	12%
Swelling	45%	7%	53%	11%	29%	3%	50%	10%
Bleeding	20%	3%	25%	3%	17%	0%	27%	0%

a: These occurred during treatment with open-label CDDP/epi gel.

The number of treatments before the occurrence of the peak severity of local cytotoxic effects was evaluated. In all treatment groups, the most severe effects were noted after one or two treatments. The incidence of local cytotoxic effects was generally greatest 2 weeks after the start of treatment and resolved over the next 3 to 12 weeks. Patients originally randomized to placebo gel then treated with open-label CDDP/epi gel during extended follow-up had longer times to resolution for all events than did the patients originally randomized to CDDP/epi gel; these patients had nearly a doubling of their tumor volume during placebo treatment and could be expected to exhibit slower resolution of local cytotoxic effects.

7.5 Clinically Significant Adverse Reactions

In the clinical studies with CDDP/epi gel the most clinically significant adverse reactions were cerebrovascular events (CVE) and hemorrhage. The occurrence of these as study-drug related events was eliminated after implementation of modified patient selection criteria and/or study drug administration procedures. Because of their clinical interest and possible significance they are further discussed in this section together with some episodes of cardiovascular events and allergy.

7.5.1 Cerebrovascular Events

Local injection of CDDP/epi gel may be associated with a risk of cerebrovascular events (CVEs) in patients whose tumors involve the carotid artery. Possible contributing factors include: Tissue damage, needle trauma to the artery, mechanical pressure from a large injected volume, local inflammation and swelling, and/or tumor progression. As reflected in its product labeling, systemic CDDP itself has been associated with vascular toxicities including CVEs. There is a high incidence of underlying carotid artery disease in this population, which may be partly be due to obvious risk factors, but also more specifically to neck irradiation.^{25,26}

Prior to amending the protocol, six patients in study 414 experienced a CVE (5 CDDP/epi gel, 1 placebo) either during or shortly after treatment (Table 57). These events were treatment related and most likely caused by carotid artery vasospasm, with needle trauma to the artery, chemical irritation, tissue damage, or mechanical pressure from a large injected volume as possible precipitating factors. Review of the cases revealed that close proximity or involvement of the carotid artery by tumor was a likely principal factor.

Table 57: Patients Who Experienced a Cerebrovascular Event

Patient No.	Treatment at Time of Event	Relationship to Treatment	Date of Event	Tumor location	Injection Volume (mL)	Outcome
4044	Placebo	Related	4-Apr-97	Neck	3.9	Recovered
1870	CDDP/epi gel	Related	18-Mar-97	Encasing carotid	2.2	Died
4034	CDDP/epi gel	Related	19-Nov-96	Base of tongue	2	Withdrew
4023	CDDP/epi gel	Probably	24-Jan-96	Base of tongue	5	Partially Recovered
2207	CDDP/epi gel	Related	23-Jan-96	Peristomal	3.5	Partially Recovered
1798	CDDP/epi gel	Possibly	29-Nov-95	Neck	3.9	Died

A total of 107 patients with HNSCC have been treated since protocol amendment V that excluded patients with tumors involving or immediately adjacent to the carotid artery and there have been no similar events related to CDDP/epi gel. There was, however, a single patient (No. 5081) who experienced a vertebro-basilar CVE which was not attributed to treatment. Neither the tumor nor the injection of CDDP/epi gel was near the vertebral artery, and, in the opinion of the investigator the event was not treatment related. Matrix agrees with the investigator in the evaluation of this event.

7.5.2 Hemorrhage

Life-threatening hemorrhage is part of the natural history of HNSCC in a significant fraction of patients. In the Phase III studies, hemorrhage occurred in 15% of patients treated with CDDP/epi gel versus 8% of patients treated with placebo gel. Most of these events were mild or moderate in severity. In three cases, severe hemorrhage resulted in death. One of these cases (Patient 1870) was also reported as a CVE. This patient had tumor known to be encasing the carotid artery. The other two patients (2324 and 4094) were in Stratum 3 and had larger tumors (150 and 39 cm³ respectively). Patient 2324 also had cirrhosis, portal hypertension, borderline platelet counts and had received non-steroidal anti-inflammatory class medications. Patient 4094 had known tumor encasement of the carotid artery, but it was unclear whether the bleeding was from erosion of the carotid or was superficial from necrotic tumor surface.

