

Summary of Statistical Review and Evaluation

NDA # : 21-236

Applicant : Matrix Pharmaceutical, Inc.

Name of the Drug: IntraDose (cisplatin/epinephrine) Injectable Gel

Indication : Squamous Cell Carcinoma of the Head and Neck

Documents Reviewed : Vols. 3.165-3.167, 3.175- 3.179, 3.194, 3.200, 3.204, 3.315, 3.14

Medical Reviewer : Gregory Frykman, M.D.

Statistical Reviewers : Jasmine Choi, M.S., Rajeshwari Sridhara, Ph.D.

I.C.H. E-9 Guidelines: Section 2.1.2, Confirmatory Trial:

*"...the key hypothesis of interest follows directly from **the trial's primary objective, is always pre-defined**, and is the hypothesis that is subsequently tested when the trial is complete. In a confirmatory trial it is equally important to estimate with due precision the size of the effects attributable to the treatment of interest and to relate these effects to their clinical significance."*

I.C.H. E-9 Guidelines: Section 2.2.2, Primary and Secondary Variables:

" To avoid multiplicity concerns arising from post hoc definitions, it is critical to specify in the protocol the precise definition of the primary variable as it will be used in the statistical analysis. In addition, the clinical relevance of the specific primary variable selected and the validity of the associated measurement procedures will generally need to be addressed and justified in the protocol."

I.C.H. E-9 Guidelines: Section 2.2.3, Composite Variables:

" The method of combining the multiple measurements should be specified in the protocol, and an interpretation of the resulting scale should be provided in terms of the size of a clinically relevant benefit."

I.C.H. E-9 Guidelines: Section 2.2.5, Multiple Primary Variables:

*" The effect on the type I error should be explained because of the potential for multiplicity problems; the method of controlling type I error should be given in the protocol. The extent of intercorrelation among the proposed primary variables may be considered in evaluating the impact on type I error. **If the purpose of the trial is to demonstrate effects on all of the designated primary variables, then there is no need***

for adjustment of the type I error, but the impact on type II error and sample size should be carefully considered."

Major Statistical Problems in the Studies

- There are two co-primary efficacy endpoints in each of the two randomized studies (Studies 414 and 514), namely, objective tumor response rate and patient benefit. The understanding between the agency and sponsor was that the trials will demonstrate effect on both of the primary variables, thus not requiring adjustment of type I error for multiplicity (I.C.H. E-9 Guidelines, section 2.2.5). The sponsor claims significant treatment (Intradose) effect with respect to objective tumor response rate. However, the sponsor's analyses demonstrate no significant treatment effect with respect to patient benefit.
- In addition to significant tumor response, the agency also required that significant correlation between objective tumor response and patient benefit should be established. There is no statistically significant association between objective tumor response and patient benefit in Study 414 (US study), where as there appears to be nominal significant association in Study 514 (Europe study). This apparent association is weak due to large number of patients classified both as non-responders and non-benefiters. Study 414 and Study 514 demonstrate that in these two studies it does not provide a good measure of predictability of benefit using tumor response. A preferred measure of association between patient benefit and tumor response is sensitivity (probability of benefit and response), and this was < 50% in each of the studies and in the combined study data.
- Patient benefit, one of the co-primary endpoints, is retrospectively defined as a decrease in symptom score by one point. Furthermore, the treatment goal differed from patient to patient.
- Palliative symptom benefit is assessed as equivalent to preventive benefit. Preventive benefit is not a measure of symptom benefit, but a measure of progression of disease.
- Blinded comparison of patient benefit between the treatment arms is questionable because the pattern of treatment conformity in the blinded phase differs between the active treatment and the placebo arms. This could potentially bias the benefit scores, particularly preventive goal scores.
- Dosing scheme of Intradose was modified after approximately 50% of the patients had been enrolled into the two studies. Because tumor response is a primary endpoint and the proposed treatment is a local treatment, there is a potential for dose-response relationship to play an important role in determining efficacy of the drug.

1. Background

Cisplatin/epinephrine (CDDP/epi or Intradose) injectable gel is proposed to be used for the **local treatment** of recurrent or refractory squamous cell carcinoma of the head and neck (SCC H&N) in patients who are considered not curable with surgery or radiotherapy. The

intent of this injectable gel system is to place the product directly into the tumor tissue, providing high local concentrations of the active drug (cisplatin) that are maintained in the tumor (i.e., at or near the site of administration) over an extended time period. The function of the collagen is to provide a dense meshwork that gives the formulation its physical and drug retention properties. This viscous 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 concomitant drug clearance. The formulation also contains epinephrine, acting as an adjuvant to effect local vasoconstriction, further inhibiting cisplatin clearance from the administration site by restricting local blood flow, and providing additional enhancement of local drug retention. CDDP/epi gel is intended for intratumoral injection only. Solid tumors that can be seen, palpated, or visualized with established imaging techniques or accessed directly or by means of minimally invasive techniques, may be potentially treated.

2. Description of Trials

2.1 General Description of All Studies

- a) Study 39-92-P: Phase I, open-label, multi-center dose escalation/dose-confirmation study in patients with accessible tumors of any histology (45 patients studied in US).
- b) Study 403-93-2: Phase II, open-label multicenter study in patients with recurrent or refractory accessible tumors of any histology except Kaposi's sarcoma and squamous cell carcinoma of the head and neck (67 patients studied in US).
- c) Study 503-93-2: Phase II, open-label multicenter study in patients with recurrent or refractory accessible tumors of any histology except Kaposi's sarcoma and squamous cell carcinoma of the head and neck (59 patients studied in Europe and South Africa).
- d) Study MP 414-94-2: Phase III, randomized, double-blind, placebo-controlled, multicenter study with an open-label extended follow-up phase for patients with squamous cell carcinoma of the head and neck (110 patients in US and Canada).
- e) Study MP 514-94-2: Phase III, randomized, double-blind, placebo-controlled, multicenter study with an open-label extended follow-up phase for patients with squamous cell carcinoma of the head and neck (115 patients in Europe and Israel).

Reviewer's Comments:

Studies 39-92-P, 403-93-2 and 503-93-2 are non-randomized, single arm open-label studies. Hence, this review will focus only on the two randomized studies, MP 414-94-2 and MP 514-94-2, and specifically on the efficacy aspect of these two studies.

2.2 Detailed Description of Studies MP 414-94-2 and MP 514-94-2

Study MP 414-94-2 was conducted in U.S. & Canada (44 study centers), and Study MP 515-94-2 was conducted in Europe & Israel (28 study centers). Both the studies MP 414-94-

2 (here after referred as Study 414) and MP 514-94-2 (here after referred as Study 514) were designed identically as phase III, randomized, double-blind, multi-center, placebo-controlled studies to evaluate efficacy and safety of the treatment with CDDP/epi gel in patients with recurrent or refractory squamous cell carcinoma of head and neck. Patients were stratified according to baseline volume of the pre-specified Most Troublesome Tumor (MTT) or the primary target tumor (Stratum 1: $MTT \leq 5 \text{ cm}^3$; Stratum 2: $MTT >5 \text{ but } \leq 20 \text{ cm}^3$) and then randomized in a 2:1 ratio to receive either CDDP/epi gel or the placebo. A stratum 3 ($MTT > 20 \text{ cm}^3$) was included to study safety in expanded use but not included as part of the pivotal analysis of safety and efficacy. Enrollment of patients to Stratum 3 was closed as of April 4, 1997 (Study period was from June 1995 to March 2000). Per protocol, prior to enrollment of the patient into the study, the investigator was required to identify the patient's most troublesome tumor (MTT) and one improvable primary treatment goal (palliative or preventative) (see Treatment Goal Questionnaire in Appendix 1) for that tumor. The patient could also identify a most troublesome tumor and may select one primary treatment goal (palliative), for this tumor. Patient's selected tumor and treatment goal could differ from the investigator's selection. If multiple tumors were associated with the primary palliative or preventive treatment goal and one tumor could not be singled out as the MTT, then the largest tumor was identified as the MTT.

Patients were treated (Appendix II) with 0.25 mL gel/cm^3 of tumor volume weekly for 6 treatments within an 8-week period (Blinded Treatment Phase) or until patient objective complete response, whichever occurred first. Patients were evaluated weekly for 4 weeks after the last treatment and this completed the blinded treatment phase. Complete or partial responders were followed monthly for an additional 5 months or until disease progression. Patients who maintained a complete response at the end of 5 months continued to be observed monthly in the Extended Follow-up Phase (open-label). Patients with a partial response or relapse and those who required re-treatment in other tumors at the end of the treatment phase could enter the Extended Follow-up Phase and be retreated, if in the opinion of the investigator the patient could benefit from treatment. Also at treatment visit 4 or beyond, patients with progressive disease of the MTT could enter extended follow-up to receive open-label Intradose for a total of up to 6 treatments.

The Treatment Goal Questionnaire for palliation was required to be administered to the patient and the investigator at the screening visit and the beginning of every subsequent visit. The Treatment Goal Questionnaire for prevention was administered to the investigator at the screening visit, last evaluation (week 4) visit, last follow-up (month 5) visit, and last visit on study.

Reviewer's Comments:

1. Per original protocol, the assigned dose was 0.5 mL of CDDP/epi gel or placebo gel per cm^3 tumor volume per treatment. However, the protocol was amended (Amendment V, May 2, 1997) for safety reasons to reduce the assigned dose to 0.25 mL/cm^3 . At the time of amendment 72 patients were enrolled in strata 1 & 2 of Studies 414 and 514.

Furthermore, the assigned dose for each treated tumor was recalculated at each treatment visit based on tumor volume at the time following the Amendment V, where as, prior to the amendment, tumor dose was calculated using the tumor volume at first treatment. Tumors smaller than 0.5 cm³ received a fixed dose of 0.1 mL per treatment.

2. This change of dosing schedule was not taken into account in the primary efficacy analyses of response data.

2.2.1 Objectives

The study objectives of both the studies 414 and 514 were: 1) To compare the effect of CDDP/epi gel to placebo gel on local tumor volume. 2) To assess achievement of an identified primary treatment goal selected for the most troublesome tumor (identified by the investigator) in patients with recurrent or refractory squamous cell carcinoma of the head and neck following up to 6 weekly intratumoral treatments of CDDP/epi gel compared to placebo gel. 3) To compare the effect of CDDP/epi gel to placebo gel on total local tumor volume per patient. 4) To evaluate the time to response and the time to progression for MTT after local treatment with CDDP/epi gel as compared to placebo gel. 5) To assess improvement or stabilization in quality of life as measured by FACT-H&N. 6) To compare the histopathology of injected lesions that respond to local treatment. 7) Pharmacokinetics: To determine plasma platinum levels in patients receiving CDDP/epi gel.

2.2.2 Sample Size Considerations

A total sample size of 120 patients (80 evaluable patients in CDDP/epi gel treatment group and 40 patients in placebo gel treatment group), was computed in each of the Studies 414 and 514, which provides power of 0.8 or greater to detect a difference in response rates conditional on most troublesome tumor volume, using a two-sided alpha of 0.05, and based on the following assumptions: 1) Patients would be stratified by most troublesome tumor volume. The number of patients in each substrata would not be less than 20 and more than 30; 2) Response rate would be 10% or less in substrata treated with placebo gel; 3) Response rates in substrata treated with CDDP/epi gel would be between 40% and 70% in patients with MTT volume ≤ 5 cm³, and between 30% and 50% in patients with MTT volume > 5 to ≤ 20 cm³; 4) Response rates in patients with MTT volume > 20 cm³ would be 20% or less. The primary efficacy analyses of tumor response would be performed excluding this stratum. Furthermore, it was estimated that 88 patients would be needed to provide 80 evaluable patients in the CDDP/epi gel treated group, and 44 patients would be needed to provide 40 evaluable patients in the placebo gel treated group.

Reviewer's Comments:

1. The sample size calculations were based on testing the hypothesis of detecting a 10% difference in MTT objective response rate between the two treatment groups. No

hypothesis was stated in the protocol with respect to patient benefit or the treatment goal (palliative or preventive) response.

