2. SYNOPSIS

Name of Sponsor/Company: SillaJen, Inc.	Individual Study Table Referring to part of the Dossier	(for National Authority Use only)
Name of Finished Product: Pexa-Vec	Volume:	
Name of Active Ingredient: Pexastimogene Devacirepvec (Pexa-Vec)	Page:	

TITLE OF STUDY: Single-Arm, Open-Label, Phase 2 Study of Pexa-Vec (JX-594; Vaccinia GM-CSF / Thymidine Kinase-Deactivated Virus) Administered by Weekly Intravenous (IV) Infusions in Sorafenib-naïve Patients with Advanced Hepatocellular Carcinoma (HCC)

INVESTIGATOR AND STUDY SITE: Four study sites in the following countries: South Korea (2 sites) and the United States of America (USA; 2 sites).

STUDY DATES:

From: 29 June 2012

To: 21 June 2013

PHASE OF DEVELOPMENT: Phase 2a

PROTOCOL VERSIONS: Original: 07 February 2012

OBJECTIVES:

Primary Objective:

- Determine radiographic response rate (RR; based on modified response evaluation criteria in solid tumors [mRECIST] and modified Choi [mChoi] criteria) for HCC.

Secondary Objectives:

- Determine the safety of Pexa-Vec administered by multiple IV infusions in patients with advanced HCC.
- Determine time-to-tumor progression (TTP) on Pexa-Vec therapy according to mRECIST criteria for HCC.
- Determine overall survival (OS).

METHODOLOGY:

This was a Phase 2a, two-staged, single-arm, open-label study in sorafenib-naïve patients with advanced HCC. Patients received 5 weekly IV infusions of Pexa-Vec and could have continued to receive IV infusions of Pexa-Vec every 3 weeks until progressive disease (PD).

NUMBER OF PATIENTS:

Planned number of patients: 21 patients

Thirteen patients were to be enrolled in the first stage of study prior to an interim analysis. If the futility interim analysis succeeded (at least 3 patients demonstrated a mRECIST and/or mChoi response per Simon's 2-stage minimax design), an additional 8 patients were to be enrolled in the second stage, for a study total of 21 patients. While results warranted continuation to the second stage of the study, the Sponsor made the decision not to continue enrollment.

Number of patients enrolled and analyzed:

- Intent to Treat (ITT) Population: 16 patients,
- Safety Population: 16 patients,
- Per Protocol Population (PPP): 16 patients.

Name of Sponsor/Company: SillaJen, Inc.	Individual Study Table Referring to part of the Dossier	(for National Authority Use only)
Name of Finished Product: Pexa-Vec	Volume:	
Name of Active Ingredient: Pexastimogene Devacirepvec (Pexa-Vec)	Page:	

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Patients were at least 18 years of age and had histologically/cytologically-confirmed advanced HCC; measurable tumor in the liver (at least one tumor with ≥1 cm longest diameter of contrast-enhancement during the arterial phase on computed tomography [CT] scanning); Child-Pugh Class A, or Class B7 without clinically significant ascites; expected survival of approximately 12 weeks or longer; Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2; and adequate liver function and hematological parameters.

TEST PRODUCT, DOSE, MODE OF ADMINISTRATION, AND BATCH NUMBER:

Pexa-Vec was administered by IV infusion at a dose of 1 x 10^9 plaque-forming units (pfu).

Pexa-Vec batch numbers administered: , , and .

DURATION OF TREATMENT:

Days 1, 8, 15, 22, and 29

Patients received an IV infusion of Pexa-Vec in approximately 250 mL buffered saline (200 mL sterile normal saline [0.9% NaCl] and 50 mL molar bicarbonate [8.4% $NaHCO_3$]) over 60 minutes (±5 minutes). Patients were observed in the clinic and/or hospital for a minimum of 20 hours after the infusion.

Treatments 2–5 were administered at 7-day intervals (±1 day). If a treatment was not given within the +7 day window, it was considered missed (e.g., the patient did not receive the infusion, but future protocol specified treatments were administered as originally scheduled per protocol).

Pre-Medication and Post-Treatment Symptom Management on all Treatment Days

Patients received approximately 1 liter of solute-containing fluids (e.g., normal saline) IV or orally within 12 hours of Pexa-Vec treatment initiation (unless medically contraindicated). In addition, during the observation period post-treatment, patients received IV normal saline or other appropriate IV solution as needed for blood pressure support.

All patients were pre-medicated with acetaminophen (or equivalent, unless contraindicated) on each treatment day. For example, the following regimen could be used:

- 650 mg 2 hours pre-infusion/injection,
- 650 mg 4 hours post-procedure,
- 650 mg every 6 hours thereafter, as needed, for up to 22 hours total post-treatment (the total acetaminophen dose was to be carefully assessed to avoid cumulative toxicity).

Anti-rigor medication (e.g., meperidine) was used as needed.

