



A Phase 3 Randomized, Open-Label Study Comparing Pexa-Vec (Vaccinia GM-CSF / Thymidine Kinase-Deactivated Virus) Followed by Sorafenib Versus Sorafenib in Patients with Advanced Hepatocellular Carcinoma (HCC) Without Prior Systemic Therapy

STUDY PROTOCOL NUMBER: JX594-HEP024

INVESTIGATIONAL PRODUCT: Pexastimogene Devacirepvec (Pexa-Vec)

PHASE: 3

IND NUMBER: BB-IND 6486

EudraCT NUMBER: 2014-001985-86

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PROTOCOL DATE: 17 February 2015

AMENDMENT 1: 3 October 2017

AMENDMENT 2: 26 June 2019

Confidentiality Statement

This document contains confidential information. It is intended solely for the use of the principal investigator, co-investigators, staff, appropriate institutional review boards or ethical committees, and other required regulatory bodies.

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 Kyoungsoo Ha
 Medical Monitor

27 JUN 2019

 Date

INVESTIGATOR SIGNATURE PAGE

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I have read and understand the protocol and I agree that it contains all the ethical, legal and scientific information necessary to conduct this study. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated. I will work according to the principles of Good Clinical Practice (GCP) as described (for the US) in the Code of Federal Regulations (CFR) Section 21, Parts 11, 50, 54, 56, and 312, The Declaration of Helsinki (2008), and GCP as described in the International Conference on Harmonization (ICH) document "Guidance for Industry – E6 Good Clinical Practice: Consolidated Guidance". Further, I will conduct the study in keeping with local and regulatory requirements.

I will provide copies of the protocol and access to all relevant information to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the drug and the study.

Principal Investigator Signature

Date

Principal Investigator Name (Printed)

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1 **LIST OF ABBREVIATIONS**

Abbreviation	Definition
AASLD	American Association for the Study of Liver Diseases
ACE	Angiotensin Converting Enzyme
ADR	Adverse Drug Reaction
AE(s)	Adverse Event(s)
AFP	Alfa-Fetoprotein
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Transaminase
BCLC	Barcelona Clinic Liver Cancer
BID	Twice daily (bis in die)
BSC	Best Supportive Care
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CDC	Centers for Disease Control and Prevention (United States)
CFR	Code of Federal Regulations (United States)
CI(s)	Confident Interval(s)
CLIP	Cancer of the Liver Italian Program
CR	Complete Response
CRO	Contract Research Organization
CSRI	Client Service Receipt Inventory
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCE MRI	Dynamic Contrast-Enhanced Magnetic Resonance Imaging
DCR	Disease Control Rate
DLT(s)	Dose Limiting Toxicity(ies)
DMC	Data Monitoring Committee
DoR	Duration of Response
EASL	European Association for the Study of the Liver
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form

Abbreviation	Definition
EGF(EGFR)	Epidermal Growth Factor (Receptor)
EORTC	European Organization for Research and Treatment of Cancer
FACT-Hep	Functional Assessment of Cancer Therapy – Hepatobiliary
FDA	Food and Drug Administration (United States)
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FHSI-8	Cancer Therapy–Hepatobiliary Symptom Index 8
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GLP	Good Laboratory Practices
GM-CSF	Granulocyte-Macrophage Colony Stimulating Factor
HCC	Hepatocellular Carcinoma
hGM-CSF	Human Granulocyte-Macrophage Colony Stimulating Factor
HIPAA	Health Insurance Portability and Accountability Act
HLA	Human Leukocyte Antigen
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
IB	Investigators’ Brochure
IBC	Institutional Biosafety Committee
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Institutional Ethics Committee
INN	International Nonproprietary Name
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
IT	Intratumoral
ITT	Intent-To-Treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LD	Longest Diameter
LDH	Lactate Dehydrogenase
LMWH	Low Molecular Weight Heparin

Abbreviation	Definition
mChoi	Modified Choi
MedDRA	Medical Dictionary for Regulatory Activities
MFD	Maximum Feasible Dose
mRECIST	Modified RECIST
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute (United States)
NIH	National Institutes of Health (United States)
ORR	Overall Response Rate
PBS	Phosphate Buffered Saline
PD	Progressive Disease
PEG-IFN	Pegylated Interferon
PEIT	Percutaneous Ethanol Injection Therapy
PET	Positron Emission Tomography
PET-CT	Positron Emission Tomography-Computerized Tomography
Pexa-Vec	Pexastimogene Devacirepvec, JX-594
PFS	Progression Free Survival
pfu	Plaque Forming Units
PP	Per Protocol
PR	Partial Response
PROs	Patient Reported Outcomes
PT/INR	Prothrombin Time/International Normalized Ratio
PTT	Partial Thromboplastin Time
QoL	Quality of Life
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
RFA	Radiofrequency Ablation
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SCID	Severe Combined Immunodeficiency
SD	Stable Disease
SLD	Sum of Longest Diameters
SmPC	Summary of Product Characteristics

Abbreviation	Definition
SOC	Standard of Care
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUV	Standardized Uptake Value
TACE	Transcatheter Arterial Chemoembolization
TIR	Time to Initial Response
TK	Thymidine Kinase
TSP	Time-to-Symptomatic Progression
TTP	Time To Progression
UFH	Unfractionated Heparin
ULN	Upper Limit of Normal
US	United States
VEGFR 1, 2, 3	Vascular Endothelial Growth Factor Receptor 1, 2, 3
VIG	Vaccinia Immune Globulin
WBC	White Blood Cell
WNL	Within Normal Limits

2 PROTOCOL SYNOPSIS

Title	A Phase 3 Randomized, Open-Label Study Comparing Pexa-Vec (Vaccinia GM-CSF / Thymidine Kinase-Deactivated Virus) Followed by Sorafenib Versus Sorafenib in Patients with Advanced Hepatocellular Carcinoma (HCC) Without Prior Systemic Therapy
Investigational Product	<p>The following products are considered as Investigational Product (IP):</p> <ul style="list-style-type: none"> • Pexa-Vec • Sorafenib (standard of care [SOC]) <p>Pexa-Vec</p> <p>Pexa-Vec (pexastimogene devacirepvec; investigational product code: JX-594) is a replication-competent, transgene-expressing therapeutic vaccinia virus derived from the Wyeth vaccine strain (Dryvax[®], Wyeth Laboratories). Three genetic modifications are included:</p> <ol style="list-style-type: none"> 1. thymidine kinase (TK) gene deactivation, 2. granulocyte macrophage colony stimulating factor (GM-CSF) gene insertion under control of the synthetic early-late promoter, and 3. lac-Z gene insertion under control of the p7.5 promoter. <p>Sorafenib</p> <p>Sorafenib belongs to the pharmacotherapeutic group of antineoplastic agents, protein kinase inhibitors, ATC code: L01XE05.</p> <p>Sorafenib is a multi-kinase inhibitor which has demonstrated both anti-proliferative and anti-angiogenic properties <i>in vitro</i> and <i>in vivo</i>.</p> <p>Sorafenib is approved for the treatment of advanced HCC and is the SOC of this disease.</p>
Phase	3
Objectives	<p>Primary Objective</p> <ul style="list-style-type: none"> • To determine and compare the overall survival of patients with advanced HCC without prior systemic therapy, treated with Pexa-Vec followed by sorafenib (Arm A) versus sorafenib (Arm B) <p>Secondary Objectives:</p> <ul style="list-style-type: none"> • To determine and compare the 2 treatment arms response based on central assessments using modified Response Evaluation Criteria in Solid Tumors (mRECIST) for HCC for the following endpoints: <ul style="list-style-type: none"> ❖ Time-to-progression (TTP) ❖ Progression free survival (PFS) ❖ Overall response rate (ORR) ❖ Disease control rate (DCR) • To determine and compare the safety profiles of the 2 treatment arms • To determine and compare the time-to-symptomatic progression (TSP) of the 2 treatment arms

	<ul style="list-style-type: none"> • To determine and compare the Quality of Life (QoL) of the 2 treatment arms <p>Exploratory Objectives:</p> <ul style="list-style-type: none"> • To determine and compare the 2 treatment arms response based on both local and central assessments using RECIST 1.1 for the following endpoints: <ul style="list-style-type: none"> ❖ TTP ❖ PFS ❖ ORR ❖ DCR • To evaluate and compare the effect of treatment with Pexa-Vec followed by sorafenib (Arm A) versus sorafenib (Arm B) on the following endpoints, (based on local and central assessments for radiology endpoints): • Time to Initial Response (TIR) and Duration of overall Response (DoR) • Tumor size over time by reference to the sum of the longest diameters of the target lesions at screening • Efficacy (overall survival, PFS, TTP) in patient subgroups to be defined in the Statistical Analysis Plan (SAP) • Overall survival, PFS, TTP in patients subdivided according to the presence or not of an objective response (complete response [CR], partial response [PR] and/or at least 3 months of stable disease) (if the number of patients is sufficient) • To determine and compare changes in clinical laboratory parameters in the 2 treatment arms including standard safety laboratory parameters, alpha-fetoprotein (AFP), and CD4/CD8 counts • To determine and compare the 2 treatment arms for overall survival by reference to the date of introduction of sorafenib • To describe the effects of Pexa-Vec on the immune response and identify biomarkers of response • To evaluate the comparative cost-effectiveness of Pexa-Vec followed by sorafenib versus sorafenib alone by collecting patient-level resource and service-use information
<p>Study Design</p>	<p>This is a Phase 3 multi-center, randomized, open-label study of Pexa-Vec followed by sorafenib (Arm A) versus sorafenib (Arm B) in patients with advanced HCC without prior systemic therapy.</p> <p>A total of 600 patients will be randomized between one of 2 treatment arms in a 1:1 ratio (300 in each arm) to reach at least 570 evaluable patients.</p> <p>Patients will be allocated to each arm via a dynamic stochastic minimization procedure performed independently for Asian and non-Asian patients. The following criteria will be used:</p> <ol style="list-style-type: none"> 1. Center 2. Main etiology: hepatitis C, hepatitis B, alcohol or other reasons (such as hemochromatosis, Wilson’s disease, type 2 diabetes, NASH) 3. Presence of extrahepatic disease or not 4. Vascular invasion or not 5. Performance status 0 or 1 6. AFP levels (<200, 200–400 or >400 ng/mL)

	<p>In experimental Arm A, Pexa-Vec will be administered as 3 bi-weekly intratumoral (IT) injections (Day 1, Week 2, Week 4). A radiological assessment will be performed at Screening, Week 6 and repeated every 6 weeks. Sorafenib will be started daily at Week 6 or 2 weeks after the last IT injection but no earlier than Week 6.</p> <p>In Arm B, sorafenib will be started daily on Day 1. Radiological assessments will be performed at Screening, on Week 6 and every 6 weeks.</p> <p>In both arms, if a patient discontinues the treatment phase prior to documented radiographic progression (e.g., permanently stops taking the study medication), the patient will perform PFS follow-up visits every 6 weeks for radiology evaluation until documented progression or until premature study discontinuation.</p> <p>Sorafenib is allowed and continued as long as the patient is clinically benefiting from the treatment and at least until progression or until unacceptable toxicity occurs.</p> <p>Beyond 12 months of treatment, the radiological evaluations will be performed every 12 weeks until first occurrence of documented progression.</p> <p>When study treatments are permanently stopped (Pexa-Vec or sorafenib), patients will perform an End of Treatment Visit and a Safety Follow-Up Visit at least 28 days (and no more than 2 months) after last study treatment administration.</p> <p>For patients in both arms, a site reader will perform local tumor assessments based on RECIST 1.1 for patient management and radiological endpoints assessment. An independent central review is also planned for blinded central assessment of all radiological endpoints, based on mRECIST for HCC and RECIST 1.1.</p> <p>Two interim analyses are planned; one futility analysis at 40% of the death events and one efficacy analysis at 80% of the events.</p> <p>A Data Monitoring Committee (DMC) will be in charge of reviewing safety and efficacy data regularly during the course of the study and at the time of the interim and final analyses. The activities of the DMC are defined in the DMC Charter document. The DMC's main objective will be to ensure that the safety of the patients, to evaluate the benefit versus risk and the integrity of the data are respected at all times throughout the study and to give recommendations on its further conduct.</p>
<p>No. of Patients</p>	<p>A total of 600 patients will be enrolled to obtain 570 evaluable patients:</p> <ul style="list-style-type: none"> • Arm A: 300 patients • Arm B: 300 patients
<p>Study Population</p>	<p>Inclusion Criteria:</p> <ol style="list-style-type: none"> 1. Male or female patients, age ≥ 18 years old 2. Histological/cytological diagnosis of primary HCC 3. Advanced stage HCC (Barcelona Clinic Liver Cancer [BCLC] Stage C or B per American Association for the Study of Liver Disease [AASLD] guidelines) eligible for systemic therapy excluding cholangiocarcinoma, hepatocholangiocarcinoma, fibrolamellar carcinoma and hepatoblastoma 4. Tumor status (as determined by radiology evaluation): At least one measurable viable tumor in the liver, ≥ 1 cm longest diameter (LD), using a dynamic imaging technique (arterial phase of triphasic computerized tomography [CT] scan, or dynamic contrast-enhanced magnetic resonance imaging [MRI]), and injectable under imaging-guidance (CT and/or ultrasound) 5. At least one tumor that has not received prior local-regional treatment, or that has exhibited $>25\%$ increase in viable tumor size since prior local-regional treatment