2. Study MP-414-94-2 enrolled a total of 110 patients. Eighty-seven patients (as opposed a planned sample size of 132 patients) were enrolled in Strata 1 and 2 (CDDP/epi gel, 62 (31 in each stratum); placebo, 24 (12 in each stratum). Thus the actual patient allocation was 2.6:1 rather than the planned 2:1 per protocol. The 23 patients enrolled in Stratum 3 (CDDP/epi gel, 14; placebo, 9) were not part of the core analysis. The sponsor excluded one patient (ID # 2231 stratum 2, placebo) who did not receive study drug. This patient after starting the injection at the first treatment visit had to be withdrawn immediately due to severe pain. This patient was included in the safety analysis. Thus, a total of 86 patients in Stratum 1 and 2 were included in the efficacy analysis.
3. Study MP-514-94-2 enrolled a total of 116 patients. Ninety-two patients (as opposed a planned sample size of 132 patients) were enrolled in Strata 1 and 2 (CDDP/epi gel, 57 (31 in stratum 1 and 26 in stratum 2); placebo, 35 (17 in stratum 1 and 18 in stratum 2)). Thus the actual patient allocation was 1.5:1 rather than the planned 2:1 per protocol. The 24 patients enrolled in Stratum 3 (CDDP/epi gel, 17; placebo, 7) were not part of the core analysis. The analyses excluded one patient (ID# 4089 stratum 3, placebo) because this patient died the day after the screening visit and therefore was never treated. The total number of patients who were included in the efficacy analysis of this study was 92.
4. Subsequent to recommendations by the agency, a second primary efficacy variable (patient benefit) was added post-hoc. The understanding of the agency has been that the purpose of this trial is to demonstrate effects on both the designated primary variables, and hence adjustment of the type I error for multiplicity was not expected and therefore, both primary hypotheses could be tested at 0.05 level of significance (faxes sent by the Agency on (1) March 8, 2000 to sponsor in response to March 24, 2000 correspondence/request for feedback, and (2) April 28, 1998 reviewer comments on sponsor's submission of Sn 115, Feb. 24, 1998).
5. No interim analysis was planned in both the studies.

2.2.3 Randomization

Each investigator received a block of patient numbers corresponding to a centralized randomization. Patients in stratum 1 were assigned numbers in a sequential order (from lowest to highest). Patients in stratum 2 were assigned numbers in reverse order (from highest to lowest). A separate block of randomized numbers were provided for all patients in stratum 3. Patients in stratum 3 were assigned numbers in sequential order. A patient number was assigned once that patient had completed all screening procedures and was deemed eligible for study entry.

Reviewer's Comments:

1. The following patients were reclassified into a different stratum post-randomization. The final analyses of the data were conducted based on the reclassified stratum allocation. All patients including reclassified patients in stratum 3 were excluded from efficacy analyses.

Study 414:

<u>I.D.#</u>	<u>Original classification</u> <u>At Screening Visit</u>	<u>Reclassified at visit 1</u>	<u>Treatment</u> <u>Received</u>
1823	Not recorded	Stratum 3	CDDP/epi
1870	Stratum 3	Stratum 2	Placebo
1989	Stratum 2	Stratum 3	CDDP/epi
2137	Stratum 1	Stratum 2	Placebo
2158	Stratum 1	Stratum 2	CDDP/epi
5036	Stratum 1	Stratum 2	CDDP/epi

Study 514:

<u>I.D.#</u>	<u>Original classification</u> <u>At Screening Visit</u>	<u>Reclassified at Visit 1</u>	<u>Treatment</u> <u>Received</u>
2275	Stratum 2	Stratum 3	Placebo
2352	Stratum 1	Stratum 2	CDDP/epi
2356	Stratum 1	Stratum 2	CDDP/epi
2545	Stratum 1	Stratum 2	CDDP/epi
5493	Stratum 2	Stratum 3	CDDP/epi

2.2.4 Efficacy Endpoints

The primary efficacy endpoint, per original protocol, was objective response to treatment as measured by change in tumor volume for the MTT (volume 3.172, Section 4.3, page 18). A complete response (CR) was defined as total disappearance of all clinically detectable and evaluable malignant disease, maintained for at least 4 weeks (25-28 days). A partial response (PR) was defined as 50% or greater reduction in detectable and evaluable malignant disease, maintained for at least 4 weeks (25-28 days). A stable disease was defined as < 50% reduction in detectable and evaluable malignant disease, or increase of < 25% detectable malignant disease and no significant change in measurable disease. A progressive disease was defined as 25% or greater increase in detectable and evaluable malignant disease. The overall objective response rate in each treatment arm was computed by combining the complete and partial responses. All the responses were evaluated with respect to the pre-selected MTT only.

Another endpoint that was designated as co-primary endpoint subsequent to agency's request (12/3/97 meeting minutes), was achievement of identified primary treatment goal and unforeseen

additional benefit, as determined by the investigator and the patient. The investigator was required to select an improvable primary treatment goal for the patient's MTT from one of the following palliative or preventative categories: wound care, pain control, ability to see, hear or smell, physical appearance, obstructive symptoms, mobility, prevention of obstruction, invasion, or subcutaneous tumors breaking through the skin. The patient could also identify an improvable primary treatment goal (palliative only) for a MTT. Patient's selection of the MTT and treatment goal could differ from the investigator's selection. The achievement of treatment goal was measured by administering the Treatment Goal Questionnaire (Appendix I) to the investigator and the patient. The palliative goal was measured on a scale of 1-4 and the preventive goal was measured on a scale of 0-1 (met or unmet) (Appendix 1).

The following secondary efficacy endpoints were also evaluated in the two studies:

- 1) rate of objective response of all tumors treated during the blinded treatment phase,
- 2) duration of and time to response of all tumors treated during the blinded treatment phase,
- 3) time to progression of all tumors treated during the blinded treatment phase,
- 4) improvement or stabilization in quality of life as measured by the Karnofsky Performance Status,
- 5) improvement or stabilization in quality of life as measured by the FACT-H&N.

Reviewer's Comments:

1. The agency recommended strongly to the sponsor to consider symptomatic response as the primary efficacy endpoint in order to evaluate patient benefit from the proposed treatment (12/3/97 meeting with the sponsor and fax communication by the Agency to the sponsor on April 28, 1998 reviewer comments on sponsor's submission of Sn 115, Feb. 24, 1998). Furthermore, the agency recommended to analyze the association of treatment goal attainment and MTT response. The Patient Benefit was to be based on the attainment of prospectively chosen primary treatment goals. Subsequently, the sponsor submitted an analysis plan in which patient benefit was described as an improvement of one scale point or more from baseline in the treatment goal. The agency expressed to the sponsor that a change in one scale point might not be sufficient to determine patient benefit (10/28/99 meeting).
2. The agency also recommended that the sponsor should analyze tumor response and patient benefit as co-primary endpoints (fax communication by the Agency to the sponsor on March 8, 2000 to sponsor in response to March 24, 2000 correspondence/request for feedback).
3. Achievement (post-hoc definition) of the prospectively identified primary treatment goal required either: i) an improvement of one scale point or more from baseline in the investigator or patient selected primary palliative treatment goal sustained for at least 4 weeks (25-28 days) or ii) absence of failure of the investigator- defined primary preventive treatment goals sustained for at least 4 weeks (25-28 days). Failure of the palliative

primary treatment goal was defined as an increase in score of one point or more for two or more consecutive visits.

4. It is to be noted that the patient benefit was defined post-hoc as a change of one scale point. Furthermore, this change has not been validated prospectively to correspond to a significant patient benefit. Also, the palliative and prevention treatment goals are measured on different scales. The sponsor did not pre-specify ***the method of combining the multiple measurements in the protocol, and an interpretation of the resulting scale was not provided in terms of the size of a clinically relevant benefit.***

2.2.5 Interim Analysis

Per protocol no interim analysis was planned.

Reviewer's Comments:

The minutes of the 12/3/97 meeting of the agency with the sponsor indicates that a blinded interim analysis was performed. The DSMB reviewed sequential unblinded analyses of data at intervals of approximately six months. To enable these analyses and remain blinded, Matrix used the services of an intermediary (Covance Clinical and Periapproval Services, Inc.).

Following an organizational meeting on 28-Jan-97, the DSMB held six meetings between March 1997 and November 1999 at which it reviewed unblinded data in closed session. After each session, the DSMB announced its recommendations about whether study enrollment should continue. It also made recommendations for the safe participation of study patients. When the last patient completed the Treatment Phase and the study itself was unblinded, Matrix obtained the minutes of the six data review meetings. A final DSMB meeting was held on 21-Aug-00, when the unblinded results were openly discussed with Matrix for the first time.

No interim analyses were conducted by Matrix. Matrix remained blinded to patients' treatment assignments until all patients had completed the Treatment Phase and all results for objective response and outcome of treatment goals were entered and locked in the database. No changes in objective response or outcome of treatment goals were made after the study was unblinded.

2.2.6 Efficacy Analysis Methods

Patients who received at least one treatment were to be considered evaluable for the intent-to-treat efficacy analysis. Patients who received six treatments to the MTT, patients who had a complete response for the MTT in less than six treatments, and patients who withdrew from treatment early for a study-related reason were to be evaluable for a per-protocol (efficacy analyzable fraction) analysis. Only tumors measuring 0.5 cm³ or larger were considered evaluable for efficacy. At the time the protocol was amended to include patients with tumors

greater than 20 cm³ (Stratum 3), it was noted that these patients would not be part of the efficacy analysis.

Analysis of MTT response was to be performed for patients in Strata 1 and 2 only. Patients in Stratum 3 were not to be included in the primary efficacy analysis. Response of the investigator-selected MTT was to be determined by the maximum decrease in MTT volume between baseline and four weeks after the end of treatment (or the last measured volume for patients who terminated early). The mean, median, standard deviation, and range for absolute and percent change in most troublesome tumor volume were to be presented for all patients by stratum (excluding Stratum 3) and treatment group, and, as sample size permitted, by age, sex, disease history, and treatment history. The best percent change in MTT volume at four weeks post-treatment, conditional on baseline tumor volume, was to be calculated and compared across treatment groups using ANOVA or ANCOVA. A secondary analysis was to assess the difference between treatment groups at the time of best response, i.e., when the maximum decrease of MTT volume occurred. Each patient's best MTT response at the end of Follow-up (or at early termination) was to be recorded.

The percentage of patients with a CR, PR, SD or PD as best response of the MTT were to be compared across treatment groups conditional on baseline tumor volume stratum, using the Mantel-Haenszel chi-squared test. In addition, comparisons of CR + PR (responders) vs. SD + PD (non-responders) were to be made across treatment arms, adjusted for tumor volume baseline stratum, using the Mantel-Haenszel chi-squared test. Population response rates (for CR and CR + PR) for both treatment groups were to be estimated using two-sided 95% confidence intervals. Where sample size permitted, inter-group comparisons of MTT response were also to be made for subgroups defined by age, sex, disease history, and treatment history.

Time to CR of the MTT was to be compared across treatment groups using the Kaplan-Meier method with baseline total tumor volume as a covariate. Time to CR + PR were to be similarly compared. In all time-to-response analyses, patients who failed to respond, including early terminators, were to be censored. Recurrence of disease after CR was defined as the return of the MTT or the incidence of a new tumor or tumors in the treated area ("treated area" as defined by the investigator). Duration of response was defined as the time from the beginning of a CR of the MTT to recurrence. Time to recurrence (equivalent to duration of response) was to be calculated for each CR as precisely as the visit schedule allowed. Time to recurrence following CR was to be compared between treatment groups using the Kaplan-Meier method, which would also provide estimates of recurrence rate by treatment group.

Disease progression of the MTT was defined as a 25% or greater increase in MTT volume from any previous measurement. Progression could occur at any time after the first treatment, and could be preceded by a CR or PR. Time to disease progression was to be compared across treatment groups using the Kaplan-Meier method. The Follow-up and Extended Follow-up periods were to be designed to enable estimation of time to disease progression for all patients except those having very durable responses. The patient responses of patients initially treated

with placebo and subsequently treated with open-label CDDP/epi gel in Extended Follow-up were to be contrasted using a paired design.

The statistical methods used for the MTT response were also to be used to evaluate total patient response, i.e., the change in volume of all treated tumors. Responses in treated tumors other than the MTT were to be assessed descriptively. The number and percent of tumors classified as CR, PR, SD or PD at the end of the Treatment Phase were to be tabulated by treatment group.

