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PROTOCOL CLN-001 Amendment 5

Phase 2, Open-Label, Single-Arm Safety, Tolerability, Anti-Tumor Effects, Systemic Exposure, and Device Technical Effects of PRV111 (Cisplatin Transmucosal System) in Subjects with Oral Squamous Cell Carcinoma

STATISTICAL ANALYSIS PLAN

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CONFIDENTIAL

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE(s)	Adverse Event(s)/Adverse Experience(s)
ANCOVA	Analysis of Covariance
BUN	Blood urea nitrogen
CBC	Complete Blood Count
CFB(s)	Change(s) from Baseline
CFR	Code of Federal Regulations
CLP	Cisplatin-Loaded [redacted] Particles
CR	Complete response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG PS	Eastern Collaborative Oncology Group Performance Status
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
LFT	Liver function test
LOCF	Last Observation Carried Forward
NRI	Non-responder Imputation
ORR	Objective Response Rate (Tumor volume change from baseline assessment of CR or PR)
PCFB	Percent change from baseline
PD	Progressive disease
PE	Permeation enhancer
PI	Principal Investigator
PK	Pharmacokinetics
PR	Partial response
PRV111	Cisplatin Transmucosal System
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SCC	Squamous cell carcinoma
SD	Stable disease/ Standard deviation for statistical summaries
SOC	Standard of care / MedDRA System Organ Class for AE assessment
TEAE	Treatment Emergent Adverse Events
VAS	Visual analog scale

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1 Introduction

This Statistical Analysis Plan (SAP) is based on study procedures and analyses described in the protocol (Amendment 5 dated 25 MAR 2020). Table shells and mock listings corresponding to the contents of this document will be included with the final version.

1.1 Background

Squamous cell carcinomas (SCC) of the head and neck include tumors that occur in the oral cavity. Most lip and oral cavity cancers originate in squamous cells, the thin flat cells that line the lips and oral cavity. Risk factors for oral cancer include chronic heavy use of alcohol and tobacco, long periods of exposure to natural or artificial sunlight, and exposure to human papillomavirus. The 5-year survival rate for oral cancer is approximately 60%; diagnosis at an early stage significantly increases the 5-year survival rate. Oral cancer has a high rate of recurrence (18%–76% for subjects who undergo standard treatment). Approximately 1/3 of subjects treated with surgery and adjuvant therapy will experience local or regional recurrence and/or distant metastasis.

The most common chemotherapy drugs for advanced oral cancer includes cisplatin, methotrexate, carboplatin, 5-fluorouracil, paclitaxel, and docetaxel, which when administered alone or in combination have been shown to provide clinical benefit with demonstrated improvement in overall survival.

PRV111 (Cisplatin Transmucosal System) is a thin, 2-layer, self-adhesive transmucosal patch embedded with cisplatin and a non-woven fabric adhesive backing. In addition to the PRV111 drug product, a separately packaged Permeation Enhancer Powder for Reconstitution is used in conjunction with the PRV111 drug product. The reconstituted Permeation Enhancer Solution is applied prior to the administration of PRV111 to improve the absorption of the cisplatin active ingredient.

Privo's PRV111 is intended as a local induction chemotherapy, to improve the local control of the disease prior to surgery by shrinking the tumor size. Local cisplatin delivery may result in larger and more effective doses of cisplatin delivered to the tumor while significantly reducing or eliminating the systemic toxicities and side effects traditionally associated with intravenous (IV) cisplatin chemotherapy. Treatment with cisplatin which is targeted to the tumor site and not administered systemically may reduce the dose-limiting systemic toxicities that are observed with IV cisplatin administration. If proven safe and effective for the treatment of SCC of the oral cavity, PRV111, in association with the standard care, may decrease the risk of local tumor recurrence.

2 Trial Design

2.1 Study Objectives

Primary Objectives

- Determine a safe and efficacious dose of PRV111 (Cisplatin Transmucosal System) (cisplatin drug-loaded patch + permeation enhancer [PE]) under the conditions of the trial.

Secondary Objectives

- Evaluate tumor volume shrinkage
- Assess long-term safety of the treatment
- Evaluate device technical success including the residual cisplatin level in the patch after the application period
- Evaluate systemic, tumor and lymph node (if available) platinum levels following administration

2.2 Study Design

This is a two-stage adaptive design. The First stage with 6 patients focuses on determining a safe dose, while stage 2 expands the study at the previously determined dose. See the Protocol section on synopsis.

Methodology: This is a Phase 1/2, open-label, prospective, single-arm study of the safety and efficacy dose-finding, systemic exposure, and device technical success of PRV111 (Cisplatin Transmucosal System) (cisplatin drug-loaded patch+PE) in subjects with oral squamous cell carcinoma (SCC) amenable to surgery.

Study Design: This is a 2-stage adaptive study. For Stage 1, up to 10 subjects will be enrolled for the purpose of 5 evaluable subjects for the 1st stage of the study to determine a safe and efficacious dose. For Stage 2, the target goal is up to 11 evaluable subjects for the efficacy analysis of the final dose. If the dose remains the same as Stage 1, Stage 2 will target 6 additional evaluable subjects but up to 21 subjects will be recruited if the dose is changed between Stage 1 and 2.

For the purpose of dose selection, tolerable dose is defined as a dose where fewer than 33% of subjects being evaluated within the safety population present with dose-limiting toxicities (DLTs). Effective dose is determined based on the evaluable population as described in the Statistical Methods section.

The 2 stages of the study are described below:

Stage 1: Up to 10 subjects will be enrolled for the purpose of 5 evaluable subjects and undergo 3 treatment applications at each of the 4 planned treatment visits. Each treatment visit will include 1 application of the PE. Starting approximately 5 minutes after application

of the PE, 1 or 2 patches (depending on tumor size) will be applied. A total of 3 treatment applications of patches will occur. These successive applications will span approximately 35 minutes. The 3 applications provide a total of 6 mg of cisplatin per visit (12 mg if 2 patches are applied at the same time). The 4 treatment visits will be separated by 2 to 4 days (at least 48 hours).

The following decisions will be made based on safety and efficacy of the dose:

Dosing Rules for Stage 1:

1) If fewer than 2 subjects experience DLTs, then the following scheme will be considered for stage 2 dosing:
   a. If fewer than or equal to 2 of the evaluable subjects have a response (Defined in the efficacy table) the dose will be escalated from 3 to 5 treatment applications per treatment visit for Stage 2.
   b. If 3 or more evaluable subjects have a response (CR or PR), the dose will remain the same for Stage 2 (3 applications per treatment visit).
2) If 2 or more subjects experience DLTs at any time during Stage 1, the following scheme will be considered for dose de-escalation in Stage 2:
   a. If there are 6 evaluable subjects in Stage 1:
      - If out of 6 evaluable subjects, 2 or more subjects have a response (CR or PR), the dose will be de-escalated to 2 applications per treatment visit.
      - If out of 6 evaluable subjects, fewer than 2 have a response (CR or PR), the dose will be considered intolerable and the study will be stopped.
   b. If Stage 1 dosing was stopped prior to having 6 evaluable subjects, the dose will be de-escalated from 3 applications to 2 applications per treatment visit.

Stage 2: In case of dose escalation or de-escalation, Stage 2 will be conducted in 2 parts: Stage 2a and Stage 2b.

Subjects will receive 2, 3, or 5 treatment applications at each of the 4 planned treatment visits, depending on the results of Stage 1. Up to 21 additional subjects will be enrolled in Stage 2 if necessary, for the purpose of 16 total evaluable subjects at the final dose for the efficacy analysis.

Stage 2a: This stage will include 6 subjects (Stage 2a flowcharts). In this stage, only safety outcomes will be considered for determining the dosing regimen for the set of subjects to be enrolled in Stage 2b. All subjects enrolled in this stage will be monitored for possible DLTs.

1) If fewer than 2 subjects with DLTs in Stage 2a, enrollment will continue for the remaining number of subjects required in Stage 2b at the same dose.
2) If 2 subjects experience DLTs in Stage 2a, dosing will be re-considered. It may be stopped or, when possible, decreased for the remaining subjects enrolled in Stage 2b:
   a. If "Stage 2a - Escalated Dose", the original dose will be used for up to 10 additional evaluable subjects enrolled for Stage 2b.
   b. If "Stage 2a - Same Dose", dosing will be stopped. Additional subjects, for up to 10 evaluable subjects, will be enrolled for Stage 2b at a lower dose, consisting of 2 applications per treatment visit.

c. If "Stage 2a – De-escalated Dose", the study will stop, as no safe dose could be determined.