	<p>6. Child-Pugh Class A. NOTE: paracentesis, albumin infusion or diuretic treatment cannot be used to downscore Child-Pugh score (e.g., to improve from severe to moderate/mild or from moderate to mild ascites)</p> <p>7. Performance status 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale</p> <p>8. Adequate hematological, hepatic, and renal function:</p> <ol style="list-style-type: none"> a. Hemoglobin ≥ 9 g/dL b. Platelet count $\geq 75 \times 10^9/L$ c. International normalized ratio (INR) ≤ 1.7 d. White blood cell (WBC) count $\geq 2 \times 10^9/L$ e. Absolute neutrophil count (ANC) $\geq 1 \times 10^9/L$ f. Albumin ≥ 2.8 g/dL, total bilirubin ≤ 3.0 mg/dL (51.3 $\mu\text{mol/L}$); alanine aminotransferase (ALT), aspartate transaminase (AST) ≤ 5 times upper limit of normal (ULN) g. Serum chemistries sodium, potassium, and calcium within normal limits (WNL) or Grade 1 h. Serum creatinine < 2.0 mg/dL or creatinine clearance > 60 mL/min according to Cockcroft-Gault formula <p>9. For patients who are sexually active: willing to use adequate barrier contraception method for at least 6 weeks after each treatment of Pexa-Vec, during sorafenib treatment, and for 2 weeks after sorafenib discontinuation</p> <p>10. Life expectancy of at least 3 months</p> <p>11. Written informed consent</p> <p>Exclusion Criteria:</p> <ol style="list-style-type: none"> 1. Major surgery within 4 weeks of study treatments (minor surgical procedures are allowed e.g., intravascular access line or Port-a-Cath®) 2. Local-regional therapy of HCC within 4 weeks prior to randomization 3. Histological diagnosis of cholangiocarcinoma, hepatocholangiocarcinoma, fibrolamellar carcinoma and hepatoblastoma 4. History of moderate or severe ascites, bleeding esophageal varices, hepatic encephalopathy or pleural effusions related to liver insufficiency within 6 months of screening 5. Bulky disease patients - tumors encompassing $> 50\%$ of the liver volume and / or inferior vena cava invasion 6. Known significant immunodeficiency due to underlying illness (e.g., HIV/AIDS) and/or immune-suppressive medication including high-dose corticosteroids (defined as ≥ 20 mg/day prednisone or equivalent which is ongoing at the time of randomization and/or was taken for more than 4 weeks within the preceding 2 months of study treatment) 7. Ongoing severe inflammatory skin condition (as determined by the Investigator) requiring medical treatment 8. History of severe eczema (as determined by the Investigator) requiring medical treatment
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	<p>9. Tumor(s) invading a major vascular structure (e.g., carotid artery) or other key anatomical structure (e.g., pulmonary airway) in the event of post-injection tumor swelling and/or necrosis (hepatic and portal vein involvement allowed)</p> <p>10. Clinically significant and/or rapidly accumulating ascites, pericardial and/or pleural effusions. Mild ascites that does not preclude safe IT injection of Pexa-Vec is allowed at the discretion of the treating physician.</p> <p>11. Symptomatic cardiovascular disease, including but not limited to significant coronary artery disease (e.g., requiring angioplasty or stenting) or congestive heart failure within the preceding 12 months</p> <p>12. Current or past history of cardiovascular disease (e.g., past history of myocardial infarction, ischemic cardiomyopathy) unless cardiology consultation and clearance has been obtained for study participation</p> <p>13. Medical conditions, per the investigator's judgment, that predispose the patient to untoward medical risk in the event of volume loading (e.g., intravenous [IV] fluid bolus infusion), tachycardia, or hypotension during or following treatment with Pexa-Vec</p> <p>14. Viable central nervous system malignancy (history of completely resected or irradiated brain metastases allowed)</p> <p>15. Prior systemic therapy for HCC (NOTE: Patients receiving 7 days or less exposure to systemic therapy are allowed)</p> <p>16. Known contraindications to sorafenib according to the drug prescribing information and/or severe hypersensitivity to sorafenib or any other component of sorafenib, or known intolerance to sorafenib</p> <p>17. Other medical condition or laboratory abnormality or active infection that in the judgment of the Principal Investigator may increase the risk associated with study participation or may interfere with interpretation of study results and/or otherwise make the patient inappropriate for entry into this study</p> <p>18. Hepatitis C virus therapy including interferon/pegylated interferon or ribavirin that cannot be discontinued within 14 days prior to any Pexa-Vec injection. Medical Monitor should be consulted if the patient is taking any other antiviral medications to determine eligibility.</p> <p>19. Prior malignancies are not allowed except for the following: adequately treated basal or squamous cell skin cancer, <i>in situ</i> cervical cancer, adequately treated cancer from which the patient has been disease-free for at least 3 years, unless Medical Monitor approval has been obtained for study participation.</p> <p>20. Significant bleeding event within the last 12 months that places the patient at risk for intrahepatic IT injection procedure based on Investigator assessment</p> <p>21. Anticoagulant or anti-platelet medication that cannot be interrupted prior to Pexa-Vec IT injections, including:</p> <ul style="list-style-type: none"> • Aspirin that cannot be discontinued for 7 days prior to Pexa-Vec IT injections • Coumadin that cannot be discontinued for 7 days prior to Pexa-Vec IT injections • Low molecular weight heparin (LMWH) that cannot be discontinued >24 hours prior to Pexa-Vec IT injections • Unfractionated heparin (UFH) that cannot be discontinued >4 hours prior to Pexa-Vec IT injection • Oral direct thrombin inhibitor (dabigatran) or direct Factor Xa inhibitor (rivaroxaban, apixiban, and endoxaban) that cannot be discontinued for 4 days prior to Pexa-Vec IT injection
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	<p>NOTE: LMWH or UFH may be used to transition patients on and off of the above anti-coagulants (if deemed appropriate by the treating physician) prior to Pexa-Vec treatments as long as the last dose of LMWH is administered >24 hours prior to treatments and last dose of UFH is administered >4 hours prior to treatments.</p> <p>Please contact the Sponsor for questions regarding the management of other anticoagulant prior to treatments.</p> <p>22. Inability to suspend treatment with anti-hypertensive medication (including but not limited to: diuretics, beta-blockers, angiotensin converting enzyme [ACE] inhibitors, aldosterone antagonists, etc.) for 48 hours prior to and 48 hours after each Pexa-Vec injection.</p> <p>23. Any prior or planned organ transplant (e.g., liver transplant)</p> <p>24. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation. Child-bearing potential patients with a positive hCG laboratory test (>10 mIU/mL) at screening and/or a urinary pregnancy test at Baseline will perform an ultrasound to confirm the pregnancy.</p> <p>25. Patients who experienced a severe systemic reaction or side-effect as a result of a previous vaccination with vaccinia</p> <p>26. Participation in a clinical study and treatment with an active IP within 4 weeks prior to randomization</p> <p>27. Patient unable or unwilling to comply with the protocol requirements</p> <p>28. Previous treatment with Pexa-Vec or other vaccinia vector based treatment</p> <p>29. Pulse oximetry O₂ saturation <90% at rest on room air</p>
<p>Drug Dosage</p>	<p>Pexa-Vec: 1×10^9 plaque-forming units (pfu) (equivalent to 9.0 Log pfu) per treatment</p> <p>Sorafenib: 400 mg twice daily (BID), according to the package insert (including dose reductions)</p>
<p>Treatment Plan</p>	<p>Arm A</p> <p>Three IT injections (Day 1, Week 2, Week 4) of Pexa-Vec suspended in buffered saline will be made into 1 to 5 intrahepatic tumors by a qualified and trained Interventional Radiologist or other trained physician using imaging-guidance (ultrasound and/or CT). As much as possible viable, safely injectable tumors ≥ 1 cm LD must be treated with a maximum of 5 tumors treated on a given treatment day. Different tumors may be treated on each treatment day. The total prepared injection volume will be divided proportionally between 1 to 5 tumors, relative to individual tumor volumes (specific instructions are described in IT Injection Manual and Worksheet).</p> <p>Patients will be observed in the clinic or hospital for a minimum of 8 hours after each IT injection. Longer hospitalization is permitted based on Investigator decision.</p> <p>Patients will be eligible for each of the 3 Pexa-Vec injections if all of the following criteria are met prior to each treatment:</p> <ul style="list-style-type: none"> • The patient continues to meet the following clinical and laboratory criteria: <ul style="list-style-type: none"> ❖ Adequate liver function (total bilirubin ≤ 3 mg/dL [51.3 μmol/L]; ALT and AST $\leq 5 \times$ ULN) ❖ Platelets $\geq 75 \times 10^9/L$ (correction with transfusion or thrombopoietin based therapy allowed to meet re-treatment eligibility criteria)

	<ul style="list-style-type: none"> ❖ Hemoglobin ≥ 9 g/dL (correction with transfusion or erythropoietin based therapy allowed to meet re-treatment eligibility criteria) ❖ INR ≤ 1.7 (correction with plasma protein support allowed to meet re-treatment eligibility criteria [e.g., fresh-frozen plasma]) ❖ Patient is still expected to have at least one viable, injectable intrahepatic tumor ≥ 1 cm LD ❖ No clinically significant and/or rapidly accumulating ascites, pericardial and/or pleural effusions. Minimal ascites that does not preclude safe IT injection of Pexa-Vec is allowed at the discretion of the treating physician <p>Sorafenib will be started daily at Week 6, or 2 weeks after the last IT injection (whichever is later) and no earlier than Week 6. Sorafenib is allowed as long as the patient is clinically benefiting from the treatment and at least until progression or until unacceptable toxicity occurs.</p> <p>Arm B</p> <p>Daily sorafenib will be initiated on Day 1 and continued as long as the patient is clinically benefiting from the treatment and at least until progression or until unacceptable toxicity occurs.</p>
<p>Pre-Medications and Supportive Care</p>	<p>The use of the following drugs will not be restricted during the course of the study: thrombopoietin, erythropoietin, G-CSF, antiemetics, antipyretics, antidepressants, steroids (NOTE: oral or parenteral steroids are not allowed during the Pexa-Vec treatment period, and for 1 week prior to and 2 weeks after Pexa-Vec treatment), topical therapies for symptomatic relief of hand-foot skin reaction and rash related to sorafenib, bisphosphonates, vitamin B12, and vitamin D.</p> <p>Antihypertensives (including diuretics) must be discontinued at least 48 hours prior to each Pexa-Vec injection and restarted no earlier than 48 hours after the injection.</p> <p>All patients in experimental Arm A should be pre-medicated with acetaminophen (paracetamol) or equivalent antipyretics (e.g., NSAIDs) at the discretion of the treating physician, (unless contraindicated) on each Pexa-Vec treatment day. For acetaminophen, the following regimen may be used:</p> <ul style="list-style-type: none"> • 500–1000 mg at 2 hours pre-infusion/injection, • 500–1000 mg at 4 hours post-procedure, • 500–1000 mg every 6 hours thereafter, as needed (the total acetaminophen dose should be carefully assessed to avoid cumulative toxicity). <p>Fevers may be associated with onset of rigors. Meperidine or equivalent may be used for severe rigors.</p> <p>Patients should also be pre-hydrated with approximately 1 L of solute-containing fluids IV or orally within 12 hours of treatment initiation. In addition, during the post-treatment observation period, patients should receive IV solute-containing fluids or other appropriate treatment as needed for blood pressure support.</p>
<p>Protocol Assessments</p>	<p>Safety and Clinical Laboratory Assessments:</p> <p>Clinical assessments include laboratory assessments (hematology, biochemistry, coagulation, AFP, CD4/CD8 counts), physical examination and vital signs. Adverse events (AEs) and serious adverse events (SAEs) will be reported and graded according to National Cancer Institute’s Common Toxicity Criteria for Adverse Events (NCI CTCAE), version 4.03. From signature of informed consent up to IP initiation, only SAEs caused by a protocol-required</p>

	<p>procedure will be collected. After IP initiation, all SAEs/AEs will be collected up to 28 days after last IP administration (Pexa-Vec or sorafenib).</p> <p>Hematology and biochemistry will be assessed every 2 weeks until Week 6, every 3 weeks during the Long Term Follow-Up phase, at the End of Treatment Visit and at the Safety Follow-Up Visit. Coagulation will be assessed every 2 weeks until Week 6 and at the End of Treatment Visit.</p> <p>AFP levels will be assessed at Screening, at Week 6, every 6 weeks during the Long Term Follow-Up phase and at the End of Treatment Visit. CD4/CD8 counts will be assessed at Screening, at Week 6 and at the End of Treatment Visit.</p> <p>All laboratory analyses will be performed in central laboratories except for the clinical investigational sites participating in China where laboratory testing will be completed by the local laboratory at each site.</p> <p>Radiographic Assessments:</p> <p>Patients will undergo imaging of the chest, abdomen and pelvis using helical/spiral contrast-enhanced CT scanning (preferentially) or MRI with non-contrast CT of the chest at Screening, at Week 6 and every 6 weeks thereafter. If study treatments are stopped before documented radiological progression, PFS visits (scan collected) will be performed for every 6 weeks to continue radiological assessment until documented progression. Beyond 12 months of treatment, the evaluations will be performed every 12 weeks. Radiographic assessments will be completed locally as per current practice according to RECIST 1.1. All radiographic images will also be reviewed centrally in an independent and blinded manner according to mRECIST for HCC and RECIST 1.1 as defined in the imaging charter document.</p> <ul style="list-style-type: none"> • CT Scan: Tri-phasic contrast-enhanced imaging of the liver will include pre-contrast, arterial, and portal venous phases. If additional delayed phase imaging is performed, these images should also be provided for independent evaluation. • MRI Scan: on either a 1.5T or 3T MRI scanner using a body array coil. Gadolinium should be administered as an IV bolus. <p>Symptomatic Assessments:</p> <p>Symptomatic progression will be assessed through the disease-specific questionnaire FACT Hepatobiliary Symptom Index 8 (FHSI-8), a subset of the FACT-Hep questionnaire (Herdman 2011; Scalone 2012) and through the ECOG performance status.</p> <p>Questionnaires will be completed prior to any other visit procedures at Screening (for ECOG performance status only), at Baseline, at Week 6, and then every 6 weeks until symptomatic progression is determined. These protocol-specified assessments must be performed regardless of whether a Pexa-Vec or sorafenib treatment is given or cancelled (missed) for any reason.</p> <p>After symptomatic progression is determined, active patients will continue to visit the hospital/clinic for scheduled protocol visits but symptomatic progression will no longer be assessed.</p> <p>Quality of Life:</p> <p>Generic and disease-specific measures are essential to provide a comprehensive picture of Health-Related Quality of Life (HRQoL) in HCC. Patients will complete the FACT-Hep that is a 45-item questionnaire designed to measure HRQoL in patients with HCC. The FACT-Hep consists of 27-item FACT-General (FACT-G), which assesses generic HRQoL concerns using 5 subscales, and the 18-item hepatobiliary subscale, which assesses specific symptoms of hepatobiliary cancer and side effects of treatment.</p>
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	<p>Patient utility will be assessed with the EQ5D-3L questionnaire (<i>Herdman 2011; Scalone 2012</i>).</p> <p>All questionnaires will be completed by the patient prior to any other visit procedures at Baseline, at Week 6, and then every 6 weeks. Beyond 12 months of treatment, the questionnaires should be completed every 12 weeks. Questionnaires will also be completed at the End of Treatment Visit.</p> <p>Biomarker Analysis:</p> <p>Serum samples collected at Baseline, 8 hour post-IT (Arm A only), at Week 6 and at End of Treatment Visit, will be archived. These samples will allow further assessments of immune response and identification of response biomarkers.</p> <p>Pharmacoeconomic Assessments:</p> <p>To determine a trial-based economic evaluation, patient-level resource and service-use will be collected to evaluate the comparative cost-effectiveness of Pexa-Vec followed by sorafenib versus sorafenib alone. Detailed costs related data will be collected during the Phase 3 trial using data entered in electronic Case Report Forms (eCRF), hospital invoices, pharmacy worksheet and 2 other questionnaires: “health care resource utilization” and “patient accommodation and transport” derived from client service receipt inventory (CSRI) (<i>Beecham 2001</i>).</p> <p>The questionnaire “health care resource utilization” is designed to capture direct-medical costs related data non-documented neither in the CRF nor in hospital invoices. The questionnaire will be completed by the patient prior to any other visit procedures at Baseline, Week 6, and then every 6 weeks until End of Treatment Visit. Beyond 12 months of treatment, the questionnaires should be completed every 12 weeks until end of treatment visit.</p> <p>The “patient accommodation and transport” covers all expenses related to indirect-medical costs. The questionnaire will be completed by the patient prior to any other visit procedures at Baseline, at Week 12, and at the End of Treatment Visit.</p> <p>Utility values collected throughout the EQ5D-3L, the QoL questionnaire will also be used to produce generic measure for economic appraisal.</p>
<p>Endpoints:</p>	<p>For secondary endpoints, central radiological assessments will be evaluated with mRECIST for HCC.</p> <p>For exploratory endpoints, local and central radiological assessments will be used and evaluated with RECIST 1.1.</p> <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Overall Survival: time from date of randomization to the date of death due to any cause. If a patient is not known to have died at the cut-off date for analysis, survival will be censored at the date of last contact. <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> • Time to Progression (TTP): time from randomization to the date of first documented radiographic tumor progression; TTP does not include deaths. If a patient has not had a TTP event at the cut-off date for analysis, TTP will be censored at the date of last evaluable tumor assessment before the cut-off. • Progression Free Survival (PFS): time from randomization to the date of first documented radiographic tumor progression or death due to any cause, whichever occurs first. If a patient has not had a PFS event at the cut-off date for analysis, PFS will be censored at the date of last evaluable tumor assessment before the cut-off.