7.5.3 Cardiovascular Events Other than Cerebrovascular Events

One patient with a history of cardiac arrest of unknown etiology, hypertension, and atherosclerotic peripheral vascular disease experienced a non-fatal cardiopulmonary arrest following injection with CDDP/epi gel. The etiology of this event was not determined.

Clinically significant increases in blood pressure during dosing were defined as a > 20 mmHg rise in systolic or diastolic pressure, or an increase in systolic to ≥ 150 from < 150, or an increase in diastolic to ≥ 100 from < 100. Fifty percent of the group randomized to CDDP/epi gel experienced at least one clinically significant increase in blood pressure during dosing. Among the patients randomized to

placebo, increases in blood pressure were seen both during the blinded treatment phase and in the extended follow-up phase of the studies, when these patients received CDDP/epi gel. However, almost half of the patients randomized to placebo gel had no increases in blood pressure during placebo gel treatment, but did have increases during CDDP/epi gel treatment.

There was only one case of hypertension associated with CDDP/epi gel treatment that was a serious adverse event and considered to be related to the drug; the patient recovered.

7.5.4 Allergy

Serious allergic reactions have been reported in 2 patients treated with CDDP/epi gel. In this case, an anaphylactoid reaction to intravenous CDDP occurred after therapy with i.t. CDDP/epi gel was completed. It is believed that the patient may have developed sensitivity to CDDP following local treatment with CDDP/epi gel.

7.6 Serious Adverse Events

Forty-two events meeting the regulatory definition of a serious adverse event (SAE) were reported to Matrix and entered into the ClinTrace™ safety database. More SAEs were reported in Study 414 than in Study 514 and more of these were considered possibly, probably, or definitely related to drug in Study 414. Nineteen of the 42 events (45%) occurred in Stratum 3 prior to this stratum being closed to further enrollment. Thirty-two (76%) of the events occurred prior to reducing the dose to 0.25 mL/cm³ tumor volume.

Table 58: Serious Adverse Events Reported to Matrix

Patient Number	Treatment Group	Dose	Strata	COSTART Term*	Days since last Rx	Relationship
414-94-2						
Died						
1870	Placebo Gel ^a	0.5	2	Neuropathy & Hemorrhage	< 1	Probable
1798	Placebo Gel ^a	0.5	2	Cerebrovascular Accident	< 1	Possible
Withdrew						
2183	CDDP/epi Gel	0.5	2	Fistula pharyngocutaneous	12	Related
1895	CDDP/epi Gel	0.5	2	Pain	< 1	Probable
1869	CDDP/epi Gel	0.5	2	Pain	< 1	Possible
4034	CDDP/epi Gel	0.5	3	Cerebrovascular Accident	< 1	Possible
Partially Recovered						
2207	CDDP/epi Gel	0.5	2	Cerebrovascular Accident	< 1	Related
4023	CDDP/epi Gel	0.5	3	Cerebral Infarct	< 1	Probable
Recovered						
4028	CDDP/epi Gel	0.5	3	Hemorrhage	5	Possible
4028	CDDP/epi Gel	0.5	3	Hemorrhage	3	Possible
1871	CDDP/epi Gel	0.5	3	Hypertension	< 1	Related
4041	CDDP/epi Gel	0.5	3	Pain	< 1	Related
4041	CDDP/epi Gel	0.5	3	Pain	< 1	Possible

