CLINICAL PROTOCOL

CTIX-BRI-205

Phase 2, Multi-center, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Brilacidin Oral Rinse Administered Daily for 7 Weeks in Attenuating Oral Mucositis in Patients with Head and Neck Cancer Receiving Concurrent Chemotherapy and Radiotherapy

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PROTOCOL SYNOPSIS

Name of Sponsor/Company: Innovation Pharmaceuticals Inc. (formerly Cellceutix Corporation)
Name of Finished Product: Brilacidin Solution, 50 mg/ml (free base)
Name of Active Ingredient: Brilacidin tetrahydrochloride
Title of Study: Phase 2, Multi-center, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Brilacidin Oral Rinse Administered Daily for 7 Weeks in Attenuating Oral Mucositis in Patients with Head and Neck Cancer Receiving Concurrent Chemotherapy and Radiotherapy
Study Centers: Approximately 20 sites in the United States will participate in the study
Number of Subjects Planned: Approximately 60 subjects with head and neck cancer receiving concurrent chemotherapy and radiotherapy
Study Duration per subject: Approximately 17 weeks
Phase of Development: 2
Primary Objective(s): • To evaluate the efficacy of topically applied brilacidin administered three times daily by oral rinse for approximately 7 weeks (treatment week is defined as a 7-day period, irrespective of the day of the week that the 7-day period begins) compared to placebo in reducing the incidence of severe OM (defined as grade 3 or 4 on the WHO Oral Mucositis scale, WHO Grade ≥3) in subjects with head and neck cancer (HNC) receiving concomitant chemoradiation therapy (CRT). • To evaluate the safety and tolerability of topically applied brilacidin administered three times daily by oral rinse for approximately 7 weeks (treatment week is defined as a 7-day period, irrespective of the day of the week that the 7-day period begins).

Secondary Objectives:

- To evaluate the efficacy of topically applied brilacidin in reducing the duration of severe OM (WHO Grade ≥3) in subjects with HNC receiving concomitant chemoradiation therapy.
- To evaluate the efficacy of topically applied brilacidin in delaying the onset of severe OM (WHO Grade ≥3) in subjects with HNC receiving concomitant chemoradiation therapy.

Design and Methodology:

The study is a Phase 2, randomized (1:1 ratio), double-blind, placebo-controlled, 2-arm trial to be conducted in patients receiving chemoradiation for the treatment of squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or supraglottic larynx. Patients with this diagnosis whose anticipated treatment includes chemoradiation therapy (CRT) and who consent to participate will enter a screening period of up to 45 days prior to the anticipated initiation of CRT. If eligible, subjects will be randomized to one of the two blinded study treatments and will enter the treatment phase of the study (approximately 11 weeks in duration).

For entry into the study, eligible patients will have recently-diagnosed (in the previous 6 months), pathologically-confirmed, non-metastatic squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or supraglottic larynx. Tumor staging for eligibility, using AJCC Tumor Staging Guidelines, or as determined by institutional tumor board review may be determined from scans (CT, PET, and/or MRI) obtained within 120 days prior to consent for screening. Scan interpretation should follow Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 criteria (Appendix E).

Patients must be scheduled to receive a continuous course of intensity-modulated radiation therapy (IMRT) with a minimum cumulative dose of 55 Gray (Gy) and maximum cumulative dose of 72 Gy over approximately 7 weeks (treatment week is defined as a 7-day period, irrespective of the day of the week that the 7-day period begins). Planned radiation treatment fields must include at least two oral sites (buccal mucosa, floor of mouth, ventral/lateral tongue, soft palate). The treatment plan must include chemotherapy with cisplatin administered in standard weekly (30-40 mg/m^2) or approximately every 21 days (80-100 mg/m^2) regimens. No other chemotherapy is allowed during radiotherapy unless intolerance to cisplatin is demonstrated during study participation. In this case, with medical monitor approval, carboplatin may be substituted.

Eligible subjects will be randomized to receive one of the following study drug regimens during participation in the study (1:1 ratio):

Arm A: Placebo (WFI) [oral rinse tid]

Arm B: Brilacidin 3 mg/mL in WFI [oral rinse tid]

