Privo technologies.
Tougher on Cancer, Easier on the Patient

CLINICAL STUDY PROTOCOL

Title:	Phase 1/2, 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
Test Product:	PRV111 (Cisplatin Transmucosal System) Drug Product
Protocol Identification:	CLN-001
Sponsor Name, Address, and Telephone Number:	Privo Technologies 200 Corporate Place, Suite 6B, Peabody, MA 01960 Phone : 978-587-2322 Fax : 978-278-5114
Compliance Statement:	The trial will be conducted in accordance with standards of Good Clinical Practice, as defined by the International Council for Harmonization and all applicable national and local regulations.
Date of Original Protocol:	3 August 2017
Date of Amendment 1: **Date of Amendment 2:** **Date of Amendment 3:** **Date of Amendment 4:** **Date of Amendment 5:**	17 October 2017 11 May 2018 26 March 2019 24 May 2019 23 March 2020
[redacted]	[redacted] [redacted] Date: March 23, 2020
[redacted]	[redacted] Signature Date : March 23, 2020

Confidential Information

PROTOCOL SIGNATURE PAGE

Protocol : CLN-001

Title: Phase 1/2, Open-Label, Single-Arm Safety and Efficacy Dose-Finding, Systemic Exposure, and Device Technical Effects of PRV111 (Cisplatin Transmucosal System) in Subjects with Oral Squamous Cell Carcinoma

Amendment 5: 23 March 2020

Investigator Statement: I have received and completely reviewed the above-named protocol, including all appendices and amendments. As Investigator, I agree to conduct the trial in accordance with all stipulations of the protocol and in accordance with 21 Code of Federal Regulations (CFR) Part 50, International Council for Harmonization (ICH) Guidelines for Good Clinical Practices (GCP), and the Declaration of Helsinki.

INVESTIGATOR SIGNATURE AND CONTACT INFORMATION	
Investigator (signature)	
Investigator (please print)	
Date of Signature	
Investigator's Address	
City, State, Country, Zip Code	
Telephone No.	
Fax No.	
Email	

Signature on this page assures Privo Technologies that, to the best of the Investigator's knowledge, the affiliated Institutional Review Board operates in accordance with applicable local and national regulations, and that the Investigator understands and agrees to abide by all regulatory obligations and ICH GCP Guidelines while conducting this clinical trial.

Once signed, the original of this form should be detached from the protocol and returned to the Sponsor.
(Please retain a copy for your files)

STUDY CONTACT INFORMATION

Unless otherwise instructed, Serious Adverse Event and Serious and Unexpected Suspected Adverse Reaction reports are to be submitted to:

[redacted]

Who will forward a copy to:

Medical Monitor:
[redacted]

1 SYNOPSIS

Name of Sponsor/Company: Privo Technologies

Name of Finished Product: PRV111 (Cisplatin Transmucosal System)

Name of Active Ingredient: Cisplatin

Title of Study: Phase 1/2, Open-Label, Single-Arm, Safety and Efficacy Dose-Finding, Systemic Exposure, and Device Technical Effects of PRV111 (Cisplatin Transmucosal System) in Subjects with Oral Squamous Cell Carcinoma

Phase of Development: Phase 1/2

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

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 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 ml of the PE which will be applied pre and post patch application (see Pharmacy Manual for details). 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 6 days (at least 48 hours apart).

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

Dosing Rules for Stage 1:

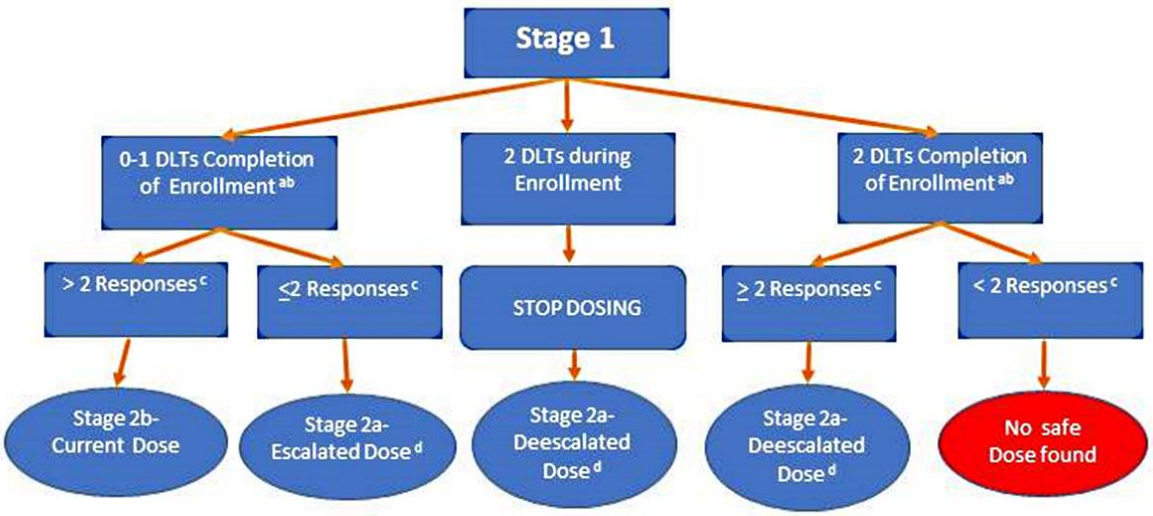
1) If fewer than 2 subjects experience DLTs, then the following scheme will be considered for stage 2 dosing:
   a. If fewer than or equal to 2 of the evaluable subjects have a response (Tumor volume change from baseline (CFB) expressed as percent change from baseline (PCFB) complete response [CR], strong response [SR] or partial response [PR]) the dose will be escalated from 3 to 5 treatment applications per treatment visit for Stage 2.

Name of Sponsor/Company: Privo Technologies
Name of Finished Product: PRV111 (Cisplatin Transmucosal System)
Name of Active Ingredient: Cisplatin

b. If 3 or more evaluable subjects have a response (as tumor volume PCFB complete response [CR], strong response [SR] or partial response [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 5 evaluable subjects in Stage 1:
      - If out of 5 evaluable subjects, 2 or more subjects have a response (as tumor volume PCFB complete response [CR], strong response [SR] or partial response [PR]), the dose will be de-escalated to 2 applications per treatment visit.
      - If out of 5 evaluable subjects, fewer than 2 have a response (as tumor volume PCFB complete response [CR], strong response [SR] or partial response [PR]), the dose will be considered ineffective and the study will be stopped.
   b. If Stage 1 dosing was stopped prior to having 5 evaluable subjects, the dose will be de-escalated from 3 applications to 2 applications per treatment visit.

Stage 1 Dose Determination Scheme:



a) Stage 1 Enrollment Goal: 5 Evaluable Subjects. See section "Evaluable Subject"
b) 2 subjects with DLTs, evaluated based on Safety Subjects
c) Response based on evaluable subjects
d) Target Dose for Stage 2a

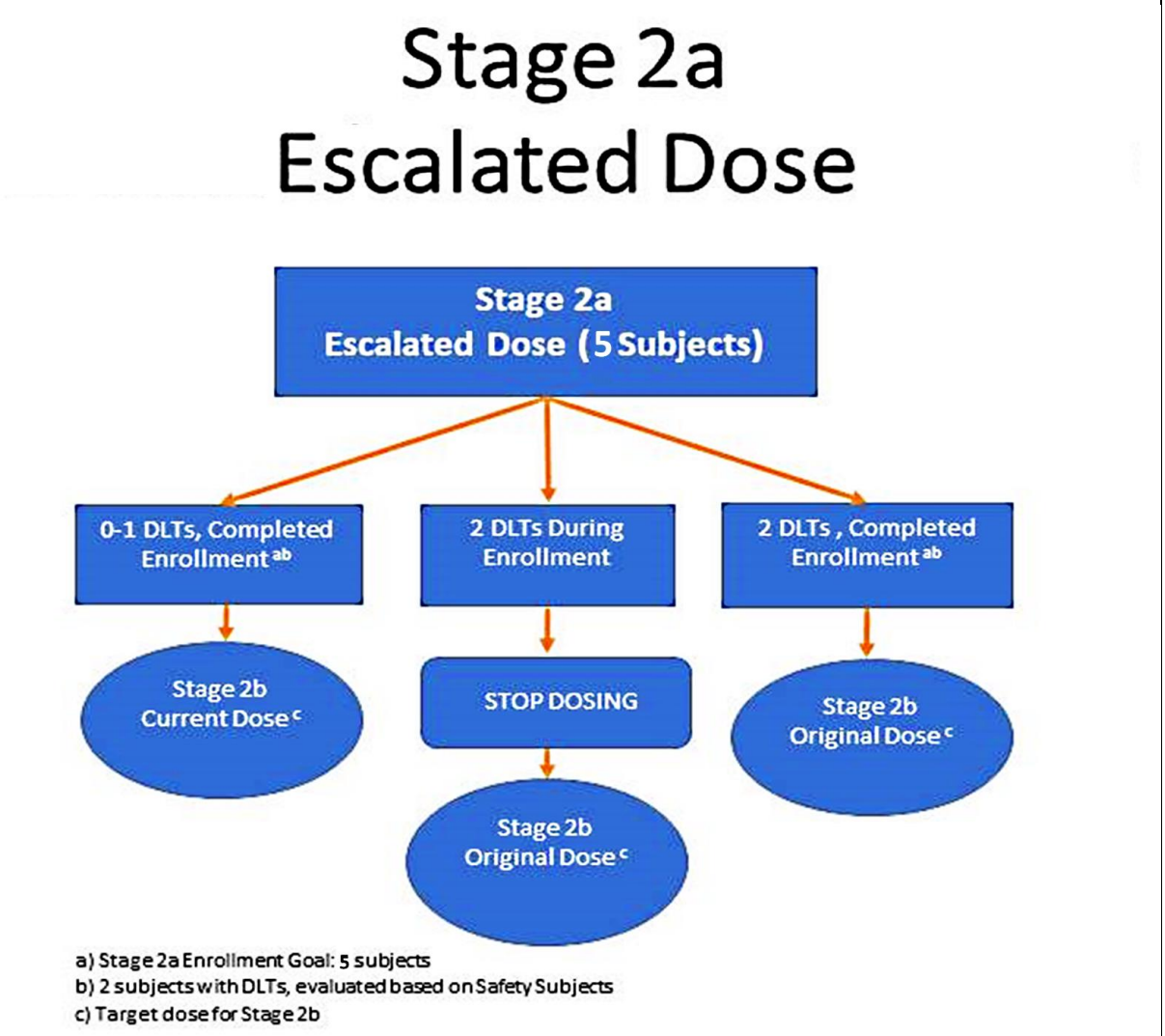
Stage 2: In case of dose escalation or de-escalation, Stage 2 will be conducted in 2 parts: Stage 2a and Stage 2b.
Subjects will receive 2, 3, or 5 treatment applications at each of the 4 planned treatment visits, depending on the results of Stage 1. [redacted]

Stage 2a: This stage will include 5 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.

