Appendix 1: Treatment Goal Questionnaire and Patient Benefit

1 Introduction

The Treatment Goals Questionnaire© (TGQ) was developed by Matrix Pharmaceutical, Inc. to assess improvements in patient function, amelioration of symptoms, and the prevention of undesirable outcomes frequently observed with uncontrolled local disease. Development of the TGQ was suggested by the FDA at an end-of-stage-II meeting in December 1994. The purpose of the TGQ was to assess the benefits directly attributable to control of local disease. The TGQ was developed over the next several months as a collaborative effort of Matrix Pharmaceutical, experts in oncology and quality-of-life assessment, and the FDA. The TGQ has been independently validated by the Center for Outcomes Research (COR), Chapel Hill, NC.

Patient Benefit was assessed using an algorithm developed in conjunction with FDA to allow a single assessment of whether benefit was achieved by each patient. The Patient Benefit Algorithm combines the outcome of both the patient's and investigator's primary treatment goal to classify patient as "benefiter" or "non-benefiter".

2 Content of the Treatment Goals Questionnaire

The TGQ consisted of eight palliative and three preventive goals. Investigators were required to select at least one attainable goal for each patient before beginning treatment; while multiple goals could be selected, one had to be designated as the investigator's primary treatment goal. Patients were strongly encouraged to also select one or more attainable goals and to designate one goal as primary if more than one goal was chosen. Both the patient and the investigator were instructed to select goals that were related to the Most Troublesome Tumor (MTT), such that successful treatment of the MTT could be reasonably expected to result in goal attainment.

Patients and investigators were not required, or even encouraged, to select the same goals. Progress towards the selected goals was evaluated by investigators and patients at regular intervals throughout the studies. Palliative goals could be chosen either by the patient or by the investigator. Preventive goals could only be selected by the investigator.

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Primary Treatment Goal	Patient	Investigator
Palliative		
Pain control	X	X
Wound care	X	X
Obstructive symptom	X	X
Physical appearance	X	X
Ability to see	X	X
Ability to smell	X	X
Ability to hear	X	X
Mobility	X	X
Preventive [a]		
Prevention of tumors breaking skin		X
Prevention of invasion (of vital structure and/or blood vessel)		X
Prevention of obstruction		X

[a] Only investigators were allowed to choose preventive goals.

2.1 Palliative Goals

Palliative goals were graded on a four-point scale, with worse conditions indicated by higher numbers. The following four palliative goals were those selected most often by the patient and investigator. Presented with each goal are the descriptive categories that represented a patient's current condition.

Pain control

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

Wound care

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

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Obstructive symptom

1. Patient's illness does not interfere with ability to talk, breath, or eat
2. Because of the illness, the patient has minor trouble talking, breathing, or eating. For example, the patient can't eat everything he/she likes because of trouble swallowing.
3. Because of the illness, the patient has a lot of trouble talking, breathing, or eating. For example, the patient can eat only soft foods or liquids because he/she has trouble swallowing.
4. Because of the illness, the patient can't talk, or the patient needs a tube to breath, or the patient must be fed through a tube.

Physical appearance

1. The illness has not changed the patient's appearance much.
2. Patient has some scars from the illness, but no one can tell that he/she is ill.
3. People can tell by looking at the patient that he/she is ill, but this does not stop the patient from going out and meeting people.
4. Patient doesn't like to go out in public because of the effect illness has had on the way the patient looks.

A palliative goal was considered to be "attained" (or "met") if there was improvement of at least one scale point, sustained for 28 days or more. A palliative goal was considered to be "worse" if the score increased by one scale point or more at two or more consecutive study visits. Goals were otherwise categorized as "Same". An observation period of 28 days or more was required to categorize a palliative goal as "attained" or "same"; if a patient was observed for less than 28 days and the goal score did not meet the criteria for "worse", the goal was considered to be "not evaluable". Patients with palliative goal outcomes of "worsened", "same", and "not evaluable" were combined into the general category "goal not met". Patient progress in achievement of palliative treatment goals was evaluated weekly.

Better	Improvement (decrease) in score by one or more scale points for a period of at least 28 days.
Worse	Worsening (increase) in score by one or more scale point at two or more consecutive study visits.
Same	Neither of the above. Note that "same" does not mean that there was no change from baseline, rather it indicates that there was neither a sustained improvement nor sustained worsening. It can indicate that the patient was observed for less than 28 days and hence goal attainment could not be adequately evaluated.
Not evaluable	Post-baseline scores not available

2.2 Preventive Goals

Preventive goals could only be selected by the investigator. Preventive goals were assessed at five time points during the study:

- Screening visit
- First visit in the 4-week evaluation period after completing the blinded treatment
- Last visit in the 4-week evaluation period
- End of Follow-Up Phase
- End of Extended Follow-Up Phase

Assessment of the preventive goals consisted of determining whether the undesirable outcome had been prevented. If the goal was not prevented, the date of failure was recorded. A goal that was not met was not assessed further and remained unmet for the duration of the study for that patient.

Preventive goals were defined as "attained" (or "met") if the undesirable outcome was prevented for at least 28 days from first treatment with study drug. Patients who were observed for less than 28 days, and whose goal did not fail, were classed as "not evaluable". The preventive goal was considered to have failed if the undesirable outcome occurred in the first 28 days of treatment. Patients with preventive goal outcomes of "failed" and "not evaluable" were combined into the category "goal not met".