The study drug will be administered as an oral rinse three times daily (approximately 6 hours between oral rinses) beginning on the first day of radiotherapy and continuing each day (including weekends) until the completion of the course of chemoradiation. The

subject will be instructed to use the study oral rinse three times each day with approximately 6 hours between each use, whenever possible. Subjects will be instructed to perform the oral rinse for 1-minute and *spit out the rinse after each use, avoiding swallowing any of the rinse*. The first use of oral rinse on the first day of study drug treatment must be witnessed by a member of the study staff. Subjects will be told not to eat, brush their teeth, chew gum, or suck on hard candy, cough drops, etc., for at least 10 minutes before each oral rinse. A subject should rinse his/her mouth with plain water prior to administering the oral rinse. Subjects will be told not to eat, drink, brush their teeth, chew gum, or suck on hard candy, cough drops, etc., for 30 minutes following each use of the oral rinse. Subjects who use allowed non-study oral rinse(s) (i.e., Gelclair®, saline solutions) during the study period should ensure that the study oral rinse is used at least 60 minutes after use of a non-study oral rinse and that a non-study oral rinse is not used until at least 60 minutes after use of the study rinse.

Note: Although chemoradiation is complete (i.e. the end of radiation therapy (ERT) visit has occurred), subjects are to complete the full 7 days of study drug for Week 7.

The treatment phase of the study will include: (1) the period of RT treatment with concomitant chemotherapy and (2) all assessments occurring after the last dose of RT, through and including a Week 4 Post-RT follow-up visit (the EOS visit).

- During the CRT treatment period, subjects will be assessed twice weekly for the presence and severity of OM by trained evaluators using the WHO grading scale for OM. Subjects will complete a daily study diary (including weekend days). The diary contains Question 2 of the Oral Mucositis Daily Questionnaire (OMDQ), a record of daily analgesic use for mouth and/or throat pain, a record of the study drug oral rinses performed each day, and the subject's assessment of mouth sensations. The diary will be reviewed by a member of the study staff each day during the first week (at least 5 days) of study treatment to ensure that the subject is appropriately completing the diary. If subject diary completion is satisfactory, then the diary will be reviewed at least once weekly during the remainder of the study. At weekly intervals (on the same day of each week), subjects will complete the FACT-H&N instrument to record quality of life responses.
- Single samples (venous blood) for assessment of brilacidin plasma concentrations will be obtained from each subject at weekly intervals during the CRT treatment period. These blood samples may be obtained at the time of the venipuncture for clinical laboratory tests as specified by the protocol.
- For those subjects who have consented to gene analysis, samples of venous blood will be obtained at baseline, during week 3, and on the last day of radiation.
- All subjects will be evaluated at 1 week after RT completion (or withdrawal from the study) for assessment of the presence and severity of OM and other safety assessments. Subjects having an WHO OM Grade $\geq$2 at this post-treatment visit will return to the clinic at weekly intervals until mucositis resolves to WHO OM Grade <2; subjects having a WHO OM Grade $\leq$1 may be followed by weekly phone call instead. During the post-RT period, subjects will continue to complete the daily study diary

that contains Question 2 of the OMDQ as well as recording analgesic use and subjects will complete the FACT-H&N QOL instrument weekly until 4 weeks (± 2 days) post-RT. In most instances the last study related visit, the End of Study (EOS) visit, will be at Week 4 post-RT.

Patient Eligibility:

- Patients with recently diagnosed (within previous 6 months), pathologically-confirmed, non-metastatic squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or supraglottic larynx.
- Patients scheduled to receive a continuous course of IMRT over approximately 7 weeks (treatment week is defined as a 7-day period, irrespective of the day of the week that the 7-day period begins) with a minimum cumulative dose of 55 Gray (Gy) and maximum cumulative dose of 72 Gy. (IMRT is typically administered as 35 separate radiation treatments).
- Planned radiation treatment fields must include at least two oral sites (buccal mucosa, floor of mouth, ventral/lateral tongue, soft palate). The treatment plan must include chemotherapy with cisplatin administered in either a standard weekly (30-40 mg/m^2) or approximately every 21 days (80-100mg/m^2) regimen. No other chemotherapy is allowed during radiotherapy unless intolerance to cisplatin is demonstrated. In this case, with medical monitor approval, carboplatin may be substituted.

Inclusion Criteria:

1. Willing and able to read, understand, and sign an informed consent form (ICF) for the study approved by the Investigator's local or a central Institutional Review Board (IRB) or Independent Ethics Committee (IEC) prior to the initiation of any study-related procedures.
2. Males or females aged ≥18 years on day of consent.
3. Have recently-diagnosed (within previous 6 months pathologically-confirmed, non-metastatic squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or supraglottic larynx. The treatment planned will utilize CRT therapy as first line non-surgical treatment. Scans (CT, PET, and/or MRI) obtained within 120 days prior to consent for screening can be used to determine the patient's eligibility.