2.3 Sample Size

[redacted]

2.4 Selection and Withdrawal of Subjects

2.4.1 Inclusion Criteria

Subjects must meet the following inclusion criteria:

1. Adult subjects, men and women, defined by age ≥18 years at the time of screening.
2. Pathologically proven and clinically confirmed T1 (<2 cm) or T2 (>2 cm but ≤4 cm) SCC of the lip or oral cavity (anterior 2/3 of the tongue, floor of mouth, lower and upper gingiva, salivary gland, hard palate, and buccal mucosa).
3. Tumor must be easily accessible, with no evidence of infection or active bleeding, encroaching major vessels or clinical evidence of neural invasion. Tumors should not have been previously irradiated.
4. Tumor must be amenable to surgical resection no later than 42 days post Visit 1.
5. Clinically and/or radiologically measurable tumor.
6. Eastern Collaborative Oncology Group Performance Status of ≤2.
7. Adequate renal function as demonstrated by renal creatinine clearance ≥50 mL/min (calculated using the Cockcroft-Gault formula).
8. Adequate organ function defined as: ANC ≥1000/µL, platelet ≥100,000/µL; hemoglobin ≥9.0 g/dL; AST and ALT ≤2.5 times the upper limit of normal (ULN), serum bilirubin ≤1.5 times the ULN or direct bilirubin ≤ULN for subjects with total bilirubin >1.5 times the ULN.
9. Candidates for standard of care treatment consisting of surgery.
10. Male and female subjects of childbearing potential must agree to use 2 methods of effective contraception from screening and for at least 30 days after the final dose of investigational product. Appropriate birth control is defined as barrier methods with spermicides, oral or parenteral contraceptives and/or intrauterine devices, or naturally or surgically sterile (with documentation in the subject's medical records). Postmenopausal women are defined as presenting at least 12 months' natural spontaneous amenorrhea, or at least 6 weeks following surgical menopause (bilateral oophorectomy). Females of childbearing potential must be non-lactating and have a negative serum hCG within 14 days of treatment initiation.
11. Absence of any serious underlying medical conditions which could impair the ability of the subject to participate in the study.

12. Have a life expectancy of ≥3 months.
13. Willing and able to provide written informed consent.
14. Able to return to study site for treatment and follow-up visits as defined in the Protocol.

2.4.2 Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

1. Known distant metastasis of the SCC of the oral cavity
2. Prior radiation and/or systemic chemotherapy for the treatment of SCC of the head and neck less than 2 years prior to screening
3. Concurrent malignancy, with the exception of localized squamous cell carcinomas of the skin
4. Exposure to any investigational agent within 3 months prior to screening
5. Known allergy or hypersensitivity to platinum-containing agents, or known intolerance to a prior platinum-containing agent, or to any of the excipients, which, in the judgement of the physician will preclude re-exposure to platinum-containing agent
6. Active, uncontrolled infection requiring systemic therapy, such as but not limited to HIV, Hepatitis B or C
7. Uncontrolled intercurrent illness that would risk subject safety, interfere with the objectives of the protocol, or limit subject compliance with study requirements, as determined by the Investigator
8. Known or suspected pregnancy, planned pregnancy, or lactation
9. Any medical or psychiatric condition that may compromise the ability to give written informed consent

2.5 Criteria for Individual Subject Discontinuation of Protocol Therapy

Subjects should be discontinued from protocol therapy, while follow-up as per protocol, for the following reasons:

- Completion of the scheduled PRV111 therapy
- Meets 1 of the stopping rules for an individual subject
- Pregnancy
- Noncompliance with trial or follow-up procedures
- Withdrawal at the Investigator's request for any reason that the Investigator believes continuation of study drug therapy would not be in the subject's best interest
- Subjects may be withdrawn at any time for drug intolerability, disease progression, availability of other therapeutic options, or subject judgment

2.6 Criteria for Individual Subject Discontinuation from the Trial

Subjects may withdraw from further participation in the study at any time and for any reason without prejudice. The degree to which a subject withdraws can vary and efforts will be made to collect important safety data if feasible and the subject agrees. A subject will be considered to be withdrawn from the trial for the following reasons:

- Withdrawn consent from all treatment and follow-up

- Death
- Lost to follow-up
- Termination of the trial by the Sponsor

2.7 Handling of Subject Withdrawals or Subject Discontinuation of Study Intervention

If a subject withdraws consent for the treatment, the Investigator will make every effort to complete all final evaluations and procedures required by the Protocol. The subject will be asked to return to the clinic for a follow-up visit to assess overall safety prior to study completion. In the event a subject withdraws for safety reasons (adverse event/serious adverse event [AE/SAE], National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events [CTCAE] toxicity related events, etc.), every effort will be made to continue to follow-up with the subject until the documented condition resolves to protocol-established grades.
The reasons for discontinuation of dosing must be clearly documented on the case report form (CRF).

2.8 Replacement of subjects

Subjects will not be replaced.

2.9 Treatments Administered

a. Description of Test Product

PRV111 (Cisplatin Transmucosal System) (referred to as PRV111) consists of:

- PRV111 4 cm^2 patch containing 2 mg of cisplatin (0.5 mg/cm^2) backed with a pressure sensitive acrylic adhesive non-woven fabric backing.
- PE Powder for Reconstitution [redacted]

b. Dosing and Administration

Each treatment visit will include 1 mL application of the PE. Starting 5 minutes after application of the PE, 1 or 2 patches (depending on tumor size) will be applied. For Stage 1, a total of 3 treatment applications of patches will occur. These successive applications will span approximately 35 minutes. The 3 applications provide a total of 6 mg of cisplatin per visit (12 mg if 2 patches are applied at the same time).

In Stage 2 (Stage 2a and Stage 2b), subjects will receive 2, 3, or 5 treatment applications at each of the 4 planned treatment visits, depending on the results of Stage 1.
Refer to the Pharmacy Manual for detailed instructions on applying the PRV111 patches.
Table 1 presents definition used for dosing and treatment in this study. Treatment is expected to be approximately 35 minutes for each treatment visit.

Table 1. Dosing Terminology

Term	Definition
Treatment visit	Two to 6 days apart, during which PRV111 patches will be administered.
Treatment application	Three patch applications will occur during each treatment visit in Stage 1. Two, 3, or 5 patch applications will occur during each treatment visit in Stage 2.

2.10 Dose-limiting Toxicity (Stopping Rules for an Individual Subject)

Toxicity will be graded and recorded according to the NCI CTCAE version 4.03 (US Department of Health and Human Services, 2010), which are considered at least possibly related to PRV111 Patch. A DLT is defined as a clinically significant Treatment-Emergent AE (TEAE) or laboratory abnormality unrelated to disease progression, concurrent illness, or concomitant therapy and that meets any of the following criteria:

- Grade 3 or 4 non-hematologic toxicity excluding alopecia
- Grade 3 or 4 nausea, vomiting, or diarrhea, lasting >48 hours, despite standard prophylaxis and/or treatment
- Grade 4 neutropenia lasting >5 days.
- Febrile neutropenia, defined as absolute neutrophil count <1000/mm^3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour.
- Grade 4 thrombocytopenia or thrombocytopenia with clinically significant bleeding (ie, bleeding that requires blood or platelet transfusion or other medical intervention, or that may cause disability or death, such as cerebral hemorrhage).
- Any grade 3 or 4 toxicity related to the study drug that precludes administration of at least 3 of the 4 planned applications.
- Grade 4 local toxicity- oral mucositis according to World Health Organization scale:
  - Grade 0 - No oral mucositis
  - Grade 1 - Erythema and soreness
  - Grade 2 - Ulcer, able to eat solids
  - Grade 3 - Ulcers, requires liquid diet (due to mucositis)
  - Grade 4 - Ulcers, alimentation not possible (due to mucositis)
- Any treatment related AE leading to surgery delay for more than 96 hours is a DLT