	<ul style="list-style-type: none"> • Overall response rate (ORR): proportion of patients whose best overall response during their participation in the study is either CR or PR. The best overall response is the best response recorded from the randomization until disease progression. • Disease control rate (DCR): proportion of patients whose best overall response during their participation in the study is either CR, PR, or stable disease (SD). • Safety: assessed by the NCI CTCAE (version 4.03). Incidence of AEs and SAEs will be reported. • Time to Symptomatic Progression (TSP): time from randomization until the first documented event of symptomatic progression defined as a decrease of 4 points or more from baseline in the FHSI-8 questionnaire (sub-part of the FACT-Hep questionnaire) or a decrease in performance status to 4, or death. • Changes in the QoL assessed by changes in the FACT-Hep and EQ5D-3L questionnaires. <p>Exploratory Endpoints:</p> <ul style="list-style-type: none"> • TTP, PFS, ORR, and DCR as described above will also be assessed centrally. • Duration of overall Response (DoR): applies only to patients whose best overall response is CR or PR. The start date is the date of first documented response (CR or PR) and the end date is the date of first documented disease progression or the date of death due to underlying cancer. • Time to Initial Response (TIR): the start date is the date of randomization and the end date is the date of first documented response (CR or PR). • Relative change of tumor size over time. Baseline tumor size is defined as the sum of the longest diameters for all target lesions as identified during screening. • Changes in clinical laboratory parameters will be described including standard safety assessments, AFP levels, CD4 and CD8 counts (all assessed centrally). • Additional immunology assays may be performed on archived samples to further assess the immune mechanisms involved and identify biomarkers of response. Pharmacoeconomy: information obtained from questionnaires collecting patient-level resource and service-use (Health Care Resource Utilization, Patient accommodation and Transport and EQ5D-3L questionnaires) will be analyzed. Detailed costs collected using data in eCRF, hospital invoices and pharmacy worksheet data will also be used as information for pharmacoeconomy analyses.
<p>Statistical Considerations</p>	<p>This is a multicenter, randomized, open-label, Phase 3 study, comparing Pexa-Vec followed by sorafenib to sorafenib. The primary efficacy population is defined as the Intent to Treat (ITT) population, which consists of all randomized patients. All primary efficacy analyses will be performed based on data from this population. Following the ITT principle, patients will be analyzed according to the treatment arm they were assigned to at randomization. The Safety Population will consist of all patients who received at least one dose of the study treatment (Pexa-Vec or sorafenib). For safety analyses, patients will be analyzed according to treatment actually received.</p> <p>The analyses of the primary and secondary efficacy endpoints will be performed on the ITT population and on a subset of the more significant endpoints repeated on the Per Protocol (PP) population which consists of patients without any major protocol deviations.</p> <p>It is assumed that Pexa-Vec does not reduce the hazard of death during the first 6 months of treatment (hazard ratio [HR] = 1.00 for the first 6 months), while it reduces the hazard by 40% thereafter (HR = 0.6 after 6 months). The median overall survival in the control arm is expected to be approximately 11 months.</p> <p>Based on the aforementioned assumptions, and assuming a 1:1 randomization a total of 474 events of death should be observed to reject the null hypothesis of no Pexa-Vec effect</p>

	<p>with a power of 86% (assuming that HR = 1 for the first 6 months and 0.6 thereafter) using a stratified log-rank test at a 1-sided cumulative 2.5% level of significance. This corresponds to a HR smaller than or equal to 0.83 at the final analysis to declare a significant treatment benefit. At the final analysis, the p-value of the re-randomization test (based on the stratified log-rank test) will be computed and compared to the threshold defined as 0.021 (if the analysis is performed at 474 events exactly) due to the alpha adjustment induced by the interim analysis for efficacy (as presented below). If the p-value is lower than this boundary, the treatment will be considered as effective.</p> <p>A first interim analysis for futility will be performed when 190 deaths (40% of the required events for final analysis) are documented in the ITT population with a stopping boundary defined as HR = 1.1. The p-value of the re-randomization test (based on the stratified log-rank test) will be computed and compared to the threshold corresponding to HR = 1.1. If exactly 190 events are considered in this analysis, the boundary for the p-value is defined as 0.744. If the p-value computed is higher than this threshold, the futility boundary will have been crossed.</p> <p>A second interim analysis for efficacy will be performed when 379 deaths (80% of the required events for final analysis) are documented in the ITT population. An α-spending function due to Lan-DeMets with O'Brien-Fleming type stopping boundary (as implemented in EAST® 6.3) will be used for the interim efficacy analysis. If the interim analysis is performed after exactly 379 events, the O'Brien-Fleming boundary for efficacy consists in using a significance level equal to 0.012, (corresponding to a HR equal to 0.79). If the p-value of the re-randomization test (based on the stratified log-rank test) is lower than this threshold, the efficacy boundary will have been crossed.</p> <p>The nominal p-values and critical values used to declare statistical significance at the time of interim analysis may be slightly different as based on the actual number of deaths that have been documented at the time of analysis.</p> <p>Assuming a non-uniform enrolment and about 5% loss to follow-up or withdrawal of consent rate, a total of 600 patients should be recruited in 19 months. It is estimated that the required 190 and 379 deaths for the interim analyses will be observed approximately 21 months and 34 months respectively after starting the trial. Likewise, it is estimated that the required 474 events for final analysis will be observed approximately 29 months after the inclusion of the last patient.</p> <p>The primary analysis (overall survival) will be done using a stratified re-randomization test.</p> <p>For secondary endpoints, a hierarchical testing strategy will be adopted, TTP will be compared between the 2 treatment arms if the primary endpoint overall survival is statistically significant. If TTP is statistically significant (i.e., $p < 0.025$) then PFS will be compared between the treatment groups and finally ORR will be analyzed. This approach ensures that the overall Type I error rate of the study is maintained at 2.5% (one-sided).</p>
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3 BACKGROUND

3.A HEPATOCELLULAR CARCINOMA (HCC)

Hepatocellular carcinoma (HCC) is estimated to be the third most common cause of cancer-related deaths world-wide (*Ferlay 2010; Hoos 2012*), the 5th most common cancer diagnosis in men worldwide and the 7th most common cancer in women (*El-Serag 2012*). Approximately 750,000 people develop HCC world-wide each year with ~80% of cases reported in developing countries which have a high prevalence of hepatitis (*El-Serag 2012*). However, HCC is one of the only cancers whose incidence is increasing in developed countries (*Siegel 2014; El-Serag 2001; Goodgame 2003; Deuffic 1998*). Approximately 25,000 new cases of HCC are diagnosed annually in the United States (US) (*Siegel 2014*). The incidence of HCC is 1,550 new cases in Canada (*Canadian Cancer Society 2008*) and approximately 50,000 in Europe (*Ferlay 2013*). Most HCC cases (approximately 90%) develop in the context of liver disease, in particular hepatocellular cirrhosis (*Simonetti 1991; Bosch 1999*). The most common causes of cirrhosis include chronic hepatitis B or C, and chemical substances such as excessive alcohol or aflatoxins (*Chen 2003*). Nonalcoholic steatohepatitis, a liver disease triggered by enhanced fat deposition in the liver, may also be a risk factor for the development of HCC (*Hashimoto 2009; Mori 2004*). The risk of death from HCC is increased both in males and females with increasing body mass index class, linking obesity to development of HCC (*Calle 2003*). Furthermore, diabetes has been shown to lead to increased risk of development of HCC in the presence of hepatitis B, hepatitis C, or alcoholic cirrhosis (*El-Serag 2001*). Hemochromatosis, a disease which results from inappropriate iron absorption, leading to excessive iron deposition in liver (leading to liver cirrhosis) and other organs, is another risk factor for the development of HCC (*Niederau 1985*). Patients with HCC generally present with advanced disease with a poor prognosis of 6 to 9 months median survival (*Yoo 2003*). Therefore, development of effective methods for the prevention and early diagnosis of HCC methods are critical. In addition, there exists a continued need for new therapies that will further improve survival of patients with HCC.

3.A.1 *Current Treatment for HCC*

Surgical resection and liver transplant are the only curative treatments for HCC. Small HCC tumor(s) (less than 3 cm in diameter) can be resected by hepatectomy, the most effective treatment. Surgery is associated with a reported 50–60% five-year survival rate, but unfortunately is feasible in only 10–15% of cases; most patients present with disease that is either too advanced or disease is accompanied by extensive cirrhosis that precludes surgery (*Gondolesi 2004*). Resection in cirrhotic patients carries high morbidity and mortality.

For patients with unresectable HCC and who cannot receive liver transplantation, a large array of local-regional therapies are available including percutaneous ethanol injection therapy (PEIT), radiofrequency ablation (RFA), transarterial chemoembolization (TACE), Yttrium-90 and/or radio-embolization. The choice of local-regional therapy depends on the size and location of the intrahepatic tumors and on the underlying liver function (*Bruix 2005*).

Sorafenib is the only systemic therapy approved for the treatment of patients with advanced HCC. Sorafenib is a small molecule which inhibits growth signaling and pro-angiogenic pathways (*Wilhelm 2004; Chang 2007*) by targeting the serine/threonine kinases Raf-1 and B-Raf as well as receptor tyrosine kinases platelet-derived growth factor receptor β (PDGFR- β) and vascular endothelial growth factor receptors 1, 2, and 3 (VEGFR1, 2, 3) (*Wilhelm 2004; Chang 2004*). These sorafenib targets have been shown to be involved in the pathogenesis of HCC (*Ito 1998; Villanueva 2007; Calvisi 2006; Semela 2004*). Results of a Phase 3 randomized trial with sorafenib conducted in 21 countries (n = 602; SHARP Trial) demonstrated a statistically significant survival advantage for sorafenib over placebo treatment (10.7 months versus 7.9 months, respectively; p < 0.001). Partial response by response evaluation criteria in solid tumors (RECIST) criteria was demonstrated in 2% of the sorafenib group and no patients had a complete response (*Llovet 2008b*). A subsequent Phase 3 randomized trial with sorafenib was completed in sites in Asia (n = 226 patients; Asia-Pacific Trial). Results demonstrated a statistically significant survival advantage for sorafenib (n = 150 patients) over placebo (n = 76 patients) (median 66.5 months versus 4.2 months, respectively; p = 0.014) (*Cheng 2009*). The disease control rate (DCR) with sorafenib was 35% (confirmed at 12 weeks after treatment initiation); disease control was defined as an objective response (partial or complete) or stable disease (SD) that lasted at least 44 weeks. The objective response rate (by RECIST criteria) was only 3% on sorafenib. Sorafenib is now approved in multiple countries for patients with unresectable HCC.

Nevertheless, despite a 2–3 month survival benefit in the front-line setting, sorafenib has significant toxicities and dose-reductions or treatment discontinuation is often required; this is currently being studied under non-protocol practice conditions on the GIDEON trial (*Lencioni 2013; Lencioni 2012*). In addition, disease stabilization is transient and tumor progression occurs in all patients (*Cheng 2009; Llovet 2008a*).

Several other systemic therapeutic agents have been tested in advanced HCC patients. In the 1st line setting, 3 receptor tyrosine kinase inhibitors – sunitinib, brivanib, linifanib – have been compared directly against sorafenib (*Cainap 2012; Cheng 2011; Johnson 2013*). In a fourth 1st line Phase 3 trial of a tyrosine kinase inhibitor (SEARCH), the combination of erlotinib plus sorafenib was compared to placebo plus sorafenib (*Zhu 2014a*). In these trials sorafenib had a

consistent performance, demonstrating a median overall survival of 8.5–10 months. None of the investigational therapies were however able to demonstrate superiority to sorafenib, or, in the case of brivanib and sunitinib, not even non-inferiority. Most trials also showed a worse safety profile of experimental agents compared to sorafenib.

3.B ONCOLYTIC IMMUNOTHERAPY

Oncolytic immunotherapy employs viruses that are designed to preferentially replicate in and lyse cancer cells and in this process trigger anti-tumor immunity. Following the first description of a virus engineered to replicate selectively in cancer cells over 20 years ago, the field of oncolytic immunotherapy has expanded dramatically. Over 10 different viral species have entered clinical trials. One oncolytic virus-based product (Onyx-015 adenovirus) entered a Phase 3 clinical trial in the US, and a similar virus, H101, was approved for use in combination with chemotherapy as a treatment for head and neck cancer by the Chinese State Food and Drug Administration in November 2005. More recently, a Phase 3 pivotal trial of *talimogene laherparepvec* (T-VEC), an oncolytic herpes virus expressing granulocyte-macrophage colony stimulating factor (GM-CSF) in patients with advanced melanoma met its primary endpoint, demonstrating a significant improvement in durable response rate versus GM-CSF alone (16% vs 2%, $p < 0.0001$) ([Andtbacka 2013](#)). Furthermore, a Phase 3 trial of an oncolytic reovirus in combination with standard chemotherapy is currently underway in advanced head and neck cancer.

Oncolytic immunotherapies kill cancer cells through a novel mechanism of action “oncolysis”, or virus replication-associated necrosis ([Parato 2005](#); [Kirn 2009](#)) and can be targeted to cancer cells with activated genetic pathways and/or loss of tumor suppressor function ([Heise 1997](#); [Stojdl 2000](#); [Martuza 1991](#)). Selective intratumoral (IT) replication of the virus leads to lysis of the infected cancer cell and spread to adjacent cancer cells. In addition, these viruses can kill through other mechanisms, including induction or amplification of a tumor-specific cytotoxic T-lymphocyte response. Oncolytic immunotherapies can also be armed for expression of therapeutic transgenes ([Chase 1998](#); [Todo 2001](#); [Hermiston 2002](#); [Hermiston 2005](#)). The latter can lead to bystander cell killing via enhanced immune response to the tumor (e.g., expression of cytokines such as GM-CSF). Oncolytic immunotherapies expressing additional therapeutic transgenes have the potential to effectively treat cancers that have become refractory to currently-approved treatments.

3.B.1 Pexa-Vec: Selective Tumor Infection and Active Immunotherapy

Pexa-Vec (Pexastimogene Devacirepvec, JX-594) is an oncolytic and immunotherapeutic vaccinia virus engineered to express GM-CSF. Pexa-Vec mechanisms-of-actions include tumor cell infection and lysis (*Breitbach 2011; Kim 2006; Park 2008*), anti-tumor immune response induction (*Heo 2013; Kim 2013*) as well as acute vascular disruption (*Breitbach 2013*). Pexa-Vec is derived from the commonly used Wyeth vaccine strain (Dryvax[®], Wyeth laboratories).

Three genetic modifications are included in Pexa-Vec:

1. thymidine kinase (TK) gene deactivation,
2. GM-CSF gene insertion under the control of the synthetic early-late promoter, and
3. lac-Z gene insertion under control of the p7.5 promoter.

Selective targeting of tumor cells by Pexa-Vec is attributed to both engineered mechanisms as well as to inherent vaccinia selectivity for cancers (*Parato 2012*). TK gene inactivation renders viral replication dependent on the high cellular TK activity that is a hallmark of cancer cells (*Hengstschlager 1998*). Vaccinia vaccine strains have been shown to be inherently tumor targeting (*Thorne 2007; Yu 2004*). This may be attributable to the fact that many of the hallmarks of cancer (*Hanahan 2000*) (e.g., blocks in apoptotic pathways, dysregulation of cell cycle control and immune evasion) are also optimal cellular conditions for successful vaccinia virus replication. Furthermore, vaccinia replication and spread is dependent on epidermal growth factor receptor (EGFR) signaling (*Katsafanas 2004*), a pathway that is activated in most cancers (*Hanahan 2000*).

GM-CSF is reportedly an effective cytokine for stimulating tumor-specific anti-tumoral immunity (*Dranoff 1993*). Furthermore, the combination of vaccinia infection with GM-CSF production has been shown to result in enhanced efficacy in preclinical models, presumably due to additional immune stimulation due to GM-CSF expression within the tumor microenvironment (*Thorne 2007*). GM-CSF is also expressed by other oncolytic viruses like T-Vec or Oncos-102. In addition, in melanoma patients GM-CSF when added to ipilimumab led to an improved outcome (*Hodi 2013*).

Protective anti-tumor immunity has been demonstrated following vaccinia infection of murine tumors *in vivo* (*Kirn 2007*). Pexa-Vec has also been shown to function as an immunotherapeutic in patients. GM-CSF expression was associated with increased neutrophil, monocyte and eosinophil production in Pexa-Vec treated patients (*Breitbach 2011; Park 2008*). Furthermore, inflammatory cell infiltration into tumors was also demonstrated with Pexa-Vec treatment (*Hwang 2011; Mastrangelo 1999*). Finally, functional anti-tumor antibodies mediating

complement dependent cytotoxicity were induced after Pexa-Vec treatment of patients with liver tumors (*Heo 2013; Kim 2013*).