Name of Sponsor/Company: Privo Technologies
Name of Finished Product: PRV111 (Cisplatin Transmucosal System)
Name of Active Ingredient: Cisplatin

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 - De-escalated Dose", the study will stop, as no safe dose could be determined.

Stage 2a Safety Scheme in Case of Escalated Dose Decision:

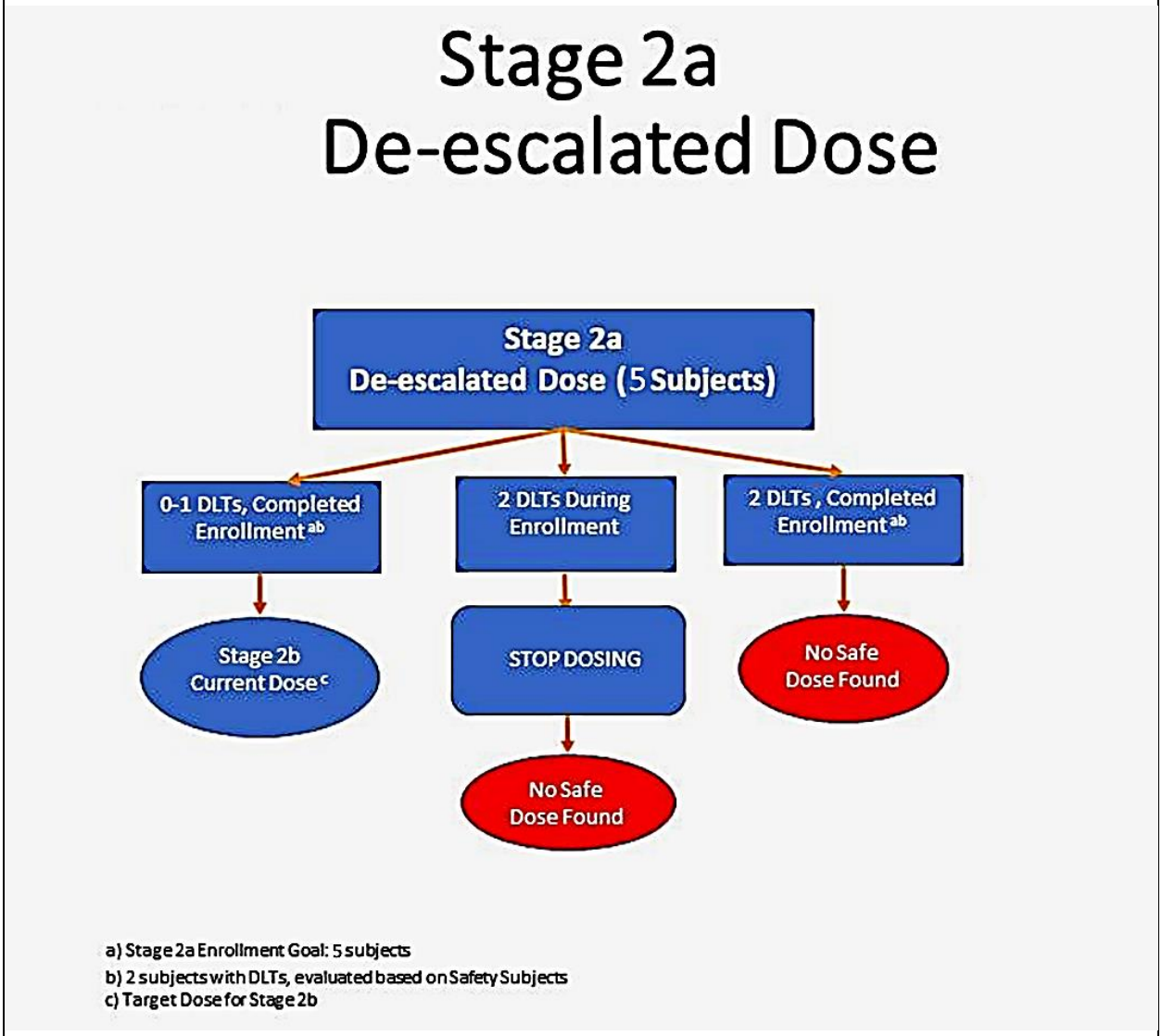


Name of Sponsor/Company: Privo Technologies

Name of Finished Product: PRV111 (Cisplatin Transmucosal System)

Name of Active Ingredient: Cisplatin

Stage 2a Safety Scheme in Case of De-escalated Dose Decision:



Stage 2b: In this stage both safety and efficacy will be evaluated. All subjects will be monitored for possible DLTs (Stage 2b – All Doses flowchart).

Stopping Rules at Stage 2b:

If 3 subjects with DLTs, no additional subjects will be dosed.

Efficacy Rules at Stage 2b:

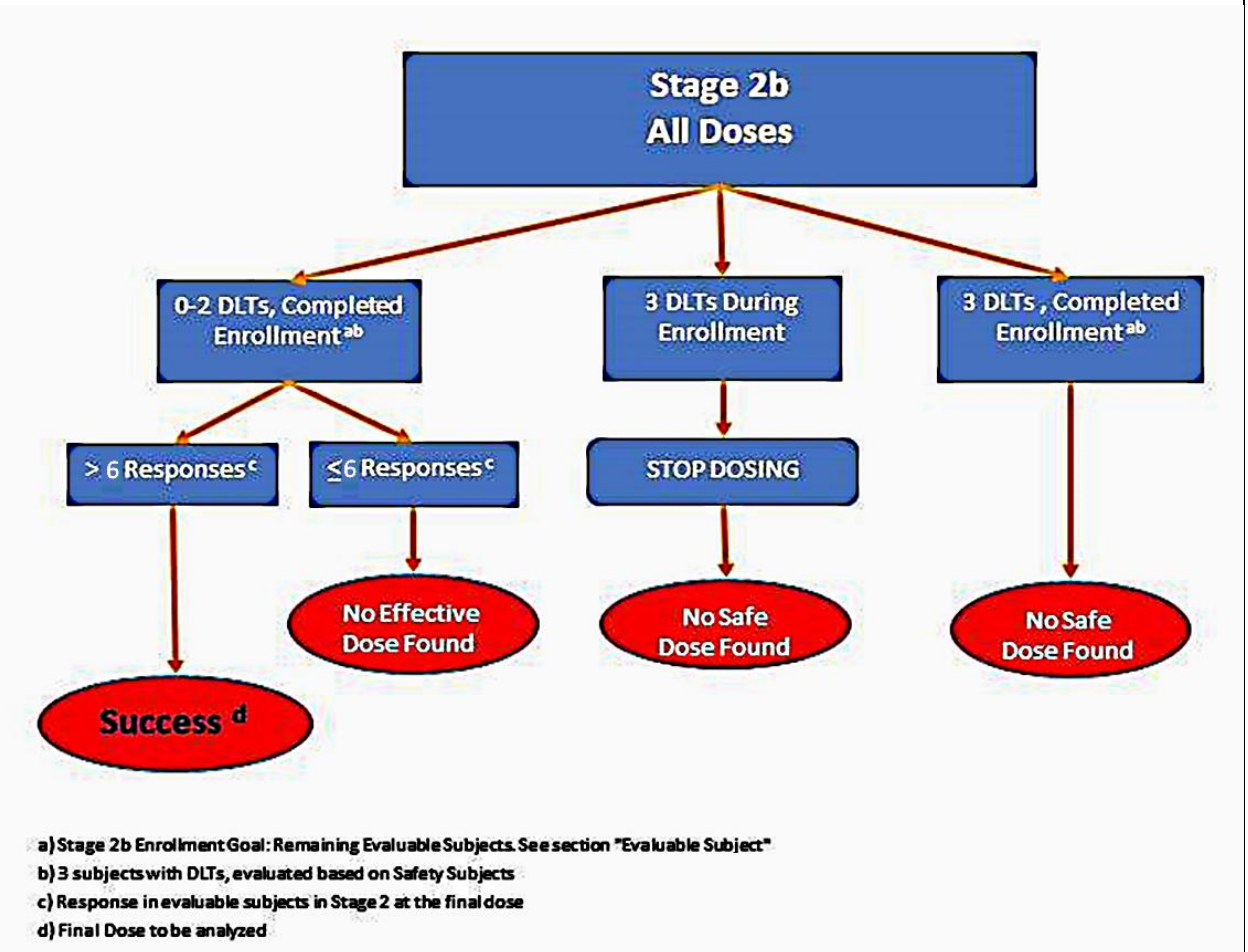
Efficacy rules are described in the statistical plans for this stage since it is end of the study.

Name of Sponsor/Company: Privo Technologies

Name of Finished Product: PRV111 (Cisplatin Transmucosal System)

Name of Active Ingredient: Cisplatin

Stage 2b Safety and Efficacy Scheme:



Note: The PRV111 treatment should not cause a delay to the scheduled surgery. Visit 1 can be performed within 42 days prior to the scheduled surgery.
All subjects will subsequently undergo standard of care, surgical ablation of the tumor and satellite nodes, and possibly additional radiotherapy and chemotherapy. All subjects will be followed for up to 6 months post-surgery at 3 visits: 1 month, 3 months, and 6 months or standard of care (discretion of the investigator) post-surgery for loco-regional response and safety.

[redacted]

Diagnosis and Main Criteria for Inclusion:

In order to be eligible to participate in the study, an individual must meet all of the following criteria:

1. Adult subjects, men and women, defined by age ≥18 years at the time of screening.

Name of Sponsor/Company: Privo Technologies

Name of Finished Product: PRV111 (Cisplatin Transmucosal System)

Name of Active Ingredient: Cisplatin

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.