2.11 Schedule of Events

Table 2. Schedule of Events

	Screening Within 28 Days Prior to Visit 1	**Days**						**Months Post Surgery**
		Treatment Visits				**Post Treatment Pre-Op**	**Surgery**	**Standard of Care (SOC) Follow-up**
		Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visits 7, 8, 9**
	0	**1**	**≥48 and ≤ 144 hours, post previous visit**			**≥72 hours post last treatment**	**≤42 days post Visit 1**	**1, 3, & 6 months (all can be +/-3 weeks) SOC visits**
Confirmed SCC	X							
Informed consent	X							
Inclusion/exclusion criteria	X	X[a]						
Schedule study visits	X	X	X	X	X	X		
Demographic, medical/history	X							
Physical examination,[b,s] VS[c]	X	X[a]	X[a]	X[a]	X[a]	X		X
Anti-emetics		X[a]	X[a]	X[a]	X[a]			
[redacted]	X							
Oral cavity examination[d]	X	X[a]	X[a]	X[a]	X[a]	X		X
Neck lymph nodes exam	X	X[a]	X[a]	X[a]	X[a]	X		X
ECG [s]	X					X		
[redacted]	X					X		
Clinical labs[f]	X	X[a]		X[a]		X	X[o]	
HPV [s]	X[g]							
Pregnancy test	X[h]	X[a]			X			
PK sampling		X[i]	X[j]	X[j]	X[i]			
Tumor resection							X[k]	

	Screening Within 28 Days Prior to Visit 1	Days					Surgery	Months Post Surgery
		Treatment Visits				Post Treatment Pre-Op		Standard of Care (SOC) Follow-up
		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visits 7, 8, 9
	0	1	≥48 and ≤ 144 hours, post previous visit			≥72 hours post last treatment	≤42 days post Visit 1	1, 3, & 6 months (all can be +/-3 weeks) SOC visits
PRV111 patch treatment		X[p]	X[p]	X[p]	X[p]			
Tumor measurements[q]		X[a]	X[a]	X[a]	X[a]	X		
Tumor Volume change from baseline (CFB) criteria			X[a]	X[a]	X[a]	X		
Tumor photographs		X[l]	X[l]	X[l]	X[l]	X		
Loco-regional recurrence								X
Histology[s]	X[m]						X[m]	
Technical success[n]		X	X	X	X			
Concomitant therapy	X	X	X	X	X	X		X
AE assessment	X	X	X	X	X	X[r]		

Abbreviations: AE=adverse event; [redacted]; ECG=electrocardiogram; HPV=human papilloma virus; [redacted]; PE=permeation enhancer; PK=pharmacokinetics; SCC=squamous cell carcinoma; VS=vital signs.

a Performed prior to dosing.

b If a physical exam was performed within 14 days prior to the screening visit, it does not need to be repeated at the screening.

c VS: seated blood pressure and pulse will be measured after the subject has been sitting for at least 3 minutes, respiration, temperature, height and weight will be recorded at every visit. VS will be obtained pre-dose at all visits and subject will also be monitored at 30+5 minutes, 60+5 minutes and 120+5 minutes following application of the last patch applied at Visits 1 and 4 and at 30+5 minutes post last patch application at Visits 2 and 3.

d Take photos of the tumor region for further assessment of tumor shrinkage.

e Every attempt should be made to use the same test for each subject for both timepoints.

f CBC and chemistry panel (creatinine to determine the creatinine clearance, BUN, LFT, electrolytes (potassium, magnesium, calcium, and sodium), urinalysis.

g Tissue will be collected at Screening but the HPV status will be ascertained at any time during the study using immunohistochemistry for p16 according to institutional clinical protocols.

h Serum pregnancy test to establish eligibility for female subjects of childbearing potential. A negative urine pregnancy test must be documented within 7 days prior to the first treatment visit, and at Visit 5.

i Visit 1 & 4: PK blood samples for total platinum collected pre- treatment (time -15 to 0 minutes), and 30±5 minutes, 60±5 minutes and 120±5 minutes post removal of last patch.

j Visit 2 & 3: PK blood samples for total platinum collected pre- treatment (time -15 to 0 minutes), and 30±5 minutes, post removal of last patch and PE application.

k Sampling for tumor and lymph nodes (if available) platinum levels.

l Photos need to be taken prior to patch application.

m Confirmation of tumor histology by a clinical pathologist is required prior to enrollment. A final pathology report, issued by a clinical pathologist is required following surgical resection of the tumor specimen.

n Taste of the PE solution and patch, adhesion, peel-off, residual cisplatin level in the patch.

o Performed after surgery if possible

p PE should be applied to the tumor area prior to first patch and allow to stay for 5 minutes. Then applied again to the tumor area for 1 minute. Note that the mouth should be kept open for the saliva not wash off the PE.

q Use “0.05” cm for the “Height” of a flat tumor. If a concave tumor, the “Height” can be shown as a negative number. If a non-measurable dent, use “-0.05” cm.

r Only SAEs within 30 days post visit 5 need to be recorded.

s. May use historical SOC information prior to consent if collected within 28 days prior to first treatment.

2.12 Study Endpoints

2.12.1 Primary Endpoints

The primary endpoints for the study involve determination of a safe and efficacious dose of PRV111 (Cisplatin Transmucosal System) (cisplatin drug-loaded patch + PE) under the conditions of the trial. Therefore, the primary endpoint is based on the incidence of DLTs and tumor volume change from baseline (CFB).

2.12.2 Secondary Endpoints

Based on secondary objectives, the secondary endpoints are:

- Evaluate tumor response
  - [redacted]
  - [redacted]
- Assess short and long-term safety of the treatment
  - Loco-regional control: subjects will be followed-up for disease recurrence and safety following surgery
  - Incidence of recurrence at 6 months
- Total platinum assessment in blood, tumor and lymph nodes (if available)
- Technical Success
  - Successful adhesion of the patch to the target lesion
  - Successful delivery (including release and permeation) of the drug to the target lesion, without getting to surrounding oral surfaces
  - Successful peel of the used patch after 10 minutes without damaging the target lesion underneath
  - Adhesion of the backing to the polymeric matrix embedded CLPs
  - Taste of the PE solution
  - Taste of the PRV111 patch
  - Residual cisplatin level in the patch after the application period

3 Efficacy Assessments

Efficacy outcomes include:

- Response to treatment evaluated by Tumor volume change from baseline (CFB)
- [redacted]
- Incidence of recurrence at 6 months
- Histological effect of PRV111 on the tumor tissue

3.1 PRIMARY: Tumor Photography and Measurements

The primary lesion will be photographed before PRV111 treatment. This will be done to allow for a clinical assessment of response to treatment. For details refer to Study Manual for instructions.
The tumor will be measured in cm to 1 digit to the right of the decimal point using a disposable plastic ruler or caliper. Three dimensions must be recorded (Length x Width x Height).

Note: If tumor or cancerous lesion is flat, a small number (0.05 cm) will be recorded for the Height. If the tumor is a concave, a negative Height is recorded. If the height is an unmeasurable dent, it can be recorded as (-0.05 cm). The volume calculations use the heights absolute value. The following formula will be used to calculate tumor volume (cm^3)

$$L \times W \times H \times \pi/6$$

3.1.1 PRIMARY: Response and Non-Response (Tumor Volume Change from Baseline Criteria)

The terms "response" and "non-response" will be defined according to the tumor volume change from baseline (CFB) criteria:

PCFB = % tumor volume change from the baseline

Response will be defined as CR, SR, or PR. Non-Response will be defined as SD or PD.

Clinical Response to Treatment

Table 2. The Efficacy Criteria

Complete Response (CR)	Disappearance of primary lesion.
Partial Response (PR)	PCFB: ≥30% to 69% decrease in the total tumor volume shrinkage (as determined by clinical measurement, **taking as reference the baseline volume.**
Strong Response (SR)	PCFB: ≥70% to 99% decrease in the total tumor volume shrinkage (as determined by clinical measurement, **taking as reference the baseline volume.**
Progressive Disease (PD)	PCFB: At least a 20% increase tumor volume as determined by clinical measurement **taking as reference the baseline volume** (Note: the appearance of one or more new lesions is also considered progression).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the volume determined by clinical measurement **at baseline**

3.1.2 Primary Efficacy Analysis

The primary efficacy variable is response according to the Tumor Volume criteria per agreement from the FDA. (Section 7.3.1), where a response is CR, SR or PR (ORR; Objective Response Rate) and a non-response is SD or PD (See Efficacy Criteria table). The primary analysis is the analysis using the Efficacy Population and tumor volume change from baseline (CFB). Include 95% CI for CFB tumor size. The study will be deemed a success if at least 7 of the up to 11 evaluable subjects achieve a minimum of a PR.