3.C PRECLINICAL EXPERIENCE WITH PEXA-VEC

3.C.1 Efficacy of Pexa-Vec in Rabbit VX-2 Carcinoma Model and Rat Carcinogen-Induced Primary Liver Tumors

Efficacy of Pexa-Vec as a single agent was studied in 2 liver cancer models. The transgene product expressed by Pexa-Vec, hGM-CSF, is biologically active in rabbits, a species in which vaccinia virus replicates. Accordingly, the virus was tested versus the transplantable orthotopic rabbit carcinoma VX-2 model in which cells are implanted under the liver capsule forming liver tumors and metastases in liver and lung (*Kim 2006*). Tumor-bearing rabbits were treated with a single dose of 10^9 plaque forming units (pfu) of Pexa-Vec via IT or intravenous (IV) injection. Seven weeks post therapy, mean tumor volume in both Pexa-Vec treated groups was significantly smaller when compared to the phosphate buffered saline (PBS) control group. Furthermore, Pexa-Vec treatment prevented formation of metastases. Median survival time of rabbits in the PBS control group was 50 days while median survival was not reached in either Pexa-Vec treated group at 70 days (*Kim 2006*). Rabbits treated with Pexa-Vec exhibited weight gain while control rabbits lost weight over the course of the study, presumably due to tumor progression. The dose response of the effects of Pexa-Vec treatment was determined by comparing the efficacy of a single IV dose of 10^8 pfu used in a subsequent study with the results discussed above with application of 10^9 pfu. Whereas a dose of 10^9 pfu resulted in 88% inhibition of primary tumor growth and 100% inhibition of metastases at 7 weeks, the lower dose of 10^8 pfu inhibited primary growth by only 10%, while inhibiting the incidence of metastases by 48%.

Pexa-Vec efficacy against primary liver tumors was investigated in an orthotopic primary liver tumor model. Cirrhosis and liver cancers were induced in rats by chronic oral administration of N-nitrosodiethylamine and N-nitrosomorpholine (*Kim 2006*). Tumor-bearing rats received 3 IV infusions of Pexa-Vec every 2 weeks. Over 10 weeks, 5 of 6 animals treated with Pexa-Vec exhibited complete responses by ultrasound while tumors in all PBS control animals increased in size. These preclinical studies provide rationale for the use of Pexa-Vec as a novel therapy for HCC (refer to the Investigator's Brochure [IB] for further details).

3.C.2 Efficacy of Repeated Doses of Pexa-Vec Followed by Sorafenib Therapy in a Human Tumor Xenograft Model of Hepatocellular Carcinoma

Preclinical *in vitro* and *in vivo* data on the combination of Pexa-Vec and sorafenib were obtained. Sorafenib, when given concomitantly with Pexa-Vec, had a highly significant inhibitory effect on Pexa-Vec replication at clinically-relevant concentrations in cancer cell lines *in vitro*, including human HCC cell lines. This effect was not unexpected since sorafenib inhibits the EGFR-ras signal transduction pathway by blocking raf kinase, and the dependence of vaccinia virus on activation of this pathway has been definitively demonstrated (Yang 2005). Therefore, as with other inhibitors of this EGFR pathway, sorafenib can be utilized to block Pexa-Vec replication (Heo 2011).

As a result, different Pexa-Vec and sorafenib treatment sequences were explored. *In vivo* experiments were carried out with Pexa-Vec and sorafenib in a HepG2 (human HCC cancer cell line) xenograft tumor model in severe combined immunodeficiency (SCID) mice once tumors reached a size of approximately 900 mm³. Two doses of Pexa-Vec administered prior to daily sorafenib therapy was superior to PBS control or daily sorafenib therapy alone in terms of tumor growth and time-to-tumor progression, and superior to Pexa-Vec alone in terms of time-to-tumor progression. In addition, this sequence was superior to sorafenib followed by Pexa-Vec and to simultaneous treatment. Of note, as predicted given the inhibitory effect of sorafenib on Pexa-Vec replication *in vitro*, simultaneous treatment resulted in efficacy that was equivalent to sorafenib alone (Heo 2011).

3.C.3 Toxicity and Biodistribution of Single or Repeated IV Doses of Pexa-Vec in the Rabbit

An exploratory study in New Zealand White rabbits was conducted. Animals in this study received one (n = 1M, 1F) or 3 (n = 3M, 3F) weekly IV doses of Pexa-Vec (10¹⁰ pfu/dose; approximately 4 × 10⁹ pfu/kg). The treatments were well-tolerated: no overt clinical signs were observed throughout the 92 days of the study, with the following exception. For the animals receiving multiple doses, following the first injection of Pexa-Vec on Day 1, the treated animals lost approximately 5% of their body weight by Day 6. Thereafter, body weight rose intermittently until the end of measurements on Day 33. Control animals gained weight steadily throughout the study (Kim 2006). While the numbers of animals in this exploratory study are limited, histological and hematological findings are consistent with vaccinia virus infection. Reversible lymphoid depletion in the thymus and lymphoid hyperplasia with red pulp expansion in the spleen were also considered physiopathological adaptations. All of these findings appeared to be resolved by

Day 92 and none are considered to be of toxicological significance (refer to the IB for further details).

A study entitled “*Toxicity and Biodistribution of Recombinant Vaccinia Virus Pexa-Vec in the Rabbits*” has been conducted in compliance with Good Laboratory Practices (GLP) guidelines. Nine groups of 5 rabbits/sex/group received IV administrations of a clinical lot (Lot No. C173-3) at doses of 3×10^6 and 3×10^7 pfu/kg (~0.2 and 2-fold the 10^9 pfu/patient dose on a pfu/kg basis). Rabbits were assigned to groups that received 3 weekly infusions of low dose or high dose Pexa-Vec or a single high dose Pexa-Vec. Rabbits in a vehicle control group received 3 infusions. Pexa-Vec triggered treatment-related inappetence, and dose-related, reversible, early loss of body weight at both dose levels. There were some mild, dose-related, reversible changes in hematology and clinical chemistry parameters. Mild anemia was considered secondary to spleen enlargement. At the high dose only, abscesses were observed in the testes. All of the observed changes appear to be reversible (refer to the IB for further details).

3.D CLINICAL EXPERIENCE

3.D.1 Overview of Clinical Experience with Pexa-Vec

Pexa-Vec has been evaluated in 21 completed and ongoing clinical trials to date. Over 500 patients have been treated by IV infusion and/or IT injection with >900 IV infusions and >900 IT injections.

**Table 1:
Pexa-Vec Clinical Development**

Study	Indication / administration	Phase	Status	No. of Patients
	Melanoma Mastrangelo, investigator initiated / IT	1	Completed	7
HEP001	Liver metastases: dose escalation / up to 8 doses IT	1	Completed	14
IV011	Solid tumors / 1 dose IV	1	Completed	23
MEL005	Melanoma / 6 doses IT	1/2	Completed	10
P009	Pediatric tumors / 1 dose IT	1	Stopped	6
HEP012	CRC – neoadjuvant therapy / 1 dose IT or IV	2a	Stopped	2

Study	Indication / administration	Phase	Status	No. of Patients
HEP007	HCC primarily 1st line: 2 dose levels / 3 doses IT	2a	Completed	30
HEP016	HCC 2nd line / 1 dose IV + 2 doses IT f/b Sorafenib	2	Enrolment completed; data analysis ongoing	25
HEP021	HCC 1st line / 5 doses IV	2	Enrolment completed; data analysis ongoing	16
HEP018	TRAVERSE (RCT): 1 dose IV + 5 doses IT (randomized 2:1) Arm A: JX594 + BSC Arm B: BSC	2b	Completed	129 Arm A: 86
CRC014	CRC: dose escalation / 4 doses IV	1	Completed	15
CRC019	CRC: single agent & combo (irinotecan) / 5 doses IV + 3 doses IT	1/2a	Enrolment completed; data analysis ongoing	52
REN022	RCC / 5 doses IV	1/2	Enrolment completed; data analysis ongoing	17
HEP024	PHOCUS (HCC): 3 doses IT vs Sorafenib	3	Ongoing	186
REN026	RCC Part 1 = 4 IV infusions at 2 dose levels in combo with anti-PD-1 Part 2 = 3 doses IT or 4 IV injections in combo with anti-PD-1	1b	Ongoing	6

The most common adverse events (AEs) reported were acute, transient flu-like symptoms, including fever and chills. Transient, hypotension responsive to fluid administration was also noted in a subset of patients within 24 hours of treatment. Pexa-Vec related skin pustules were observed in less than 15% of patients receiving IT injections (1.6% of all IT treatments). The

pustules were self-limited and resolved without sequela within 2–3 weeks of treatment, consistent with the timeline for pustule resolution utilizing wild-type vaccinia vaccine. Evidence of anti-tumor activity was observed in patients treated across all studies with Pexa-Vec, as will be discussed in the next sections.

Radiographic signals of efficacy for Pexa-Vec were primarily assessed utilizing modified RECIST (mRECIST) or mChoi response criteria. In HCC, conventional RECIST responses are uncommon following systemic treatment. In the absence of decreased tumor size as measured by RECIST criteria, alternative methods for assessing anti-tumor response have been developed. Modified RECIST criteria for HCC focuses on the contrast enhancing (or viable) portions of tumor with response defined as a $\geq 30\%$ decrease in the sum of longest diameter (SLD) of the contrast enhancing areas of target tumors in the absence of non-target progression, progressive disease (PD) as $\geq 20\%$ increase in the SLD of target tumors or the non-target progression, and SD as those not qualifying as PD (*Llovet 2008b; Lencioni 2010*). Of note, Pexa-Vec replication in tumors may trigger an acute, local inflammatory response within tumors which may lead to transient tumor swelling (termed an “oncolytic flare response” or “pseudoprogression”). In addition, the modified Choi (mChoi) criteria is a more qualitative radiographic assessment measures which incorporates the impact of anti-cancer treatment on tumor viability and necrosis. The Choi response (*Choi 2004; Choi 2007*) is a measure of decreased tumor density and is defined as a decrease in 10% or more of the longest diameter (LD) of the tumor and/or a decrease of 15% or more in the average tumor enhancement. Despite potential transient tumor swelling due to edema and/or inflammation, Pexa-Vec has demonstrated anti-tumor activity based on mChoi or mRECIST for HCC criteria.

3.D.2 Pexa-Vec Evaluation in Non-HCC Indications

Pexa-Vec was initially evaluated in patients with metastatic melanoma and was well-tolerated in a total of 17 patients treated by IT injection either weekly or twice weekly on 2 clinical trials (*Mastrangelo 1999; Hwang 2011*). Evidence of tumor infection and anti-tumor activity was observed in both injected and non-injected tumors.

An IV dose escalation study (JX594-IV-011) has been completed and results published (*Breitbach 2011*). A total of 23 patients were treated and a maximum feasible dose (MFD) of 3×10^7 pfu/kg was reached without definition of a maximum tolerable dose (MTD). Pexa-Vec delivery to tumors following IV infusion of Pexa-Vec was demonstrated in tumor biopsies of 7 of 8 evaluable patients treated at a dose of $\geq 1 \times 10^9$ pfu and in no patients treated at $< 1 \times 10^9$ pfu. Delayed reemergence of Pexa-Vec in blood was demonstrated in a subset of patients and was

associated with GM-CSF expression and white blood cell induction. Furthermore, tumor response, disease control, and suppression of new tumor outgrowth were observed more frequently in higher dose cohorts than in patients receiving lower systemic doses of Pexa-Vec.

Additional information on non-HCC studies can be found in the IB.

3.D.3 Treatment of Solid Tumors within the Liver with Pexa-Vec

3.D.3.a Phase 1 Liver Tumor Trial

A Phase 1 dose-escalation trial of Pexa-Vec in patients with primary or metastatic liver tumors (JX594-IT-HEP001) has been completed and the results published (*Park 2008*). Pexa-Vec was administered by IT injection every 3 weeks in patients with refractory, injectable tumors within the liver at one of 4 dose levels (1×10^8 pfu to 3×10^9 pfu). Patients were scheduled to receive 2–4 treatments but could subsequently receive an additional 4 treatments if there was evidence response or clinical benefit. Fourteen patients, including 3 HCC patients were enrolled and treated.

Pexa-Vec was well-tolerated in study patients. All patients treated with Pexa-Vec experienced mild-to-moderate flu-like symptoms, which included fever, chills, anorexia, aches/pain, fatigue, headache, and/or nausea. No significant organ toxicity was reported. Two patients were treated at the 3×10^9 pfu dose and both patients experienced dose limiting toxicities (DLTs) after a single treatment with Pexa-Vec. The DLTs experienced by these study patients included asymptomatic Grade 3 hyperbilirubinemia ($n = 2$), and Grade 3 anorexia and right upper quadrant pain ($n = 1$). Hyperbilirubinemia was apparently due to tumor swelling post-treatment and occlusion of the adjacent bile duct. The maximum-tolerated dose on the study was therefore defined as 1×10^9 pfu.

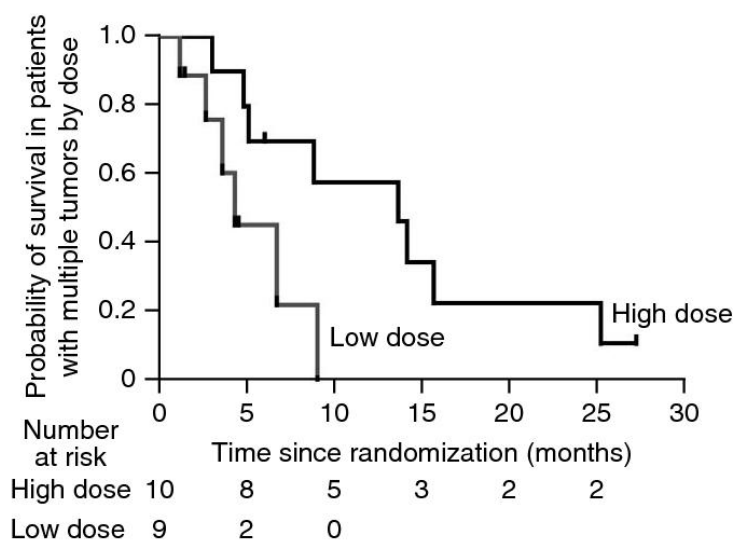
Response and/or stable disease were observed in 9 out of the 10 evaluable patients. Target tumor responses were demonstrated in 8 patients by RECIST criteria and/or Choi criteria. Responding patients had various tumor types, including HCC. In 3 cases positron-emission tomography – computed tomography (PET-CT) scans demonstrated a decrease in injected tumor metabolic activity (10–100% decrease standardized uptake value [SUV]). Eight patients (57%) survived for at least 8 months, and up to 72+ months. The median cancer-specific survival was 9 months.

3.D.3.b Phase 2 Liver Cancer (HCC) Trial (JX594-IT-HEP007)

A Phase 2 randomized dose-finding trial of Pexa-Vec in patients with liver cancer (HCC) (JX594-IT-HEP007) has been completed and the results published (*Heo 2013*). Pexa-Vec was administered by IT injection every 2 weeks for 3 total doses in patients with injectable tumors

within the liver. Study dose levels were 1×10^8 pfu (Arm A) and 1×10^9 pfu (Arm B). Thirty patients were treated (16 patients in Arm A, 14 patients in Arm B). Twenty-nine patients received all 3 planned injections; one low-dose patient received 2 Pexa-Vec treatments. IT injection was well-tolerated at both dose levels in this population of patients with HCC. One treatment-related serious adverse event (SAE) was reported in the high-dose group (nausea and vomiting requiring prolonged hospitalization). Flu-like symptoms (Grade 1–2) occurred in all patients over the first 12–24 hours after treatment, including fever, rigors, nausea or vomiting. Four patients responded to treatment based on mRECIST criteria (1 complete response; 3 partial responses). Responses were observed in injected and non-injected tumors. Further, overall survival was significantly longer in the high-dose arm compared with the low-dose arm (median 14.1 months versus 6.7 months, hazard ratio [HR] 0.39; p-value 0.020, Gehan-Breslow-Wilcoxon test; 1-sided test for superiority of high-dose [Figure 1]). The median overall survival was 9.0 months for the entire population.