Criteria for Exclusion:

An individual who meets any of the following criteria will be excluded from participation in the study:

1. Known distant metastasis of the SCC of the oral cavity
2. Systemic chemotherapy for the treatment of SCC of the head and neck less than 2 years prior to Screening
3. Concurrent documented malignancy, with the exception of localized SCCs 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

Test Product, Dose and Mode of Administration: PRV111 (Cisplatin Transmucosal System) consists of:

- PE solution [redacted] to be applied superficially to the malignant tumor to improve the drug permeation into the tumor (1 mL at each treatment visit) (Refer to the Pharmacy Manual).

Name of Sponsor/Company: Privo Technologies

Name of Finished Product: PRV111 (Cisplatin Transmucosal System)

Name of Active Ingredient: Cisplatin

- Patch with [redacted] polymeric matrix, embedded cisplatin-loaded [redacted] particles (CLPs), and a non-permeable backing. Each 2 cm x 2 cm PRV111 topical patch covers a tumor region of 4 cm^2 and contains 0.5 mg/cm^2 (total 2 mg) of cisplatin.

patch(es). The number of patches used for each subject should remain consistent throughout treatment. Refer to the Pharmacy Manual for detailed instructions for use.

Duration of Treatment: Up to 6 weeks of treatment prior to the scheduled resection of the tumor and 6 months post-surgical follow-up. ***Note:*** The PRV111 treatment should not cause a delay to the scheduled surgery. Visit 1 can be performed within 42 days prior to the scheduled surgery.

Criteria for Evaluation:
Safety/Tolerability evaluation based on:

- Adverse events
- Physical examination, vital signs, and weight
- Blood and urinary tests: complete blood count, chemistry panel, and urinalysis
- Electrocardiogram
- Oral examination: including observation for mucositis and other signs of local reaction to the test article
- Neck lymph nodes examination

Efficacy, based on:

- Tumor volume change from baseline clinical assessment (CR, PR, SR, SD, or PD). Response defined as CR, SR, or PR; non-response defined as SD or PD.
- Ruler or caliper measurements of tumor volume
- [redacted]
- Tumor photography and measurements
- Loco-regional control: subjects will be followed-up for disease recurrence and safety following surgery

Pharmacokinetics:

- Whole blood samples will be assessed for total platinum content

Technical Success will be defined as:

- 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.

Statistical Methods:

Safety outcomes resulting in a DLT 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.

Name of Sponsor/Company: Privo Technologies

Name of Finished Product: PRV111 (Cisplatin Transmucosal System)

Name of Active Ingredient: Cisplatin

- 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, SR or PR will be tested using a 1-sided test exact binomial test at level 0.018.
- [redacted]
- Systemic and tumor and lymph nodes (if available) platinum levels will be summarized using descriptive statistics.
- Variables measuring technical success (including residual cisplatin level in the patch) will be summarized using descriptive statistics.

All summaries will be presented by dose, as appropriate. Incidence of pre-surgery AEs will be summarized using number and percent for each System Organ Class and Preferred Term (MedDRA), including Investigator assessment of relatedness and severity grade.

All assessments will be listed and summarized using mean, standard deviation, median, minimum, and maximum for continuous variables and using number and percent for categorical assessments.

Data from this study will be summarized at 2 timepoints:

- Final report at End of Stage 2: after all subjects complete PRV111treatment, efficacy, pharmacokinetics, and technical data will be analyzed, including all available safety data from the long-term follow-up.
- Long term safety report: after all subjects complete all observations.

Power and Sample Size

[redacted]

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. Additional subjects will be accrued for a total of 11 evaluable subjects at the final dose.

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.

Based on Simon's 2-stage procedure, the null hypothesis that the true response rate is 0.30 will be tested against a one-sided alternative. The null hypothesis will be rejected if **7** or more responses are observed at the final dose. This design yields a type I error rate of 0.018 and power of 96.44% when the true response rate is 0.85.

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*

[redacted]

Table 1. 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]	
PRV111 patch treatment		X[p]	X[p]	X[p]	X[p]			
Tumor measurements[q]		X[a]	X[a]	X[a]	X[a]	X		

	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
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
[redacted]	[redacted]						[redacted]	
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.

[redacted].

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. [redacted]

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. [redacted] 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 TABLE OF CONTENTS

2.1 List of Tables

2.2 List of Figures

3 LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	Adverse Event/Adverse Experience
AUC	Area under the curve
BUN	Blood urea nitrogen
CBC	Complete Blood Count
CFB	Change from Baseline
CFR	Code of Federal Regulations
CLP	Cisplatin-Loaded [redacted] Particles
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CR	Complete response
CRF	Case Report Form
[redacted]	[redacted]
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
HPV	Human papillomavirus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IRB	Institutional Review Board
IV	Intravenous
LFT	Liver function test
[redacted]	[redacted]
NCI	National Cancer Institute
PCFB	Percent change from baseline
PD	Progressive disease
PE	Permeation enhancer
PI	Principal Investigator

Abbreviation	Definition
PK	Pharmacokinetics
PR	Partial response
PRMC	Protocol Review and Monitoring Committee
PRV111	Cisplatin Transmucosal System
QA	Quality Assurance
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SCC	Squamous cell carcinoma
SD	Stable disease
SUSAR	Serious and Unexpected Suspected Adverse Reaction
$t_{1/2}$	Half life
TEAE	Treatment emergent adverse event
[redacted]	[redacted]
ULN	Upper limit of normal
US	United States
VS	Vital signs

4 INTRODUCTION

4.1 Background of Disease

Squamous cell carcinomas (SCC) of the head and neck include tumors that occur in the oral cavity (lips, buccal mucosa, anterior tongue, floor of the mouth, hard palate, upper gingiva, lower gingiva, buccal mucosa and retromolar trigone) (Brockstein, 2016). 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 (HPV). Statistics also show that males and those of low socioeconomic background are at a higher risk of developing oral cancer than other demographics (Brockstein, 2016; da Silva, 2012).

In 2017, an estimated 50,000 new cases of oral and pharynx cancer will be reported in the United States (US); approximately 11.1 adults per 100,000 will develop oral and pharynx cancer per year (National Cancer Institute, 2016). The median age of diagnosis is 62 years. The incidence of oral cancer increases with age (National Cancer Institute, 2016; National Institute of Dental and Craniofacial Research, 2016).

The 5-year survival rate for oral cancer is approximately 60%; diagnosis at an early stage significantly increases the 5-year survival rate (83% for Stage I versus 10%–22% for Stage IV) (da Silva, 2012; National Cancer Institute, 2016; National Institute of Dental and Craniofacial Research, 2014). Approximately 30% of subjects have early (Stage I or II) localized disease, with most subjects diagnosed with advanced disease (Brockstein, 2016; da Silva, 2012; National Cancer Institute, 2016).

Oral cancer has a high rate of recurrence (18%–76% for subjects who undergo standard treatment), and is considered the major cause of poor survival rates. Recurrence can vary by tumor location, with a median time to recurrence of 9.5 months (range 2–79 months) for tongue, 8 months (range 2–120 months) for buccal tumor, and 5–8 months for lip tumors (da Silva, 2012; Gurudutt, 2011; Kelner, 2014). The median time to recurrence across all oral cancer sites is 7.5 months, with most recurrences (86%) occurring within 24 months (da Silva, 2012).

Approximately 1/3 of subjects treated with surgery and adjuvant therapy will experience local or regional recurrence and/or distant metastasis. Local and regional recurrences account for up to 90% of treatment failures post-surgery and radiotherapy (da Silva, 2012). An estimated 9,700 deaths will occur due to oral and pharynx cancer in the US in 2017 (National Cancer Institute, 2016).

The treatment and management of oral cancer is dependent upon the stage of disease. Standard treatment for localized early disease is surgery with or without radiation (Brockstein, 2016). For subjects with pathologically loco-regionally advanced disease (Stage III/IV), or for those treated with surgery for early stage disease identified to have close or positive margins, or positive lymph nodes, adjuvant postoperative radiotherapy with or without chemotherapy is recommended (Brockstein, 2016). Typical treatment approaches for loco-regionally advanced disease will include neoadjuvant chemotherapy or radiotherapy, primary surgery followed by adjuvant radiotherapy or chemoradiotherapy, or chemotherapy or chemoradiotherapy without

surgery (Brockstein, 2016; da Silva, 2012; Gregoire, 2010; Marta, 2015; Seiwert, 2007). Salvage surgery, adjuvant radiation, re-irradiation, and/or palliative chemotherapy is recommended for subjects with locally recurrent disease (Milano, 2015). For subjects with locally recurrent metastatic disease, palliative chemotherapy, immunotherapy, and/or supportive care are recommended (Brockstein, 2016). 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 (da Silva, 2012; Gregoire, 2010; Vermorken, 2010).

4.2 Privo's PRV111 Patch

PRV111 (Cisplatin Transmucosal System) is a thin, 2-layer, matrix-type, non-sterile transmucosal patch consisting of a [redacted] matrix layer embedded with cisplatin loaded [redacted] particles (CLPs) and a non-woven fabric adhesive unidirectional backing, which is applied to the matrix layer during manufacturing (Figure 1). The patch is self-adhesive.

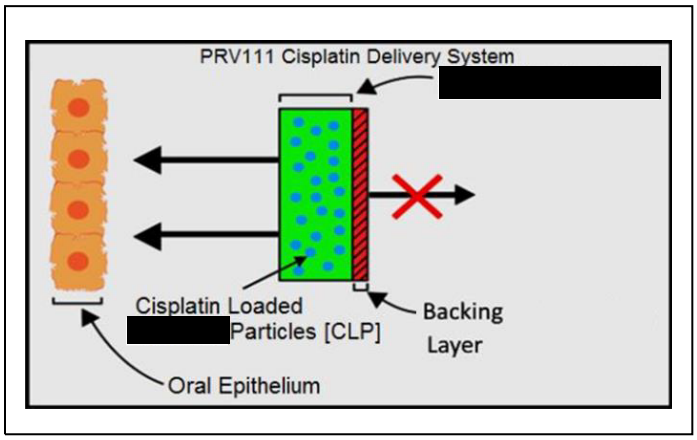


Figure 1. PRV111 (Cisplatin Transmucosal System)

In addition to the PRV111 drug product, a separately packaged Permeation Enhancer (PE) Powder for Reconstitution (a vial [redacted] [redacted] to be reconstituted at the clinical site with 1 mL of Water for Injection) is used in conjunction with the PRV111 drug product. The reconstituted PE Solution is intended to improve the absorption of the cisplatin active ingredient and will be applied pre and post patch application (see Pharmacy Manual for details).

4.3 Rationale for Use of the Product

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. 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.