Achievement of the palliative primary treatment goal selected by the patient and investigator for the MTT was to be assessed by examining trends in scores on the Treatment Goal Questionnaire (TGQ) over the Treatment, Follow-up, and Extended Follow-up Phases. At each patient visit (Screening, Treatment, Follow-up) the scores for the selected treatment goals were to be recorded. Scores from screening and Visit 1 were to be averaged to obtain a baseline primary treatment goal score. Within each treatment goal category, scores for the primary treatment goal were to be compared across treatment groups at the end of the treatment period using analysis of variance (ANOVA) or analysis of covariance (ANCOVA) with baseline total tumor volume as a covariate. Other treatment goals selected by the investigator and patient were also to be scored at each visit and compared across treatment groups within treatment-goal categories. Mean per-patient scores for all identified goals and scores for all primary treatment goals across all categories were also to be examined.

Medians and ranges for goals scores by category and overall were to be represented graphically by treatment group over time, to identify trends during Treatment, Follow-up, and Extended Follow-up Phases. If appropriate, the General Estimating Equations method was to be used to examine the long-term effect of treatment on the primary treatment goal and other individual treatment goals. The effect of baseline tumor volume and treatment history on achievement of palliative treatment goals was to be examined. Other analyses of treatment goal outcomes were to include the examination of treatment goal scores at the time of maximum response for the MTT and repetition of the analysis described above for the subgroup of patients classified as having complete response of the MTT at the end of the treatment period, and for those having complete patient response at the end of study.

The reliability of the Palliative Treatment Goal questionnaire was to be investigated by comparing the Screening and Visit 1 responses using McNemar's test. An attempt was to be made to validate the questionnaire by examining the association of change in questionnaire score for the primary treatment goal with changes in volume of the MTT and changes in FACT-H&N score occurring during the same time period. The physician options for treatment goals also included prevention. Performance on preventive goals was to be assessed at the fourth weekly visit following the end of randomized treatment, the 5-month Follow-up visit, and study completion. The proportion of patients failing the preventive goal at each evaluation timepoint was to be compared across treatment groups for all prevention categories combined and, if sample sizes permitted, within specific categories, using the Mantel-

Haenszel chi-squared test. If possible, the effect of baseline total tumor volume and treatment history on the success of preventive treatment goals was to be examined. An attempt was to be made to validate the preventative goal section of the questionnaire by examining the association of prevention/non-prevention with changes in tumor volume for the most troublesome tumor and changes in the FACT-H&N score occurring during the same time period. The extent of agreement between patient and physician was to be evaluated in the sub-sample of patients, in which the patient and investigator selected the same goal, using the kappa statistic.

To evaluate the impact of treatment on global quality of life, each patient was to complete the FACT-H&N quality of life assessment regularly while on study. This instrument included a subscale specific to head and neck cancer. FACT-H&N responses at each visit were to be scored as described in the FACT Manual. Missing responses were to be pro-rated as permitted by the Manual. Individual scores obtained on the six subscales, and the overall FACT-H&N score, were to be summarized and examined by visit, by the response status of the MTT, and by treatment group. Nonparametric analysis of variance and tests for trend were to be used to identify significant differences between treatment groups in FACT-H&N overall and subscale scores over time. Changes from baseline in FACT-H&N scores were to be compared across treatment groups at the 1-week and 4-week post-treatment visits, the 5-month Follow-up visit, and study completion. The associations between subscale and overall FACT-H&N responses and KPS score over the study period were to be examined using Spearman's correlation coefficient.

Many new analyses listed below were added since the efficacy analysis plan was completed in 1998:

- The response of other treated tumors relative to the response of the MTT to be examined;
- A logistic regression model, exploring the relationship between MTT response and baseline patient and disease characteristics to be provided;
- Analysis of the relationship between MTT response and Patient Benefit was expanded to include exploration of the reasons patients maybe classified as benefitters in the absence of MTT response.

The following additions to the analysis plan were specified in the NDA:

Pairs of binomial proportions (for instance, Stratum 1 CDDP/epi gel and placebo MTT response rates) were compared using Pearson's (large-sample) chi-squared test and Fisher's exact test, as implemented in SAS procedure FREQ. Fisher's exact test was also used to compare CDDP/epi gel rates across patient subgroups: for instance, MTT response rates across centers. For stratified comparisons, the hypothesis that CDDP/epi gel and placebo rates are equal within each stratum was tested using large-sample and exact Cochran-Mantel-Haenszel tests. The large-sample approximations were obtained using FREQ and the exact p-values were obtained using SAS procedure MULTTEST (code supplied by Peter Westfall, one of the authors). Exact Clopper-Pearson confidence intervals for binomial rates were computed. Cramér's V statistic, which for 2x2 contingency tables is the signed square root of [Pearson

statistic / n], was used as a measure of association of binary variables, such as MTT response (responder, non-responder) and Patient Benefit (benefitter, non-benefitter).

SAS procedure GENMOD was used to fit an exploratory no-interaction logistic regression model to the blinded-phase MTT response status of CDDP/epi gel patients in Stratum 1 and Stratum 2. Variables such as age and time from original diagnosis of primary disease to first treatment visit were categorized in the same way they were categorized for the corresponding one-variable-at-a-time MTT response summary tables.

With the intention of conducting analysis based on combined-studies results, cutpoints for continuous variables were chosen to be approximately equal to tertiles or quartiles of the combined distribution of CDDP/epi gel and placebo groups. The no-interaction model and one-variable-at-a-time models were fitted solely to explore which variables should be included in the combined-trials model and the results should not be used as a basis for conclusions about which factors predict response.

Three types of time-to-event (“survival”) summaries were computed. Where possible, time-to-event distributions were estimated by the Kaplan-Meier method, as implemented in SAS procedure LIFETEST. Statistics such as estimated median time to event, estimated mean time, and the estimated standard error of the mean estimator are those calculated by LIFETEST with the default options. Time-to-event summaries were also computed for exact times only. For instance, time to MTT response was summarized for MTTs with CR or PR, and time to MTT response for CDDP/epi gel responders was compared across patient subgroups using Wilcoxon’s rank sum tests or Kruskal-Wallis tests, as implemented in SAS procedure NPAR1WAY, using the EXACT statement where feasible.

Reviewer's Comments

1. Although the primary analysis was conducted in all the randomized patients to strata 1 and 2, the data was analyzed per re-classification of some of the patients to different strata (see reviewer's comments in section 2.2.3 above).
2. It appears from the statement underlined in the analysis plan specified above, that the Treatment Goal Questionnaire is not prospectively validated instrument for measuring a meaningful clinical patient benefit. The sponsor's submission of the validation of the treatment goals questionnaire (vol. 3.14) is based on 12 investigators and 15 patients from one single institution, who were not entered in the trial. None of these 15 patients selected pain as the most important treatment goal (vol. 3.14, page 28). However, patients in the current studies under review most commonly (34%) selected pain as the primary or most important treatment goal.
3. Furthermore, it appears that in the initial plan of analysis, the palliative and preventative goals were to be assessed and validated separately with respect to FACT-H&N scores. However, in the NDA application an algorithm was presented where in the results of the two goals are combined as presented below.

4. Plan for comparing treatments with respect to patient benefit when there is differential number of treatments in the CDDP/epi gel and Placebo gel was not discussed.
5. Analysis plan accounting for the change in dose assignment after Amendment V is not specified.

Sponsor's Algorithm for Evaluating Patient Benefit

<i>Evaluation of Primary Treatment Goal by:</i>		<i>Patient Benefit?</i>	<i>Comment</i>
<i>Investigator</i>	<i>Patient</i>		
↑	↑	YES	If either goal is met and neither goal fails, then Patient Benefit is achieved
↑	—		
—	↑		
—	—	NO	If one or both goals are not met, then Patient Benefit is not achieved
↑	↓		
↓	↑		
↓	—		
—	↓		
↓	↓		

↑ Primary Treatment Goal is achieved.

— Either there was no change in status, the patient did not select a goal, or the Primary Treatment Goal was not evaluable or not evaluated.

↓ Failure to achieve Primary Treatment Goal.

3. Efficacy Results of Study MP 414-94-2 and MP 514-94-2

3.1 Demographic and Other Baseline Characteristics

MTT volume, number of tumors at the start of the study, treatment history, baseline Karnofsky performance status, FACT H&N score, and age were recorded at the study entry. There appears to be no significant imbalance with respect to these baseline factors between the CDDP/epi gel arm and the placebo arm. Demographic and other baseline characteristics are summarized in Table 1a and 2a, respectively, for Studies 414 and 514.

Table 1a: Summary of Demographic and Other Baseline Characteristics of Study 414

Characteristic	Stratum 1		Stratum 2		Stratum 1&2	
	Placebo	CDDP/epi gel	Placebo	CDDP/epi gel	Placebo	CDDP/epi gel
Age						
N	12	31	12	31	24	62
Mean (Std. Dev.)	64.3 (11.8)	61 (11.7)	57.4 (10.5)	63.2 (11.1)	61.5 (11.5)	62.6 (11.7)
Median (Range)	61 (46-84)	62 (37-82)	60 (43-81)	65 (41-81)	61 (40-82)	63 (33-87)
Gender						
N	12	31	12	31	24	62
Male	9 (75.0%)	23 (74.2%)	8 (66.7%)	27 (87.1%)	17 (70.8%)	50 (80.6%)
Female	3 (25.0%)	8 (25.8%)	4 (33.3%)	4 (12.9%)	7 (29.2%)	12 (19.4%)
Ethnicity						
N	12	31	12	31	24	62
White	10 (83.3%)	26 (83.9%)	8 (66.7%)	25 (80.7%)	18 (75%)	51 (82.3%)
Black	0 (0.0%)	3 (9.7%)	1 (8.3%)	1 (3.2%)	1 (4.2%)	4 (6.5%)
Hispanic	0 (0.0%)	2 (6.5%)	1 (8.3%)	4 (12.9%)	1 (4.2%)	6 (9.7%)
American Indian	1 (8.3%)	0 (0.0%)	1 (8.3%)	1 (3.2%)	2 (8.3%)	1 (1.6%)
Asian	1 (8.3%)	0 (0.0%)	1 (8.3%)	0 (0.0%)	2 (8.3%)	0 (0.0%)
Karnofsky Status						
N	12	30	12	31	24	61
Mean (Std. Dev.)	83.3 (13.7)	78.0 (13.0)	79.2 (16.8)	78.7 (13.0)	81.3 (15.1)	78.4 (12.8)
Median (Range)	85 (60-100)	80(50-100)	85 (40-100)	80 (50-100)	85 (40-100)	80 (50-100)
FACT-H&N Score						
N	11	29	12	31	23	60
Mean (Std. Dev.)	108.6 (31.2)	97.1 (19.6)	107.0 (19.6)	101.3 (17.8)	107.8 (25.2)	99.3 (18.6)
Median (Range)	124.3 (60.4-142)	97.1 (63.5-134)	104.2 (71.4-139)	99 (75.7-146)	108.3 (60.4-146)	97.6 (63.5-139)
MTT volume						
N	12	31	12	31	24	62
Mean (Std. Dev.)	1.6 (1.1)	1.9 (1.2)	11.7 (4.7)	11.9 (5.0)	6.6 (6.1)	6.9 (6.2)
Median (Range)	1.2 (0.125-3.64)	1.5 (0.49-4.69)	10.0 (6-18.25)	11.3 (6-20)	4.8 (0.1-18.8)	5.3 (0.5-20)
Number of Tumors						
N	12	31	12	31	24	62
Mean (Std. Dev.)	1.8 (1.4)	2.3 (2.2)	1.4 (0.5)	1.4 (1.0)	1.6(0.9)	1.8 (1.7)
Median (Range)	1 (1-4)	1 (1-10)	1 (1-2)	1 (1-5)	1 (1-4)	1 (1-10)
Treatment History						
N	12	31	12	31	24	62
RT	1	1	1	0	2	1
Surgery only	1	1	0	1	1	2
CT& RT	1	0	0	1	1	1
Surgery & RT	7	15	5	11	12	26
Surgery & CT	0	0	0	1	0	1