Figure 1: Kaplan-Meier Plot of Overall Survival by Dose



3.D.3.c Phase 2 Study of HCC Patients Treated IV and IT with Pexa-Vec Prior to Sorafenib (JX594-HEP016)

Twenty-five patients were enrolled on this Phase 2 study investigating one IV dose of Pexa-Vec, followed by 2 IT injections (one week and 3 weeks after the IV infusion), prior to initiation of standard sorafenib therapy. Twenty patients were resistant to sorafenib therapy before Pexa-Vec treatment. Transient flu-like symptoms following Pexa-Vec treatments were the most common

AEs. Subsequent therapy with sorafenib was well-tolerated. The 2 agents were not used simultaneously, as sorafenib inhibits Pexa-Vec replication and can potentially impair its activity.

Transient decreases in white blood cell (WBC) counts, in particular neutrophils and lymphocytes, may occur within the first 24 hours following each Pexa-Vec treatment dose. Modified Choi responses and/or disease stabilization were observed following IV and IT Pexa-Vec therapy prior to and following standard sorafenib therapy. One patient exhibited a partial response by RECIST criteria in addition to a response by Choi criteria.

3.D.3.d Phase 2b Randomized Trial of Pexa-Vec Plus Best Supportive Care Versus Best Supportive Care in Patients with Advanced Hepatocellular Carcinoma Who Have Failed Sorafenib Treatment (JX594-HEP018/TRAVERSE)

One hundred and twenty-nine patients having failed previous sorafenib therapy were enrolled on this Phase 2b study and randomized 2:1 to receive either Pexa-Vec plus best supportive care (BSC) or BSC alone. Eighty-six patients were assigned to the Pexa-Vec arm and were to receive one IV dose followed by up to 5 IT injections (1, 3, 6, 12, and 18 weeks after the IV infusion), and 43 to BSC-only arm.

The most common AEs related to Pexa-Vec experienced by patients in Arm A included: pyrexia (78.6%), chills (50.0%), pustular rash (28.6%), hypotension (26.2%), and nausea (25%). These AEs were generally mild-to-moderate in severity and tolerable with the exception of hypotension, which was more severe than previously observed in other trials of Pexa-Vec.

Grade 3 AEs possibly or probably related to Pexa-Vec included pyrexia (8.3%), hypotension (8.3%), blood bilirubin increased (4.8%), anemia (3.6%), blood aspartate transaminase (AST) increased (3.6%); fatigue, hepatic encephalopathy, hypertension, platelet count decreased, vomiting, (2.4% for each event); abdominal pain and blood alanine aminotransferase (ALT) increased (1.2% for each event). Two Grade 4 or Grade 5 events were noted: respiratory failure (Grade 4) and hepatic failure (Grade 5).

Six patients presented with at least one Grade 3–4 AE possibly or probably related to IT injection procedure (7.1%): these AEs included hypotension (2.4%), upper abdominal pain, acute respiratory failure, anemia, ascites, fluid overload, hepatic hemorrhage, pleural effusion, acute renal failure, staphylococcal sepsis, and troponin increase (1.2% for each event). No procedure-related AE resulted in the patient's death.

The most frequent Pexa-Vec-related SAE, which occurred in 6 patients (8 SAEs) was severe hypotension defined as a systolic blood pressure <90 mmHg, lasting and requiring a medical treatment for at least 24 hours after Pexa-Vec administration. Notably, anti-hypertensive medication was ongoing at the time of treatment with Pexa-Vec prior to the development of hypotension in the majority of these patients, thereby possibly exacerbating the potential for hypotension.

Treatment with Pexa-Vec did not improve overall survival or other efficacy measures, compared with BSC, in patients with advanced HCC in this open-label study. No significant improvement of overall survival was shown in Arm A compared to Arm B ($p = 0.426$, stratified log-rank test) for the Intent-to-Treat (ITT) population. Median overall survival was 4.2 (95% confidence interval [CI]: 3.3 to 5.4 months) vs 4.4 months (95% CI: 3.2 to 6.0 months) for Arm A vs Arm B, respectively. HR observed was 1.19 (95% CI: 0.78 to 1.80). The overall disease control rate (proportion of patients with complete response [CR], partial response [PR], or SD) during the study was 13% (95% CI: 7% to 22%) vs 19% (95% CI: 8% to 33%) for Arm A vs Arm B, respectively. Notably, the majority of patients in TRAVERSE did not receive the complete protocol specified treatment regimen of JX-594. In Arm A, 12 of 86 randomized patients (13.9%) received all 6 planned treatments; and only half of the patients (51.2%) received at least 3 IT treatments (1 IV plus 3 IT) as administered in previous JX-594 HCC trials.

The limited number of patients completing treatment on Arm A in conjunction with the significantly shorter median overall survival (~4.2 vs 4.4 months on Arms A and B, respectively) observed in this study versus studies of other agents for second line HCC (~7–9 months) suggests a relatively more advanced HCC patient population was included in TRAVERSE ([Llovet 2013](#); [Zhu 2014b](#)).

3.E RATIONALE

3.E.1 Rationale for Study

Novel therapies are desperately needed for patients with advanced, unresectable HCC. The only approved agent for advanced HCC, sorafenib, prolongs survival by only a few months, is not curative, and is generally cytostatic. Furthermore, several agents with similar mechanisms-of-action to sorafenib (including brivanib, sunitinib and linifanib) have failed to demonstrate improved outcome for advanced HCC patients when compared to sorafenib. Pexa-Vec exhibits multiple different and complementary mechanisms-of-action to sorafenib. By exploiting novel,

alternative mechanisms-of-action of Pexa-Vec relative to other investigational agents, Pexa-Vec administration prior to sorafenib may provide additional clinical benefit to sorafenib therapy alone.

The rationale for Pexa-Vec treatment of HCC is based on:

1. Exploiting novel, alternative mechanisms-of-action of Pexa-Vec relative to sorafenib as well as investigational agents in HCC.
2. Preclinical liver cancer models that have demonstrated significant tumor responses with Pexa-Vec treatment ([Section 3.C.1](#)).
3. Preclinical evidence that Pexa-Vec replication is driven by activated EGFR/Ras signaling ([Section 3.B.1](#)).
4. Preclinical and clinical evidence suggest that anti-tumor activity of Pexa-Vec is dependent on targeting of the tumor endothelium and that Pexa-Vec spread within and between tumors is dependent upon the IT vasculature ([Section 3.B.1](#)). High level tumor vascularity and angiogenesis is well established in HCC (*Forner 2012*).
5. In Phase 1 and 2 clinical trials of Pexa-Vec for HCC, IT administration to hepatic tumors has been associated with both local and distant tumor responses ([Section 3.D.3](#)).
6. Improved survival with high-dose IT injections of Pexa-Vec in advanced HCC patients ([Section 3.D.3.b](#)).
7. Long survival of sorafenib naïve patients who have received Pexa-Vec prior to sorafenib initiation ([Section 3.D.3.c](#)).

NOTE: The rationale for sorafenib therapy after completion of Pexa-Vec therapy is outlined below.

Results from this pivotal trial will determine whether Pexa-Vec followed by sorafenib increases survival duration in advanced HCC patients compared to treatment with sorafenib alone, and whether sequential dosing with Pexa-Vec followed by sorafenib has a favorable safety profile.

3.E.2 Rationale for Pexa-Vec Dose and Schedule and Sequential Sorafenib Therapy

3.E.2.a Pexa-Vec Dose, Route and Interval Rationale

Due to the high rate of accessible tumors and clinical relevance of locoregional therapy in HCC, IT treatment is well established in all locoregional therapies. IT injection of Pexa-Vec into liver tumors was well-tolerated at both the 1×10^8 pfu and the 1×10^9 pfu dose (equivalent to 9.0 Log

pfu) in HCC patients treated in the JX594-IT-HEP007 protocol regimen (3 IT injections, each 2 weeks apart) (Section 3.D.3.b) (*Heo 2013*). Of interest, overall survival was significantly longer in the high-dose arm compared with the low-dose arm (median 14.1 months versus 6.7 months, HR 0.39; p-value 0.020, Gehan-Breslow-Wilcoxon test; 1-sided test for superiority of high-dose). Therefore, the 1×10^9 pfu dose level administered 3 times every 2 weeks appears to have the highest likelihood of benefiting patients with advanced HCC while maintaining a tolerable safety profile of Pexa-Vec.

3.E.2.b Rationale for Sequential Therapy with Sorafenib

Pexa-Vec and sorafenib cannot be used simultaneously since sorafenib inhibits Pexa-Vec replication and can potentially impair its activity. Therefore, sequential treatment appears as an appropriate option for therapeutic combination of the 2 agents.

The sequential use of Pexa-Vec and sorafenib holds the potential for additive activity of these 2 agents with unique mechanisms of action in HCC. Preclinical and preliminary clinical data supports this hypothesis (*Heo 2011*). Pexa-Vec acutely induces viral lytic effects and tumor vascular shutdown; in addition, Pexa-Vec is designed to induce a tumor-specific cytotoxic T lymphocyte response. In contrast, sorafenib is generally cytostatic (<5% objective tumor response rate) with its main clinical impact elicited via inhibition of raf kinase signal transduction and angiogenesis (via inhibitory effects on the VEGF receptor in tumors). The sequential combination of the two may lead to up-front Pexa-Vec mediated cell lysis and induction of systemic anti-tumor immunity followed by further sorafenib induced tumor control and prevention of regrowth.

Sorafenib is currently the standard of care (SOC) and only approved systemic therapy for subjects with advanced HCC. Based on the non-overlapping toxicity profile of the 2 agents, and the sequential design of the therapeutic regimen, the anticipated safety profile of the combination is expected to be tolerable. This hypothesis is supported by data from a Phase 2 study of 25 HCC patients utilizing sequential Pexa-Vec followed by sorafenib which demonstrated no significant safety concerns (Section 3.D.3.c). Pexa-Vec has not resulted in sorafenib-associated toxicities with the exception of nausea/reduction of appetite, and specifically has not been associated with the dose-limiting rash or diarrhea frequently associated with sorafenib dosing. The most clinically important Pexa-Vec side effects (flu-like symptoms) occur within the first 24 hours post-dosing. Therefore, no additive toxicities are expected when in the timeframe sorafenib is initiated in this protocol.

4 OBJECTIVES

4.A PRIMARY OBJECTIVE

- To determine and compare the overall survival of patients with advanced HCC without prior systemic therapy, treated with Pexa-Vec followed by sorafenib (Arm A) versus sorafenib (Arm B)

4.B SECONDARY OBJECTIVES

- To determine and compare the 2 treatment arms response based on central assessments using mRECIST for HCC for the following endpoints:
 - ❖ Time to Progression (TTP)
 - ❖ Progression Free Survival (PFS)
 - ❖ Overall Response Rate (ORR)
 - ❖ Disease Control Rate (DCR)
- To determine and compare the safety profiles of the 2 treatment arms
- To determine and compare the Time to Symptomatic Progression (TSP) of the 2 treatment arms
- To determine and compare the Quality of Life (QoL) of the 2 treatment arms

4.C EXPLORATORY OBJECTIVES

- To determine and compare the 2 treatment arms response based on both local and central assessments using RECIST 1.1 for the following endpoints:
 - ❖ Time to Progression (TTP)
 - ❖ Progression Free Survival (PFS)
 - ❖ Overall Response Rate (ORR)
 - ❖ Disease Control Rate (DCR)
- To evaluate and compare the effect of treatment with Pexa-Vec followed by sorafenib (Arm A) versus sorafenib (Arm B) on the following endpoints (based on local and central assessments for radiology endpoints):

- ❖ Time to Initial Response (TIR) and Duration of overall Response (DoR)
- ❖ Tumor size over time by reference to the sum of the longest diameters of the target lesions at screening
- ❖ Efficacy of Pexa-Vec (overall survival, PFS, TTP) in patient subgroups to be defined in the Statistical Analysis Plan (SAP)
- ❖ Overall survival, PFS, TTP in patients subdivided according to the presence or not of an objective response (CR, PR and/or at least 3 months of SD [if the number of patients is sufficient])
- To determine and compare changes in clinical laboratory parameters in the 2 treatment arms including standard laboratory parameters, alpha-fetoprotein (AFP) and CD4/CD8 counts
- To determine and compare the 2 treatment arms for overall survival by reference to the date of introduction of sorafenib
- To describe the effects of Pexa-Vec on the immune response and identify biomarkers of response
- To evaluate the comparative cost-effectiveness of Pexa-Vec followed by sorafenib versus sorafenib alone by collecting patient-level resource and service-use information

5 STUDY DESIGN

5.A STUDY OVERVIEW

This is a multi-center, randomized, open-label, Phase 3 study comparing Pexa-Vec followed by sorafenib (Arm A) versus sorafenib (Arm B) in patients with advanced HCC without prior systemic therapy.

A total of 600 patients will be randomized between the 2 treatment arms in a 1:1 ratio (300 in each arm) to reach at least 570 evaluable patients.

This study is expected to start in Q3 2015 with recruitment to be completed by Q1 2020. The study treatment phase is expected to be completed by Q1 2021.

It is understood that this accrual rate is based on reasonable planning expectations. The actual accrual rate should be compared to the expected rate on an ongoing basis. If problems of recruitment are identified (by the Contract Research Organization [CRO] through monthly reports or by the Data Monitoring Committee [DMC]) this should be discussed between the Sponsor, the CRO and the Investigators as early as possible in order to define actions to meet the above timelines.

Patients will be allocated to each arm via a dynamic stochastic minimization procedure performed independently for Asian and non-Asian patients. The following criteria will be used:

1. Center
2. Main etiology: hepatitis C, hepatitis B, alcohol or other reasons (such as hemochromatosis, Wilson's disease, type 2 diabetes, NASH)
3. Presence of extrahepatic disease or not
4. Vascular invasion or not
5. Performance Status 0 or 1 on the ECOG scale.
6. AFP levels (<200, 200–400, >400 ng/mL)

Two interim analysis are planned; one futility analysis at 40% of the death events and one efficacy analysis at 80% of the events.

5.B STUDY ENDPOINTS

5.B.1 *Primary Endpoint*

- Overall survival: time from date of randomization to the date of death due to any cause. If a patient is not known to have died at the cut-off date for analysis, survival will be censored at the date of last contact.

5.B.2 *Secondary Endpoints*

- **Central radiological assessments** will be assessed with mRECIST for HCC:
 - ❖ Time to Progression (TTP): time from randomization to the date of first documented radiographic tumor progression; TTP does not include deaths. If a patient has not had a TTP event at the cut-off date for analysis, TTP will be censored at the date of last evaluable tumor assessment before the cut-off.
 - ❖ Progression Free Survival (PFS): time from randomization to the date of first documented radiographic tumor progression or death due to any cause, whichever occurs first. If a patient has not had a PFS event at the cut-off date for analysis, PFS will be censored at the date of last evaluable tumor assessment before the cut-off.
 - ❖ Overall response rate (ORR): proportion of patients whose best overall response during their participation in the study is either CR or PR. The best overall response is the best response recorded from the randomization until disease progression.
 - ❖ Disease control rate (DCR): proportion of patients whose best overall response during their participation in the study is either CR, PR, or SD.
- **Safety** will be assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; version 4.03). Incidence of AEs and SAEs will be reported.
- **Time to Symptomatic Progression (TSP)** is the time from randomization until the first documented event of symptomatic progression defined as a decrease of 4 points or more from baseline in the FHSI-8 questionnaire (sub-part of the FACT-Hep questionnaire) or a decrease in Eastern Cooperative Oncology Group (ECOG) performance status to 4, or death.
- **Changes in QoL** will be assessed by the changes in the FACT-Hep and EQ5D-3L questionnaires.

5.B.3 Exploratory Endpoints

Both central and local radiological assessments will be evaluated with RECIST 1.1.

- TTP, PFS, ORR, and DCR as described above will also be assessed centrally.
- Duration of overall Response (DoR): applies only to patients whose best overall response is CR or PR. The start date is the date of first documented response (CR or PR) and the end date is the date of first documented disease progression or the date of death due to underlying cancer.
- Time to Initial Response (TIR): the start date is the date of randomization and the end date is the date of first documented response (CR or PR).
- Relative change of tumor size over time: Tumor size is defined as the sum of the longest diameters for all target lesions as identified at screening.