Cisplatin (cis-diamminedichloroplatinum) has been approved in the US for 38 years as an antineoplastic agent and is commonly administered systemically IV as a standard of care chemotherapy for the treatment of oral cancer, alone and in combination with other chemotherapies (da Silva, 2012; Vermorken, 2007; Vermorken, 2010). However, systemic treatment with cisplatin can lead to dose-limiting toxicities (DLTs) and significant side effects, including renal toxicity, ototoxicity, and myelosuppression, which can limit the extent and duration of treatment (WG Critical Care, 2015). These side effects of IV cisplatin administration can be dose-limiting, reducing the dosage and length of cisplatin treatment for subjects. 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.

The antineoplastic activity of cisplatin can be primarily attributed to its ability to bind and modify nuclear and mitochondrial DNA, forming multiple intrastrand and interstrand DNA adducts, which leads to the activation of the p53 apoptotic pathway and subsequently cell death (Galluzzi, 2014; Johnstone, 2015). Cisplatin has also been linked to inducing chemokine and T-cell infiltration of tumor sites, thereby impeding tumor growth (Hong, 2011).

4.4 Rationale for Dose Selection

The maximum total planned PRV111 cisplatin dose if dose escalation proceeds as planned in Stage 2 (10 mg per treatment visit for 5 single patch applications, and 20 mg per treatment visit for 5 double patch applications) is approximately 9 to 18 times lower than the recommended dose of IV cisplatin (180 mg for an 80 kg person) (WG Critical Care, 2015).

Version 10 of the drug product will be used for this clinical trial since it has shown good safety and efficacy in 4 nonclinical studies. This version has the optimal dose per patch as 2 mg (0.5 mg/cm^2) that balances the quality, drug release and uniformity of the patch.

5 TRIAL OBJECTIVES

5.1 Primary Objective

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

5.2 Secondary Objectives

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

6 INVESTIGATIONAL PLAN

6.1 Overall Trial Design and Plan: Description

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 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 DLTs. Effective dose is determined based on the evaluable population as described in the Section 10.2.

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 involve application of 1 ml of the permeation enhancer and will be applied pre and post patch application (see Pharmacy Manual for details) (One ml vial of PE per visit, see Pharmacy Manual). 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 6 days (at least 48 hours apart).

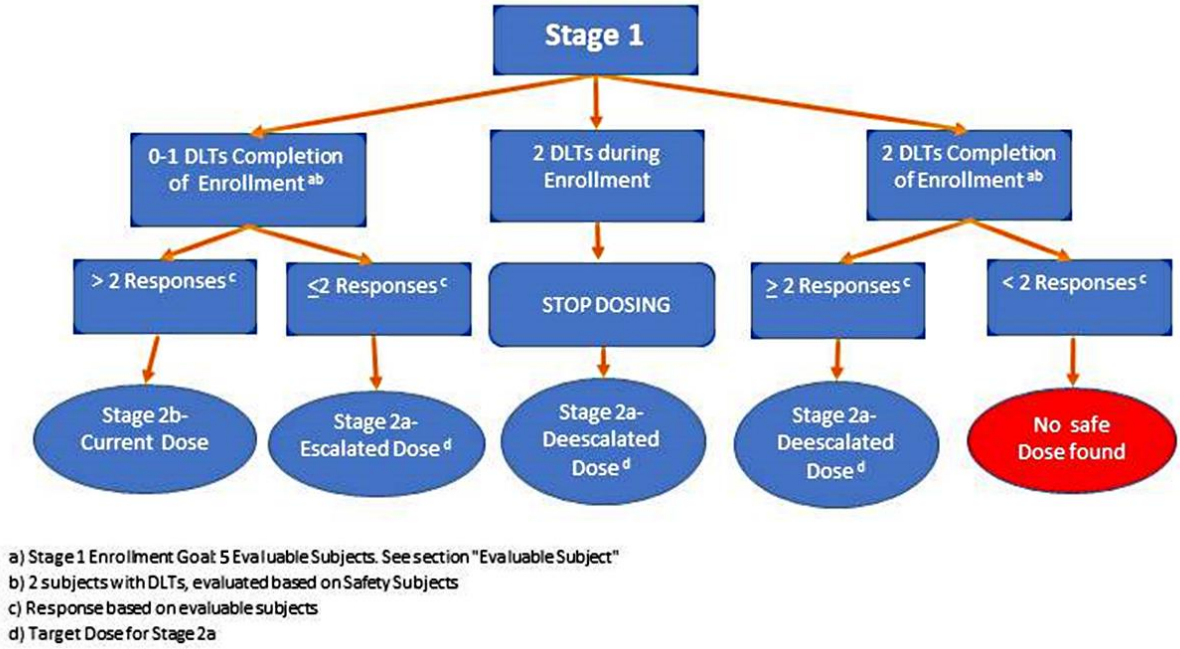
The following decisions will be made based on safety and efficacy of the dose:

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 (as tumor volume PCFB complete response [CR], strong response [SR] or partial response [PR])) 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 (as tumor volume PCFB complete response [CR], strong response [SR] or partial response [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 5 evaluable subjects in Stage 1:
      - If out of 5 evaluable subjects, 2 or more subjects have a response (as tumor volume PCFB complete response [CR], strong response [SR] or partial response [PR])), the dose will be de-escalated to 2 applications per treatment visit.
      - If out of 5 evaluable subjects, fewer than 2 have a response (as tumor volume PCFB complete response [CR], strong response [SR] or partial response [PR])), the dose will be considered intolerable and the study will be stopped.
   b. If Stage 1 dosing was stopped prior to having 5 evaluable subjects, the dose will be de-escalated from 3 applications to 2 applications per treatment visit.

c.

Figure 2. Stage 1 dose determination scheme



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 11 total evaluable subjects at the final dose for the efficacy analysis.

Stage 2a:

This stage will include 5 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 on the remaining patients.