Surgery, CT & RT	2	14	6	17	8	31
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Table 2a: Summary of Demographic and Other Baseline Characteristics of Study 514

Characteristic	Stratum 1		Stratum 2		Stratum 1&2	
	Placebo	Treatment	Placebo	CDDP/epi gel	Placebo	Treatment
Age						
N	17	31	18	26	35	57
Mean (Std.Dev)	60.9 (12.5)	57.4 (12.0)	62.7 (9.7)	62.2 (11.5)	62.3 (11.0)	60.1 (11.6)
Median (Range)	60 (48-82)	54 (33-84)	64 (40-70)	62.5 (42-87)	61 (43-84)	57 (37-82)
Gender						
N	17	31	18	26	35	57
Male	13 (76.5%)	21 (67.7%)	17 (94.4%)	24 (92.3%)	30 (85.7%)	45 (79.0%)
Female	4 (23.5%)	10 (23.5%)	1 (5.6%)	2 (7.7%)	5 (14.3%)	12 (21.0%)
Ethnicity						
N	17	31	18	26	35	57
White	17 (100%)	31 (100%)	18 (100%)	26 (100%)	35 (100%)	57 (100%)
Karnofsky Status						
N	17	31	18	26	35	57
Mean (Std.Dev)	80.6 (13.5)	85.5 (11.5)	75 (16.2)	75 (12.4)	77.7 (15.0)	60.1 (11.6)
Median (Range)	90 (60-100)	90 (50-100)	75 (40-100)	70 (50-100)	80 (40-100)	57 (37-82)
FACT H&N Score						
N	17	30	16	25	33	55
Mean (Std.Dev)	102.5 (21.5)	101.0 (19.7)	99.6 (17.7)	102.0 (20.0)	101.1 (19.5)	101.5 (19.7)
Median (Range)	102.6 (67.2-132)	107.5 (66-134.2)	100.1 (62.3-126.7)	101.7 (64.7-136)	102.6 (62.3-132)	104.7 (64.7-136)
MTT volume						
N	17	31	18	26	35	57
Mean (Std.Dev)	2.7 (1.3)	2.9 (1.4)	11.1 (5.3)	12.7 (3.9)	7.0 (5.8)	7.4 (5.7)
Median (Range)	2.6 (0.5-5)	2.9 (0.75-5)	9.0 (5.3-20)	12.2 (6-19.9)	5.3 (0.5-20)	4.9 (0.8-19.9)
Number of Tumors						
N	17	31	18	26	35	57
Mean (Std.Dev)	1.5 (1.2)	1.2 (0.6)	1.4 (1.0)	1.4 (0.8)	1.5 (1.1)	1.3 (0.7)
Median (Range)	1 (1-5)	1 (1-3)	1 (1-5)	1 (1-4)	1 (1-5)	1 (1-4)
Treatment History						
N	17	31	18	26	35	57
No prior therapy	0	0	0	1	0	1
RT	2	1	3	2	5	3
Chemo(CT)	0	1	0	1	0	2
Surgery only	1	1	0	1	1	2
CT & RT	1	2	2	2	3	4
Surgery & RT	6	16	6	12	12	28
Surgery & CT	0	0	0	0	0	0
Surgery, CT & RT	7	10	7	7	14	17

Table 1b : Summary of Demographic and Other Baseline Characteristics of Study 414 with Original Randomization (FDA Analysis)

Characteristic	Stratum 1		Stratum 2		Stratum 1&2	
	Placebo	Treatment	Placebo	CDDP/epi gel	Placebo	Treatment
Age						
N	13	33	10	30	23	63
Mean (Std. Dev.)	65.3 (12.1)	61.3 (12.3)	56.5 (9.8)	63.6 (11.2)	61.5 (11.8)	62.6 (11.8)
Median (Range)	62 (48-82)	62 (33-84)	57 (40-70)	64 (44-87)	60 (40-82)	63 (33-87)
Gender						
N	13	33	10	30	23	63
Male	10 (76.9%)	25 (75.8%)	7 (70.0%)	26 (86.7%)	17 (73.9%)	51 (81.0%)
Female	3 (23.1%)	8 (24.2%)	3 (30.0%)	4 (13.3%)	6 (26.1%)	12 (19.1%)
Ethnicity						
N	13	33	10	30	23	63
White	10 (76.9%)	27 (81.8%)	7 (70.0%)	24 (80.0%)	17 (73.9%)	51 (81.0%)
Black	0 (0.0%)	3 (9.1%)	1 (1.0%)	2 (6.7%)	1(4.4%)	5 (7.9%)
Hispanic	1 (0.0%)	3 (9.1%)	0 (0.0%)	3 (10.0%)	1 (4.4%)	6 (9.5%)
American Indian	1 (7.7%)	0 (0.0%)	1 (1.0%)	1 (3.3%)	2 (8.7%)	1 (1.6%)
Asian	1 (7.7%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	2 (8.7%)	0 (0%)
Karnofsky Status						
N	13	32	10	30	23	62
Mean (Std. Dev.)	83.9 (13.3)	78.8 (12.9)	76.0 (16.5)	78.5 (12.8)	80.4 (14.9)	78.5 (12.7)
Median (Range)	90 (60-100)	80(50-100)	80 (40-90)	80 (50-100)	80 (40-100)	80 (50-100)
FACT-H&N Score						
N	12	31	10	30	22	61
Mean (Std. Dev.)	111.7 (31.6)	98.4 (20.4)	102.2 (16.3)	100.3 (16.6)	107.4 (25.7)	99.6 (18.4)
Median (Range)	127.6 (60.4-146)	97.1 (63.5-139)	101.3 (75.7-132.1)	99 (71.4-138.9)	107.7 (60.4-146)	98.5 (63.5-1389)
MTT volume						
N	13	33	10	30	23	63
Mean (Std. Dev.)	2.0 (1.9)	2.5 (2.8)	11.6 (4.7)	12.5 (5.6)	6.17 (5.9)	7.9 (8.7)
Median (Range)	1.2 (0.125-7.5)	1.5 (0.49-15.3)	10.0 (6-18.75)	11.3 (6-26.4)	3.64 (0.2-18.8)	6 (0.5-52.5)
Number of Tumors						
N	13	33	10	30	23	63
Mean (Std. Dev.)	1.7 (1.1)	2.2 (2.1)	1.5 (0.5)	1.4 (1.0)	1.6 (0.9)	1.8 (1.7)
Median (Range)	1 (1-4)	1 (1-10)	1 (1-2)	1 (1-5)	1 (1-4)	1 (1-10)
Treatment History						
N	13	33	10	30	23	63
RT	1	1	1	0	2	1
Surgery only	1	1	0	1	1	2
CT& RT	1	0	0	2	1	2

Surgery & RT	8	16	4	10	12	26
Surgery & CT	0	0	0	1	0	1
Surgery, CT & RT	2	15	5	16	10	31

Table 2b: Summary of Demographic and Other Baseline Characteristics of Study 514 with Original Randomization (FDA Analysis)

Characteristic	Stratum 1		Stratum 2		Stratum 1&2	
	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment
Age						
N	17	34	19	24	36	58
Mean (Std.Dev)	61.3 (11.8)	58.9 (11.9)	63.7 (10.4)	61.9 (10.8)	62.6 (11.0)	60.1 (11.5)
Median (Range)	60 (46-84)	55 (37-82)	66 (43-81)	62 (41-79)	61 (43-84)	57 (37-82)
Gender						
N	17	34	19	24	36	58
Male	13 (76.5%)	24 (70.6%)	17 (89.5%)	22 (91.7%)	30 (83.3%)	46 (79.3%)
Female	4 (23.5%)	10 (29.4%)	2 (10.5%)	2 (8.3%)	6 (16.7%)	12 (20.7%)
Ethnicity						
N	17	34	19	24	36	58
White	17 (100%)	34 (100%)	19 (100%)	24 (100%)	36 (100%)	58 (100%)
Karnofsky Status						
N	17	34	19	24	36	58
Mean (Std.Dev)	80.6 (13.5)	84.7 (11.4)	74.7(15.8)	75.4(13.2)	77.5 (14.8)	80.9 (12.9)
Median (Range)	90 (60-100)	90 (50-100)	70 (40-100)	70 (50-100)	80 (40-100)	80 (50-100)
FACT H&N Score						
N	17	33	18	22	35	55
Mean (Std.Dev)	102.5 (21.5)	100.3 (19.3)	101.1(18.3)	103.2 (20.0)	101.8 (19.7)	101.5 (19.5)
Median (Range)	102.6 (67.2-132)	106 (66-134.2)	104 (62.3-126.7)	104.7 (64.7-136)	103.3 (62.3-132)	105.1 (64.7-136)
MIT volume						
N	17	34	19	24	36	58
Mean (Std.Dev)	2.7 (1.3)	3.4 (2.3)	11.6 (5.6)	13.9 (5.1)	7.4 (6.1)	7.8 (6.4)
Median (Range)	2.6 (0.5-5)	3.2 (0.75-11.3)	9.4 (5.3-20.4)	13.0 (6-30.0)	5.4 (0.5-20.4)	4.9 (0.75-29.9)
Number of Tumors						
N	17	34	19	24	36	58
Mean (Std.Dev)	1.5 (1.2)	1.32 (0.76)	1.4 (1.0)	1.24 (0.58)	1.4 (1.1)	1.3 (0.6)
Median (Range)	1 (1-5)	1 (1-4)	1 (1-5)	1 (1-3)	1 (1-4)	1 (1-4)
Treatment History						
N	17	34	19	24	36	58
No	0	0	0	1	0	1
RT	2	1	3	2	5	3
Chemo(CT)	0	2	0	0	0	2
Surgery only	1	2	0	0	1	2
CT & RT	1	2	2	2	3	4
Surgery & RT	6	16	6	13	12	29
Surgery & CT	0	0	0	0	0	0
Surgery, CT & RT	7	11	8	6	15	17

Reviewer's Comments:

1. The mean and median MTT volume in stratum 1 is larger in the Study 514 compared to Study 414.
2. Median MTT volume in the placebo arm was smaller than the CDDP/epi arm in Stratum 2 of Study 514.
3. The summary of demographic data presented in Tables 1b and 2b, respectively, for studies 414 and 514, are as per the original randomization scheme (for difference in patient numbers in the two strata compared to Tables 1a and 1b, see reviewer's comments, section 2.2.3). There appears to be no apparent difference between the two sets of data (Table 1a vs. 1b and Table 2a vs. 2b).

3.2 Primary Efficacy Evaluation

3.2.1 Objective Tumor Response

The following Tables 3a & 4a, compare the objective tumor (CR + PR) response rate per Sponsor's evaluation during the blinded treatment phase of the study, respectively, for Studies 414 and 514. During the blinded period, rates of MTT response of the CDDP/epi gel arm and the placebo arms per sponsor's analyses were significantly different. In Study 414, 34% of patients with CDDP/epi gel had tumor responses while no patient with placebo had response (p= 0.001). In Study 514 the tumor response rates in the CDDP/epi gel and placebo gel arms were, respectively, 25% and 3% (p= 0.007).

**Table 3a: Rate of MTT Response (per Sponsor) of Study 414 (Volume 3.166, p102)
(Sponsor's Analysis-Strata Allocation Modified Post-Randomization)**

	Number of Response	p-value
Stratum 1&2		
Treatment (n=62)	21 (34%)	0.001*
Placebo (n=24)	0 (0%)	
Stratum 1		
Treatment (n=31)	13 (42%)	0.008 [#]
Placebo (n=12)	0 (0%)	
Stratum 2		
Treatment (n=31)	8 (26%)	0.082 [#]
Placebo (n=12)	0 (0%)	

**Table 4a: Rate of MTT Response (per Sponsor) of Study 514 (Volume 3.193, p101)
(Sponsor's Analysis-Strata Allocation Modified Post-Randomization)**

	Number of Response	p-value
Stratum 1&2		
Treatment (n=57)	14 (25%)	0.007*
Placebo (n=35)	1 (3%)	
Stratum 1		
Treatment (n=31)	10 (32%)	0.070 [#]
Placebo (n=17)	1 (6%)	
Stratum 2		
Treatment (n=26)	4 (15%)	0.130 [#]
Placebo (n=18)	0 (0%)	

* Cochran-Mantel- Haenszel test (exact)

[#] Fisher's exact test

Reviewer's Comments:

1. The MTT response rates in both the studies as evaluated by the FDA Medical Reviewer (most conservative: responses not counted in patients with incorrect dosing, duration of response < 4 weeks, etc., and least conservative) are presented in Tables 3b and 3c, and Tables 4b and 4c, respectively, for Studies 414 and 514. In both the Studies according to the Medical Reviewer's assessment of tumor response, there is no significant difference between the CDDP/epi gel and placebo gel arms, when the most conservative approach is considered (Tables 3b and 4b).