Change of tumor volume will be summarized for each visit, however the final efficacy determination will be based on CFB from V1 to V5.

A frequency distribution of efficacy based on overall response rate (ORR) at each visit will be provided evaluable population. A one-sided test of response (CR, PR, SR) rate less than 30% will be calculated at each visit.

Photographs from V1 vs V5 will be presented

[redacted]

3.2.2 SECONDARY: Loco-regional Control

Subjects will be followed-up for 6 months, and the incidence of local and regional (nodes) tumor recurrence will be recorded.

[redacted]

A summary table will show if any tumor recurred in the evaluable patients at 1,3, and 6 month follow up visits. The final analysis will include the summary of the incidence of tumor recurrence and survival status for the Efficacy of Evaluable Population.

Time to recurrence and time to death will be summarized, with Kaplan-Meier curves will be described in the CSR and corresponding summary statistics at months 1, 3 and 6.

3.2.3 SECONDARY: Technical Success

Technical assessment data will include:

- Taste of the PE solution
- Taste of the PRV111 patch
- Adhesion, including the time of adhesion of PRV111 patch
- PRV111 patch peel-off
- Residual cisplatin level in the patch after the application period. All PRV111 patches will be assessed for the amount of residual cisplatin in each patch after each application period. If the product detaches prematurely, the residual cisplatin will be assessed and the time of detachment will be noted.

Results will be summarized using descriptive statistics.

[redacted]

4 Safety Assessments

Safety observations and measurements including study drug exposure, AEs, laboratory data, physical examination findings, VS, weight, and concomitant therapy will be summarized and presented in tables and listings SAEs will be collected within 30 days post-surgery. Certain key parameters such as "Expected" and "Related to treatment" will be recorded. AEs that occur from visit 1 to visit 5 are documented. AEs (not SAEs) during or after surgery are not documented since the oral tumor and reconstructive surgeries can result in many AEs. The list of expected SAEs due to oral cancer surgery and reconstructive surgery is included in the Investigator Brochure. Laboratory parameters will be summarized using descriptive statistics and data listings. The incidence of clinically significant abnormalities will be summarized. Physical examinations, VS, and weight will be summarized by changes from baseline values using descriptive statistics.

AEs occurring after the start of treatment are TEAEs. The severity of the TEAEs will be graded according to the CTCAE criteria, version 4.0. The severity of oral mucositis will be graded according to the WHO grade. The number and percentages of subjects experiencing TEAEs will be tabulated by system organ class and preferred term. Assessments of TEAEs will include characterization of the type, incidence, severity, seriousness, and relationship to treatment. Summary subject listings will be provided for subjects with dose modification, SAEs, TEAEs resulting in study discontinuation, and deaths. The rates of local tolerability and oral mucositis will be reported.

Safety assessments include:

- Physical Examination, Vital Signs, Weight
- Oral Cavity Examination
- Neck Lymph Nodes Examination
- Safety Laboratory Assessments
- Electrocardiograms
- Adverse events

4.1 *Physical Examination, Vital Signs, Weight*

A complete physical examination will be performed by the Investigator or Sub-investigator.

The physical examination will include a review of all body systems (head, eyes, nose and throat, cardiovascular, respiratory, gastrointestinal, musculoskeletal, neurological, lymph nodes, dermatological, extremities/joints), and weight.

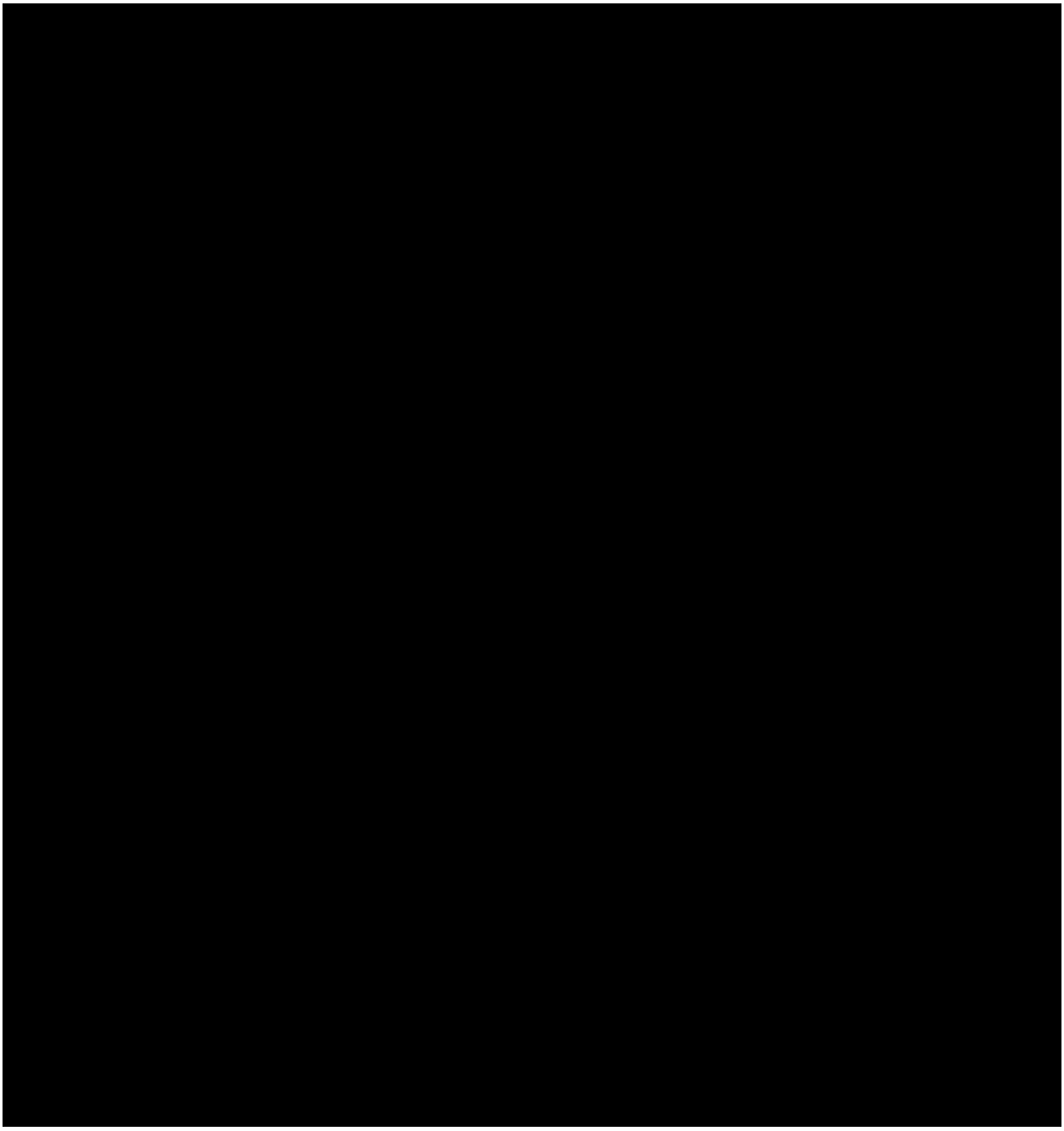
Seated blood pressure (mmHg), pulse (beats per minute) and temperature (degrees Celsius) will be measured after the subject has been sitting for at least 3 minutes.

Neuropathy and ototoxicity will be assessed via clinical examination since cisplatin can potentially cause neurotoxicity and ototoxicity. Questions will be asked to document symptoms such as tinnitus, pain in the extremities, or loss of sensation in the eCRFs.

4.1.1 Physical Examinations Analysis:

A complete general physical examination, including height and weight and vital signs (VS), will be assessed and recorded. Seated blood pressure (mmHg), pulse (beats per minute) and temperature (degrees Celsius) will be measured after the subject has been sitting for at least 3 minutes. Measured values of all vital signs and the corresponding CFBs (Change from baseline) will be summarized with descriptive statistics by visit. All observed vital signs and corresponding CFB will be presented in a listing. All abnormal physical examination findings will be included in the adverse events listings and summary tables.