Treatment Extension

Starting at the Week 6 CT scan response assessment, patients with a mChoi or mRECIST response or with stable disease (SD) and otherwise appeared to be clinically benefitting from Pexa-Vec treatment, could have continued to receive IV infusion of Pexa-Vec every 3 weeks until PD. In order to undergo re-treatment, patients continued to meet initial eligibility criteria.

Patients not clinically benefitting or with PD discontinued Pexa-Vec treatment. Immediate initiation of sorafenib, the current first line standard of care for patients with HCC, was strongly recommended.

REFERENCE THERAPY, DOSE, MODE OF ADMINISTRATION, AND BATCH NUMBER:

A reference therapy was not used in this study.

Name of Sponsor/Company: SillaJen, Inc.	Individual Study Table Referring to part of the Dossier	(for National Authority Use only)
Name of Finished Product: Pexa-Vec	Volume:	
Name of Active Ingredient: Pexastimogene Devacirepvec (Pexa-Vec)	Page:	

CRITERIA FOR EVALUATION:

Primary Endpoints:

- Radiographic RR (complete response [CR] or partial response [PR]) based on mRECIST criteria for HCC and mChoi criteria as determined by Independent Central Review.

Secondary Endpoints:

- Safety of Pexa-Vec according to National Cancer Institute – Common Toxicity Criteria for Adverse Events (NCI-CTCAE) Version 4.03.
- TTP based on mRECIST criteria for HCC.
- OS duration.

Other Endpoints:

- Pharmacodynamics: Change over time in peripheral white blood cell (WBC) count (with differential).
- Radiographic: Change in contrast-enhancement on CT scans over time (including, but not limited to, mChoi response criteria); 3 dimensional (3D) tumor viability response (3D segmentation analysis to assess volume of viable versus non-viable tumor over time); immune-related response criteria to evaluate imaging changes due to immune therapy activity; change from Baseline in contrast-enhancement on magnetic resonance imaging (MRI) scans; disease control rate (DCR) by mRECIST and mChoi; (optional) change from Baseline over time in standard uptake value on positron emission tomography (PET)-CT scans.

STATISTICAL METHODS:

Pexa-Vec activity was evaluated in terms of radiological response (mRECIST or mChoi) with the decision rule of the study based on the proportion of patient who were responders. The study was a Simon 2-stage minimax design that assumed the null proportion (inactivity cut-off) was equal to 20% (H_0) and that alternate proportion (activity cut-off) was equal to 45% (H_A) where r was the RR. Thus the hypotheses of interest were H_0: r<20% against H_A: r>45%. The type I error rate (α; probability of accepting an insufficiently active treatment, a false positive outcome) was 5% and the type II error rate (β; probability of rejecting an active treatment, a false negative outcome) was 20%. Under these assumptions, a maximum of 21 evaluable patients were required and the interim analysis for futility was 13 evaluable patients.

The ITT Population consisted of all patients deemed eligible, who signed the informed consent form, and were enrolled in the study. The Safety Population consisted of all patients who received at least 1 treatment of Pexa-Vec and had at least one valid post-Baseline safety assessment. The PPP consisted of all patients in the ITT Population who had no major protocol deviations, were evaluable for efficacy (had a best overall response assessment different then 'unknown'), and received at least 3 treatments of Pexa-Vec. However, if a patient progressed (as per Investigator's decision and was therefore withdrawn), discontinued due to an adverse event (AE), or died before the minimum exposure requirement was met or before they became evaluable for efficacy, the patient was still included in the PPP. The ITT Population was used for summaries of demographic and baseline variables. The Safety Population was used for safety, drug exposure, and concomitant medication analyses. All efficacy endpoints were analyzed using the ITT (main analysis) and PPP.

All data collected during this study for enrolled patients were displayed in data listings, unless otherwise specified. Data listings were sorted by patient identifier. Screen failures were listed. In addition, listings included all relevant derived variables.

Summary statistics for continuous variables include the number of patients, mean, standard deviation (StD), median, first quartile (Q1), third quartile (Q3), minimum, and maximum values. Continuous variables are generally presented with the mean, median, Q1, and Q3 to 1 decimal more than individual data, and StD to 2 decimals more than individual data. Data with more than 3 decimal places (if any), may not follow this rule.

Name of Sponsor/Company: SillaJen, Inc.	Individual Study Table Referring to part of the Dossier	(for National Authority Use only)
Name of Finished Product: Pexa-Vec	Volume:	
Name of Active Ingredient: Pexastimogene Devacirepvec (Pexa-Vec)	Page:	

Categorical variables were summarized using counts and percentages. Percentages were based on all available observations. Proportions were presented with their exact (binomial) 95% confidence intervals (CIs) when appropriate.

Kaplan-Meier (KM) methods were used to summarize time-to-event analysis.

In general, missing data were not imputed or carried forward. All data summaries and tabulations were prepared with SAS® Version 9.2 or higher. Medical history was coded using the Medical Dictionary for Drug Regulatory Affairs (MedDRA), Version 14.1 and was presented for the ITT Population.