Table 3b: Rate of MTT Response (per FDA Medical Reviewer Most Conservative Assessment) of Study 414 (Strata Allocation Used as Modified Post-randomization by the Sponsor)

	Number of Response	p-value(Fisher's Exact)
Stratum 1&2		

Treatment (n=62)	3 (5%)	0.557
Placebo (n=24)	0 (0%)	

Table 4b: Rate of MTT Response (per FDA Medical Reviewer Most Conservative Assessment) of Study 514 (Strata Allocation Used as Modified Post-randomization by the Sponsor)

	Number of Response	p-value(Fisher's Exact)
Stratum 1&2		
Treatment (n=57)	6 (11%)	0.246
Placebo (n=35)	1 (3%)	

Table 3c: Rate of MTT Response (per FDA Medical Reviewer Least Conservative Assessment) of Study 414 (Strata Allocation Used as Modified Post-randomization by the Sponsor)

	Number of Response	p-value(Fisher's Exact)
Stratum 1&2		
Treatment (n=62)	17 (27%)	0.002
Placebo (n=24)	0 (0%)	

Table 4c: Rate of MTT Response (per FDA Medical Reviewer Least Conservative Assessment) of Study 514 (Strata Allocation Used as Modified Post-randomization by the Sponsor)

	Number of Response	p-value(Fisher's Exact)
Stratum 1&2		
Treatment (n=57)	12 (21%)	0.015
Placebo (n=35)	1 (3%)	

2. Randomization in both the studies was done based on the stratification factor, MTT volume measured at screening. However, some of the patients in each of the studies were reclassified to other strata based on their MTT volume at the first treatment visit. In Study 414, three patients were switched from Stratum 1 to 2, one patient was switched from

Stratum 2 to 3, and one patient was switched from Stratum 3 to 2. In Study 514, there were three patients who were switched from Stratum 1 to 2, and two patients were switched from Stratum 2 to 3. The sponsor's analyses presented in Tables 3a and 4a are based on the modified strata allocation. The reviewers conducted analyses using the original strata allocation (ITT population). It appears that the changes made by the sponsor did not significantly affect the overall objective response rate results in both the studies.

3. Two patients from each studies had chosen a different MTT from the investigator selected MTT. These two patients' tumors had the same response to the treatments as the response to investigator chosen MTT.
4. Apart from the changes in the dosing scheme in the middle of the study (After Amendment V), dose violation was also commonly observed throughout the study (please refer to the medical officer's review). Table 3d and 4d present the response rates in the CDDP/epi gel arm, prior and post amendment of the dosing schedule. These results indicate that there was no significant difference in the response rates between pre and post amendment V in both the US Study 414 and the Europe Study 514. However, *the direction of the response rate was reversed* in the Europe Study 514 compared to the US Study 414 (Table 3d and 4d). Although, the sponsor had specified in the amended data analysis plan that all analyses will take into account the change in dose assignment described in Amendment V (Vol. 3.172 pages 7 and 27 Section 9.5.5), the sponsor has not presented data adjusting for this change in dose assignment.

Table 3d: Rate of MTT Response (per Sponsor) in the CDDP/epi Arm of Study 414 (FDA's Analysis-Pre and Post Amendment V)

	Number of Response	p-value (Fisher's Exact)
Pre-amendment V (Dose = 0.5 mL/cm³)	7/24 (29%)	0.591
Post-amendment V (Dose = 0.25 mL/cm³)	14/38 (37%)	

Table 4d: Rate of MTT Response (per Sponsor) in the CDDP/epi Arm of Study 514 (FDA's Analysis-Pre and Post Amendment V)

	Number of Response	p-value (Fisher's Exact)
Pre-amendment V (Dose = 0.5 mL/cm³)	6/21 (29%)	0.751
Post-amendment V (Dose = 0.25 mL/cm³)	8/36 (22%)	

3.2.2 Primary Treatment Goal

Tables 5 & 6 presented below, compare the patient benefit response rate per Sponsor's evaluation during the blinded treatment phase of the study, respectively, for Studies 414 and 514. Both the studies did not show any significant differences of Patient Benefits between the treatment arms. In Study 414, 21/62 (34%) CDDP/epi gel-treated patients compared with 4/24 (17%) placebo-treated patients achieved Patient Benefit. The difference between the treatment groups did not reach statistical significance ($p=0.18$). In Study 514, 11/57 (19%) CDDP/epi gel-treated patients compared with 3/35 (9%) placebo-treated patients achieved Patient Benefit. This difference was not statistically significant ($p=0.24$).

The sponsor claims that in the blinded period, 27% of CDDP/epi gel-treated patients attained Patient Benefit compared to 12% of placebo gel-treated patients, using the combined studies data, and that the difference between the two groups was marginally significant (exact Cochran-Mantel-Haenszel $p = 0.046$, volume 3.164, section 3.1.3.4.2.1, p 167).

**Table 5: Number of Patient Benefitters in Study 414
(Sponsor's Analysis-Strata Allocation Modified Post-randomization)**

	Benefitters	p-values
Stratum 1&2		
Treatment (n=62)	21 (34%)	0.18*
Placebo (n=24)	4 (17%)	
Stratum 1		
Treatment (n=31)	13 (42%)	0.48#
Placebo (n=12)	3 (25%)	
Stratum 2		
Treatment (n=31)	8 (26%)	0.40#
Placebo (n=12)	1 (8%)	

* Cochran-Mantel-Haenszel test (exact)

Fisher's exact test

**Table 6 : Number of Patient Benefitters in Study 514
(Sponsor’s Analysis-Strata Allocation Modified Post-randomization)**

	Benefitters	p-values
Stratum 1&2		
Treatment (n=57)	11 (19%)	0.24*
Placebo (n=35)	3 (9%)	
Stratum 1		
Treatment (n=31)	7 (23%)	0.46#
Placebo (n=17)	2 (12%)	
Stratum 2		
Treatment (n=26)	4 (15%)	0.63#
Placebo (n=18)	1 (6%)	

* Cochran-Mantel- Haenszel test (exact)

Fisher’s exact test

Reviewer’s Comments:

1. The sponsor’s analysis of evaluating patient benefit is based on the assumption that a change in one point score of the palliative goal (for example from a score of 2 to 1) to be clinically significant and meaningful. This change of the score by one point was not pre-specified, and has not been prospectively validated to correspond to patient benefit by comparing to existing validated instruments. A change in score of one point is questionable to be a significant change that may correspond to a meaningful clinical benefit to the patient. Furthermore, the results in Tables 7 & 8 suggest that majority of the patients did not have any change in the symptom scores. Of those who did have a change in score, in the CDDP/epi gel arm, Study 414, only one patient had a decrease in the score (benefit) by one point, where as 6 patients had an increase in the score (worsening of the symptom) by one point (Table 7). Similarly in the CDDP/epi gel arm, Study 514, 5 patients had a decrease in the score (benefit) by one point, and 5 other patients also had an increase in the score (worsening of the symptom by one point) (Table 8). This suggests that a change in

score by one point may not be meaningful. It should also be noted that the treatment goals differed from patient to patient. This amounted to, for example, a patient with a primary treatment goal 'obstruction' and a change in score of 1, as being equivalent to a patient with a primary treatment goal 'pain' and same change of score of 1.

Table 7: Change of Palliative Treatment Goal Scores in Study 414

Change in Score	CDDP/epi gel	Placebo gel
-2	0	0
-1	<i>1</i>	0
0	23	11
+1	6	0
+2	0	0
Not Evaluable	1	0

Table 8: Change of Palliative Treatment Goal Scores in Study 514

Change in Score	CDDP/epi gel	Placebo gel
-2	2	0
-1	5	1
0	31	20
+1	5	2
+2	2	0
+3	1	0
Not Evaluable	0	2

2. The algorithm used by the sponsor for combining the ‘patient’s and the ‘investigator’s assessment of the achievement of the treatment goal is presented in section 2.2.6 of this review. The validity of this Algorithm is questionable. The palliative treatment goals were measured using a four-point scale while the preventive treatment goals were measured as either met or not met. These two different goals which are different in nature and measurement criteria, were treated equally by Patient Benefit Algorithm. Furthermore, “met” of the preventive goals, which indicated absence of disease progression, and “better” of the palliative goals, which indicated palliation of certain symptoms, were interpreted with an equal weight by applying this Algorithm. For example, a patient with the stable symptoms through out the study, could have preventive goal as the primary treatment goal according to the investigator and benefit assessed as “met” by the investigator. i.e., for this patient preventive benefit could be recorded as “met” and as “same” for the palliative

benefit. This combination by the sponsor’s algorithm would then lead to classifying the patient as a benefitter. Among 39 benefitters claimed by the sponsor from both the studies, 64% (25/39) had “met” from investigators’ preventive goal assessment and “same” or missing value from the patients’ palliative goal assessment.

- Furthermore, in Study 414, the investigators selected in 44/86 (51.2%) patients preventive goal as the primary treatment goal, where as in 42/86 (48.8%) palliative goal was selected as the primary treatment goal. In 26/44 (59%) of patients with the preventive goal as the primary treatment goal, the investigators recorded for the treatment goal to be “met”, where as, **only one patient** (2%) of 42 patients with palliative goal as primary treatment goal was assessed to be “better”. In Study 514, the investigators selected preventive goal as the primary treatment goal in 21 patients. Of those 29% were assessed as “met”. In this 514 study, the investigators selected palliative goal as the primary treatment goal in 71 patients. Of these patients 11% were assessed as “better”. There appears to be a selection bias in the Study 414 investigators in choosing preventive versus palliative goal as the primary treatment goal. As the results presented in Tables 9a and 9b indicate, the attainment of Patient Benefit is greatly influenced by the investigator’s selection of the primary treatment goal. Furthermore, patients with preventive primary treatment goal were more likely to be assessed as Benefitters, which raises concern regarding investigator selection bias in selecting a primary treatment goal.

Table 9a: Number of Patients Assessed as “Met” or “Better” in the CDDP/epi gel Arm

	Investigator treatment goal	Total	Met/Better
Study 414	Palliative goals	31	1 (3%)
	Preventive goals	31	22 (71%)
Study 514	Palliative goals	46	7 (15%)
	Preventive goals	11	4 (36%)

Table 9b: Number of Patients Assessed as “Met” or “Better” in the Placebo gel Arm

	Investigator treatment goal	Total	Met/Better
Study 414	Palliative goals	11	0 (0%)
	Preventive goals	13	4 (31%)
Study 514	Palliative goals	25	1 (4%)
	Preventive goals	10	2 (20%)

- Due to questionable validity of the sponsor’s algorithm of combining the palliative and preventive goals, and combining patients’ and investigators’ assessments, the patients’ and the investigators’ palliative goals were analyzed separately by the reviewers. Sixty-eight

patients in Study 414 and 84 patients in Study 514 had chosen their own primary treatment goals (palliative goals). Forty-two patients in Study 414 and 71 patients in Study 514 had palliative goals as the primary treatment goal as selected by the investigator. As shown in Tables 10 & 11, very small numbers of patients were assessed as “better” in the CDDP/epi gel arm as well as the placebo arm in Study 414 for the palliative treatment goal both by the patients and investigators ($\leq 5\%$). Furthermore, the percentages of the placebo-treated patients assessed as “same” were similar or higher (79% vs. 74%, 100% vs. 74%) than the ones of the CDDP/epi gel arm, and even smaller proportions (11% vs. 20%, 0% vs. 19%) of the placebo-treated patients were assessed as “worse”. **These results of the Study 414 clearly demonstrate that there was no significant symptom or palliative benefit to patients treated with CDDP/epi gel compared to placebo gel** and more significantly, more patients felt worse in the CDDP/epi gel arm compared to the placebo gel arm, possibly due to its toxicity. In Study 514, slightly higher percentages of patients from the CDDP/epi gel arm were assessed as “better” (17% and 15%) than the patients in Study 414. However, it was not significantly higher than the number of patients in the placebo arm. Furthermore, the proportion of patients who were assessed as “worse” were higher than the ones assessed as “better” (21% and 17%). As demonstrated in Study 414, in Study 514 also, the placebo arm had higher proportion of patients assessed as “same”, and lower proportion of patients assessed as “worse” compared to the CDDP/epi gel arm (Tables 10 & 11).