   Note: Post-surgical subjects may be enrolled provided any head/neck surgical sites (including sites of dental extractions) are sufficiently healed.
4. Have a plan to receive a continuous course of conventional external beam irradiation delivered by intensity-modulated radiation therapy (IMRT) as single daily fractions of 2.0 Gy to 2.2 Gy with a cumulative radiation dose ≥55 Gy and ≤72 Gy. Planned radiation treatment fields must include at least two oral sites (buccal mucosa, floor of mouth, ventral/lateral tongue, soft palate)

   Note: The independent RTQA consultant must confirm that the planned radiation treatment meets the protocol criteria.

5. Have a plan to receive a standard cisplatin chemotherapy regimen administered weekly (30-40 mg/m^2) or approximately every 21 days (80-100 mg/m^2)
6. Have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2. However, potential subjects with an ECOG Performance Status of 3 may be enrolled provided their condition does not preclude performing the actions required by study participation (e.g. opening medication bottles, swishing the oral rinse and spitting out, completing or participating in completion of daily diaries and FACT-H&N forms).
7. Have adequate hematopoietic, hepatic, and renal function at screening:
    a. Hematopoietic function
        i. Hemoglobin ≥ 9 g/dL
        ii. Absolute neutrophil counts (ANC) ≥ 1.5 x 10^3/uL
        iii. Platelet count ≥ 100 x 10^3/uL
    b. Hepatic function
        i. Total bilirubin ≤ 1.5 times the upper limit of normal (ULN)
        ii. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.0 times the ULN
    c. Renal function
        i. Either a serum creatinine concentration within the site laboratory's normal limits or a calculated creatinine clearance > 60 mL/min
8. Urine or serum pregnancy test: negative for female patients of childbearing potential. If pregnancy test is performed more than 10 days prior to the start of radiotherapy, the test must be repeated prior to Day 1.
9. Female subjects with reproductive potential must agree to use reliable means of contraception (e.g., abstinence, double barrier method, oral/implantable/transdermal contraception, Depo-provera, intrauterine device, or physical barrier) throughout study participation and for 90 days after the last use of study oral rinse.

    A female is considered of reproductive potential unless she is premenarchal, without a uterus and/or both ovaries, or has had a bilateral tubal ligation, has undergone the Essure procedure with confirmation of tubal blockage, or is postmenopausal. Females identified as postmenopausal for less than 2 years must have serum Follicle Stimulating Hormone (FSH) of 40 mIU/mL or greater at the Screening visit to be considered postmenopausal.

Exclusion Criteria:

1. Has tumor(s) of the lips, sinuses, salivary glands, nasopharynx, glottic larynx, subglottic larynx, or unknown primary tumor
2. Has metastatic disease (M1) Stage IV C
3. Has had prior radiation to the head and neck for any reason/condition
4. Plan to be treated with cetuximab (Erbitux®) and not cisplatin as the component of chemoradiation

5. Planned use of cisplatin as induction chemotherapy.
6. Has a history of other malignant tumors within the last 5 years, except non-melanoma skin cancer or in situ cervical carcinoma curatively excised
7. Has had a major surgical procedure, other than for HNC, or significant traumatic injury within 4 weeks prior to the initiation of RT; anticipation of need for major surgical procedure during the course of the study
8. Will have incompletely healed sites of dental extractions on first day of chemoradiation treatment
9. Has a 12-lead ECG obtained at screening visit which shows medically significant abnormality(ies) (e.g. left bundle branch block, frequent premature ventricular contractions, QTc interval prolongation > 450 msec for males and > 470 msec for females)
10. Has untreated hypertension or has hypertension under treatment meeting one of the following definitions:
    a. Age ≥ 60 years: SBP ≥ 150 mmHg and/or DBP ≥ 90 mmHg
    b. Age < 60 years: SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg
    c. All ages with diabetes: SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg

    NOTE: Medical therapy for untreated hypertension may be initiated or existing treatment for hypertension may be optimized during the Screening Phase if clinically indicated. Blood pressures will then be reassessed before Day 1 to confirm eligibility. Blood pressure criteria need to be met at screening and/or prior to dosing on Day 1.
11. Has active infectious disease undergoing systemic treatment, excluding oral candidiasis
12. Has oral mucositis (of any severity) prior to initiation of radiotherapy
13. Has a diagnosis of an immunosuppressive illness or a condition requiring chronic immunosuppression
14. Has known seropositivity for HIV or hepatitis C antibody, or known to be hepatitis B surface antigen positive (testing for these serologic markers is not required for enrollment in this protocol)
15. Use of any investigational agent within 30 days of randomization
16. Is pregnant or breastfeeding
17. Has known allergies or intolerance to brilacidin, cisplatin, or carboplatin
18. Has inability to give informed consent or comply with study requirements
19. Has any other condition or prior therapy that in the opinion of the Investigator would make the patient unsuitable for the study and/or unable to comply with requirements for follow-up visits.
20. Is unwilling or unable to agree to swish and spit the study oral rinse three times per day during the study period