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

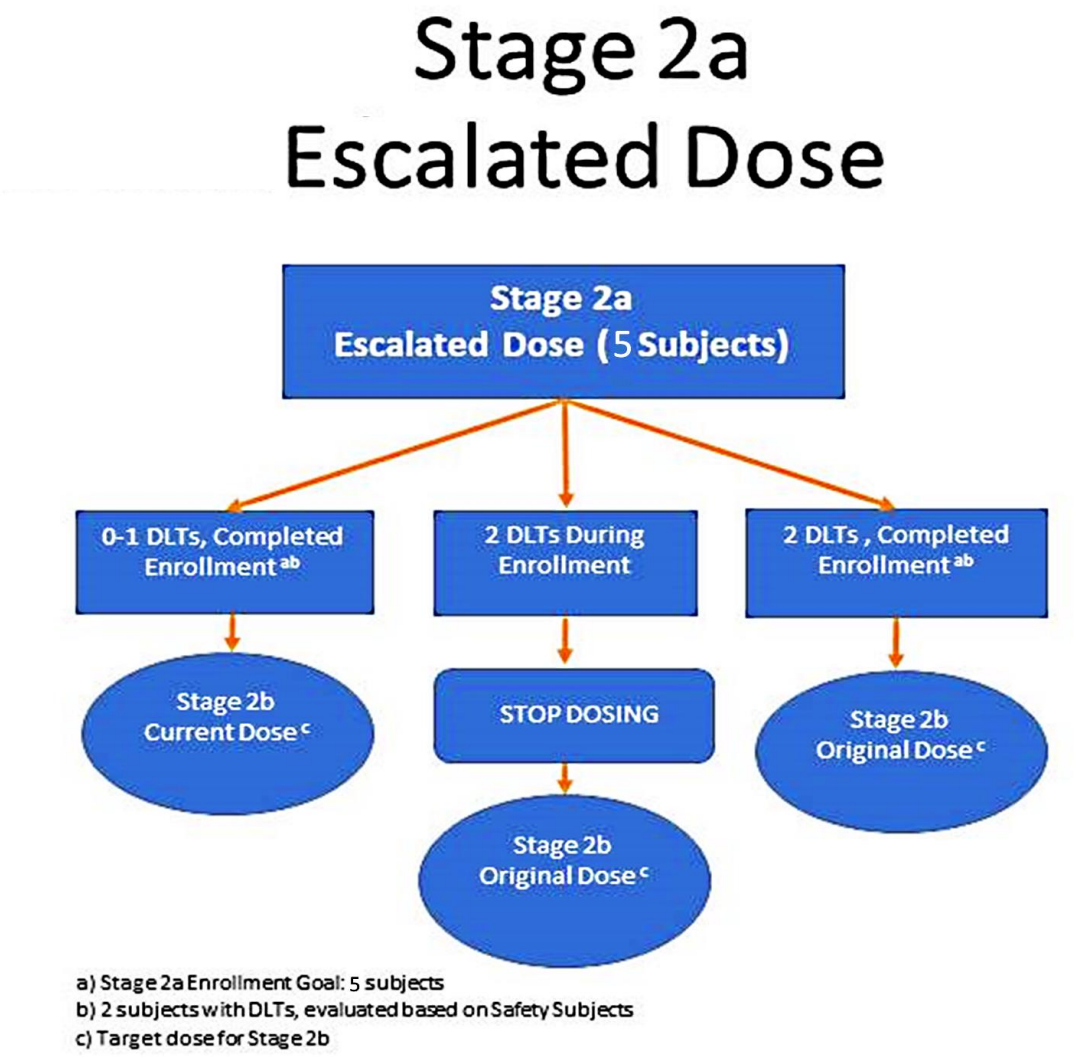


Figure 3. Stage 2a safety scheme in case of escalated dose decision

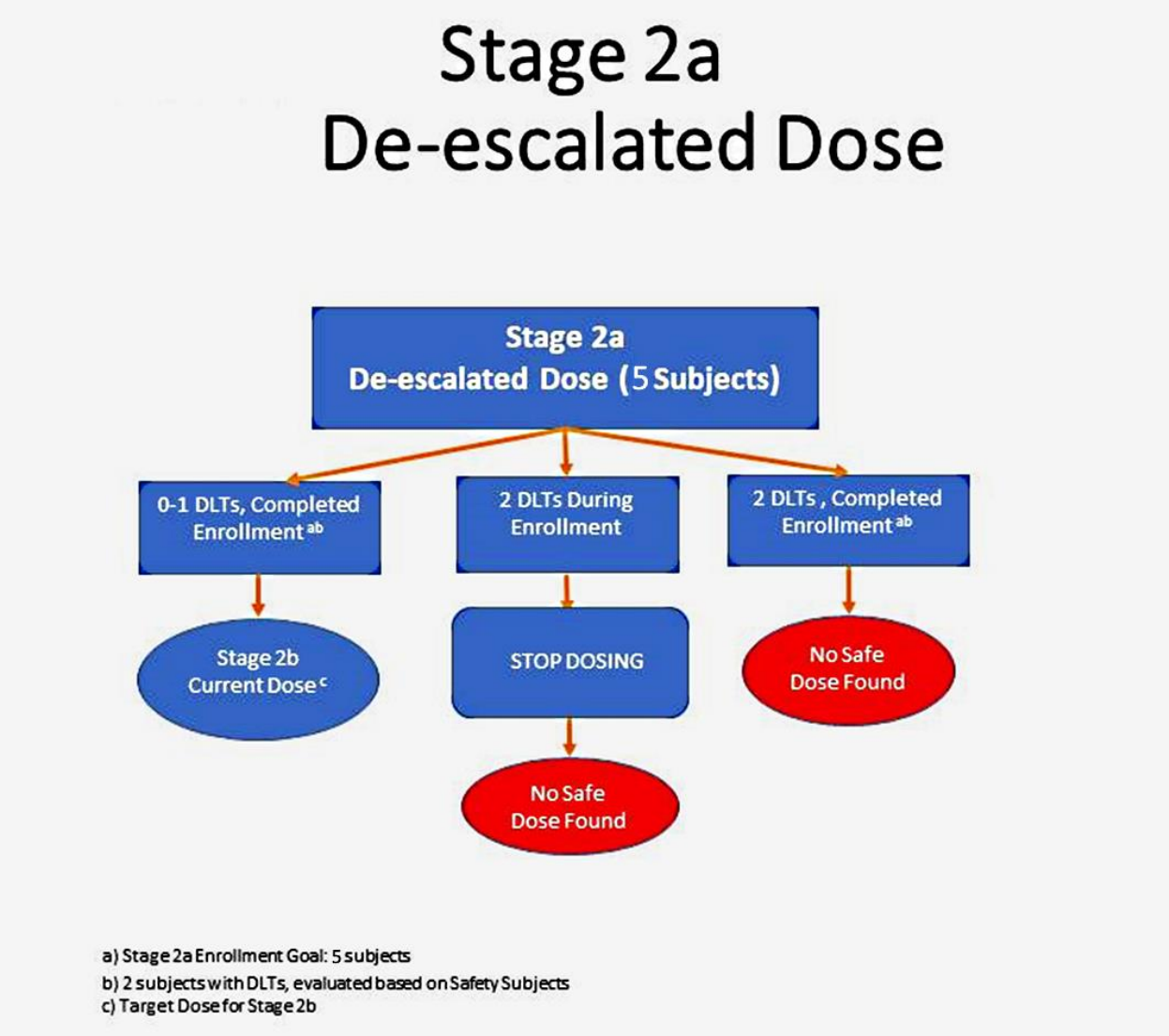


Figure 4. Stage 2a safety scheme in case of de-escalated dose decision

Stage 2b: In this stage both safety and efficacy will be evaluated. All subjects will be monitored for possible DLTs (Stage 2b – All Doses flowchart).

Stopping Rules at Stage 2b:
If 3 subjects with DLTs, no additional subjects will be dosed.

Efficacy Rules at Stage 2b:
Efficacy rules are described in the statistical plans for this stage since it is end of the study.

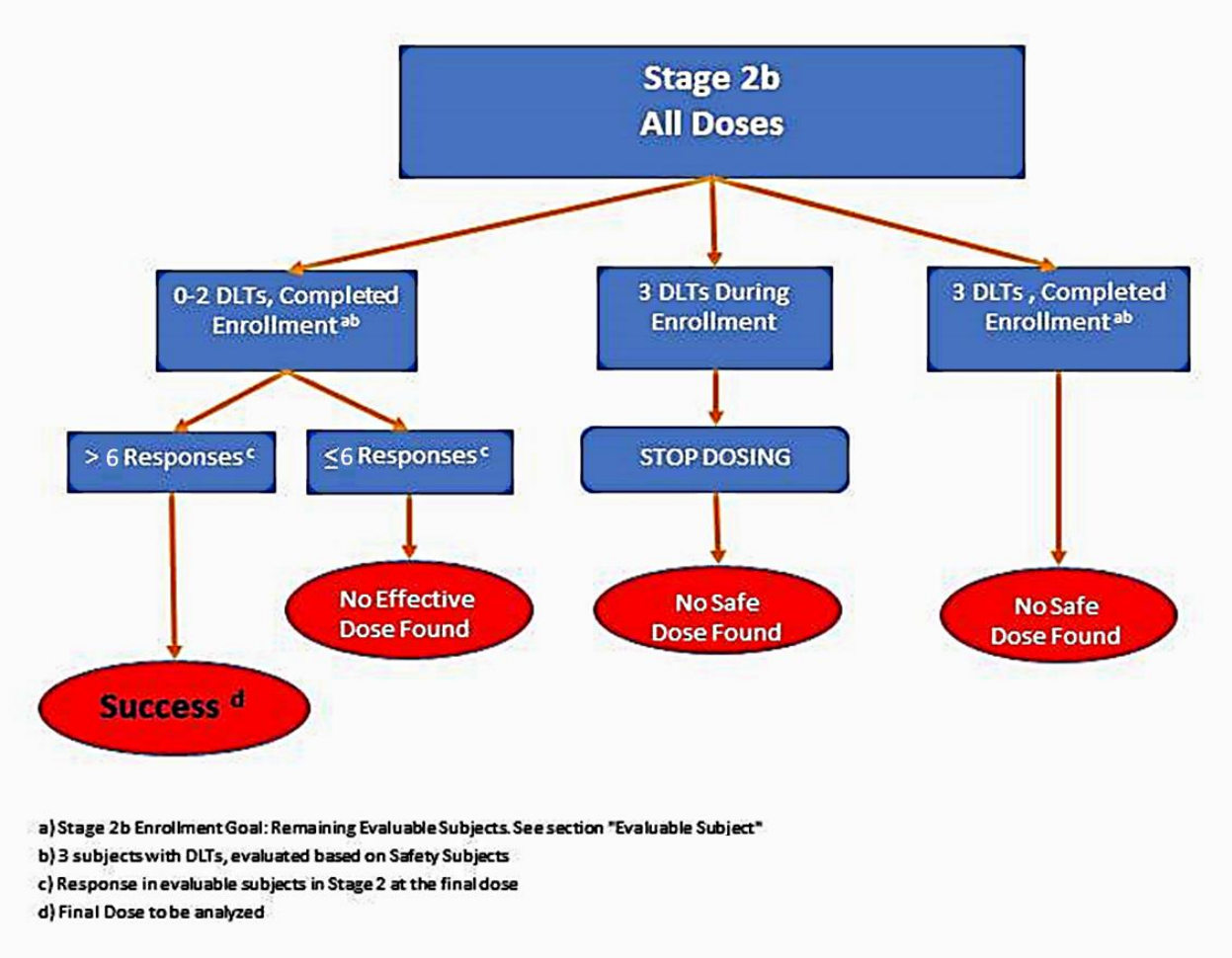


Figure 5. Stage 2b safety and efficacy scheme

Note: The surgery is to be performed no later than 42 days post Visit 1.

All subjects will subsequently undergo standard of care, surgical ablation of the tumor and satellite nodes, and possibly additional radiotherapy and chemotherapy. All subjects will be followed for up to 6 months post-surgery at 3 visits: 1 month, 3 months, and 6 months post-surgery for loco-regional response and safety. Follow-up visits may coincide with standard of care follow-up visits, if deemed appropriate by the Principal Investigator.

6.2 Discussion of Trial Design

This study is intended to establish the first-in-human safety and efficacy observations and the optimal dose of the PRV111 (Cisplatin Transmucosal System) prior to the surgical removal of SCC tumors of the oral cavity.

[redacted]

7 SELECTION OF SUBJECTS

7.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for the trial:

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. Tumor 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 (ECOG PS) 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; Hb ≥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 during the entire duration of the study and for at least 30 days after the final dose of investigational product. An 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

7.2 Exclusion Criteria

Subjects meeting any of the following criteria are ineligible for the trial:

1. Known distant metastasis of the SCC of the oral cavity
2. Systemic chemotherapy for the treatment of SCC of the head and neck less than 2 years prior to Screening
3. Concurrent documented malignancy, with the exception of localized SCC 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

7.3 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 (Section 8.2)
- 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

7.4 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

7.5 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).

7.6 Premature Termination or Suspension of Study

The study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to Privo, Institutional Review Board (IRB), US FDA, and appropriate committees. If the study is prematurely terminated or suspended, the Principle Investigator (PI) will be required to promptly inform the IRB and provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Determination of futility
- Excessive study treatment toxicity leading to delays in the scheduled surgery

7.7 Replacement of Subjects

Subjects will not be replaced.

8 TREATMENTS

Study treatment is to be administered only to subjects who have provided informed consent and have met the criteria outlined in Sections 7.1 and 7.2.

8.1 Treatments Administered

8.1.1 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]

8.1.2 Packaging

The PRV111 4 cm^2 patch and PE Powder for Reconstitution is packaged in a self-sealing pouch, 2.25” x 4.0” (constructed of medical grade paper). The primary pouch is enclosed in a secondary heat sealed triple laminated Mylar foil pouch (to protect the patch from light and moisture).

All components are packaged in a quaternary cardboard carton which is labeled appropriately.

8.1.3 Labeling

The proposed labeling of the PRV111 patch (Cisplatin Transmucosal System) study drug is described in the Pharmacy Manual.

8.1.4 Preparation

Refer to the Pharmacy Manual for a complete description of preparation. Each investigational site, and all site personnel handing the PRV111 patch, will be trained on application and handling.

8.1.5 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 2 presents definition used for dosing and treatment in this study. Treatment is expected to be approximately 35 minutes for each treatment visit.

Table 2. 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.

8.2 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 (refer to Section 8.7 for a list of suggested anti-emetic medications)
- 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 toxicity 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 related AE leading to surgery delay for more than 96 hours is a DLT

8.3 Dose Modification

If in the clinical judgment of the Medical Monitor and the PIs, clinically relevant safety issues are identified, the dose regimen (number of patches/visit and/or number of visits) may be reduced at any time during the conduct of the study.