Changes in clinical laboratory parameters, including standard safety assessments, AFP levels, CD4/CD8 counts (all assessed centrally).

Additional immunology assays may be performed on archived samples to further assess the immune mechanisms involved.

Pharmacoeconomy analyses include all information obtained from questionnaires collecting patient-level resource and service-use (Health Care Resource Utilization questionnaire, patient accommodation and transport questionnaire derived from client service receipt inventory [CSRI] and EQ5D-3L questionnaire). Detailed costs collected using data entered in electronic Case Report Form (eCRF), hospital invoices and pharmacy worksheet data will also be used as information for pharmacoeconomics analyses.

5.C DOSE AND REGIMEN

Refer to [Section 10](#) for more information about study treatments.

Arm A (Pexa-Vec followed by sorafenib):

Pexa-Vec: Three IT Pexa-Vec treatments are planned. Each IT Pexa-Vec treatment will be administered at a dose of 1×10^9 pfu (equivalent to 9.0 Log pfu). This dose will be suspended in sterile normal saline buffered in sodium bicarbonate. Refer to [Section 10.A.8](#) for additional details. Pexa-Vec has to be administered within a specified treatment window of -1 and +7 days.

While the IT treatment can be performed anytime within the allowed window, it is preferred that it occurs in the beginning of the treatment window.

Sorafenib: sorafenib dosing of 400 mg (oral, twice daily [BID]) will be administered and managed according to the registered Summary of Product Characteristics (SmPC). Treatment will be initiated at the visit Week 6, 2 weeks after the third Pexa-Vec IT (whichever is later). If not all 3 Pexa-Vec IT were performed, sorafenib should start no earlier than Week 6.

Arm B (sorafenib):

Sorafenib dosing of 400 mg (oral, BID) will be started on Day 1 and managed according to the registered SmPC.

5.C.1 Dose Modifications, Delays, and Cancellations

5.C.1.a Dose Modifications

Pexa-Vec: No Pexa-Vec dose modifications are allowed.

Sorafenib: Dose modification will be allowed according to the registered SmPC.

5.C.1.b Dose Delays

Pexa-Vec: Pexa-Vec must be administered within the specified treatment window (-1/+7 days) and there are no Pexa-Vec dose delays planned outside of this window.

Sorafenib: Sorafenib will be managed according to the registered SmPC.

5.C.1.c Dose Cancellations

Pexa-Vec: If for any reason a Pexa-Vec IT treatment is not given within the allowed treatment window, it will be cancelled (i.e., missed for that time point), but then IT treatments should be resumed at the next scheduled treatment visit if re-treatment eligibility criteria are met as outlined in [Section 6.C.2](#).

Sorafenib: Sorafenib will be taken by the patient at home. Drug accountability will be recorded by designated site personnel. The patient should be counseled on the importance of not missing doses unless instructed by the Investigator (e.g., due to toxicity).

5.C.1.d Treatment Withdrawal

All patients should remain on study until progression or until unacceptable toxicity occurs.

Sorafenib treatment is allowed as long as the patient is clinically benefiting according to the registered SmPC.

If, however sorafenib and/or Pexa-Vec treatment is withdrawn (i.e., no further treatment will be administered at future visits), prior to Investigator determination of clinical benefit (e.g., patient withdrew consent, AE, concurrent prohibited medical condition, etc.) patients should complete an End of Treatment Visit. Reason for treatment withdrawal should be recorded in the eCRF. Patients should also return to the clinic for a safety follow-up visit at least 28 days after the last study treatment received.

5.D OVERALL STUDY DURATION

Overall study duration will consist of an active study participation phase (which includes: the Treatment Phase, the Long-Term Follow-Up Visits ([Section 7.C.1](#)), an End Of Treatment Visit ([Section 7.D](#)), a Safety Follow-Up ([Section 7.E](#)), and PFS visits ([Section 7.F](#)) if applicable) and a survival follow-up phase (consisting of patient and/or caregiver contact every 4 weeks).

5.D.1 *Active Study Participation Phase*

The treatment phase is the first part of the active study participation phase: will last from the first day of study administration until the last study treatment administration. After this phase, i.e., at treatment discontinuation (Pexa-Vec and/or sorafenib), an End of Treatment visit will be performed, followed by a safety follow-up at least 28 days after the last study drug administration.

- Patients in both Arm A and Arm B will remain in active study phase until they are no longer clinically benefiting from the treatment and at least until radiographic progression or unacceptable toxicity occurs. In case a patient discontinues the treatment phase (e.g. permanently stops taking the study medication) prior to documented radiographic progression, the patient will perform PFS follow-up visit(s) every 6 weeks for radiology evaluation, until documented progression or until premature study discontinuation (refer to [Section 6.C.4](#)).

5.D.2 *Survival Follow Up Phase*

After the active study participation phase, patients in both Arm A and Arm B will enter survival follow-up. During this phase, patients and/or their specified contacts will be contacted approximately every 4 weeks with the window of ± 7 days for follow-up and collection of information on subsequent anti-cancer therapy received (e.g., type of therapy, start/stop date, or ongoing, etc.) until the patient dies, is lost to follow-up, or specifically withdraws consent for further survival contacts.

6 SELECTION OF PATIENTS

6.A INCLUSION CRITERIA

Patients must meet the following inclusion criteria:

1. Male or female patients, age ≥ 18 years old
2. Histological/cytological diagnosis of primary HCC
3. Advanced stage HCC (Barcelona Clinic Liver Cancer [BCLC] Stage C or B per American Association for the Study of Liver Disease [AASLD] guidelines) eligible for systemic therapy excluding cholangiocarcinoma, hepatocholangiocarcinomas, fibrolamellar carcinoma and hepatoblastoma.
4. Tumor status (as determined by radiology evaluation): At least one measurable viable tumor in the liver (≥ 1 cm LD and enhancing on arterial phase of triphasic CT scan or MRI), and injectable under imaging-guidance (CT and/or ultrasound)
5. At least one tumor that has not received prior local-regional treatment, or that has exhibited $>25\%$ increase in viable tumor size since prior local-regional treatment
6. Child-Pugh Class A. **NOTE:** paracentesis, albumin infusion or diuretic treatment cannot be used to downscore Child-Pugh score (e.g., to improve from severe to moderate/mild or from moderate-to-mild ascites)
7. Performance status 0 or 1 on the ECOG scale
8. Adequate hematological, hepatic, and renal function:
 - a. Hemoglobin ≥ 9 g/dL
 - b. Platelet count $\geq 75 \times 10^9/L$
 - c. International normalized ratio (INR) ≤ 1.7
 - d. WBC count $\geq 2 \times 10^9/L$
 - e. Absolute neutrophil count (ANC) $\geq 1 \times 10^9/L$
 - f. Albumin ≥ 2.8 g/dL, total bilirubin ≤ 3.0 mg/dL (51.3 $\mu\text{mol/L}$); ALT, AST ≤ 5 times upper limit of normal (ULN)
 - g. Serum chemistries sodium, potassium, and calcium within normal limits (WNL) or Grade 1

- h. Serum creatinine <2.0 mg/dL or creatinine clearance >60 mL/min according to Cockcroft-Gault formula
9. For patients who are sexually active: willing to use adequate barrier contraception method for at least 6 weeks after each treatment of Pexa-Vec, during sorafenib treatment and for 2 weeks after sorafenib discontinuation
10. Life expectancy of at least 3 months
11. Written informed consent

6.B EXCLUSION CRITERIA

Patients must not meet any of the following exclusion criteria:

1. Major surgery within 4 weeks of study treatment (minor surgical procedures are allowed e.g., intravascular access line or Port-a-Cath[®])
2. Local-regional therapy of HCC within 4 weeks prior to Arm assignment
3. Histological diagnosis of cholangiocarcinoma, hepatocholangiocarcinomas, fibrolamellar carcinoma and hepatoblastoma
4. History of moderate or severe ascites, bleeding esophageal varices, hepatic encephalopathy or pleural effusions related to liver insufficiency within 6 months of Screening
5. Bulky disease patients- tumors encompassing >50% of the liver volume and or inferior vena cava invasion.
6. Known significant immunodeficiency due to underlying illness (e.g., HIV/AIDS) and/or immune-suppressive medication including high-dose corticosteroids (defined as ≥ 20 mg/day prednisone or equivalent which is ongoing at the time of randomization and/or was taken for more than 4 weeks within the preceding 2 months of study treatment)
7. Ongoing severe inflammatory skin condition (as determined by the Investigator) requiring medical treatment
8. History of severe eczema (as determined by the Investigator) requiring prior medical treatment

9. Tumor(s) invading a major vascular structure (e.g., carotid artery) or other key anatomical structure (e.g., pulmonary airway) in the event of post-injection tumor swelling and/or necrosis. Hepatic and portal vein involvement allowed.
10. Clinically significant and/or rapidly accumulating ascites, pericardial and/or pleural effusions. Mild ascites that does not preclude safe IT injection of Pexa-Vec is allowed at the discretion of the treating physician.
11. Symptomatic cardiovascular disease, including but not limited to significant coronary artery disease (e.g., requiring angioplasty or stenting) or congestive heart failure within the preceding 12 months
12. Current or past history of cardiovascular disease (e.g., past history of myocardial infarction, ischemic cardiomyopathy) unless cardiology consultation and clearance has been obtained for study participation
13. Medical conditions, per the investigator's judgment, that predispose the patient to untoward medical risk in the event of volume loading (e.g., IV fluid bolus infusion), tachycardia, or hypotension during or following treatment with Pexa-Vec
14. Viable central nervous system malignancy (history of completely resected or irradiated brain metastases allowed)
15. Prior systemic therapy for HCC. **NOTE:** Patients receiving 7 days or less exposure to systemic therapy are allowed.
16. Known contraindications to sorafenib according to the drug prescribing information and/or severe hypersensitivity to sorafenib or any other component of sorafenib, or known intolerance to sorafenib
17. Other medical condition or laboratory abnormality or active infection that in the judgment of the Principal Investigator may increase the risk associated with study participation or may interfere with interpretation of study results and/or otherwise make the patient inappropriate for entry into this study
18. Hepatitis C virus therapy including interferon/pegylated interferon or ribavirin that cannot be discontinued within 14 days prior to any Pexa-Vec injection. Medical Monitor should be consulted if the patient is taking any other anti-viral medications to determine eligibility.
19. Prior malignancies are not allowed except for the following: adequately treated basal or squamous cell skin cancer, *in situ* cervical cancer, adequately treated cancer from which the

patient has been disease-free for at least 3 years, unless Medical Monitor approval has been obtained for study participation

20. Significant bleeding event within the last 12 months that places the patient at risk for intrahepatic IT injection procedure based on Investigator assessment
21. Anticoagulant or anti-platelet medication that cannot be interrupted prior to Pexa-Vec IT injections, including:
 - a. Aspirin that cannot be discontinued for 7 days prior to Pexa-Vec IT injections
 - b. Coumadin that cannot be discontinued for 7 days prior to Pexa-Vec IT injections
 - c. Low molecular weight heparin (LMWH) that cannot be discontinued >24 hours prior to Pexa-Vec IT injections
 - d. Unfractionated heparin (UFH) that cannot be discontinued >4 hours prior to Pexa-Vec IT injections
 - e. Oral direct thrombin inhibitor (dabigatran) or direct Factor Xa inhibitor (rivaroxaban, apixiban, and endoxaban) that cannot be discontinued for 4 days prior to Pexa-Vec IT injection

NOTE: LMWH or UFH may be used to transition patients on and off of the above anti-coagulants (if deemed appropriate by the treating physician) prior to Pexa-Vec treatments as long as the last dose of LMWH is administered >24 hours prior to treatments and last dose of UFH is administered >4 hours prior to treatments.

Please contact the Sponsor for questions regarding the management of other anticoagulant prior to treatments.

22. Inability to suspend treatment with anti-hypertensive medication (including but not limited to: diuretics, beta-blockers, angiotensin converting enzyme [ACE] inhibitors, aldosterone antagonists, etc.) for 48 hours prior to and 48 hours after each Pexa-Vec injection
23. Any prior or planned organ transplant (e.g., liver transplant)
24. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation. Child-bearing potential patients with a positive hCG laboratory test (>10 mIU/mL) at Screening and/or a positive urinary test at Baseline will perform an ultrasound to assess the pregnancy.

25. Patients who experienced a severe systemic reaction or side-effect as a result of a previous vaccination with vaccinia
26. Participation in a clinical study with an active investigational product within 4 weeks prior to randomization
27. Patient unable or unwilling to comply with the protocol requirements
28. Previous treatment with Pexa-Vec or other vaccinia vector based treatment
29. Pulse oximetry O₂ saturation <90% at rest on room air

6.C SCREENING, ELIGIBILITY, ARM ASSIGNMENT, STUDY COMPLETION, AND STUDY DISCONTINUATION

6.C.1 Screening

Screening assessments will begin after the patient has signed the informed consent and a Patient Study Identification Number will be generated. The Day 1 visit may occur within 21 days of the first screening procedure. Screening window can be extended beyond 21 days with prior Sponsor's approval.

6.C.1.a Screen Failures

The status and reason for failure will be reported in the eCRF. Patients who do not meet all eligibility criteria during Screening should be screen-failed. Any patients who are deemed "screen failures" cannot be re-screened for participation unless prior Sponsor's approval was granted.

6.C.2 Eligibility

The Principal Investigator is ultimately responsible for ensuring and endorsing that patient(s) meet all eligibility criteria (Inclusion/Exclusion Criteria) prior to randomization

Patients will be eligible for each of the 3 Pexa-Vec IT injections if all of the following clinical and laboratory criteria are met prior to each Pexa-Vec IT treatment:

- Adequate liver function (total bilirubin ≤ 3.0 mg/dL [51.3 μ mol/L]; ALT and AST $\leq 5 \times$ ULN)

- Platelets $\geq 75 \times 10^9/L$ (correction with transfusion or thrombopoietin based therapy allowed to meet re-treatment eligibility criteria)
- Hemoglobin ≥ 9 g/dL (correction with transfusion or erythropoietin based therapy allowed to meet re-treatment eligibility criteria)
- INR ≤ 1.7 (correction with plasma protein support allowed to meet re-treatment eligibility criteria [e.g., fresh-frozen plasma])
- Patient is still expected to have at least one viable, injectable intrahepatic tumor ≥ 1 cm LD
- No clinically significant and/or rapidly accumulating ascites, pericardial and/or pleural effusions. Minimal ascites that does not preclude safe IT injection of Pexa-Vec is allowed at the discretion of the treating physician and interventional radiologist.

6.C.2.a Laboratory Eligibility

Blood samples drawn at Screening to determine study eligibility must be sent to the central laboratory except for the clinical investigational sites participating in China where laboratory testing will be completed by local laboratory at each site. Local laboratory results may be used to determine patient re-treatment eligibility before each Pexa-Vec IT injection (i.e., not for study eligibility); however, blood samples will need to be sent to the central laboratory in parallel which will prevail over the local laboratory results.

During the screening period, hematology parameters can be re-tested after an authorized therapy.

6.C.3 *Patient Allocation to Treatment Arms*

A total of 600 patients will be randomized between one of 2 treatment arms in a 1:1 ratio (300 in each arm). Patients will be allocated to each arm via a dynamic stochastic minimization procedure performed independently for Asian and non-Asian patients. The following criteria will be used:

1. Center
2. Main etiology: hepatitis C, hepatitis B, alcohol or other reasons (such as hemochromatosis, Wilson's disease, type 2 diabetes, NASH)
3. Presence of extrahepatic disease or not

4. Vascular invasion or not
5. Performance status 0 or 1 on the ECOG scale
6. AFP levels (<200, 200–400 or ≥400 ng/mL)

6.C.4 *Premature Study Discontinuation*

Premature discontinuation from active study participation may occur at any time due to any of the following reasons:

1. Any situation where, in the opinion of the Investigator or the Medical Monitor, continued participation in the study would not be in the best interest of the patient.
2. Patient initiates other anti-cancer therapy. The anti-cancer therapy will be documented in the medical record and eCRF.
3. An intercurrent illness develops that precludes objective clinical assessments.
4. Prohibited concomitant medications are required or used.
5. Patient is unable or unwilling to comply with study procedures.
6. Consent for active study participation is withdrawn.
7. Termination of the study by the Sponsor.
8. Request by a Health Authority.