Met	Prevention sustained for at least 28 days.
Not Met	Prevention failed in less than 28 days.
Same	The patient was observed for less than 28 days and hence goal attainment could not be adequately evaluated
Not evaluable	Post-baseline scores not available

8 Primary Treatment Goals

Selection of primary treatment goals by patient and investigator are tabulated in Table A1-1. When investigators chose a palliative primary treatment goal, the patient selected the same primary treatment goal in 74% of cases (75% for the CDDP/epi gel group and 72% for the placebo gel group). For both investigator- and patient-selected primary treatment goals, the distribution across treatment groups and strata (similar percentages of chosen goals) was balanced.

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Table A1-1: Distribution of Primary Treatment Goals Selected

Primary Treatment Goal	Patient		Investigator	
Palliative	n	%	n	%
Pain control	60	34%	40	22%
Wound care	35	20%	36	20%
Obstructive symptom	39	22%	29	16%
No goal selected [a]	26	15%	0	0%
Physical appearance	12	7%	6	3%
Ability to see	2	1%	2	1%
Ability to smell	1	1%	0	0%
Ability to hear	1	1%	0	0%
Mobility	2	1%	0	0%
Preventive [b]				
Prevention of tumors breaking the skin			33	19%
Prevention of invasion (of vital structure and/or blood vessel)			20	11%
Prevention of obstruction			12	7%

[a] Patients were not required to select a Primary Treatment Goal.
[b] Only investigators were allowed to choose preventive goals.

3 Analysis of the Treatment Goal Questionnaire

Results of the TGQ were used to compare patients treated with CDDP/epi gel in the blinded phase of the studies to patients treated with placebo. The proportion of patients with a "met" investigator primary goal was compared in the CDDP/epi gel and placebo groups. Goal attainment rates were also compared for each specific goal (whether primary or secondary) for all patients for whom the investigator had selected that goal. Patient-selected goals were analyzed in the same way. It was expected that if CDDP/epi gel provided clinical benefit other than tumor response, the rates of attainment of investigator-selected and patient-selected goals would be higher in patients treated with CDDP/epi gel than in patients treated with placebo. This was indeed the case in both studies.

4 Validation of the Treatment Goals Questionnaire

An investigation of the content validity, internal validity, inter-observer reliability, test-retest reliability, and performance characteristics of the TGQ was carried out by the Center for Outcomes Research (COR), Chapel Hill, NC. The TGQ was found to be valid and reliable. Physicians experienced with the TGQ from participation in the HNSCC clinical trials and patients with HNSCC who had not enrolled in the clinical studies were included in the validation study. A particularly important finding

of the validation process was that both patients with HNSCC and physicians who treat HNSCC agreed that the 4-point scale used to score the palliative goals did indeed represent different levels of functioning, and that a change of one scale point was important and meaningful. Also, both the patients and physicians interviewed in the validation process agreed that all the goals used in the TGQ were important to at least some HNSCC patients.

5 The Patient Benefit Algorithm

The Patient Benefit Algorithm was developed in 1998 following discussions with the FDA regarding the number of quality-of-life and clinical-benefit outcomes, including the TGQ and FACT-H&N, that were specified in the study protocols. The FDA requested that Matrix Pharmaceutical submit a plan to distill some or all of these outcomes into a single quality-of-life endpoint. With input and assistance from the FDA, the Patient Benefit Algorithm was developed to combine the outcomes of the patient's and investigator's primary treatment goals to classify patients into one of two categories, "benefiter" or "non-benefiter". The attribution of Patient Benefit was based only on the patient's and investigator's primary treatment goal in the TGQ. The classification mechanism is shown in the schema below:

Note that the Patient Benefit Algorithm allows a patient to be classified as a benefiter only if the patient's and/or investigator's primary treatment goal is met, and neither primary goal worsens (if palliative) or fails (if preventive).

Patient Benefit Algorithm

Primary Treatment Goal		Patient Benefit	Comment
Investigator	Patient		
↑	↑	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 (met).

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

↓ Failure to achieve Primary Treatment Goal (not met).

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6 Analysis of Patient Benefit

The proportion of patients attaining benefit in the blinded treatment phase was compared for patients treated with CDDP/epi gel and placebo gel. Results in both studies were consistent with the hypothesis that patient benefit was more likely to be achieved in patients treated with CDDP/epi gel. The two individual studies did not reach statistical significance, but both trended strongly in the same direction with twice the rate of benefit in the CDDP/epi gel arm versus the placebo gel arm. When the studies were combined, the relationship between treatment and benefit was statistically significant ($p=0.047$, CMH test). In the combined studies and in study 514, the attainment of patient benefit was also significantly associated with MTT response, providing support for the hypothesis that control of local disease resulted in a clinical benefit.

7 Use of the TGQ and Patient Benefit Algorithm in Supportive Studies

The TGQ and Patient Benefit Algorithm have also been used in two open-label Phase II trials of CDDP/epi gel in patients with cancer other than HNSCC. In these studies, meaningful benefit rates (in the range of 21% to 39%, depending on the type of cancer treated) were observed, and benefit attainment was statistically associated with response of the MTT.