Table 58: Serious Adverse Events Reported to Matrix

Patient Number	Treatment Group	Dose	Strata	COSTART Term*	Days since last Rx	Relationship
4041	CDDP/epi Gel	0.5	3	Pain	< 1	Possible
4040	CDDP/epi Gel	0.5	3	Chest Pain	8	Possible
4029	CDDP/epi Gel	0.5	3	Cellulitis	7	Possible
4029	CDDP/epi Gel	0.5	3	Cellulitis	6	Possible
4041	CDDP/epi Gel	0.5	3	Infection	1	Possible
5228	Placebo Gel	0.5	2	Grand Mal Convulsion	< 1	Unknown
4044	Placebo Gel	0.5	2	Hemiplegia	< 1	Possible
1967	Placebo Gel	0.5	2	Hemorrhage	< 1	Related
5302	CDDP/epi Gel	0.5	2	Dehydration	2	Possible
4989	CDDP/epi Gel	0.5	1	Infection	< 1	Possible
1989	CDDP/epi Gel	0.25	3	Pain	8	Probable
5081	CDDP/epi Gel	0.25	2	Cerebral Ischemia	6	Possible
5396	CDDP/epi Gel ^a	0.25	2	Nausea & Vomiting	< 1	Possible
5304	Placebo Gel ^a	0.25	1	Fistula pharyngocutaneous	13	Probable
2183	Placebo Gel	0.25	1	Dehydration	2	Related
514-94-2						
Died						
2324	CDDP/epi Gel	0.5	3	Hemorrhage	4	Related
4094	CDDP/epi Gel	0.5	3	Hemorrhage	1	Possibly
Withdrew						
2301	Placebo Gel ^a	0.5	1	Anemia	6	Related
2274	CDDP/epi Gel	0.5	3	Pain	7	Related
4081	CDDP/epi Gel	0.5	3	Pain	8	Related
2420	CDDP/epi Gel	0.5	2	Allergic reaction	< 1	Probably
4090	CDDP/epi Gel	0.5	3	Paralysis	2	Possibly
2545	CDDP/epi Gel	0.25	2	Pallor	< 1	Probably
Unchanged						
2636	Placebo Gel ^a	0.25	2	Blindness	< 1	Probably
Recovered						
4094	CDDP/epi Gel	0.5	3	Convulsion	3	Unknown
5420	CDDP/epi Gel	0.5	2	Swelling	4	Probably
2682	CDDP/epi Gel	0.25	2	Cardiac arrest	< 1	Possibly
2742	CDDP/epi Gel	0.25	1	Hemorrhage	6	Possibly
2373	CDDP/epi Gel	0.25	1	Edema	< 1	Probably

^aSerious adverse event occurred during open-label treatment with CDDP/epi gel

7.7 Deaths

Deaths on study and within 30 days post study were tabulated by study, treatment, and study phase, along with an assessment of relationship to treatment. Overall, there were 54 deaths (36%) among patients randomized to CDDP/epi gel and 28 deaths (37%) among patients randomized to placebo gel. Only 3 deaths possibly or probably related to study drug occurred among CDDP/epi gel randomized or open label treated patients. These are patient numbers 2324, 4094 and 1870, and have been discussed in 7.5.1 and 7.5.2. None of these patients would be eligible for treatment under current labeling recommendations. Patient No. 1798 experienced a cerebrovascular event after treatment with

CDDP/epi gel during the open-label treatment phase, however, the patient died of respiratory failure secondary to laryngeal carcinoma.

Table 59: Deaths on Study or Within 30 Days Post Study

Study Phase ^a	CDDP/epi Gel (n = 150)	Placebo Gel (n = 75)
Blinded Treatment Phase	13 (9%)	5 (7%)
Follow-up Phase	6 (4%)	0 (0%)
Extended Follow-up Phase	8 (5%)	7 (9%)
30-Days Post Study	27 (18%)	16 (21%)
All Phases	54 (36%)	28 (37%)

^a Study phases defined in section 6.1

7.8 Drop-outs due to Adverse Events

Twelve (8%) patients randomized to CDDP/epi and four (5%) patients randomized to placebo discontinued study treatment due to an adverse event. Eighteen (11%) patients discontinued treatment with open-label CDDP/epi gel due to an adverse event. There are patients for whom the investigator checked “Other” as the reason for discontinuation and then made comments indicating the concurrent presence of an adverse event and/or death; these are not included here. It is not possible to determine, in all cases, the specific adverse event(s) that led to discontinuation, although every attempt was made to gather the relevant information.

7.9 Systemic Toxicity of Cisplatin

Systemic cisplatin therapy^{27,28} has been associated with nausea and vomiting, nephrotoxicity, peripheral neuropathy, ototoxicity, and myelosuppression, at single doses of 50 mg/m². Neurotoxic and nephrotoxic effects are cumulative. As expected, based on the Phase I trial in patients with liver tumors²⁹ in which maximum serum concentrations of free platinum following treatment with CDDP/epi gel were generally lower than those typically associated with toxicity, intratumoral injection of CDDP/epi gel did not cause significant systemic toxicity in the clinical trials. As shown in Table 60, signs or symptoms of nephrotoxicity, peripheral neuropathy, ototoxicity, and myelosuppression were infrequent. Although nausea and vomiting occurred more commonly in patients treated with CDDP/epi gel as compared to patients randomized to placebo gel, the rates of nausea and vomiting were much lower than rates commonly observed with systemic platinum therapy (≈100%). This is in sharp contrast to the almost universal nausea and vomiting, frequently of a severe degree, associated with cisplatin administered intravenously.