Height is measured only at the screening visit and will not be included in the vital signs summary table but will be included in the listing.



4.2 *Oral Cavity Examination*

A systematic and thorough visual and manual oral examination will be performed. This will include a visual examination of all the soft tissues of the mouth, including manual extension of

the tongue to examine its base, a bi-manual palpation of the floor of the mouth, and a digital examination of the borders of the tongue.

Special attention must be given to the application site and the tumor, with documentation of any local adverse reactions, including documentation with photographs if warranted.

4.2.1 Oral Cavity Examination Analysis:

A systematic and thorough visual and manual oral examination will be performed. This will include a visual examination of all the soft tissues of the mouth, including manual extension of the tongue to examine its base, a bi-manual palpation of the floor of the mouth, and a digital examination of the borders of the tongue. Results will be summarized using descriptive statistics

4.3 *Neck Lymph Nodes Examination*

A cervical and local lymph nodes examination will be performed.

4.3.1 Neck Lymph Nodes Analysis

A cervical and local lymph nodes' examination will be performed. Results will be summarized using descriptive statistics.

4.4 Safety Laboratory Assessments

Clinical laboratories to be assessed will be as in Table 3.

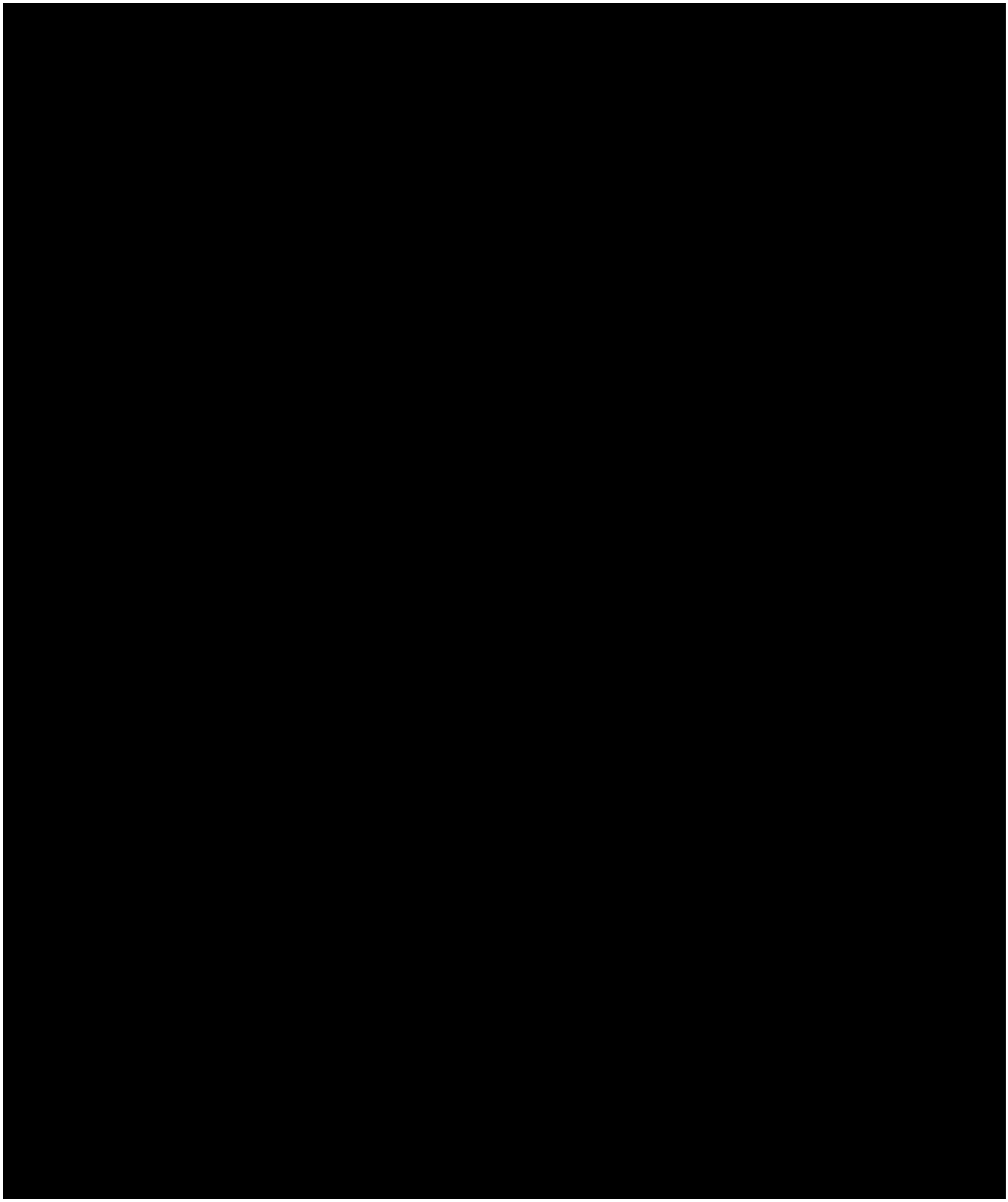
Table 3. Clinical Laboratories

COMPLETE BLOOD COUNT	CHEMISTRY PANEL	
• hematocrit • hemoglobin • platelet count • red blood cell count • white blood cell count and differential (absolute and percentage); neutrophils, lymphocytes, monocytes, eosinophils, basophils, and reticulocyte count	• alanine aminotransferase • albumin • alkaline phosphatase • aspartate aminotransferase • bilirubin (direct and total) • blood urea nitrogen • calcium • CO2	• chloride • creatinine[a] • gamma glutamyl transferase • glucose • magnesium • potassium • sodium • total protein
URINALYSIS		
• urinalysis dipstick with reflex microscopic examination for abnormalities		

[a] Creatinine Clearance will be used to assess renal function using Cockcroft-Gault Equation

4.4.1 Laboratory Tests Analysis:

Laboratory values such as routine blood chemistry, hematology, and urinalysis will be measured for each subject. Summary statistics will be provided by visit for blood chemistry and hematology and the corresponding CFBs. The calculation for CFB is described in Section9.5. If the value at Baseline is missing, then CFB will be defined as the change from the value recorded at Screening. Urinalysis results and serum and urine pregnancy test results will be included in the listings of laboratory parameters but not in the summary tables. Laboratory ranges displayed and used for normal values will be per site. If a laboratory is missing ranges, the next most-similar lab will be used. For example, if Site 001 is missing a normal range, another lab from the same site will be used as reference (i.e. Baylor HHS is missing red blood cells, the value from Baylor Austin will be used). Data will be displayed per lab and per patient.



4.5 Electrocardiograms

Electrocardiograms (ECGs) will be evaluated for clinically relevant changes from Baseline.

4.5.1 ECG Parameters Analysis:

ECG parameters will be reported as normal or abnormal per subject and per visit.

4.6 Adverse Event Definitions/Reporting Requirements

An AE (also known as an "adverse experience") is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related (US Code of Federal Regulations [CFR] 312.32).

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the drug, without any judgment about causality. A TEAE, treatment emergent adverse event is an AE that occurred on or after the start of treatment.

All clinical AEs noted during the study will be reported on the appropriate AE page of the CRF.

AEs that are serious, unexpected, and at least possibly related to study participation will be reported to the IRB and to the US FDA within the timelines described below. All other AEs, such as those that are expected, or definitely not related to the study participation, are to be reported per the IRB's policy and to FDA as part of regular data submission at the time of annual Investigational New Drug report.

4.6.1 Expected Events

Expected events are those that have been previously identified as resulting from administration of the study drug. An AE is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in the current Investigator's Brochure (IB).

4.6.2 Suspected Adverse Reaction

A suspected adverse reaction is a subset of all AEs for which there is a reasonable possibility (ie, evidence to suggest a causal relationship between the drug and the AE) that the drug caused the event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction.

4.6.3 Adverse Reaction

An adverse reaction is a subset of all suspected adverse reactions and is defined as any AE caused by a drug.

4.6.4 Adverse Device Effects

Adverse device effects are those AEs thought to be related to the use of an investigational medical device. This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition also includes any event resulting from use error or from intentional misuse of the investigational medical device.