Test Product, Dose, and Mode of Administration:

Brilacidin (45 mg/ 15mL WFI) oral rinse tid, or placebo (15mL WFI) oral rinse tid

Efficacy and Safety Endpoints:

Primary Efficacy Endpoint

Incidence of severe OM (WHO Grade ≥3) experienced during radiation therapy by subjects with HNC receiving concomitant chemoradiation therapy and a cumulative radiation dose of at least 55 Gy.

Secondary Efficacy Endpoints

- Duration of severe OM (WHO Grade ≥3), from initial WHO Grade ≥3 during radiation therapy to the first WHO Grade 2 or lower OM assessment during/after radiation therapy.
- Duration of severe OM (WHO Grade ≥3), from initial WHO Grade ≥3 during radiation therapy to the last WHO Grade ≥3 assessment during/after radiation therapy.
- Time to onset of severe OM (WHO Grade ≥3).
- Incidence of severe OM (WHO Grade ≥3) by cumulative IMRT.

Safety Endpoints

The safety and tolerability of treatment with brilacidin will be assessed through incidence, severity and type of adverse events, including serious adverse events, and changes in clinical laboratory parameters, blood pressure, heart rate, ECOG, and body weight.

Systemic Exposure/Pharmacokinetic Endpoints

Brilacidin systemic exposure will be estimated from plasma sample concentrations; samples will be obtained from each randomized subject at weekly intervals during the CRT treatment period.

Data Analysis:

Efficacy Analyses

Full details of the statistical methodology for summary and analyses of the data collected in this study will be prepared separately from this protocol in a Statistical Analysis Plan (SAP).

The primary efficacy objective is to evaluate brilacidin compared to placebo in reducing the incidence of severe OM (defined as grade 3 or 4 on the WHO Oral Mucositis scale, WHO Grade ≥3) in subjects with HNC receiving concomitant chemoradiation therapy and a cumulative radiation dose of at least 55 Gy. For this comparison the Fishers Exact Test will be used.

Time to onset of severe OM (WHO Grade ≥3) will be assessed using the log rank test. Both a scale of days, and a scale of cumulative radiation dose delivered (Gy) will be used for the

Kaplan-Meier analysis. The log rank test will be used to compare treatment groups at time of onset of severe OM. Time to onset of ulcerative OM (WHO Grade ≥2) will be explored similarly.

Duration of severe OM (WHO Grade ≥3) is evaluated two different ways: (1) Initial instance duration of severe OM is defined as the number of days from initial WHO Grade ≥3 during radiation therapy until the first WHO Grade 2 or lower OM Grade occurs; (2) Overall duration of severe OM is defined as the number of days from initial WHO Grade ≥3 during radiation therapy to the last WHO Grade ≥3 assessment during/after radiation therapy. If any subject does not experience severe OM, his/her duration will be set to 0. Subjects who experience severe OM but do not resolve to WHO Grade 2 or lower will be censored at the last study visit. The effect of treatment on the duration of severe OM will be assessed using a log rank statistic. Analyses will be done using both a scale of days, and a scale of cumulative radiation dose delivered (Gy).

Safety Analysis

All safety data, demographic and baseline characteristics will be summarized descriptively through appropriate data tabulations, descriptive statistics, and categorical summaries.

Changes in blood pressure, heart rate, and hematology and clinical chemistry parameters from baseline to the end of the study will be summarized. Treatment-emergent changes from values within normal range to abnormal values in clinical laboratory parameters will be identified by means of summary and shift tables. ECOG and body weight changes from baseline to the end of the study will also be summarized.

Interim Analysis

Ad-hoc interim analyses may be conducted to support decision making concerning the current clinical study, the Sponsor's clinical development projects in general or in case of any safety concerns. Such analyses may be unblinded, and the details will be documented in the SAP.

Sample Size

The proportion of subjects experiencing severe OM (WHO Grade ≥3) after a total cumulative radiation dose of at least 55 Gy (and no more than 72 Gy) is unknown but expected to be approximately 75% for the placebo oral rinse treatment group, and the assumption for the active Brilacidin oral rinse treatment group is estimated to reduce to approximately 35-40%. Based on these assumptions, a sample size of 23-30 subjects per treatment group is appropriate to detect the specified difference with at least 80% power.