The adverse event profile of CDDP/epi gel was expected to be better than that of systemically administered cisplatin, as the gel was designed to deliver very high concentrations of cisplatin directly

into the tumor and maintain the drug locally. Also, the addition of epinephrine in the gel was expected to lead to some transient cardiovascular consequences (e.g., elevated blood pressure and heart rate).

Table 60: Reported Adverse Events with Systemic CDDP^b, CDDP/epi gel or Placebo gel

Adverse Event	Systemic Cisplatin (Package Insert)	Studies 414 and 514	
		CDDP/epi Gel	Placebo Gel
Nephrotoxicity ^a	28-36%	< 3%	< 3%
Ototoxicity	31%		
tinnitus		2% ^b	0%
deafness		< 3% ^c	
Myelosuppression	25-30%		
anemia		11%	7%
leukopenia		< 1%	< 1%
Nausea/Vomiting	~100%		
nausea		18%	8%
vomiting		17%	3%

a: includes kidney function abnormal, kidney failure, acute kidney failure, and urinary retention.

b: Platinol®-AQ (cisplatin injection). Physicians' Desk Reference 2000, pages 877-9.

8 Risk/Benefit Assessment

Patients with early stage or previously untreated HNSCC have a wide variety of therapeutic options. In contrast, patients with locally advanced disease who have failed prior therapy have very limited therapeutic options. When HNSCC recurs, it is not unusual for one or a small number of local lesions to be the major source of the patient's symptoms. For example, lesions located at or adjacent to a tracheostomy site often cause major problems with airway function and adequate ventilation. Even small lesions can cause such problems as painful and dangerous deeper invasion, disfigurement, ulceration with malodorous drainage, pain and practical impediments to normal sleep, eating, dressing, and social functioning. Few if any of these patients are curable, but for many, local disease is the component of the malignancy that is in most urgent need of management.

In some instances, such patients' local disease can be successfully controlled by further surgery or re-irradiation, but always with trade-offs. Such salvage procedures furthermore do not always lead to permanent control. The value of systemic chemotherapy for locally recurrent disease-related problems is unclear. There are no previous trials of systemic chemotherapy documenting concrete patient benefit, as opposed to tumor response rates, which are most applicable to distant metastases. In some cases systemic chemotherapy is definitely of value, and it should be considered for suitable candidates. We all know though that nearly all patients eventually fail chemotherapy as a single modality, and unfortunately this is likely to remain true for some time. Many patients are poor candidates due to comorbidities or debilitation, or simply refuse systemic chemotherapy. *These are settings where CDDP/epi gel can have a real impact.*

Cisplatin/epinephrine gel is relatively easy to administer, and produces a response rate of 29% in tumors of up to 20 cm³ in volume. Most threatening local recurrences of HNSCC should be easily detected and treatable by CDDP/epi gel before reaching this size threshold. Importantly, the complete response rate of 19% was almost twice as high as the partial response rate of 10%. The responses were rapid in onset and also durable, with few responding patients showing subsequent progression of treated sites on study. This is very unusual for even highly effective chemotherapeutic agents, and speaks to the validity of the basic pharmacological principles upon which this product is based. Exposure to previous chemotherapy did not decrease the response rate to CDDP/epi gel. Responses were similarly obtained, even in the face of rapidly advancing disease in patients initially treated with placebo who crossed over to receive CDDP/epi gel. The trials that documented these response rates are large, relative to the number of patients with this orphan indication, and were of high quality, prospective, randomized, double-blind, and placebo controlled in design. Thus, CDDP/epi works very well in these patients, and the amount and quality of the data available provide a high level of confidence regarding the activity of this drug formulation.