An Unanticipated Adverse Device Effect is an adverse device effect, which by its nature, incidence, severity or outcome has not been identified in available information on the device.

Additional device issues, malfunctions or misuse will be documented in the electronic CRF.

4.6.5 Serious Adverse Event Definitions / Reporting Requirements

4.6.6 Serious Adverse Event or Serious Suspected Adverse Reaction

An AE or suspected adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

Death. This includes any death that occurs while the subject is on study and/or within 30 days after the last dose of study drug. An autopsy will be requested, and if performed, results will be submitted to the Sponsor.

A life-threatening AE. An AE or suspected adverse reaction is considered life-threatening if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include a reaction that had it occurred in a more severe form, might have caused death.

Inpatient hospitalization or prolongation of existing hospitalization. In the absence of an AE, hospitalization or prolongation of hospitalization should not be reported as an serious AE (SAE) in the following situations:

Hospitalization or prolongation of hospitalization is needed for a procedure required by the Protocol.

Hospitalization or prolongation of hospitalization is part of routine procedure followed by study center.

Hospitalization for survey visits or annual physicals.

For a hospitalization planned (and documented) before the start of the study for a pre-existing condition which has not worsened.

A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

4.6.7 Pregnancy

For safety reporting purposes, any pregnancy occurring during the study will be considered an "important medical event". If a study subject becomes pregnant while participating in the study, the study drug will be discontinued immediately and the pregnancy will be reported to the Sponsor. The Investigator will then report follow-up information to the Sponsor regarding the course of the pregnancy, including perinatal and neonatal outcome, regardless of the fact that the subject has discontinued the study. Once the newborn is determined to be healthy, as defined by and agreed upon by the Sponsor and Investigator, additional follow-up will no longer be required.

4.6.8 Serious Unexpected and Suspected Adverse Reaction

An unexpected AE (or serious and unexpected suspected adverse reaction [SUSAR]) is any AE or suspected adverse reaction that is not listed in the IB or is not listed at the specificity or severity that has been observed, if an IB is not required/available, is not consistent with the risk information described in the general investigational plan. This also refers to AEs or suspected

adverse reactions mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the study drug. A SUSAR requires mandatory expedited reporting to the applicable regulatory authority(ies). The Sponsor will forward the formal notification describing the SUSAR to Investigators. Each Investigator must then notify his/her IRB of the SUSAR, in accordance with the IRB's policy.

The Sponsor should be notified within 24 hours of the Investigator becoming aware of a SUSAR and the event documented on the CRF.

4.6.9 Recording Adverse Events

All AEs (including SAEs) within the 5 pre-surgery visits are to be accurately recorded on the AE/SAE page(s) of the CRF. In addition, any SAEs within 30 days of visit 5 will need to be recorded. The Investigator will carefully evaluate each AE to determine:

Duration (start and end dates)
Severity (grade)
Seriousness
Relationship to study drug (Not Related, Possible, Definite)
Action taken (none, study drug modification, medical intervention)
Outcome (resolved without sequelae, resolved with sequelae, ongoing)

The Investigator will evaluate all AEs and SAEs with regard to maximum intensity and relationship to study drug. Maximum intensity should be assigned using one of the severity grades as outlined in the NCI CTCAE v4.0. If the AE is not specifically listed in CTCAE v4.0, the following grades will be used:

Grade 1: mild
Grade 2: moderate
Grade 3: severe
Grade 4: life-threatening or disabling
Grade 5: death

4.6.10 Determining Relationship of Adverse Events to Study Drug

The Investigator must attempt to determine if an AE or SAE is related to the use of the study drug. This relationship should be described as follows:

Possible The event follows a reasonable temporal sequence from administration of the study drug and the event follows a known response pattern to the study drug BUT the event could have been produced by an intercurrent medical condition which, based on the pathophysiology of the condition and the pharmacology of the study drug, would be unlikely to be related to the use of the study drug OR the event could be the effect of a concomitant therapy.

Definite The event follows a reasonable temporal sequence from administration of the study drug, the event follows a known response pattern to the study drug and

based on the known pharmacology of the study drug, the event is clearly related to the effect of the study drug.

Not Related Based on the evidence available, causality is not possible.

4.7 Adverse Events Analysis:

All treatment-emergent adverse events (TEAE) will be summarized. Counts and percents of each observed system organ class (SOC) and preferred term as defined in the Medical Dictionary for Regulatory Activities (MedDRA) version 9.0 or later will be presented. The preferred terms will be summarized in the following sets of tables:

- Baseline AEs, occurring after enrolment and prior to treatment;
- All TEAEs;
- All serious TEAEs;
- All TEAE leading to discontinuation from study
- All TEAEs by closest relationship (related or not related). Relationship will be recorded as definitely related, probably related, possibly related, or not related to the study medication; the recorded relationship will be included in listings.

Reported severity (mild, moderate or severe) will be included in the listing. The severity of the TEAEs will be graded according to the CTCAE criteria, version 4.0 (Appendix 3), A separate table for AE of CTCAE grade greater than 2 (moderate) will be generated. The severity of oral mucositis will be graded according to the WHO grade.

A subject having the same TEAE (preferred term) more than once over the course of the study will be counted only once in the incidence calculation for that preferred term. Similarly, if a subject had more than one TEAE in a single SOC, the subject will be counted only once in the incidence calculation for that SOC. If a subject had a TEAE more than once in the study, the occurrence with the maximum severity will be used in the calculation of the incidence of individual TEAE by severity. If a subject had a TEAE more than once in the study, the occurrence with the highest relationship to treatment will be used in the calculation of the incidence of individual TEAE by relationship.

4.7.1 Deaths, Other Serious Adverse Events (SAEs), and Other Significant AEs Analysis:

Listings will be provided for

- Deaths,
- SAEs,
- Discontinuations due to TEAEs,
- Grade 4 AEs, and
- Related AEs.

4.8 Pharmacokinetics and Biodistribution Assessment

4.8.1 Pharmacokinetics Analysis:

Whole blood samples will be assessed for PK parameters and maximum concentration (C_{max}) during treatment period will be determined. PK parameters will be derived from the platinum concentrations obtained from Excite Pharma Services. Tumor and lymph node cis platinum content will be provided as well.

Summary statistics for PK data will be displayed for the following category: :

1. Tumor tissue
2. Lymph nodes
3. Blood
4. Residual Patch

C_{max} based on blood concentrations across patch treatment period as well as other summary statistics for each patient will be listed.

Systemic, tumor and lymph node (if available) platinum levels will be summarized using descriptive statistics. Analysis will be adjusted based on the number of patches applied per application (1 or 2) and total number of treatment visits.

5 Data Analysis and Statistical Considerations

Statistical analyses and summaries will be provided when all corresponding data is collected and processed, and the corresponding database portions are locked through this stage of the

study. All available data from post-operative visits for other subjects, if any, will be included. The final analysis including all available post-operative data will be performed when the last subject has reached the 6-month post-operative follow-up visit and the final database is locked.

Statistical tables, data listings and graphs will be prepared using SAS Version 9.1 or higher (SAS Institute, Cary, North Carolina, USA).

5.1 Statistical Analysis

Safety outcomes resulting in DLTs will be used during the conduct of this study to select doses being tested according to pre-defined thresholds of toxicity.

- Local and systemic safety and tolerability will be summarized using descriptive statistics.
- The number of subjects with DLTs will be capped to be fewer than 2 subjects with DLTs out of 5 new subjects enrolled.
- The treatment regimen will be deemed tolerable if fewer than a third of the subjects exposed to it present DLTs.
- Efficacy based on Tumor volume CFB criteria will be summarized, and the null hypothesis that the probability of response is at most 30%, where a response is the occurrence of CR or PR will be tested using a one-sided test exact binomial test at level 0.018.
- Other efficacy assessments such as change in tumor volume or tumor histology will be summarized using descriptive statistics.
- Variables measuring technical success (including residual cisplatin level in the patch) will be summarized using descriptive statistics.