Table 10: Patient-Selected Palliative Treatment Goals of Both the Studies

	Total	Better	Same	Worse	Not Evaluable
Study 414					
CDDP/epi gel	49	2 (4%)	36 (74%)	10 (20%)	1 (2%)
Placebo	19	1 (5%)	15 (79%)	2 (11%)	1 (5%)
Study 514					
CDDP/epi gel	53	9 (17%)	32 (60%)	11 (21%)	1 (2%)
Placebo	31	1 (3%)	23 (74%)	4 (13%)	3 (10%)

Table 11: Investigator-Selected Palliative Treatment Goals of Both the Studies

	Total	Better	Same	Worse	Not Evaluable
Study 414					
CDDP/epi gel	31	1 (3%)	23 (74%)	6 (19%)	1 (3%)
Placebo	11	0 (0%)	11 (100%)	0 (0%)	0 (0%)
Study 514					
CDDP/epi gel	46	7 (15%)	31 (67%)	8 (17%)	0 (0%)

Placebo	25	1 (4%)	20 (80%)	2 (8%)	2 (8%)
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5. The preventive goals were assessed as “same” in instances where the goal did not fail, but was not documented to have been prevented for 25 days or more. The most common example of this was when a placebo patient was terminated from the blinded period in less than 25 days and was rolled over to receive open-label CDDP/epi gel. i.e., there appears to be differential pattern and conformity between the treatment arms in the total number of treatments administered (Table 12 & 13). This could introduce bias in patient benefit assessment because of possible unblinding issues.

Table 12: Pattern of Treatment Conformity in Study 414

# of Treatments Received	CDDP/Epi.gel N = 62	Placebo N = 24
1	62 (100.0%)	24 (100.0%)
2	56 (90.3%)	23 (95.8%)
3	42 (67.7%)	17 (70.8%)
4	28 (45.2%)	6 (25.0%)
5	15 (24.2%)	1 (4.2%)
6	10 (16.1%)	0 (0.0%)

Table 13: Pattern of Treatment Conformity in Study 514

# of Treatments Received	CDDP/Epi.gel N = 57	Placebo N = 35
1	57 (100.0%)	35 (100.0%)
2	55 (96.5%)	30 (85.7%)
3	49 (86.0%)	24 (68.6%)
4	34 (59.7%)	15 (42.9%)
5	24 (42.1%)	8 (22.9%)
6	24 (42.1%)	6 (17.1%)

6. The reviewers analyzed the preventive treatment goals separately from the palliative treatment goals. Among 25 benefitters (per investigators assessment) in Study 414, 23 patients had preventive goals as the primary treatment goal, and their responses to the patient-selected treatment goals were either “same” or missing except for one patient. Among these 23 patients only three patients were in the placebo group. However, this difference was driven by the algorithm, and presence of “same” instead of efficacy of the

treatments. As shown in Table 14, about half of the patients in the placebo group were in “same”, and no patient was in “not met”. The patients with “same” in the investigator-selected treatment goals could be benefitters only if they were in “better” in the patient-selected treatment goals. However, the results presented in Tables 10 & 11 indicate that very few patients felt “better” with respect to symptom improvement regardless of the treatment received. Also, the results presented in Tables 10 & 11 demonstrate that the chances of “worsening” of a symptom was low in the placebo group. These results suggest that if the placebo-treated patients stayed in the blinded phase for 25 days or more, they would be more likely to be classified as benefitters. It should be noted that the number of patients who were assessed as “worse” or “not met” in the placebo treated patients was zero versus four patients in CDDP/epi gel treated group. This is probably due to differential number of treatments administered in the two treatment arms and it is also possible that the patients’ symptoms would remain stable without any treatment in general.

Table 14: Preventive Treatment Goals of Both the Studies

	Total	Met	Same	Not Met	Not Evaluable
Study 414					
CDDP/epi gel	31	22 (71%)	4 (13%)	4 (13%)	1 (3%)
Placebo	13	4 (31%)	6 (46%)	0 (0%)	3 (23%)
Study 514					
CDDP/epi gel	11	4 (36%)	3 (27%)	1 (9%)	3 (27%)
Placebo	10	2 (20%)	4 (40%)	1 (10%)	3 (30%)

- The sponsor pooled the two studies (414 and 514), and claimed statistically significant difference in Patient Benefit between the treatment groups (p-value = 0.046). Patient benefit is an important primary endpoint and benefit needs to be demonstrated in each study separately. Individually, neither of the studies demonstrated statistically significant difference with respect to patient benefit. Retrospective meta-analysis results are not acceptable.

3.2.3 Association between Patient Benefit and MTT Response

The association between objective tumor response and patient benefit was evaluated by the sponsor by combining the results of the two studies and these results are presented in the Table 15.

**Table 15: Association between Patient Benefit and MTT Response
(Sponsor's Analysis)**

Strata	Nonresponder Benefit Rate			Responder Benefit Rate			P-value*
	n	No. with Benefit	Benefit Rate	n	No. with Benefit	Benefit Rate	
Stratum 1	39	7	18%	23	13	57%	0.004
Stratum 2	45	9	20%	12	3	25%	1.000
Stratum 1 & 2	84	16	19%	35**	16**	46%	0.012

* Exact Cochran-Mantel Haenzel test

**Sensitivity = $16/35 = 0.457$

Reviewer's Comments:

1. The Agency had made it clear to the sponsor at various stages of the study that it was critical to establish a strong correlation between tumor shrinkage and Patient Benefit. The agency had also strongly recommended that patient benefit should be the primary efficacy parameter since the therapy considered in this study is a local therapy and was not expected to extend survival in this patient population. Therefore, tumor shrinkage without the palliation of the symptoms would not show any clinical benefit of the new treatment, CDDP/epi gel. This reviewer conducted the association analysis in both the studies separately as detailed in Tables 16a and 17a. In Study 414 there was no statistically significant association ($p=0.16$) between the tumor response and patient benefit. However in Study 514 there appears to be nominal significant association between Patient Benefit and MTT response ($p=0.018$). This nominal significant association means that the patient benefit and tumor response are dependent on each other and the observed trend is weak. The association needs to be assessed quantitatively. Because both patient benefit and tumor response are discrete variables, correlation coefficient can not be computed. However, sensitivity, which measures predictability, is an important measure of association, which is less than 50%. Furthermore, these results should be interpreted with caution, since responder's characteristics may be different from non-responders. Also, since there were far fewer patients studied in the placebo arm and most of the patients in the placebo arm did not receive more than 4 treatments (approximately 4 weeks of treatment), the placebo treated patients could not have had a complete evaluation of the benefit.

Table 16a: Association Between MTT Response and Patient Benefit in CDDP/epi gel Arm, Study 414

Patient Benefit	MTT Response	
	Responder	Non-responder
Benefitter	10	11
Non-benefitter	11	30
p-value	0.16	

Sensitivity = $10/21 = 0.476$

Table 17a: Association Between MTT Response and Patient Benefit in CDDP/epi gel Arm, Study 514

Patient Benefit	MTT Response	
	Responder	Non-responder
Benefitter	6	5
Non-benefitter	8	38
p-value	0.02	

Sensitivity = $6/14 = 0.429$

- In Study 414, according to sponsor, 10/21 responders (48%) had both tumor response and patient benefit in the CDDP/epi gel treated patients. Nine of these 10 benefitters were assessed as benefitters based on preventative goal. However only one of these 10 patients had patient benefit per the agency evaluation of the data (please see medical officer's review).
- In Study 514, according to sponsor, 6/14 responders (43%) had both tumor response and patient benefit in the CDDP/epi gel treated patients. However only one of these 6 patients had patient benefit per the agency evaluation of the data (please see medical officer's review).
- As mentioned earlier, almost all the benefitters that the sponsor has claimed are based on achievement of preventative goal. Achievement of this goal has not been validated or established to result in any significant clinical benefit to the patient and as such the agency does not consider achievement of preventative goal to be a valid measurement of patient benefit. Furthermore, there is no association between the tumor response and achievement of palliative or preventative benefit when evaluated separately in Study 414 (Tables 16b & 16c) and preventative benefit in Study 514 (Table 17c). There appears to be significant correlation between tumor response and achievement of palliative benefit in Study 514 (Table 17b).

Table 16b: Association Between MTT Response and Patient Palliative Benefit in CDDP/epi gel Arm, Study 414

Patient Benefit	MTT Response	
	Responder	Non-responder
Benefitter	1	0
Non-benefitter	9	21
p-value	0.32	

Sensitivity = $1/10 = 0.1$

Table 17b: Association Between MTT Response and Patient *Palliative* Benefit in CDDP/epi gel Arm, Study 514

Patient Benefit	MTT Response	
	Responder	Non-responder
Benefitter	5	4
Non-benefitter	7	30
p-value	0.04	

Sensitivity = $5/12 = 0.42$

Table 16c: Association Between MTT Response and Patient *Preventive* Benefit in CDDP/epi gel Arm, Study 414

Patient Benefit	MTT Response	
	Responder	Non-responder
Benefitter	9	11
Non-benefitter	2	9
p-value	0.24	

Sensitivity = $9/11 = 0.818$

Table 17c: Association Between MTT Response and Patient *Preventive* Benefit in CDDP/epi gel Arm, Study 514

Patient Benefit	MTT Response	
	Responder	Non-responder
Benefitter	1	1
Non-benefitter	1	8
p-value	0.35	

Sensitivity = $1/2 = 0.5$

5. All the above analyses of establishing association between tumor response and patient benefit should be interpreted cautiously. **The strength of association is greatly influenced by the large number of patients classified both as non-responders and non-benefiters.** A better analysis would be to evaluate the sensitivity of the two methods of evaluation. The results of these analyses are presented as footnotes in Tables 16a-17c. As these results indicate the **sensitivity is < 50%**, (probability of having a tumor response

and patient benefit is < 0.5) in all cases, except in the case of preventive benefit vs. tumor response in Study 414 (Table 16c). Sensitivity of 0.8 in this case may be due to investigator bias.

3.3 Adjusted Covariate Analyses

As an exploratory analysis, logistic regression analysis was conducted by the sponsor using combined data from Studies 414 and 514, to determine the effects of selected covariates on MTT response. The results of this analysis are presented in Table 18. Tables 19 and 20 are the logistic regression analyses results per sponsor for the individual studies. Previous platinum therapy is highly significant in the US Study 414 where as it is not significant in the Europe Study 514.

Table 18: Preliminary Examination of Objective Response of the MTT Using Logistic Regression in Patients Treated with CDDP/Epi Gel (n = 119) in Studies 414 and 514

Covariate	p-value*
Baseline KPS	0.018
MTT location	0.027
Baseline MTT volume	0.033
Time since diagnosis	0.27
Gender	0.35
Age group	0.83
Previous chemotherapy	0.83

* Type 3 likelihood ratio test for preliminary variable selection analyses.

Table 19: Logistic Regression: Effect of Covariates on MTT Response in Study 414

Covariate	p-value*
Age group	0.10
Baseline KPS	0.27
MTT location	0.11
Previous platinum-based therapy	0.009
Gender	0.13
MTT stratum	0.27
Ethnic group	0.066

* Type 3 likelihood ratio test for preliminary variable selection analyses.

Table 20: Logistic Regression: Effect of Covariates on MTT Response in Study 514

Covariate	p-value*
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Age group	0.30
Baseline KPS	0.21
MTT location	0.023
Previous platinum-based therapy	0.19
Gender	0.84
MTT stratum	0.34
Region of Europe	0.061

* Type 3 likelihood ratio test for preliminary variable selection analyses.