SUMMARY OF RESULTS AND CONCLUSIONS:

Efficacy:

- The majority of patients (81.3%) had prior local-regional therapy for HCC. The median number of prior HCC therapies was 1.5 (range: 0-3). One patient (6.3%) recieved prior systemic therapy (sorafenib).
- The RR (proportion of patients with CR or PR) based on mRECIST for HCC (*Llovet 2008; Lencioni 2010*) and/or mChoi criteria, as determined by Independent Central Review, at Week 6 was 18.8% (3/16 patients; 95% CI: 4.05 to 45.65) with the best overall response being a PR for 3 patients and SD for 5 patients. All responses were based on mChoi criteria, no mRECIST responses were observed.
- The RR based on mRECIST and/or mChoi criteria during the entire study (Week 6 or later) was 25.0% with the best overall response reported as a CR for 1 patient (6.3%), PR for 3 patients (18.8%), and SD for 4 patients (25.0%). All responses were based on mChoi criteria. Patient 17-06 had a CR based on mChoi criteria observed at Week 18 with radiological follow-up at Week 24 indicating the patient had PD.
- Six patients (37.5%) had SD as best overall response based solely on mRECIST.
- Four patients (25.0%) had a reduction in tumor size from Baseline during the study, where the best change in tumor size (mRECIST) for these 4 patients ranged from -2.3 to -20.5%.
- The KM estimate median TTP based on mRECIST 1.1 was 1.38 months (95% CI: 1.35 to 2.73) and the probability of staying progression-free at 3 months was 20%.
- The KM estimate median OS time was 7.47 months (95% CI: 4.44 to 10.64). The probability of survival at 3 months was 88% and at 12 months was 25%.

Safety:

- All 16 patients completed the treatment phase and received 5 doses of Pexa-Vec, 1 x 10^9 pfu (cumulative dose 5 x 10^9 pfu). Nine patients continued treatment during the extension phase (IV infusion of Pexa-Vec, 1 x 10^9 pfu every 3 weeks) with the number of additional infusions received ranging from 1 to 7 doses of Pexa-Vec.
- Reasons for discontinuation during the treatment extension phase included progressive disease (81.3%), AEs (12.5%), and withdrawal by patient (6.3%).
- The types and frequencies of treatment-emergent AEs (TEAEs) and Grade ≥3 (CTCAE Version 4.03) TEAEs observed were consistent with the safety profiles of Pexa-Vec (in other indications) and were otherwise similar to what might be expected in a population with advanced HCC.
- The most common all-causality TEAEs included influenza like illness (81.3%), chills (81.3%), pyrexia (56.3%), headache (43.8%), abdominal pain (37.5%), diarrhea (37.5%), and nausea (37.5%) and were considered tolerable with all events reported as ≤Grade 3 in severity.
- The most common Pexa-Vec related TEAEs included influenza like illness (81.3%), chills (81.3%), pyrexia (56.3%), headache (31.3%), and rash pustular (31.3%). Pexa-Vec related TEAEs were considered tolerable with all related events reported as ≤Grade 3 in severity.

Name of Sponsor/Company: SillaJen, Inc.	Individual Study Table Referring to part of the Dossier	(for National Authority Use only)
Name of Finished Product: Pexa-Vec	Volume:	
Name of Active Ingredient: Pexastimogene Devacirepvec (Pexa-Vec)	Page:	

- Pexa-Vec related hypotension (systolic blood pressure ≤90 mmHg) was experienced by 2 patients (12.5%), with all events reported as Grade 1 or 2. Pexa-Vec related tachycardia (heart rate ≥100 bpm) was experienced by 2 patients (12.5%), with all events reported as Grade 1.
- There were no Pexa-Vec related Grade 4 or 5 TEAEs. No Pexa-Vec related Grade 3 TEAE was experienced by more than 1 patient.
- Three deaths (18.8%) were reported during the study. All deaths were assessed as not related to Pexa-Vec and were similar to those expected in patients with HCC (hepatic failure, hepatic neoplasm malignant, and hepatorenal syndrome).
- Eight patients (50.0%) experienced a treatment-emergent serious adverse event (SAE) during the study. All SAEs were Grade 3 or 5. There were no Pexa-Vec related SAEs.
- No patient had a TEAE leading to discontinuation during the treatment phase of the study. Two patients (12.5%) experienced TEAEs that led to discontinuation of treatment during the treatment extension phase of the study, both in patients with fatal events not related to Pexa-Vec.

CONCLUSIONS:

- The AE profile in this study was generally well tolerated and consistent with the safety profile previously established for Pexa-Vec in other indications, thereby demonstrating the safety of Pexa-Vec.
- The number of patients that continued treatment in the treatment extension phase of the study further demonstrates the tolerability of Pexa-Vec.
- The RR (CR + PR) by mChoi was 25.0%.
- A reduction in tumor size from Baseline, ranging from -2.3 to -20.5%, was notable for 4 patients during the study.
- Based solely on mRECIST, 37.5% of patients had a best overall response of SD.
- Pexa-Vec did not significantly improve radiographic RR, or other efficacy measures, in patients with HCC.

DATE OF REPORT: Final CSR – 28 June 2018