At the end of Stage 2, the following is a statistical analysis of the sample size as it pertains to efficacy:

Power and Sample Size

[redacted]

Based on Simon's 2-stage procedure, the null hypothesis that the true response rate is 0.30 will be tested against a 1-sided alternative. In the first stage, 5 evaluable subjects will be accrued. If there are 2 or fewer responses in these 5 subjects, the dose will be escalated. Otherwise, the dose will remain the same or de-escalated based on safety data. [redacted] This design yields a type I error rate of 0.018 and power of 96.44% when the true response rate is 0.65.

Null response rate: P_0	Alt. response rate: P_1	Alpha one-tailed	Power	n1	r1	N	R
0.30	0.85	0.018	96.44%	5	2	11	6

N is the total number of evaluable subjects at the final dose
n_1 is the number of evaluable subjects accrued during Stage 1
r_1, if r_1 or fewer responses are observed during stage 1, escalate the dose if safety requirements are met
R, if *R* or fewer responses are observed by the end of Stage 2 in N subjects, then an effective dose is not found

Note: If the dose is not increased after Stage 1, the test will be performed using all evaluable subjects from Stage 1 and 2. If the dose is adjusted after Stage 1, the test will be performed using all evaluable subjects from Stage 2.

5.2 Treatment Analysis Guidelines

5.2.1 Efficacy Analyses

The primary efficacy analysis will be conducted after all evaluable subjects will have undergone their surgical ablation of the oral tumor, in addition to the interim analysis described below.
Note: All hypothesis tests will be performed at a 0.018 level.

5.2.2 Evaluable Population

All subjects who have **met the inclusion and exclusion criteria**, and have completed at least 75% of the total dose required for that stage will be included in the Evaluable Population*. This population will be used for the efficacy analysis. **Only subjects in the evaluable population will be assessed for tumor response.**

* 75% is defined as at least 3/4 patch application visits completed

5.2.3 Baseline Values for Tumor Measurement

The baseline values for each subject will be those recorded at Visit 1. If the value at the Baseline visit is missing, then the value from the earliest available visit will be used. For tumor measurements, if the Visit 1 measurement is missing, then the measurements from the screening CT scan will be used as baseline values.

5.2.4 Change from Baseline (CFB) and Percent Change from Baseline (PCFB)

CFB will be calculated at each post-baseline visit for all evaluable subjects as:

CFB = Post-Baseline value – Baseline value.

CFB will be reported to the same number of decimal places as the variable.

PCFB will be calculated at each post-baseline visit for all evaluable subjects as:

PCFB = 100*CFB/ Baseline value

= 100*(Post-Baseline value – Baseline value) /Baseline value.

PCFB will be reported to same number of decimal places as the variable.

5.2.5 Descriptive Summary Statistics

The following standards will be applied for each analysis unless otherwise specified. Simple summary statistics for continuous data are defined as: n (number of non-missing observations), mean, standard deviation, maximum, median, minimum. The number and percentage of subjects will be used to summarize categorical data. All data will be listed and sorted by investigator number, variable, subject number, and visit, if appropriate.

5.3 Safety Analyses

The Safety Population will be used for all summaries of safety data.
will be used in the calculation of the incidence of individual TEAE by relationship.

5.3.1 Safety Population

All subjects who have at least 1 PRV111 patch applied will be included in the Safety Population.

5.3.2 Concomitant Medication and Therapy

A listing of concomitant medications and therapy will be provided for the Safety Population.

5.3.3 Medical History, Medication History and Baseline Disease Characteristics

Medical history and baseline disease characteristics will be listed for the Safety Population.
ECOG PS (Appendix 2) will be included.

5.3.4 Subject Accountability, Demographics, and Baseline Characteristics

Subject completion status, dose modification, and study terminations will be summarized for each of the study stages and for the study overall. Subjects with major protocol violations will be listed. Demographics will be summarized along with baseline characteristics such as medical history, and baseline physical examination, weight, VS, ECOG PS, and concomitant therapy.

6 Data Handling

6.1 Pooling of Centers

This is a multi-center study. The data from all sites will be pooled for all analyses.

6.2 Handling of Missing Data

All missing data will be queried. Missing efficacy data which are not retrievable through queries will be imputed. Missing safety data will not be imputed. If the value of a vital sign assessment, ECG variable, laboratory value, or clinical tumor measurement is missing at Baseline, then CFB will be defined as the change from the value recorded at the next earliest available data point.

Non-Responder Imputation (NRI)

No missing values imputation will be applied.

6.3 Drop-outs, Withdrawals, Replacement Policy

If a subject withdraws from the study at any time, either at his or her request or at the Investigator's discretion, the reason(s) for withdrawal will be recorded on the relevant page of the CRF. Subjects withdrawn due to AEs will be monitored until resolution of all AEs. Subjects who withdraw from dosing will be not replaced. However, their data will still be used if they are considered part of the evaluable population, unless they state otherwise.

7 Changes from the Protocol

No changes from the protocol are planned.

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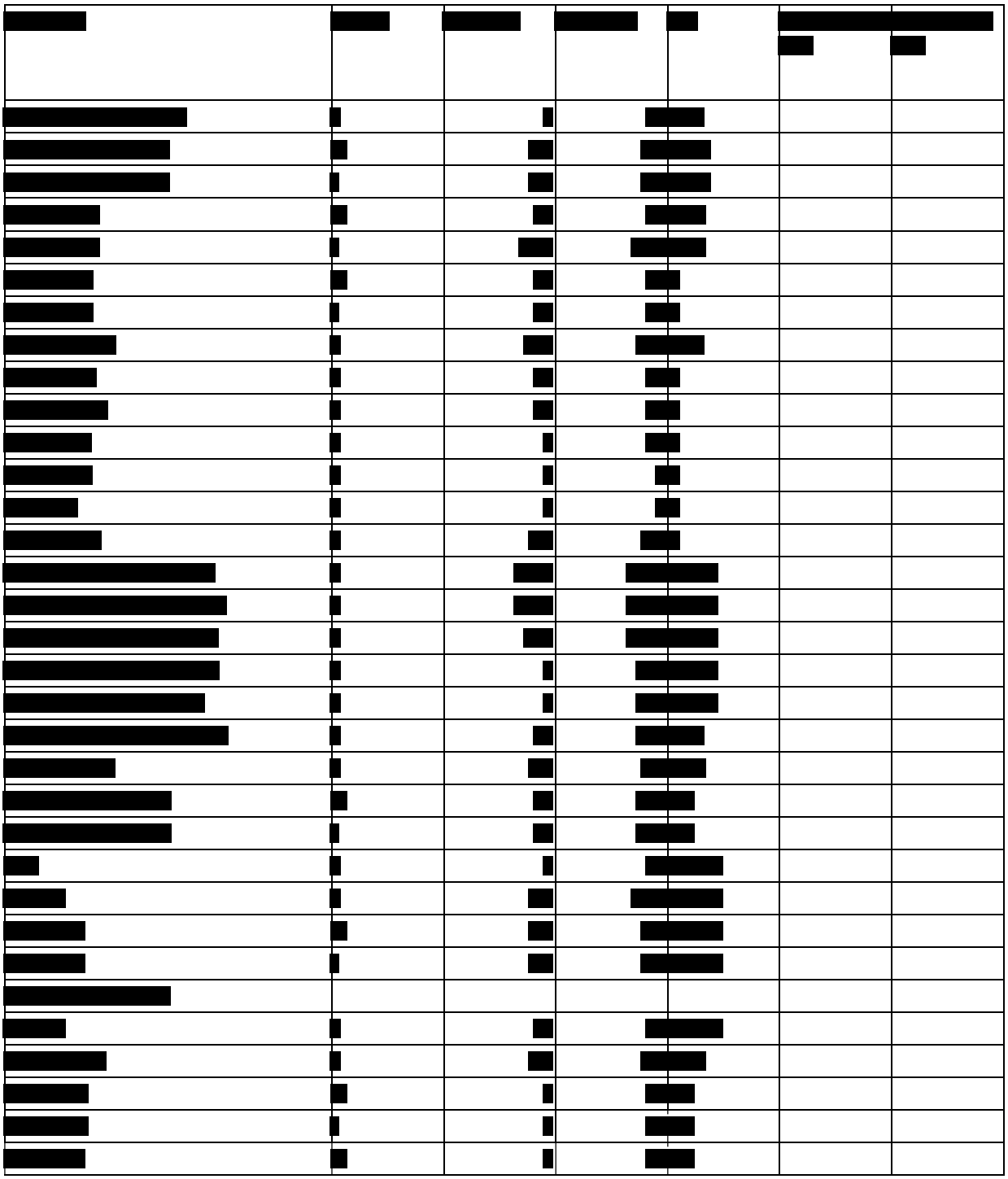