6.C.4.a Data Collection for Premature Discontinued Patients

The reason(s) for premature study discontinuation should be reported on eCRF and within the source documents. AEs should be documented according to [Section 11](#). An End of Treatment Visit should be performed and will be followed by a Safety Visit at least 28 days after the last study drug administration (Pexa-Vec or sorafenib) to allow for collection and assessment of AEs and Concomitant Medications. Refer to [Section 7.C](#) for details. Patients who discontinue treatments will continue to be followed for survival follow-up (to allow for analysis of the primary trial endpoint), collection of other anti-cancer therapy data and EQ5D-3L questionnaire completion (if the patient is at a site where EQ5D-3L questionnaire is planned to be completed).

In case a patient discontinues the treatment phase prior to documented radiographic progression (e.g., permanently stops taking the study medication), a PFS follow-up visit should be performed

every 6 weeks for radiology evaluation, until documented progression or until premature study discontinuation ([Section 6.C.4](#)).

If a patient withdraws consent from active study participation (discontinues), the site should initiate protocol-specified survival contacts every 4 weeks with the window of ± 7 days unless the patient explicitly withdraws consent for survival follow-up. This consent withdrawal will be documented in the source documents and in the eCRF.

Patients who discontinue the active study participation will not be replaced.

7 STUDY PROCEDURES AND TREATMENT

7.A SCREENING

Screening assessments will begin after:

- The signature of the informed consent form (ICF)
- A patient study identification number is obtained (via Interactive Voice Response System [IVRS] / Interactive Web Response System [IWRS]). The patient study identification number is unique and remains with the patient for the entirety of the trial.

Patient eligibility for the study will be determined up to 21 days before Day 1 for Arm A or Baseline/Day 1 for Arm B. Screening procedures may be completed in less than 21 days, which is preferred. The 21-day screening window starts when the first protocol-required screening procedure is performed and does not include the ICF signature date. Screening window can be extended beyond 21 days with prior Sponsor's approval.

Central laboratory results must be obtained prior to randomization and used for eligibility determination except for the clinical investigational sites participating in China where laboratory testing will be completed by local laboratory at each site. These results are also used for Arm A patient eligibility to receive Day 1 IT injection. Only central laboratory data can be used and will be entered into the clinical database.

At the Screening visit, the following will occur:

- Collection of detailed medical, surgical, and cancer history
- Complete physical exam including weight, height, and vital signs (blood pressure, pulse, temperature including pulse oximetry for screening only)
- CT (preferred) or MRI (if CT not possible) (refer to [Section 8.C.2](#)): tumors are numbered with unique number and identified as Target or Non-Target tumors. Tumors should be assigned the next available chronological number wherever possible.
- Electrocardiogram (ECG)
- BCLC and Cancer of the Liver Italian Program (CLIP) scoring (including Child-Pugh scoring).
- Histological HCC diagnosis. If no pathology report available, perform biopsy
- European Association for the Study of the Liver (EASL) / European Organization for Research and Treatment of Cancer (EORTC) criteria

- Blood sample collection for central laboratory eligibility/safety assessment including:
 - ❖ Hematology, chemistry, and coagulation
 - ❖ CD4 and CD8 count
 - ❖ HIV, Hepatitis B and C testing
 - ❖ AFP
 - ❖ Pregnancy test for women of child-bearing potential (if positive, an ultrasound will be performed to confirm pregnancy)

NOTE: Definition of *women of child-bearing potential* = A sexually mature woman who has not undergone hysterectomy, or tubal ligation, vasectomy, or other means of permanent sterilization or who has not been naturally post-menopausal for at least 24 consecutive months for women ≤ 55 years or 12 consecutive months for women > 55 years.

- Standard urinalysis
- ECOG performance status
- Concomitant medications reporting
- From the date of signature of the ICF and up to initiation of study treatments, only SAEs caused by a protocol-required procedure will be collected and reported to the Sponsor
- Refer to [Section 8.A.4.b](#) for treatments to be stopped prior to Pexa-Vec treatment.

7.B INITIAL TREATMENT PHASE (BASELINE AND DAY 1 UNTIL WEEK 6)

7.B.1 Randomization (Upon Investigator Confirmation of Eligibility)

After patient eligibility has been confirmed by the Investigator (and by the Sponsor, as applicable), site personnel will access the IVRS/IWRS and provide relevant minimization information to obtain randomization assignment (to Arm A or Arm B). The patient will keep the same number as the one given during the screening phase.

If a patient is randomized to Arm A, a Pexa-Vec treatment kit number will be assigned for the Day 1 IT injection. If the patient is randomized to Arm B, a sorafenib treatment kit number will be assigned for the first period. Kits' assignment to patients randomized in both Arms A and B are made through the IVRS/IWRS.

Randomization and Baseline procedures ([Section 7.B.2](#)) can be performed on the same day.

7.B.2 Arm A and Arm B: Baseline Visit

At the Baseline visit, up to 4 days before Day 1, the following will occur:

- Baseline for symptomatic progression assessments, Health-Related Quality of Life (HRQoL) assessments, and pharmacoeconomic evaluations (all questionnaires should be completed prior to any Baseline Visit protocol assessments/exams):
 - ❖ ECOG performance status
 - ❖ Functional Assessment of Cancer Therapy - Hepatobiliary (FACT-Hep) questionnaire (FHSI-8 questions for scoring of symptomatic progression obtained as a subset of the FACT-Hep questionnaire)
 - ❖ EQ5D-3L questionnaire
 - ❖ Collection of pharmacoeconomic data through the Health Care Resource Utilization questionnaire and the Patient Accommodation and Transport questionnaire
- Blood sample collection for the following testing:
 - ❖ Hematology, chemistry, and coagulation
 - ❖ Human leukocyte antigen (HLA) typing (selected sites only)
 - ❖ Urinary pregnancy test for women of child-bearing potential
 - ❖ Archival serum sample

Refer to the Central Lab Manual for details on blood sample processing and shipping instructions.

- Complete physical exam
- Vital signs (e.g., blood pressure, temperature, and pulse)
- Concomitant medications reporting
- From the date of signature of the ICF and up to initiation of study treatments, only SAEs caused by a protocol-required procedure will be collected and reported to the Sponsor
- An ultrasound may be optionally performed to assess suitability of IT injection within selected liver lesions and to select lesions for injection (Arm A); or to rule out pregnancy for patients with a positive hCG laboratory test (>10 mIU/mL).

- Pregnancy test (urine) for women of child-bearing potential (if positive, an ultrasound will be performed to confirm pregnancy)

Patient Contact Log completion: include detailed contact information for the patient, family/caregivers, and preferred (to be updated periodically during study) in compliance with local regulations.

7.B.3 Arm A and Arm B: Visit 1 (“Day 1”)

All visit dates and visit windows will be counted from Day 1

7.B.3.a Arm A: Pexa-Vec Treatment #1 (Day 1)

7.B.3.a.1 Identification of Liver Lesions for IT treatment

Using the most recent CT/MRI scan (e.g., screening CT/MRI), a qualified and trained Interventional Radiologist will identify up to 5 intrahepatic tumors, each ≥ 1 cm LD, for injection. As noted at baseline visit above, a pre-treatment ultrasound may be performed if needed to confirm ability to inject tumors under imaging guidance.

The Interventional Radiologist can select tumors for injection that were identified as target or non-target tumors and numbered with a unique number at screening.

The Interventional Radiologist will measure and document the LD of the tumors (with appropriate tumor numbers) selected for injection. Tumor numbers and measurements will be documented by the Interventional Radiologist/physician performing the injection on the Pexa-Vec IT Injection Preparation Worksheet.

The number(s) of the tumor(s) injected and the volume of solution injected into each tumor (among other data points) will be recorded in the eCRF.

7.B.3.a.2 IT Injection Procedure

The total Pexa-Vec dose for IT injection is 1×10^9 pfu (equivalent to 9.0 Log pfu) which is diluted in sterile buffered normal saline. The volume of saline used for dilution will vary according to the number and size of tumors to be injected. Each tumor will be injected with Pexa-Vec diluted in buffered normal saline solution in a volume that is approximately 25% of that tumor’s volume (percentage dependent on the size of the tumor) but will not exceed a specified upper limit. After an appropriate pre-hydration (refer to [Section 8.A.3](#)), injections will be performed by the

Interventional Radiologist or other trained physician using imaging-guidance (ultrasound and/or CT). All viable, safely injectable intrahepatic tumors ≥ 1 cm LD must be treated, with a maximum of 5 tumors treated on a given treatment day. Different tumors may be treated on each treatment day, including new intrahepatic tumors that have developed since screening evaluation. The total prepared injection volume will be divided proportionally between 1–5 intrahepatic tumors, relative to individual tumor volumes.

Injection needles designed for percutaneous insertion into tissues will be used. Depending on tumor size, either multi-pronged injection needles (provided by the Sponsor), or straight needles preferably with multiple side ports (not provided by the Sponsor), will be used.

Refer to the “*Pexa-Vec Intratumoral injection: Procedure Manual*” and to the “*Pexa-Vec Intratumoral (IT) Injection: Preparation Worksheet*” for more information about the specific calculation and preparation instructions and for the detailed injection procedure guidelines and needle use recommendations.

7.B.3.a.3 Additional Procedures

Patients will be observed in the clinic or hospital for a minimum of 8 hours after IT Pexa-Vec treatment. The following evaluations will be performed:

- Complete physical exam (before IT)
- Medical, and surgical history update with any study procedure-related SAEs that would have occurred from the signature of the ICF (before IT)
- Reporting of AEs (that occurred during or after IT) and concomitant medications
- Vital signs (blood pressure, temperature, and pulse) within 60 minutes prior to injection to establish baseline, 15 minutes (± 5 minutes) after injection completion and then every hour (± 15 minutes) for at least 8 hours after treatment
- Archival serum sample (8 hours with ± 15 minutes after treatment)

7.B.3.b Arm B: Sorafenib Treatment Start (Day 1)

For patients assigned to Arm B, sorafenib will be started at Day 1 at a dose of 400 mg BID. Dosing reductions may be performed according to the registered SmPC.

Arm B patients will complete the following procedures:

- Complete physical exam
- Vital signs (blood pressure, temperature, and pulse)
- Medical, and surgical history update with any study procedure-related SAEs that would have occurred from the signature of the ICF (before sorafenib initiation)
- AE and concomitant medications reporting from the first dose of sorafenib intake
- Sorafenib: counsel patient on use and IVRS/IWRS first kit dispensation

7.B.4 Arm A: Visit 2 (Pre-Day 15 or Pre-Week 2); Arm B: Visit 2 (Day 15 or Week 2)

7.B.4.a Arm A: Visit 2/ Pre-Day 15 or Pre-Week 2

This visit will be performed up to 4 days before Visit 3/Day 15 (Week 2). This visit must occur regardless of whether the Day 15 IT injection will be given.

The Principal Investigator is ultimately responsible for ensuring and endorsing that patient(s) meet the required clinical and laboratory criteria prior to Pexa-Vec injection.

Patients will be eligible for Treatment #2 if all of the following re-treatment criteria are met:

1. Laboratory criteria:
 - Adequate liver function (total bilirubin ≤ 3 mg/dL [$51.3 \mu\text{mol/L}$]; ALT, and AST $\leq 5 \times$ ULN)
 - Platelets $\geq 75 \times 10^9/\text{L}$ (correction with transfusion or thrombopoietin based therapy allowed to meet re-treatment eligibility criteria)
 - Hemoglobin ≥ 9 g/dL (correction with transfusion or erythropoietin based therapy allowed to meet re-treatment eligibility criteria)
 - INR ≤ 1.7 (correction with plasma protein support allowed to meet re-treatment eligibility criteria [e.g., fresh-frozen plasma])
2. The patient is still expected to have at least one viable, injectable intrahepatic tumor ≥ 1 cm LD.
3. No clinically significant and/or rapidly accumulating ascites, pericardial and/or pleural effusions. Minimal ascites that does not preclude safe IT injection of Pexa-Vec is allowed at the discretion of the treating physician.

Re-treatment eligibility assessments may be repeated until the patient becomes eligible for treatment within the specified window of $-1/+7$ days, but all eligibility criteria must be ultimately confirmed within 4 days prior to IT injection.

Arm A patients will complete the following procedures:

- Complete physical examination including weight and skin assessment
- Vital signs (blood pressure, temperature, and pulse)
- Blood sample collection for central laboratory assessment including:
 - ❖ Hematology, chemistry and coagulation (in the interest of time, local analysis may be obtained to confirm patient re-eligibility for treatment but samples should be sent to central laboratory in parallel)
- AEs and concomitant medications reporting
- If the patient meets eligibility criteria, contact the IVRS/IWRS to obtain Pexa-Vec kit number for Day 15 treatment.

7.B.4.b Arm B: Visit 2/ Day 15 (Week 2)

This visit can occur Day 15 \pm 3 days, but preferentially the closest as possible to Day 15.

Arm B patients will complete the following procedures:

- Complete physical examination including weight
- Vital signs (blood pressure, temperature, and pulse)
- Blood sample collection for central laboratory assessment including hematology, chemistry and coagulation parameters
- AEs and concomitant medications reporting
- Sorafenib: collection of returned medication and IVRS/IWRS new kit dispensation
- Update of the Patient Contact log as needed

7.B.5 *Arm A: Visit 3 / Pexa-Vec Treatment #2 (Day 15/Week 2)*

This visit can occur Day 15 $-1/+7$ days (Days 14–22) but preferentially the closest as possible to Day 15.

Pexa-Vec IT doses should be given at least 13 days apart.

Clinical and laboratory eligibility criteria should have been confirmed at previous visit. Refer to [Section 6.C.2](#).

All procedures are the same as Pexa-Vec Treatment #1 (Day 1). Patients will be observed in the clinic or hospital for a minimum of 8 hours after IT Pexa-Vec treatment and following evaluations will be performed:

- Complete physical exam (before IT)
- Vital signs (blood pressure, temperature, and pulse) within 60 minutes prior to injection to establish baseline, 15 minutes (± 5 minutes) after injection completion and then every hour (± 15 minutes) for at least 8 hours after treatment
- An ultrasound may be optionally performed to assess suitability of IT injection within selected liver lesions and to select lesions for injection
- Reporting of AEs and concomitant medications
- Update of the Patient Contact log as needed

If an IT treatment is ultimately not administered within the protocol-specified window for any reason, this treatment must be cancelled (i.e., missed for this time point), but the patient should resume follow-up visits per the Schedule of Activities and IT treatments at the next scheduled treatment visit if there is still an IT administration planned and re-treatment eligibility criteria are met as outlined above.

7.B.6 *Arm A: Visit 4 (Pre-Day 29/Pre-Week 4); Arm B: Visit 3 (Day 29/Week 4)*

7.B.6.a Arm A: Visit 4/ Pre-Day 29 (Pre-Week 4)

This visit will be performed up to 4 days before Visit 5/Day 29 (Week 4). This visit must occur regardless of whether the Day 29 IT injection will be given.

Arm A patients will complete the following procedures:

- Complete physical examination including weight and skin assessment
- Vital signs (blood pressure, temperature, and pulse)
- Blood sample collection for central laboratory assessment including:

- ❖ Hematology, chemistry and coagulation (in the interest of time, local analysis may be obtained to confirm patient re-eligibility for treatment but samples should be sent to central laboratory in parallel)
- AE and concomitant medications reporting
- Refer to [Section 6.C.2](#) for re-treatment eligibility criteria: If the patient meets eligibility criteria, contact the IVRS/IWRS to obtain Pexa-Vec kit number for Visit 4/Day 29 (Week 4) treatment.

7.B.6.b Arm B: Visit 3 / Day 29 (Week 4)

This visit can occur Day 29 \pm 3 days, but preferentially the closest to Day 29.