8.4 Dose Interruption

At the Investigator's discretion, study drug may be interrupted, for reasons not related to toxicity (eg, intercurrent illness, subject scheduling conflict). Such interruption may not last more than 144 hours and may not occur more than 1 time during the subject's treatment schedule.

Subjects who experience an AE(s) requiring interruption of study drug for ≥144 hours will be removed from treatment.

Subjects who experience a DLT will be terminated from dosing, but will remain in the study for the purpose of data collection. The DLT period will be defined as the start of treatment to 14 days after the last treatment application or the time of surgery, whichever is first.

8.5 Study Drug Handling and Accountability

The Investigator (or designee, ie, study pharmacist) at the site will be responsible for handling all study drug supplies and maintaining required documentation. The Investigator must maintain complete and current inventory and dispensing records.

The Investigator (or designee) will:

- Ensure study drug supplies (PRV111 study kits) are stored between 2º and 8º C (in an appropriately controlled limited-access room in a secure location.
- Dispense the appropriate number of study patches.
- Record pertinent information regarding the number of study kits used (eg, subject identification code, date of use, number of patches used, etc.) on the Drug Dispensing Log, or other appropriate inventory form. This inventory will be maintained throughout the trial and will be periodically reviewed by a Sponsor representative.
- All used and unused patches during a treatment visit must be sent to the pharmacokinetics (PK) lab. They should be separated into properly labeled sealing plastic bags. The used patches will be processed by the PK lab to assess the residual levels of cisplatin of each application. Preparation for shipping and shipping logistics will be found in the Laboratory Manual.

8.6 Study Drug Disposal

Periodically throughout and at the conclusion of the trial, an inventory of unused study drug kits will be conducted by a Sponsor representative. All unused study drug materials during a treatment visits must be sent to the PK lab in labelled, sealing plastic bags and they will be disposed in an appropriate manner according to the laboratory policy.

At the treatment completion, any remaining unopened and unused study drug in the kit will be sent back to the Sponsor. Preparation for shipping and shipping logistics will be found in the Pharmacy Manual. At the termination of the trial, a final drug accountability review and reconciliation must be completed and any discrepancies must be investigated and their resolution documented.

8.7 Concomitant Medications and Therapy

Concomitant medications and therapies include other prescription medications, over-the-counter drugs, or dietary supplements that a study participant takes in addition to the investigational product. Based on FDA's recommendation, anti-emetic prophylaxis will be mandatory.

Symptomatic anti-emetics will be used during the study.

All subjects will receive emesis prophylaxis, administered approximately 30 minutes before PRV111 treatment. The drug used may be either ondansetron or promethazine, the dose to be determined at the discretion of the PI. After treatment, subjects may self-administer orally or via feeding tube approximately every 12 hours for 24 to 48 hours for persistent nausea. Alternatively, subjects may receive promethazine 12.5 mg orally approximately 60 minutes before administration of the PRV111 treatment. After treatment, subjects may self-administer promethazine 12.5 mg approximately every 4 to 6 hours for 24 to 48 hours for persistent nausea.

Subjects with diarrhea will receive appropriate interventions/medications at the discretion of the treating physician consistent with current clinical practice.

Based upon the Investigator's judgment, the subject might need topical anesthetic (ie, lidocaine, Magic Mouthwash) to ameliorate discomfort or prevent accidental touching and removal of the patch.

8.8 Drugs Contraindicated with PRV111

Refer to the package insert for Platinol-AQ Injection for a list of drugs that interact with cisplatin.

Plasma levels of anticonvulsant agents may become subtherapeutic during cisplatin therapy.

9 VARIABLES ASSESSED

Refer to Table 1for scheduling of study assessments.

9.1 Eligibility Only Assessments

Refer to Table 1for for timing of assessments.

9.1.1 Confirmation of Squamous Cell Carcinoma

Subjects eligible for enrollment must have histological confirmation of SCC.

HPV, the possible etiology of SCC, will be ascertained using immunohistochemistry for p16 overexpression per institutional standards. Results are not an eligibility requirement, but should be available at some point during the subject's participation in the study.

9.1.2 Tumor Staging

The size or direct extent of the primary tumor intended for surgical resection will be assessed for eligibility (National Cancer Institute, 2015):

- Tx: tumour cannot be assessed
- Tis: carcinoma in situ
- T0: no evidence of tumour
- T1, T2, T3, T4: size and/or extension of the primary tumour

9.1.3 Demographics, Medical and Medication History

Demographic information, including age, sex, race, history of tobacco and alcohol use, and medical history will be obtained by interviewing the subject.

Baseline characteristics consist of a complete medical history and detailed disease history. Medical history includes prior and ongoing medical diagnoses and conditions, surgical procedures not related to the primary diagnosis, and medications taken within the previous 28 days. Disease history is a history of the primary diagnosis and should include the date of initial oral SCC diagnosis and staging; for recurrent cases- date of most recent relapse and/or re-staging; histologic diagnosis; prior treatments (eg, chemotherapy, radiotherapy); and any current signs and symptoms related to the primary diagnosis.

9.1.4 Pregnancy Test

A serum pregnancy test to establish eligibility for female subjects of childbearing potential will be performed. In addition, a negative urine pregnancy test must be documented within 7 days prior to the first treatment visit, and at Visit 5.

9.1.5 Eastern Collaborative Oncology Group

Performance status will be assessed using ECOG PS criteria (Table 3).

Table 3. Eastern Collaborative Oncology Group Performance Status

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, eg, 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

Abbreviations: ECOG PS=Eastern Collaborative Oncology Group Performance Status.

9.2 Efficacy Assessments

Refer to Table 1for timing of assessments.

9.2.1 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 following formula will be used to calculate tumor volume (cm^3)

$$L \; x \; W \; x \; H \; x \; \pi/6$$

9.2.2 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, PR or SR. Non-Response will be defined as SD or PD (Table 4).

Table 4. Clinical Response to Treatment Based on Tumor Volume Change*

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

* Necrosis/inflammation will not be included towards clinical tumor measurements.

9.2.3 [redacted]

[redacted]

9.2.4 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

9.2.5 Loco-regional Control

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

9.3 Safety Assessments

Refer to Table 1for timing of assessments.

9.3.1 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.

9.3.2 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.

9.3.3 Neck Lymph Nodes Examination

A cervical and local lymph nodes examination will be performed.

9.3.4 Safety Laboratory Assessments

Clinical laboratories to be assessed will be as in Table 6.

Table 6. 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	• chloride • creatinine[a] • gamma glutamyl transferase • glucose • magnesium • potassium

URINALYSIS • urinalysis dipstick with reflex microscopic examination for abnormalities	• CO2	• sodium • total protein

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

9.3.5 Electrocardiograms

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

9.3.6 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.

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.

9.3.6.1 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).

9.3.6.2 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.

9.3.6.3 Adverse Reaction

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

9.3.6.4 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.

9.3.6.5 Serious Adverse Event Definitions / Reporting Requirements

9.3.6.5.1 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 a 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.

9.3.6.5.2 Pregnancy

For safety reporting purposes, any pregnancy occurring during the study will be considered an "important medical event" (Section 9.3.6.5.1). 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.

9.3.6.5.3 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) (Section 9.3.6.8). 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.

9.3.6.6 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 the recorded 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

9.3.6.7 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.

9.3.6.8 Reporting Deaths and Other Serious Adverse Events

9.3.6.8.1 Events to Be Reported and Timeframe

Any death or other SAE experienced by the subject during treatment or within 30 days of receiving study drug, regardless of expectedness, relationship to study drug, or any death that occurs more than 30 days after receiving study drug and is believed to be study drug-related, must be promptly reported to the Sponsor (*within 24 hours (of a working day) of the Investigator becoming aware of the event*) by telephone or email transmission.

9.3.6.8.2 Governing Regulatory Requirements

Compliance with this request for prompt reporting is essential in that the Sponsor is responsible for informing the FDA and other regulatory authorities as well as all other participating Investigators of the event.

Under FDA ruling (US CFR, Title 21 CFR Part 312.32) and the International Council on Harmonisation (ICH) Guidelines for Clinical Safety Data Management Definitions and Standards for Expedited Reporting, the Sponsor is required to submit written documentation, in the form of an IND Safety Report, on the following:

- SUSARs
- Unexpected fatal or life-threatening suspected adverse reactions
- Findings from other studies that suggest a significant risk to humans exposed to drug

- Findings from animal or in vitro testing that suggest a significant risk to humans exposed to drug
- Increased rate of occurrence of serious suspected adverse reactions from what is reported in the IB or the Protocol

Written submission must be made by the Sponsor to the FDA/other regulatory authorities (and by the Investigator to the IRB) as soon as possible, and in no event later than **15 calendar days** after the Sponsor determines that the information qualifies for reporting. The Sponsor shall also inform all Investigators.

In addition, the Sponsor is further required to report, by either telephone or facsimile transmission or in writing to the FDA/other regulatory authorities the occurrence of any unexpected fatal or life-threatening event associated with the use of the drug (SUSARs) no later than **7 calendar days** after notification of the event, followed by a written report **no later than 15 calendar days** after the initial report receipt date. The Sponsor shall also inform all Investigators.

The Sponsor will provide expedited reports of the following SUSARs to the Investigators for reporting to their IRB:

- SUSARs that have arisen in the clinical trial that was assessed by the IRB.
- SUSARs that have arisen in other clinical trials of the same Sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the IRB.

Investigators are required to promptly report to the IRB all unanticipated problems involving risk to human subjects, including AEs that should be considered unanticipated problems (21 CFR 312.53(c)(1)(vii), 312.66, and 21 CFR 56.108(b)(1)).

9.3.6.9 Initial Information Provided by the Investigator

The Investigator must transmit sufficient initial information to the Sponsor (or designee) should an SAE report meet the criteria for completion of an IND Safety Report. As much of the following information about the subject and the event will be requested:

- Subject identification code, gender, and age or date of birth
- Underlying diagnosis and extent of disease
- Lot number and expiration date of study drug (if available)
- Dose, route, frequency, and duration of study drug administered
- Date of last study drug administration
- Description of event, including date of onset and duration
- Date of death (if applicable)
- Intervention(s) required
- Concomitant therapy (including regimens and indications)
- Pertinent laboratory data/diagnostic study (including dates)
- Pertinent medical history
- Study drug status (dose interrupted, discontinued)

- Did event abate after interruption of study drug administration (if applicable)?
- Did event recur after study drug was reintroduced (if applicable)?
- Severity of the AE
- Relationship of the AE to study treatment
- Outcome of the AE

9.3.6.10 Follow-up Information

Follow-up data concerning the SAE (eg, diagnostic test reports, physician's summaries, etc.) must also be submitted to the Sponsor as they become available by email as soon as they become available, and until the event resolves or stabilizes.