Reviewer's Comments:

1. All adjusted analyses are considered only as supportive to the primary efficacy analyses.
2. It is to be noted that dose, which was amended in the middle of the trial, was not included in any of the above models.

3.4 Other Efficacy Variables Evaluation

3.4.1 Association between Patient Benefit and the Change in FACT Score

The sponsor made an attempt to validate the treatment goal questionnaire by examining the association of change in questionnaire score for the primary treatment goal with changes in FACT-H&N score. Patient Benefit and the trend in FACT H&N score were independent.

Reviewer's Comments:

1. As shown in Table 21, in Study 514, patients who achieved Patient Benefit and those who did not were equally likely to have experienced a decreasing FACT H&N scores. In Study 414 the benefitters were even more likely to have decreasing FACT H&N scores. However, these results should be interpreted with caution due to the fact that more than half of FACT H&N scores were recorded as missing.

Table 21: Association between Patient Benefit and Change in FACT Score

QoL	Study 414		Study 514	
	Benefitters	Non-benefitters	Benefitters	Non-benefitters
Increase	3 (25%)	11 (44%)	3 (30%)	8 (30%)
Decrease	9 (75%)	14 (56%)	7 (70%)	19 (70%)

3.4.2 Secondary Efficacy Analyses:

Per sponsor analyses, KPS was essentially stable during the Blinded Period in both the CDDP/epi gel and placebo groups despite the longer period of observation in the former. (Patients in the placebo group had a shorter period of observation in the Blinded Period because of early treatment failure and roll-over into the Extended Follow-up Phase.) This trend was observed in both strata separately and combined.

In Study 414, a comparison of survival time in patients in each treatment group, defined as days from first randomized treatment to death, was not planned because local therapy was not expected to extend survival in this patient population. In Strata 1 and 2, the sponsor was able to obtain dates of death for 40 of 62 of patients in the CDDP/epi gel group and for 17 of 24 patients in the placebo group. As expected, survival time in the two treatment groups was similar and did not differ significantly (unstratified log rank test $p = 0.36$). Similarly in Study 514, in Strata 1 and 2, dates of death were obtained for 24 of 57 patients in the CDDP/epi gel group and for 22 of 35 patients in the placebo group. In this Study 514, median survival in the two treatment groups (CDDP/epi gel, 201 days; placebo, 107 days) did not differ significantly ($p = 0.11$, stratified log rank test).

Figure 1 is sponsor's survival analysis graph of combined survival data from Studies 414 and 514 illustrating no difference in survival between the two treatment arms.

Tables 22 and 23 describe sponsor's analysis of time to and duration of MTT response among MTT responders for Studies 414 and 514, respectively.

Tables 24 and 25 describe sponsor's analysis of time to MTT progression for Studies 414 and 514, respectively.

Reviewer's Comments:

1. All secondary efficacy analyses are considered as hypotheses generating analyses.

Figure 1: Survival Analysis of the Combined Studies 414 and 514

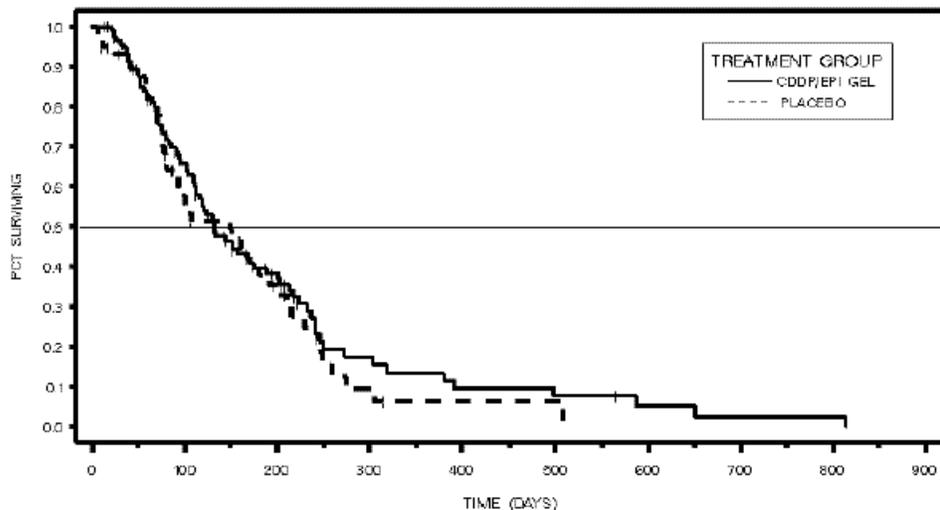


Table 22: Time to and Duration of MTT Response Among MTT Responders in Study 414

	Median Time to Response (days)	Median Duration of Response (days)	Median # of Treatments to Response
Strata 1 & 2			
CDDP/epi gel (n = 21/62)	17	85	2
Placebo (n = 0/24)	-	-	-
Stratum 1			
CDDP/epi gel (n = 13/31)	14	78	2
Placebo (n = 0/12)	-	-	-
Stratum 2			
CDDP/epi gel (n = 8/31)	21	90	2.5
Placebo (0/12)	-	-	-

Table 23: Time to and Duration of MTT Response Among MTT Responders in Study 514

	Median Time to Response (days)	Median Duration of Response (days)	Median # of Treatments to Response
Strata 1 & 2			
CDDP/epi gel (n = 14/57)	53	64	4.5
Placebo (n = 1/35)	56	54+	5
Stratum 1			
CDDP/epi gel (n = 10/31)	62	61	5.0
Placebo (n = 1/17)	56	54+	5
Stratum 2			
CDDP/epi gel (n = 4/26)	30	228	3.5

Placebo (0/18)	-	-	-
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Table 24: Time to MTT Progression in Study 414

	CDDp/epi gel arm			Placebo gel arm		
	n	Mean (days)	Range (days)	n	Mean (days)	Range (days)
Strata 1 & 2	62	58	6 to 216+	24	29	5 to 263+
Stratum 1	31	37	7 to 216+	12	24	5 to 212+
Stratum 2	31	61	6 to 154+	12	19	7 to 263+

Table 25: Time to MTT Progression in Study 514

	CDDp/epi gel arm			Placebo gel arm		
	n	Mean (days)	Range (days)	n	Mean (days)	Range (days)
Strata 1 & 2	57	128	5 to 564+	35	44	6 to 210+
Stratum 1	31	144	8 to 223	17	48	7 to 210+
Stratum 2	26	107	5 to 564+	18	34	6 to 170+

4. Summary and Conclusions

This NDA submission is to support administration of Cisplatin/epinephrine injectable gel (CDDP/epi gel) for the local treatment of recurrent or refractory squamous cell carcinoma of the head and neck in patients who are considered not curable with surgery or radiotherapy. In this NDA submission, two phase II, randomized, double-blind, multi-center, placebo controlled studies, Study MP 414-94-2 (US study) and Study MP-514-94-2 (Europe study), were conducted to evaluate the efficacy and safety of the treatment of CDDP/epi gel. The US Study 414 enrolled a total of 86 efficacy evaluable patients (62 in the CDDP/epi gel arm and 24 in the placebo gel arm) and the Europe Study 514 enrolled a total of 92 efficacy evaluable patients (57 in the CDDP/epi gel arm and 35 in the placebo gel arm). **The primary efficacy endpoint per Agency in both the studies has been patient benefit based on a pre-specified treatment goal.** However, objective MTT response was originally stated in the protocol as the primary efficacy endpoint, and therefore, in the final analyses both patient benefit and objective MTT response were considered as co-primary endpoints in these two studies. The understanding between the agency and sponsor was that the trials will demonstrate effect on both the primary variables (particularly demonstrate effect with respect clinical patient benefit), thus not requiring adjustment of type I error for multiplicity (I.C.H. E-9 Guidelines, section 2.2.5) (faxes sent by the Agency on (1) March 8, 2000 to sponsor in response to March 24, 2000 correspondence/request for feedback, and (2) April 28, 1998 reviewer comments on sponsor's submission of Sn 115, February 24, 1998). The sponsor claims a significant patient benefit favoring CDDP/epi gel treatment (p-value = 0.046), based on combining the results of the Studies 414 and 514, and that a one point change in the scale of measurement is clinically meaningful. There was no statistically significant difference between CDDP/epi gel and the placebo gel in either of the two studies (Study 414, p-value=0.18, and Study 514, p-value=0.24). The sponsor also claims significant objective MTT response in favor of the

proposed new drug, CDDP/epi gel in Study 414 (p-value = 0.001) and Study 514 (p-value = 0.007). Furthermore, the sponsor claims a significant association between the patient benefit and objective MTT response.

1. The sponsor was required to demonstrate significant effect in favor of CDDP/epi gel with respect to both the primary efficacy variables and demonstrate significant association between the two efficacy variables.
2. The co-primary efficacy endpoint, patient benefit, was the specified clinical efficacy parameter by the agency. There is **no statistically significant difference in patient benefit** in either of the two studies (Study 414, p-value=0.18, and Study 514, p-value=0.24). The sponsor pooled the two studies (414 and 514), and arrived at a smaller p-value (p = 0.046). However, **pooled analysis is not acceptable as the primary analysis**. A significant difference in the objective MTT response was demonstrated by the sponsor analysis. However, according to FDA Medical Reviewer's revised data, the significant difference is questionable.
3. The agency also required that significant correlation between objective tumor response and patient benefit should be established. There is **no statistically significant association between tumor response and patient benefit in the US Study 414** (p-value = 0.16), where as there appears to be nominally significant association in the Europe Study 514 (p-value = 0.018). The strength of this association is weak and is greatly influenced by the large number of patients classified both as non-responders and non-benefiters. **A preferred measure of association between patient benefit and tumor response is sensitivity, and this was < 50%** in each of the studies and in the combined study data. Furthermore, these results should be interpreted with caution, since **responder's characteristics may be different from non-responders**. Also, since there were far fewer patients studied in the placebo arm and most of the patients in the placebo arm did not receive more than 4 treatments (approximately 4 weeks of treatment), the placebo treated patients could not have had a complete evaluation of the benefit.
4. The primary efficacy endpoint, **patient benefit is retrospectively defined** as a decrease in symptom score by one point (I.C.H. E-9 Guidelines, sections 2.1.2 and 2.2.2). A change in symptom score by one point has not been prospectively validated to be clinically significant or meaningful. Furthermore, Palliative symptom benefit is assessed as equivalent to preventative benefit. The combination of these two measurements is questionable (I.C.H. E-9 Guidelines, section 2.2.3). There is no input by the patient towards preventative benefit score. The algorithm used by the sponsor to combine the palliative & preventative goals, and patient & investigator assessments, has not been prospectively validated. The questionnaire (Appendix I) used in these two studies has been used only in the sponsor studies.

5. Blinded comparison of patient benefit between the treatment arms is questionable because the pattern of treatment conformity in the blinded phase differs between the active treatment and the placebo arms. This could **potentially bias the benefit scores**, particularly preventive goal scores, as the criteria for assessing a patient as a benefitter included improvement in the score for a minimum of 4 weeks, and majority of the placebo arm patients did not receive assigned treatment beyond 4 weeks. Thus there is reason to believe that the comparison between the treatment arms with respect to patient benefit and particularly with respect to preventative benefit may not be a fair/adequate comparison. Furthermore, in the benefitters claimed by the sponsor in the US Study 414, 20/21 benefitters were based on investigator's assessment on preventative treatment goal as "met" and only 1/21 benefitters was assessed based on palliative treatment goal.
6. The sponsor's claim of significant difference in the objective MTT response in both the studies are mainly due to stratum 1 or in patients with MTT size $\leq 5 \text{ cm}^3$. Furthermore, per FDA medical reviewer evaluation majority of the sponsor claimed responses were not evaluable due to, for example, incorrect dosing. It is to be noted that although no significant differences in the MTT response rates between pre- and post- amendment of dosing schedule were observed (Study 414: 29% vs. 37%, p-value = 0.59, Study 514: 29% vs. 22%, p-value=0.75), **the direction of the response rate was reversed** in the Europe Study 514 compared to the US Study 414.