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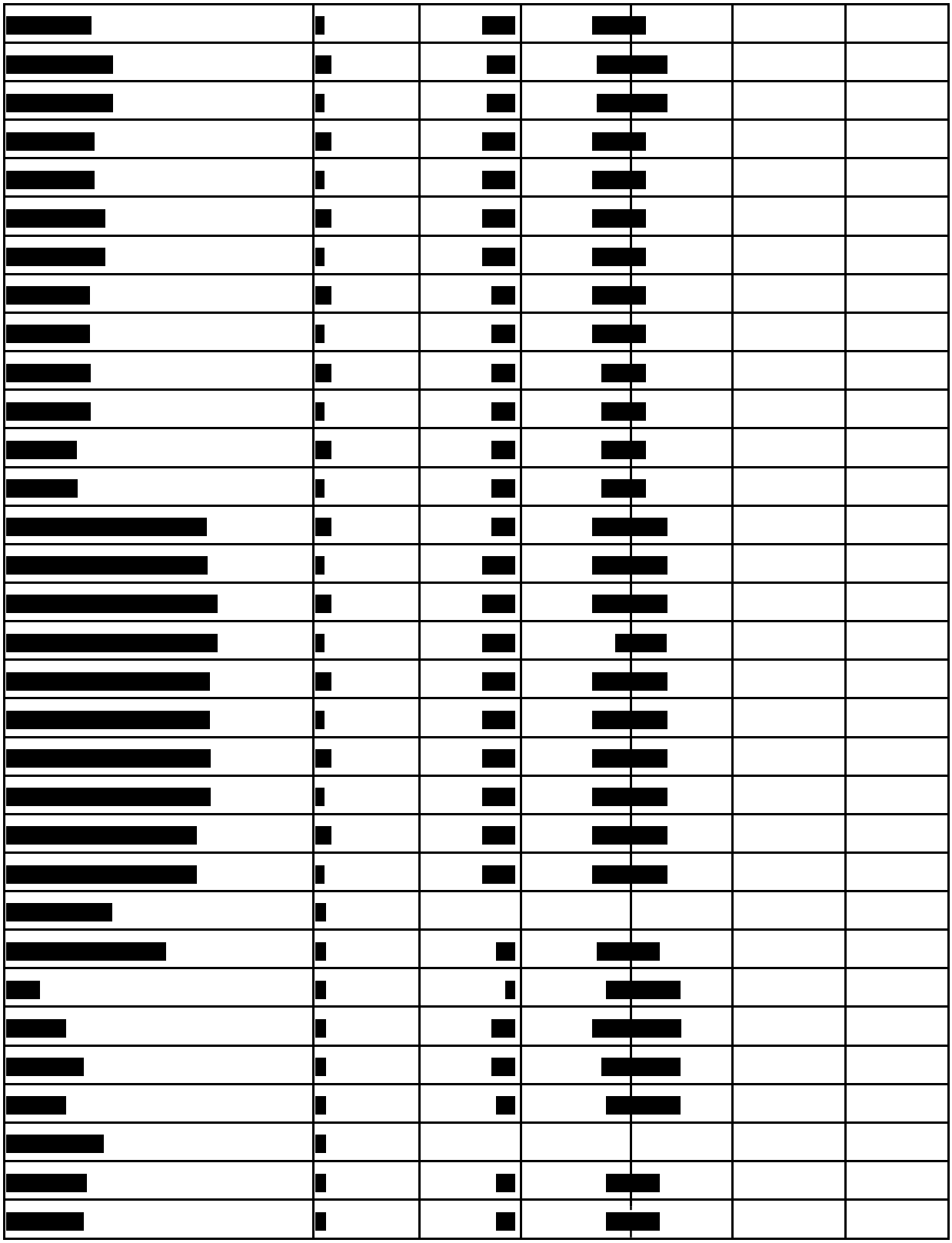

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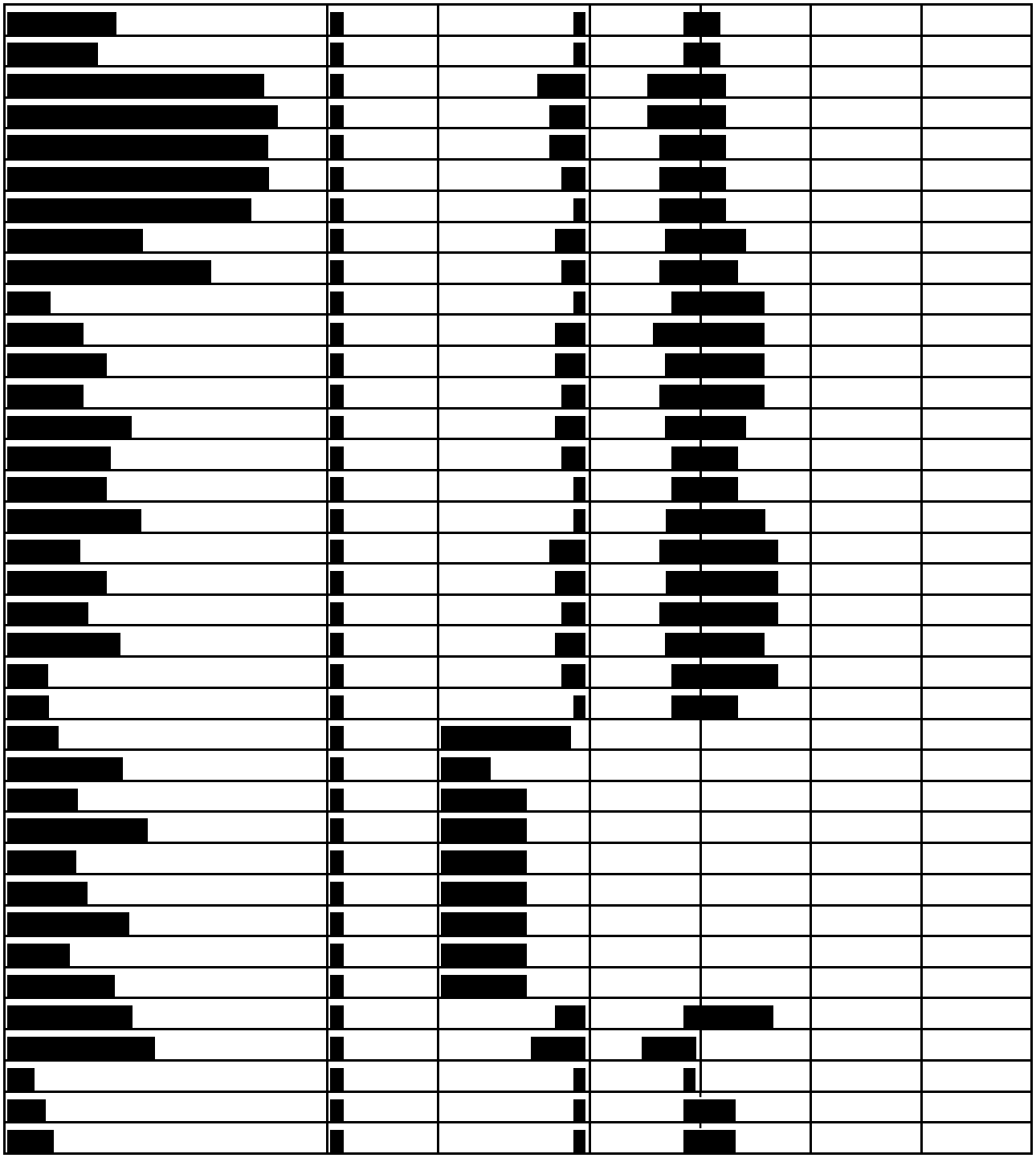

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8.2 Appendix 2: ECOG Performance Status (ECOG PS)

Performance status will be assessed using ECOG PS at Baseline for inclusion criterion.

Grade	ECOG PS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

8.3 Appendix 3: Common Terminology Criteria for Adverse Events (CTCAE)

CTCAE Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade	Severity Description
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to AE

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.