9.3.6.11 Serious Adverse Event that are Unexpected and related Serious Adverse Reaction Review that have a Potential Impact on Trial Conduct

The Investigator will review each SAE report and evaluate further the relationship of the SAE to study drug and to the subject's underlying disease.

Based on the Investigator's and Sponsor's assessment of causality of the AE and discussions with the Medical Monitor, a decision will be made by the Sponsor concerning the need for further action with respect to the future conduct of the study. The primary consideration governing further action is whether new findings affect the safety of other subjects participating in the clinical study. If the discovery of a new SAE related to study drug raises concern over the safety of its continued administration to subjects, the Sponsor will take immediate steps to notify FDA, other regulatory authorities, and all Investigators participating in clinical studies with the study drug.

Further action required may include any of the following:

- Alteration of the existing research program by modification of the Protocol
- Discontinuation or suspension of the study
- Alteration of the informed consent process by modification of the existing consent form and informing current study participants of new findings
- Modification of previously identified expected suspected adverse reaction lists to include SAEs newly identified as study drug-related

9.4 Pharmacokinetics Assessment

[redacted]

9.5 Technical Success Assessments

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.

9.6 Timing of Assessments

Refer to Table 1for a schedule of events.

9.6.1 Screening (Visit 0)

- Visit and all historical exams/tests must occur within 28 days prior to initial treatment (Visit 1). Confirmed SCC
- Obtain and document consent from potential subject on Informed Consent Form (ICF)
- Review inclusion/exclusion criteria to determine eligibility
- Review demographics, medical and medications history to determine eligibility based on inclusion/exclusion criteria
- Obtain or perform a general physical examination (must be within 14 days of first dose) and check VS
- [redacted]
- Perform a systematic and thorough visual and manual examination of the oral cavity mouth and cervical and local lymph nodes examination
- Obtain historical or perform an ECG
- [redacted]
- Perform clinical labs: blood draw for complete blood count (CBC), chemistry panel (creatinine for determining creatinine clearance, blood urea nitrogen (BUN), liver function test (LFT), electrolytes [potassium, magnesium, calcium, and sodium], hCG [serum]) for females of childbearing potential and perform urinalysis.
- AE documentation begins after subject signs the ICF
- Schedule study visits
- Obtain historical or test tissue for HPV

9.6.2 Baseline, Treatment (Visit 1)

Occurs within 28 days following Screening visit (Visit 0).**Predose Assessments (Baseline):**

- Verify inclusion/exclusion criteria
- Perform and record result of physical examination and VS

- Perform and record visual oral cavity examination and neck lymph node examination
- Perform and document baseline clinical tumor measurement
- Collect clinical labs: blood draw for CBC, chemistry panel (creatinine for determining creatinine clearance, BUN, LFT, electrolytes [potassium, magnesium, calcium, and sodium], hCG [urine] for females of childbearing potential), and perform urinalysis.
- Administer oral anti-emetics (ondansetron or promethazine, the dose to be determined at the discretion of the PI) before the start of PRV111 treatment
- Photograph the tumor
- Draw blood for PK (-15 to 0 minutes predose)
- Administer PE (refer to Pharmacy Manual for administration instructions)
    - document time of application
    - ask for taste of PE solution
- Administer PRV111 patch(es) and document time of each application and removal. Ask for taste of patch.

Postdose Assessments:

- Draw blood for PK 30±5 minutes, 60±5 minutes and 120 ±5 minutes following application of the last patch at that treatment visit.
- VS shall be monitored at 30±5 minutes, 60±5 minutes and 120 ±5 minutes following application of the last patch applied.
- Collect all used patches (include the ones that detached prematurely), record the time of the detachment of each patch, store the patches in the plastic bags supplied by the Sponsor (refer to Laboratory Manual for instructions).
- Record AEs as reported by subject or observed by Investigator
- Review any concomitant therapy
- Schedule study visits

9.6.3 Treatment (Visit 2)

Occurs at least 48 hours, up to 144 hours, after previous visit.

Predose Assessments:

- Perform and document physical examination and VS
- Perform and document visual oral examination and neck lymph node examination
- Perform and document clinical tumor measurement and Tumor volume CFB criteria
- Administer oral anti-emetics (ondansetron or promethazine, the dose to be determined at the discretion of the PI) before the start of PRV111 treatment
- Photograph the tumor
- Draw blood for PK (-15 to 0 minutes predose)
- Administer PE (refer to Pharmacy Manual for administration instructions)
    - document time of application
- Administer PRV111 patch(es) and document time of each application and removal
    - Document adherence of each patch

Postdose Assessments:

- Draw blood for PK 30±5 minutes following application of the last patch applied at that treatment visit. VS shall be monitored at 30±5 minutes following application of the last patch at that treatment visit.
- Collect all used patches (include the ones that detached prematurely), record the time of the detachment of each patch, store the patches in the plastic bags supplied by the Sponsor (refer to Laboratory Manual for instructions)
- Record AEs as reported by subject or observed by Investigator
- Review any concomitant therapy
- Schedule study visits

9.6.4 Treatment (Visit 3)

Occurs at least 48 hours , up to 144 hours, after previous visit.

Predose Assessments:

- Perform and document physical examination and VS
- Perform and document visual oral examination and neck lymph node examination
- Perform and document clinical tumor measurement and Tumor volume change from baseline
- Collect clinical labs: blood draw for CBC, chemistry panel (creatinine for determining creatinine clearance, BUN, LFT, electrolytes [potassium, magnesium, calcium, and sodium], and perform urinalysis.
- Administer oral anti-emetics (ondansetron or promethazine, the dose to be determined at the discretion of the PI) before the start of PRV111 treatment
- Photograph the tumor
- Draw blood for PK (-15 to 0 minutes predose)
- Administer PE (refer to Pharmacy Manual for administration instructions)
    - Document time of application
- Administer PRV111 patch(es) and document time of each application and removal
    - Document adherence of each patch

Postdose Assessments:

- Draw blood for PK 30±5 minutes
- VS shall be monitored for 30±5 minutes following application of the last patch applied at that treatment visit
- Collect all used patches (include the ones that detached prematurely), record the time of the detachment of each patch, store the patches in the plastic bags supplied by the Sponsor (refer to Laboratory Manual for instructions).
- Record AEs as reported by subject or observed by Investigator
- Review any concomitant therapy
- Schedule study visits for subjects

9.6.5 Treatment (Visit 4)

Occurs at least 48 hours, up to 144 hours, after previous visit.

Predose Assessments:

- Perform and document physical examination and VS
- hCG [urine] for females of childbearing potential
- Perform and document clinical tumor measurement and tumor volume change from baseline criteria
- Perform and document visual oral examination and neck lymph node examination
- Administer oral anti-emetics (ondansetron or promethazine, the dose to be determined at the discretion of the PI) before the start of PRV111 treatment
- Photograph the tumor
- Draw blood for PK (-15 to 0 minutes predose)
- Administer PE (refer to Pharmacy Manual for administration instructions)
    - document time of application
- Administer PRV111 patch(es) and document time of each application and removal
    - Document adherence of each patch

Postdose Assessments:

- Draw blood for PK 30±5 minutes, 60±5 minutes and 120±5 minutes
- VS shall be monitored at 30±5 minutes, 60±5 minutes and 120±5 minutes following application of the last patch applied.
- Collect all used patches (include the ones that detached prematurely), record the time of the detachment of each patch, store the patches in the plastic bags supplied by the Sponsor (refer to Laboratory Manual for instructions).
- Record AEs as reported by subject or observed by Investigator
- Review any concomitant therapy
- Schedule study visits

9.6.6 Post-Treatment/Pre-Op Visit (Visit 5)

- Occurs a minimum of 72 hours after the last visit and prior to surgery. Perform and document physical examination and VS
- Perform and document visual oral examination and neck lymph node examination
- [redacted]
- Perform and document clinical tumor measurement and Tumor volume CFB criteria
- ECG
- Collect clinical labs: blood draw for CBC, chemistry panel (creatinine, BUN, LFT, electrolytes [potassium, magnesium, calcium, and sodium], and perform urinalysis
- Photograph the tumor
- Record AEs as reported by subject or observed by Investigator
- Review any concomitant therapy

9.6.7 Surgery Day (Visit 6)

- Tumor resection as per the standard of care
- [redacted]
- Post-Surgery, collect clinical labs. Draw blood for CBC, chemistry panel (creatinine, BUN, LFT, electrolytes [potassium, magnesium, calcium, and sodium], and perform urinalysis. Post-surgical labs may be used, if deemed appropriate by the Principal Investigator

9.6.8 Post-Treatment Follow-Up (Visits 7, 8, & 9)

All subjects will be followed for up to 6 months post-surgery at 3 visits: 1, 3, and 6 months post-surgery for loco-regional response and safety. Follow-up visits may coincide with standard of care follow-up visits, if deemed appropriate by the Principal Investigator.

- Perform and record results of physical examination and VS
- Perform visual oral examination and neck lymph node examination to assess for signs of loco-regional recurrence
- Review any concomitant therapy

10 STATISTICAL METHODS AND PLANNED ANALYSES

10.1 General Considerations

Clinical response to treatment will be evaluated according to Table 4.

10.2 Sample Size Determination

Safety outcomes resulting in DLT 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.
- [redacted]
- 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. Additional subjects will be accrued for a total of 11 evaluable subjects at the final dose. The null hypothesis will be rejected if **7** or more responses are observed at the final dose. This design yields a type I error rate of 0.018 and power of 96.44% when the true response rate is 0.85.

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

10.3 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.Pharmacokinetics

[redacted]

10.4 Study Populations

10.4.1 Safety Population

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

10.4.2 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.

10.5 Statistical Analyses

[redacted]

[redacted]

10.5.2 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.

10.5.3 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 CFB.

10.5.4 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

10.5.5 Efficacy Data

Efficacy outcomes include:

- Response to treatment evaluated by Tumor volume change from baseline (CFB)
- [redacted]
- Incidence of recurrence at 6 months
- [redacted]

[redacted]

10.5.6 Safety Data

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.

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 4.03. The severity of oral mucositis will be graded according to the WHO grade (Section 8.2).

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.

10.5.7 Pharmacokinetics Data

[redacted]

10.5.8 Technical Data

Technical success is defined as:

- 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.