In these reviewers' opinion the study failed to demonstrate clinical patient benefit of cisplatin/epinephrine injectable gel versus placebo gel for patients with refractory squamous cell carcinoma of the head and neck in patients who are considered not curable with surgery or radiotherapy. It is also not evident from the results of the two randomized studies presented in this NDA that the objective tumor response translates into clinical benefit. Therefore, the evidence submitted in this application is not convincing and does not support approval.

Jasmine Choi, M.S.
Mathematical Statistician
Date:

Rajeshwari Sridhara, Ph.D.
Mathematical Statistician
Date:

Concur: Dr. Chen
Team Leader

Dr. Mahjoob
Deputy Division Director, DBI

Cc:
HFD-150/ Ms. Spillman
HFD-150/ Dr. Frykman
HFD-150/ Dr. Williams
HFD-710/ Dr. Sridhara
HFD-710/ Ms. Choi
HFD-710/ Dr. Chen
HFD-710/ Dr. Mahjoob
HFD-710/ Dr. Chi
HFD-700/ Dr. Anello
HFD-710/ Chron

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Appendix I

Treatment Goals

General Instructions

At the screening visit, each patient is to select one or more treatment goals from one of the eight palliative treatment goal categories: wound care, pain control, ability to see, ability to hear, ability to smell, physical appearance, obstructive symptoms, or mobility. The treatment goals should reflect the patient's desire to improve his/her physical or social functioning in a personally meaningful way as a direct result of treatment with cisplatin/epi gel.

Because the scales are designed to measure improvement, the patient should not select treatment goal categories in which he/she would place himself at the best end of the four-point measurement scale.

One to eight palliative treatment goals may be selected by the patient; the goals will be assessed at screening and the beginning of every treatment and follow up visit.

Some patients may be unable to identify any treatment goals. This would occur, for example, if the patient's self-assessment placed him at the best end of the scale in every goal category. A patient who is unable to select a treatment goal category will have the change in tumor volume of his/her treated tumors used in place of the treatment goal. The overall tumor response will also be measured on a four-point scale: complete response (100% reduction in tumor volume), partial response (50% or greater reduction in tumor volume), stable disease (less than 50% reduction or increase of less than 25% in tumor volume) and disease progression (25% or greater increase in tumor volume).

At the time the patient selects treatment goals, the physician should also select one or more treatment goals for that patient. A primary treatment goal must be identified by the physician for the patient's most troublesome goal. The patient and physician need not discuss their reasons for selecting treatment goals, and the patient and physician need not select the same goals.

The patient may select one or more treatment goals from eight palliative goals: wound care, pain control, ability to see, ability to hear, ability to smell, physical appearance, obstructive symptoms, or mobility (unless he/she is unable to select a treatment goal, as described above). The physician may select goals from the list of eight palliative goals and the list of three preventive goals: invasion, obstruction, and subcutaneous tumors breaking through the skin.

At each visit, the patient will assess his/her current status on the palliative treatment goals he/she selected at the first visit, rating his/her status on each goal on a four-point scale.

If the physician selected palliative goals for the patient, he/she will also rate the patient's status on each goal at each patient visit. Status on preventive goals will be rated by the physician on a two-point scale (prevented or failed to prevent). Preventive goals will be evaluated and rated only at screening, week 4 evaluation visit, end of follow-up (month 5), and study completion.

For patients who terminate the initial treatment stage after less than six treatments and who do not have a CR, preventive goal assessment should be done before administration of open-label drug.

1. Prevention Scales: Physician Assessment Only

1. Prevention of invasion of vital structure(s) and/or blood vessel(s).

Specify structures and/or vessels threatened by invasion:

1. At end of 4-week follow-up, tumor has not invaded vital organs or blood vessels. If patient terminates initial treatment prematurely, evaluate at last visit of initial treatment phase before administration of open-label drug.

2. At end of 4-week follow-up, tumor has invaded vital organs and/or blood vessels. If patient terminates initial treatment prematurely, evaluate at last -visit before administration of open-label drug.

Date of invasion: _____

2. Prevention of obstruction

Specify structures, areas, and/or processes threatened by obstruction:

1. At end of 4-week follow-up, tumor has not obstructed any structure, area, or process in a manner which interferes with the patient's functioning. If patient terminates initial treatment prematurely, evaluate at last visit before administration of open-label drug.

2. At end of 4-week follow-up, tumor has progressed to obstruct a structure, area, or process in a manner which interferes with the patient's functioning. If patient terminates initial treatment prematurely, evaluate at last visit before administration of open-label drug.

Date of obstruction: _____

3.Prevention of subcutaneous tumors breaking through the skin.

Specify location of at risk of breaking through the skin:

1. At end of 4-week follow-up, a subcutaneous tumor has not broken through the skin to create an ulceration, erosion, or hole. If patient terminates initial treatment prematurely, evaluate at last visit before administration of open-label drug.
2. At end of 4-week follow-up, a subcutaneous tumor has broken through the skin to create an ulceration, erosion, or hole. If patient terminates initial treatment prematurely, evaluate at last visit before administration of open-label drug.

Date tumor broke through skin: _____

II. Palliation Scales: May be Selected by Patient or Physician

I . Wound Care

Instructions to patient:

Please choose the statement below which best describes your cancer sore (or sores) over the past week [SUBSTITUTE: "since your last visit" for subsequent visits].

Please choose a response based only on the sore or sores injected with medicine as part of this study.

If some of your treated sores are worse than others, choose statement which describes the worst treated sore.

1. I do not have an open sore that oozes, bleeds, or smells bad.
2. I have an open sore that has little or no smell and does not need a bandage.
3. I have an open sore that needs a bandage and/or has a bad smell, but the smell does not stop me from being around other people, or make me feel sick to my stomach.
4. I have an open sore that needs frequent changes of bandage or packing; OR has a strong/bad smell that stops me from being around other people; OR causes me to feel sick to my stomach or to vomit.

2. Pain Control

Instructions to patient:

Please choose the statement below which best describes the pain you have felt over the past week [SUBSTITUTE: "since your last study visit" for subsequent visits].

Please answer based on only on the tumor or tumors injected with medicine as part of this study. Choose the statement that describes the pain caused by your tumor(s).

Do not include pain caused by the injection of medicine into your tumor(s), either at the time of the injection or later.

If some of your treated tumors are causing more pain than others, choose a statement that describes the treated tumor giving you the most pain.

1. I have no pain, or I have minor pain that does not require medicine.
2. I have pain that goes away when I take medicine that I can buy in the drugstore without a doctor's prescription.
3. I have pain that only goes away when I take medicine prescribed by a doctor.
4. I have pain that does not go away even when I take medicine prescribed by a doctor.

3. Ability to See

Instructions to patient:

Please choose the statement below which best describes your sight over the past week [SUBSTITUTE: "since your last study visit" for subsequent visits], compared to before your illness.

These statements are about problems you may have with your sight that are caused by one or more of the tumors being treated in this study.

Please choose the statement that most closely describes the problems with your sight caused by the treated tumor(s).

1. I can see just as well as I could before my illness.
2. I cannot see as well as I could before my illness, but I am able to do things like watch TV and read.
3. I cannot see as well as I could before my illness, and this makes it hard for me to read and watch TV.
4. I cannot see.

4. Ability to Hear

Instructions to patient:

Please choose the statement below which best describes your hearing over the past week [SUBSTITUTE: "since your last study visit" for subsequent visits], compared to before your illness.

These statements are about problems you may have with your hearing that are caused by one or more of the tumors being treated in this study.

Please choose the statement that most closely describes the problems with your hearing caused by the treated tumor(s).

1. I can hear just as well as I could before my illness.
2. I cannot hear as well as I could before my illness, but I am able to do things like watch TV, listen to the radio, and talk with people.
3. I cannot hear as well as I could before my illness, and this makes it hard for me to watch TV, listen to the radio, and talk with people.
4. I cannot hear.

5. Ability to Smell

Instructions to patient:

Please choose the statement below which best describes your sense of smell over the past week [SUBSTITUTE: "since your last study visit" for subsequent visits], compared to before your illness.

These statements are about problems you may have with your sense of smell that are caused by one or more of the tumors being treated in this study.

Please choose the statement that most closely describes the problems with your sense of smell caused by the treated tumor(s).

1. I can smell just as well as I could before my illness.
2. I cannot smell as well as I could before my illness, but it does not effect my enjoyment of food or things around me.
3. I cannot smell as well as I could before my illness, and I do not enjoy my food or things around me as much as I used to.
4. I cannot smell.

6. Physical Appearance

Instructions to patient:

Please choose the statement below which best describes how you have been feeling about the way you look over the last week [SUBSTITUTE: "since your last study visit" for subsequent visits].

Please choose your answer based only on things about the way you look that might be changed by injections with study medicine.

If you think that some things about the way you look are getting worse due to the injections but some are getting better, try to choose a sentence that best describes your overall feeling about the way you look.

1. My illness has not changed the way I look much.
2. I have some scars from my illness, but no one can tell that I am ill.
3. People can tell by looking at me that I am ill, but this does not stop me from going out and meeting people.
4. I don't like to go out in public because of the effect my illness has had on the way I look.

7. Obstructive Symptoms

Instructions to patient:

Please choose the statement below which best describes your symptom or symptoms over the last week [SUBSTITUTE: "since your last study visit" for subsequent visits].

Please choose your answer based on only symptoms you feel are caused by tumors injected with medicine as part of this study.

The answer may be about only one symptom (difficulty swallowing, for example). It may be about more than one (difficulty swallowing and also difficulty breathing, for example).

If you have more than one symptom and one is worse than the other, pick the sentence that describes the worst symptom.

1. My illness does not interfere with my ability to talk, breath, or eat.

2. Because of my illness, I have minor trouble with talking, breathing, or eating. For example, I can't eat everything I like because I have trouble swallowing.
3. Because of my illness, I have a lot of trouble talking, breathing, or eating. For example, I can eat only soft foods or liquids because I have trouble swallowing.
4. Because of my illness, I can't talk, or I need a tube to breath, or I am fed through a tube.

8. Mobility

Instructions to patient

Please choose the statement below which best describes your ability to move around and use all parts of your body (arms, legs, neck, trunk, etc.) over the past week [SUBSTITUTE: "since your last visit" for subsequent visits].

These statements are about problems with movement that are caused by one or more of the tumors being treated in this study.

Please choose the statement that most clearly describes the problem with moving around caused by the treated tumor(s).

1. I am able to move around as well as I could before my illness.
2. Because of my illness, I have some problems with moving around, but I can still carry out most of my normal everyday activities.
3. Because of my illness, I have problems with moving around that greatly affect my normal everyday activities. (Examples: I can no longer move around well enough to drive a car; I can no longer move around enough to fix a meal for myself.)
4. Because of my illness, I can no longer move around at all, or I can only move around a very little. There are almost no normal everyday activities I can carry out by myself.

What part of your body do you have problems moving?_____

Appendix II Treatment Plan

BLINDED PERIOD		OPEN-LABEL PERIOD	
<i>Treatment Phase</i>		<i>Follow-up Phase</i>	
<i>6 to 8 weeks</i>	<i>4 weeks</i>	<i>Up to 5 months</i>	
		<i>Extended Follow-up Phase</i>	
<ul style="list-style-type: none"> • Treat MTT and other selected tumors with CDDP/epi or placebo gel* for 6 weekly treatments or until 100% reduction of total treated tumor volume, whichever occurs first. • Assess disease progression. • Complete responders (100% reduction of total tumor volume) may enter Follow-up • Patients with a partial response, stable disease, or disease progression may enter Extended Follow-up to receive open label CDDP/epi gel 	<ul style="list-style-type: none"> • Evaluate response (once each week) 	<ul style="list-style-type: none"> • Follow duration of response (monthly) • Patients who maintained a complete response could enter Extended Follow-up for continued follow-up • Patients with disease progression could enter Extended Follow-up for retreatment 	<ul style="list-style-type: none"> • Follow duration of response (monthly) for responders • Retreat new, progressive, and recurrent tumors with open-label CDDP/epi gel * • Receive treatment with other cancer therapy†

* New tumors that developed during the Treatment Phase could also be treated, provided that the total assigned patient dose did not exceed 10 mL CDDP/epi or placebo gel

† Other cancer therapy was not to be administered concomitantly with CDDP/epi gel unless approved by Matrix.