Any therapeutic entity should offer the patient a clear benefit. In cases where the local lesion obstructs the airway, prevents swallowing, or causes a festering wound, the benefit of shrinking the mass is

obvious. What is not so obvious is how best to measure benefits of this type of locally directed therapy, particularly against the background of symptoms and signs due to systemic components of the malignancy. This challenge was addressed in the trials of CDDP/epi gel by assessing those goals that the patient and the treating physician identified. Goals typically selected included:

- Improved wound care
- Pain control
- Physical appearance
- Prevention of invasion or obstruction of vital structures

In this randomized and blinded clinical trial setting, a meaningful number of patients in the active treatment group, but not the placebo group, reported or attained a palliative outcome. When these data were analyzed by the rigorous study algorithm which was designed to amalgamate all of the primary goal outcomes into a single variable, "Patient Benefit", it was documented to occur among a significantly higher percentage of CDDP/epi gel than placebo gel treated patients. Patient Benefit was moreover significantly correlated with objective tumor response. The instrument used and the analytical approach taken have been thoroughly and independently validated. Thus, the studies conducted provide substantial confidence in the ability of this form of treatment to accomplish goals that the patient and medical caregiver believe to be of importance.

Treatment with CDDP/epi gel is not without toxicity. Local pain during and following the intratumoral injection was the most common problem. This was rarely severe and it is fully expected that this pain can be adequately controlled with appropriate administration of pain medications and/or local anesthetics. The most serious treatment related adverse events in these trials were 6 cerebrovascular events and 3 instances of hemorrhagic deaths. Careful review of the details of these cases led to refinements of patient selection and dosing guidelines which were successful in eliminating these occurrences from the experience with the subsequently treated 107 patients. Although not the primary goal of these phase III trials, these trials were thus successful in providing additional data to guide safe future use of this medication. The dose recommended for HNSSC has a large margin of safety in that there is a sizable experience with safe administration of higher doses for this and other cancers. Necrosis and skin breakdown are frequent consequences of progression of locally recurrent HNSSC. These manifestations are necessarily increased by any treatment which causes rapid tumor killing. Such manifestations were meticulously tracked and reported in the clinical trials. Necrosis was found to occur and have a positive correlation with tumor response. Most of these conditions were mild to moderate in severity, followed a predictable pattern, were maximal after the second or third treatment, and resolved during the following weeks with standard wound care. Finally, the systemic effects typically associated with systemic chemotherapy were milder and much reduced in this setting of local intra-tumoral treatment.

These considerations strongly support the conclusion that, in appropriately selected patients, the benefits of CDDP/epi gel treatment outweigh the risks. Specifically, this treatment produces a high

incidence of response of locally recurrent symptomatic or threatening tumors, and a documented ability to provide specific patient benefits, with little risk of serious complications, and with toxicities that are manageable and rarely severe. Cisplatin/epinephrine gel provides appropriately trained surgical and medical oncologists with an important new tool with which to address complications of local regionally recurrent HNSSC. It is practical and easy to administer in most clinical settings without usually requiring hospitalization or even necessarily advance scheduling. There is a very high probability that further therapeutic advantage can be gained by combining CDDP/epi gel with systemic chemotherapy and/or local irradiation, and this will be vigorously addressed in future clinical trials. However, the therapeutic index of CDDP/epi gel by itself is sufficient to merit approval for use as a single agent.

9 Conclusions

Matrix Pharmaceutical, Inc. conducted two multi-centered, randomized, double blind, placebo-controlled trials to evaluate the safety and efficacy of CDDP/epi gel in patients with advanced, recurrent or refractory HNSCC. The key findings from these studies are:

- CDDP/epi gel is an effective treatment option, producing a 29% response rate in symptomatic or threatening tumors, often in an irradiated field, in heavily pretreated patients.
- CDDP/epi gel provides local control in a disease where advancing local tumor often leads to morbidity.
- Tumors respond promptly (median of 21 days), providing early relief of symptoms. This allows patients and physicians to make an early assessment of efficacy in a relatively short period of time and if necessary, select another course of management.
- CDDP/epi gel provides palliative benefits to patients that improve their quality of life and well-being.
- Prior use of platinum-based systemic chemotherapy does not reduce the efficacy of CDDP/epi gel.
- Side effects from treatment with CDDP/epi gel are manageable with minimal systemic effects in contrast to intravenous chemotherapy, thereby making treatment possible for patients who are either too weak or debilitated for systemic therapies.

In conclusion, the intratumoral injection of CDDP/epi gel provides physicians with an important and effective new therapy with which to address a devastating disease.

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