11 QUALITY CONTROL AND QUALITY ASSURANCE

Quality Assurance (QA) and Quality Control systems will be implemented and maintained with Standard Operating Procedures by Privo Technologies, as appropriate, to ensure that this clinical study is conducted and data are generated, documented and reported in compliance with the Protocol, ICH E6 GCP and applicable regulatory requirements.

Before enrolling any subjects in this study, a Sponsor representative and the Investigator will review the Protocol, IB, CRFs and instructions for their completion, as well as the procedures for obtaining informed consent and for reporting TEAEs and SAEs. A qualified representative of the Sponsor will monitor the conduct of the study by visiting the site and by contacting the site by telephone and email. During site visits, the study Monitor will assure accurate and reliable data collection by verifying the information recorded on the CRFs against source documents and medical records (ie, source document verification).

Measures will be undertaken to protect the confidentiality of records that could identify subjects respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements.

12 DOCUMENTATION AND INSPECTIONS

12.1 Study Monitoring

The Sponsor has responsibility to governing regulatory authorities to take all reasonable steps to ensure the proper conduct of the study with respect to trial ethics, Protocol adherence, and data integrity and validity.

This trial will be closely monitored by Sponsor representatives throughout its duration. Monitoring will be in the form of personal visits with the Investigator and staff as well as any appropriate communications by telephone, mail, or email transmission.

The personal visits and monitoring are conducted to the extent possible however under certain circumstances such as COVID-19 pandemic, to minimize or eliminate immediate hazards or to protect the life and well-being of research staff and participants, discussions, monitoring and site closures will be performed remotely via technologies including but not limited to phone calls, email, eCRF, eTMF and file sharing on video conferencing for source documents. Sponsor and sites can utilize video and teleconferencing such as ZOOM to remotely discuss, review and approve documents. The PI sign off can be obtained and saved electronically for all eCRFs at the site.

The purpose of these contacts is to review trial progress, Investigator and subject adherence to the protocol, and to determine if there are any problems associated with the conduct of the study. The following may be assessed during site monitoring visits:

- Required regulatory documentation
- Signed ICFs
- Subject accrual and follow-up
- Study drug inventory records
- Investigator and subject compliance to the study Protocol
- Concomitant therapy uses
- AE documentation
- Protocol deviation documentation
- Data are accurate, complete, and verifiable when compared to source documents

The Investigator and study staff are expected to cooperate with monitors during such visits and provide all relevant study documents.

12.2 Audits and Inspections

All documentation pertaining to this clinical trial may be subject to a QA audit by the Sponsor, or the FDA. Upon request, the auditor will have access to inspect, copy, review, and audit all source documents, CRFs, medical records, correspondence, and ICFs pertaining to the subjects in the trial. The Investigator agrees to promptly take any reasonable steps that are requested by

the Sponsor as a result of an audit to cure deficiencies in the study documents and CRFs. Other documentation subject to QA audit includes the IRB files, certification and quality control of supporting laboratories, and records relevant to the trial in any supporting pharmacy facilities. Conditions of storage of study materials are also subject to inspection. Sponsor representatives may observe the conduct of any aspect of the clinical trial or its supporting activities both within and outside of the Investigator's institution.

13 ETHICAL AND LEGAL ISSUES

13.1 Ethical Conduct/Good Clinical Practice

This study will be conducted in accordance with the ethical principles that have their origin in the current Declaration of Helsinki and will be consistent with ICH GCP and applicable regulatory requirements.

13.2 Institutional Review Board

This study must be reviewed and approved by the IRB representing the institution prior to enrolling subjects. The IRB must be appropriately constituted and meet all requirements as described in Part 56, Title 21 of the US CFR. The review must include both the Protocol and the ICF for the trial. A copy of the Letter or Notice of Approval from the IRB must be received by the Sponsor prior to shipment of drug supplies to the Investigator. The IRB membership list must be submitted to the Sponsor with the written IRB approval and updated lists, if applicable.

The Investigator must promptly report all changes in the research activity and all unanticipated problems involving risk to the subjects or others to their IRB. The Investigator will provide progress reports as required by the IRB. The Investigator is responsible for assuring continuing review and approval of the clinical study on an annual basis and submitting documentation of renewal to the Sponsor. The Investigator will give notice to the IRB when participation in the study has been completed.

13.3 Written Informed Consent

The Investigator agrees to protect the rights, safety, and welfare of the subjects entered into the study, including obtaining written informed consent prior to performing any study-related procedures and informing each subject that the study drug is being used for investigational purposes. A copy of the IRB-approved ICF to be used during the study must be submitted for Sponsor review prior to study initiation.

Prior to entry into the study, the purpose and nature of the study and possible AEs must be explained to each patient. All questions about the study should be answered to the patient’s satisfaction or the patient’s legal representative. It is the responsibility of the Investigator or designee to obtain written informed consent from each patient, thereby attesting that consent was freely given. A copy of the signed and dated ICF will be given to the patient. Documentation of the informed consent process must be evident in the patient’s clinical files, and the original executed ICF must be available for review by the study Monitor.

13.3.1 Update of Informed Consent

In the event that modifications in the experimental design, dosages, parameters, subject selection, etc., of the Protocol are indicated or required, and in the event that such modifications substantially alter the study design or increase the potential risk to subjects, revisions to the existing ICF will be made. Such a revision will be reviewed and approved by the appropriate IRB, and documentation of this approval will be forwarded to the Sponsor for submission to the appropriate regulatory body.

In addition, all current study participants, as well as subsequent study candidates, will be informed of the study design modification or increase in potential risk, and written informed consent will be obtained as outlined in Section 13.3.

13.4 Records and Case Report Forms

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the study drug. Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained. All requested information must be entered on the CRF in the spaces provided.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirements.

The completed CRF must be promptly reviewed, signed, and dated by a qualified physician who is an Investigator or Sub-Investigator. The Investigator must retain a copy of the CRFs including records of the changes and corrections.

13.5 Protocol Deviations

The study is to be conducted as described in this Protocol without deviation unless there is a safety concern. The Protocol should not be modified for any subject without the prior consent of the Sponsor and, if necessary, the IRB responsible at the investigative site.

In the event of an important deviation, a report will be submitted to the IRB (as applicable) and site explaining the circumstances.

13.6 Retention of Records

US federal law requires that the Investigator retain copies of all files pertaining to the trial (ie, medical records, laboratory reports, drug inventory/disposition records, signed ICFs, CRFs, all correspondence, dates and reports of monitoring visits) for a period of 2 years following the date of marketing application approval of the drug for the indication investigated in the study, and until there is no pending or contemplated marketing application, or for 2 years following the Sponsor's discontinuing worldwide clinical development of the study drug, as notified by the Sponsor, whichever is longer.

If the Investigator relocates, retires, or withdraws for any reason from the study, trial records may be transferred to an acceptable designee, such as another Investigator within the institution.

Prior notice of such transfer will be provided in writing to the Sponsor. The Investigator must obtain written permission from the Sponsor prior to disposing of any records.

14 REFERENCES

Brockstein B, Stenson K, Song S. Overview of Treatment for Head and Neck. Posner M, Fried M, Brizel D, Ross M, editors. 2016. UpToDate.

da Silva SD, Hier M, Mlynarek A, Kowalski LP, Alaoui-Jamali MA. Recurrent oral cancer: current and emerging therapeutic approaches. Front Pharmacol 2012; 3:149.

Galluzzi L, Vitale I, Michels J, Brenner C, Szabadkai G, Harel-Bellan A et al. Systems biology of cisplatin resistance: past, present and future. Cell Death Dis 2014; 5:e1257.

Gregoire V, Lefebvre JL, Licitra L, Felip E. Squamous cell carcinoma of the head and neck: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010; 21 Suppl 5:v184-v186.

Gurudutt VV, Genden EM. Cutaneous squamous cell carcinoma of the head and neck. J Skin Cancer 2011; 2011:502723.

Hong M, Puaux AL, Huang C, Loumagne L, Tow C, Mackay C et al. Chemotherapy induces intratumoral expression of chemokines in cutaneous melanoma, favoring T-cell infiltration and tumor control. Cancer Res 2011; 71(22):6997-7009.

Johnstone TC, Suntharalingam K, Lippard SJ. Third row transition metals for the treatment of cancer. Philos Trans A Math Phys Eng Sci 2015; 373(2037).

Kelner N, Vartanian JG, Pinto CA, Coutinho-Camillo CM, Kowalski LP. Does elective neck dissection in T1/T2 carcinoma of the oral tongue and floor of the mouth influence recurrence and survival rates? Br J Oral Maxillofac Surg 2014; 52(7):590-597.

Marta GN, William WN, Jr, Feher O, Carvalho AL, Kowalski LP. Induction chemotherapy for oral cavity cancer subjects: Current status and future perspectives. Oral Oncol 2015; 51(12):1069-1075.

Milano M, Chmura S, Haraf D, Banuchi V, Kraus D. Treatment of Locally Recurrent Squamous Cell Carcinoma of the Head and Neck. Brizel DFMRM, editor. 2015. UptoDate.

National Cancer Institute. Cancer Staging. March 2015. Accessed 3 August 2017 https://www.cancer.gov/about-cancer/diagnosis-staging/staging.

National Cancer Institute. SEER Cancer Statistics Fact Sheet: Oral Cavivity and Pharynx Cancer. NIH, editor. 2016. 8-24-2016.

National Institute of Dental and Craniofacial Research. Oral Cancer 5-year Survival Rates by Race, Gender, and Stage of Diagnosis. 2014. 8-24-2016.

National Institute of Dental and Craniofacial Research. Oral Cancer Incidence (New Cases) by Age, Race, and Gender. 2016. NIH. 9-15-2016.

Seiwert TY, Salama JK, Vokes EE. The chemoradiation paradigm in head and neck cancer. Nat Clin Pract Oncol 2007; 4(3):156-171.

US Department of Health and Human Services. "National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.0. 2009 (v4. 03: June 14, 2010)."

Vermorken JB, Remenar E, van HC, Gorlia T, Mesia R, Degardin M et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med 2007; 357(17):1695-1704.

Vermorken JB, Specenier P. Optimal treatment for recurrent/metastatic head and neck cancer. Ann Oncol 2010; 21 Suppl 7:vii252-vii261.

WG Critical Care, LLC. Cisplatin Injection (NDA 018057), product labeling. 2015. Paramus, NJ, WG Critical Care, LLC.