Arm B patients will complete the following procedures:

- Complete physical examination including weight
- Vital signs (blood pressure, temperature, and pulse)
- Blood sample collection for central laboratory assessment including:
 - ❖ Hematology, chemistry and coagulation
- AEs and concomitant medications reporting
- Sorafenib: collection of returned medication and IVRS/IWRS new kit dispensation

7.B.7 *Arm A: Visit 5 / Pexa-Vec Treatment #3 (Day 29 / Week 4)*

This visit can occur Day 29 $-1/+7$ days (between Days 28–36), but preferentially the closest to Day 29.

Pexa-Vec IT doses must be given at least 13 days apart.

Clinical and laboratory eligibility criteria should have been confirmed at previous visit. Refer to [Section 6.C.2](#).

All procedures are the same as Pexa-Vec Treatment #1 and #2 (Day 1 and Day 15), refer to [Section 7.B.3.a](#) and [Section 7.B.5](#), respectively. Patients will be observed in the clinic or hospital for a minimum of 8 hours after IT Pexa-Vec treatment and following evaluations will be performed:

- Complete physical exam (before IT)
- Vital signs (blood pressure, temperature, and pulse) within 60 minutes prior to injection to establish baseline, 15 minutes (± 5 minutes) after injection completion and then every hour (± 15 minutes) for at least 8 hours after treatment
- An ultrasound may be optionally performed to assess suitability of IT injection within selected liver lesions and to select lesions for injection
- Reporting of AEs and concomitant medications

If an IT treatment is ultimately not administered within the protocol-specified window for any reason, this treatment must be cancelled (i.e., missed for this time point), but the patient should resume follow-up visits per the Schedule of Activities.

7.B.8 *Arm A: Visit 6 (Day 43/Week 6)/ Arm B: Visit 4 (“Day 43/Week 6”)*

7.B.8.a Arm A: Visit 6/Day 43 (Week 6)

This visit should occur between Day 41 – Day 45.

Sorafenib should be started 2 weeks (± 2 days) after the last IT injection.

Arm A patients will complete the following procedures:

- Symptomatic progression assessments, HRQoL assessments, and pharmacoeconomic evaluations (all questionnaires should be completed by all patients prior to any Visit 6 protocol assessments/exams):
 - ❖ ECOG performance status
 - ❖ FACT-Hep questionnaire
 - ❖ EQ5D-3L questionnaire
 - ❖ Collection of pharmacoeconomic data through the Health Care Resource Utilization questionnaire
- Complete physical examination including weight and skin assessment
- Vital signs (blood pressure, temperature, and pulse)
- Blood sample collection for central laboratory assessment including:
 - ❖ Hematology, chemistry and coagulation

- ❖ CD4 and CD8 count
- ❖ AFP
- ❖ Archival serum sample
- AE and concomitant medication reporting
- Update patient contact log
- Sorafenib initiation: patient counsel on use and IVRS/IWRS new kit dispensation
- CT (preferred) or MRI (if CT not possible) (refer to [Section 8.C.2](#)).

7.B.8.b Arm B: Visit 4/Day 43 (Week 6)

This visit will occur at Day 43 \pm 2 days (between Day 41 and Day 45). Arm B patients will complete the following procedures:

- Symptomatic progression assessments, HRQoL assessments, and pharmacoeconomic evaluations (*all questionnaires should be completed by all patients prior to any assessments/exams*):
 - ❖ ECOG performance status
 - ❖ FACT-Hep questionnaire
 - ❖ EQ5D-3L questionnaire
 - ❖ Collection of pharmacoeconomic data through the Health Care Resource Utilization questionnaire
- Complete physical examination including weight
- Vital signs (blood pressure, temperature, and pulse)
- Blood sample collection for central laboratory assessment including:
 - ❖ Hematology, chemistry and coagulation
 - ❖ CD4 and CD8 count
 - ❖ AFP
 - ❖ Archival serum sample

- AE and concomitant medications reporting
- Update patient contact log
- Sorafenib: collection of returned medication and IVRS/IWRS new kit dispensation
- CT (preferred) or MRI (if CT not possible) (refer to [Section 8.C.2](#)).

7.C FOLLOW-UP PHASE

7.C.1 *Long-Term Follow-Up Visits and Monitoring (Arm A and Arm B)*

7.C.1.a Every 3 Weeks \pm 4 Days: Clinical Status Visits

After Week 6, safety and clinical status will be assessed every 3 weeks \pm 4 days starting from the Week 6 visit date up to the End of Treatment visit. The following procedures will be performed for both Arm A and Arm B patients:

- Blood sample collection for central laboratory assessment including:
 - ❖ Hematology and chemistry
- AEs and concomitant medications reporting
- Update patient contact log
- Sorafenib: collection of returned medication and IVRS/IWRS new kit dispensation

7.C.1.b Every 6 Weeks \pm 7 Days: Symptomatic, QoL, and Radiographic Status Visits

After Week 6, radiographic status will be evaluated every 6 weeks \pm 7 days starting from the Week 6 visit date up to the End of Treatment Visit.

Beyond 12 months of treatment, the evaluation will be performed every 12 weeks.

Both Arm A and B patients will complete the following procedures every 6 weeks (e.g., every other follow-up visit):

- Symptomatic progression assessments, HRQoL assessments, and pharmacoeconomic evaluations (questionnaires should be completed by all patients prior to any protocol assessments/exams):
 - ❖ ECOG performance status

- ❖ FACT-Hep questionnaire
- ❖ EQ5D-3L questionnaire
- ❖ Collection of pharmacoeconomic data through the Health Care Resource Utilization questionnaire and the Patient Accommodation and Transport questionnaire (only at Week 12)
- Blood sample collection for central laboratory assessment including:
 - ❖ Hematology and chemistry
 - ❖ AFP
- Complete physical examination including weight and skin assessment for Arm A patients
- CT (preferred) or MRI (if CT not possible) (refer to [Section 8.C.2](#))
- AE and concomitant medication reporting
- Update patient contact log
- Sorafenib: collection of returned medication and new IVRS/IWRS dispensation

7.D END OF TREATMENT VISIT (ARM A AND ARM B)

This visit should be completed as soon as the last Pexa-Vec or sorafenib dose is administered. The following evaluations will be performed:

- Complete physical examination including weight (skin assessment in Arm A)
- Vital signs (blood pressure, temperature, and pulse)
- Symptomatic progression assessments, HRQoL assessments, and pharmacoeconomic evaluations:
 - ❖ ECOG performance status
 - ❖ FACT-Hep questionnaire
 - ❖ EQ5D-3L questionnaire
 - ❖ Collection of pharmacoeconomic data through the Health Care Resource Utilization questionnaire and the Patient Accommodation and Transport questionnaire
- ECG

- Blood sample collection for central laboratory assessment including:
 - ❖ Hematology, chemistry and coagulation
 - ❖ CD4 and CD8 count
 - ❖ AFP
 - ❖ Archival serum sample
- CT (preferred) or MRI (if CT not possible) (refer to [Section 8.C.2](#)).
- AE and concomitant medications reporting
- Update patient contact log

7.E SAFETY FOLLOW-UP

This visit should occur not less than 28 days and no more than 2 months after the last study drug administration (sorafenib or Pexa-Vec).

The following evaluations will be performed:

- Complete physical examination including weight (skin assessment in Arm A)
- Vital signs (blood pressure, temperature, and pulse)
- Reporting of AE having occurred within 28 days after the last study treatment administration
- Reporting of concomitant medications (including potential anti-cancer therapies) and significant non-drug therapies within 28 days after the last study drug administration
- Blood sample collection for central laboratory assessment including:
 - ❖ Hematology, chemistry

7.F FOLLOW-UP VISITS FOR PROGRESSION FREE SURVIVAL

For patients who complete the study treatment phase prior to documented radiographic progression, radiological evaluation should be obtained every 6 weeks until documented progression. Beyond 12 months, the evaluations will be performed every 12 weeks until documented progression.

NOTE: patients undergoing follow-up visits for PFS are still on the active study participation phase and may not receive other anti-cancer treatments.

7.G SURVIVAL FOLLOW-UP PHASE

After the Safety Follow-Up Visit, all patients will be monitored every month for:

- Survival
- Reporting of anti-cancer therapies

Patient consent for survival follow-up contacts is implicit when patients consent to study participation. If a patient withdraws consent from study procedures (discontinues), they will continue to be contacted for the protocol-specified survival follow-up unless the patient explicitly withdraws consent for survival follow-up.

Due diligence should be used in contact efforts including:

- At least 3 documented direct patient contact attempts and certified letter sent
- If a patient cannot be directly contacted, utilize all contact information provided by the patient on the patient contact log
- If all contact attempts are unsuccessful, death registries should be reviewed
- These patient contact procedures should be followed for at least 3 months before the patient can be considered lost to follow-up. Death registry data should be accessed for all patients until the study is completed.
- If a patient explicitly withdraws consent for survival follow-up, or if the site is unable to contact the patient, other methods to determine survival may be used, including referencing death registries, clinic/hospital visit records, primary oncologist or physician records, and/or newspaper obituaries, in compliance with local regulations.

8 PATIENT MANAGEMENT

8.A TREATMENTS

8.A.1 *Expected Toxicities of Pexa-Vec Treatment*

- **Flu-Like Symptoms (mild-to-severe fever, rigors, anorexia, aches/pain, fatigue, headache, and/or nausea)**

These flu-like symptoms typically peak during the first 12 hours after Pexa-Vec treatment. Acute, fever is expected within 4–12 hours post-treatment and has a typical duration of 18–24 hours, although these can last up to 72 hours.

- **Hypotension**

Across clinical trials and indications, mild-to-moderate transient hypotension can be observed within 24 hours following treatment with Pexa-Vec (21% of all patients as of October 2018). However, in the TRAVERSE trial (Study No. JX594-HEP018) for patients with advanced 2nd line HCC, 6 patients (8 total SAEs) have experienced severe hypotension following Pexa-Vec treatment, defined as a SBP <90 mmHg, lasting and/or requiring >24 hours of medical treatment, intensive care unit care, and vasopressor treatment. Notably, anti-hypertensive medication was ongoing at the time of treatment with Pexa-Vec prior to the development of hypotension in the majority of these patients, thereby potentially exacerbating the potential for hypotension.

A single event of severe hypotension has also been observed in JX594-HEP024, a study in sorafenib-naïve HCC. The patient required IV fluid therapy and vasopressor treatment for 36 hours. The frequency of observation of this degree of hypotension on TRAVERSE compared to other studies of Pexa-Vec may possibly be due to the more advanced status of the TRAVERSE population with respect to co-morbid cirrhosis with associated intravascular volume depletion, third space fluid accumulation and diuretic therapy as well as confounding effects of concurrent anti-hypertensive medications administration.

To mitigate risk of hypotension following Pexa-Vec treatment, the following are required:

- ❖ Prehydration with 1 liter of solute-containing fluid (p.o. or IV) prior to each treatment
- ❖ Suspension of anti-hypertensive medication (including diuretics, beta-blockers, ACE inhibitors, aldosterone antagonists, etc.) for 48 hours prior to and 48 hours after each Pexa-Vec injection
- ❖ Observation of patients for at least 8 hours following each IT injection

- ❖ For patients with a history of cardiovascular disease, cardiology consultation and creatinine clearance must be obtained prior to enrollment. **NOTE:** Patients with active cardiac disease within 12 months of study entry are excluded from study participation.

- **Hematological Events**

Transient decreases in WBC counts (including neutrophils and lymphocytes), platelets and hematocrit can occur. Transient thrombocytopenia (including reduced platelet count) occurred within days of treatment with Pexa-Vec and resolved within 1 week of treatment without medical intervention. Transient leukopenia (including reduced neutrophil and lymphocyte counts), has been observed with resolution generally occurring within 7 days of treatment. Leukopenia is a common finding associated with viral infection in general. Conversely, transient leukocytosis (including neutrophil, eosinophil, and monocyte subsets) has also been observed. An elevated WBC count is expected based on a GM-CSF mediated effect by Pexa-Vec and the infusion of an attenuated vaccinia virus.

- **Chemistry Changes**

Chemistry changes included hyponatremia and hyperglycemia; the relationship to Pexa-Vec treatment is not yet known. Dose-related direct hyperbilirubinemia (due to tumor swelling and occlusion of biliary tract drainage) has been noted in patients treated with Pexa-Vec whose liver tumors were adjacent to or impeding the biliary tract at baseline. In addition, acute respiratory distress secondary to airway obstruction was observed in one patient with HCC metastases to the lung following treatment. Therefore, patients with liver tumors in a location that would potentially result in significant clinical adverse effects if post-treatment tumor swelling were to occur, including at the site of the common bile duct, should not be included as per Exclusion Criteria 8. Biliary tract drainage should be considered as clinically indicated if biliary occlusion does not resolve quickly enough clinically. Acute post-treatment tumor swelling can result in hyperbilirubinemia within approximately one week following treatment; tumor swelling may resolve over time.

- **Rashes**

Rashes related to latent virus reactivation have been reported, both with Varicella-Zoster (i.e., “shingles”) and herpes simplex virus; whether these rashes are related to Pexa-Vec itself, or due to the fever induced, is unknown. Small (<1 cm) superficial skin or oral mucous membrane pustules containing Pexa-Vec may develop after Pexa-Vec treatment. If they develop, it is typically within 1 week after the first IV infusion only. These pustules have rarely (<10%) been seen following IT injection. These pustules generally resolve within approximately the following

2–3 weeks, a time course that is consistent with the usual course following intentional vaccination with wild-type [non-attenuated] vaccinia vaccine. All pustules to date have been self-limited and resolved without complications or the need for specific anti-viral treatment.

8.A.2 Notable Safety Findings

- **Myocardial Infarction and/or Cardiac Ischemia**

On the PHOCUS trial (Study No. JX594-HEP024), one patient experienced a Grade 2 acute myocardial infarction (MI) [MCN #2017SLU000230] approximately 8 hours following their second Pexa-Vec injection. The Investigator assessed the event possibly related to Pexa-Vec and injection procedure based on temporal association of the event with Pexa-Vec treatment and therefore, Pexa-Vec could not be ruled out as a potential cause of the event. However, the Investigator acknowledged this patient had well-established pre-existing cardiovascular risk factors including hypertension, hyperlipidaemia, diabetes, and distant tobacco use, as potentially contributing alternative etiological factors. Sponsor agreed with this assessment. Subsequently, the patient developed a recurrent MI that occurred 6 days after Pexa-Vec treatment and appeared to be not immediately temporally related and unprovoked in a patient with significant underlying cardiovascular risk factors. Approximately 2 weeks after initiation of sorafenib therapy, the patient experienced severe chest pain diagnosed as stable angina. Following recovery from the angina episode and having re-initiated sorafenib, the patient developed unstable angina requiring re-hospitalization approximately 6 weeks after original sorafenib start date. The Sponsor assessed the second episode of MI and subsequent stable angina event as unlikely related to both Pexa-Vec and sorafenib in the patient with significant CAD and previous MI. Please refer to the IB for further details.

A second patient who experienced an MI Grade 3 (MCN #2018SLU000115) was a 70-year old male with a history of hypertension, hyperlipidemia, type 2 diabetes mellitus, obesity, and a distant history of tobacco smoking. Prior to enrollment in the study, the patient was seen for an abnormal CT finding of moderately prominent coronary artery calcification and had a pre-treatment cardiac work up including a 3-minute exercise test that revealed no acute ischemic ECG changes but was overall non-diagnostic. No major cardiac dysfunction was revealed by echocardiogram or EKG. The patient was cleared for trial participation (understanding the risk of tachycardia and hypotension after treatment with Pexa-Vec). The patient developed tachycardia following Pexa-Vec treatment and prior to the development of chest pain symptoms and subsequent finding of elevated troponin blood levels. Angiogram revealed underlying CAD including significant narrowing of the ostium of one of the diagonal arteries. These findings and clinical setting were

thought consistent with demand related MI secondary to tachycardia. The patient was treated with medical therapy (atorvastatin and aspirin) for underlying CAD with discharge after an uncomplicated post-MI clinical course. The Investigator assessed the causal relationship of deviated troponin level to investigational product Pexa-Vec as possibly related, and the Sponsor agreed with the Investigator's assessment.

The analysis of cardiac events demonstrated an incidence rate of under 1% of MI following treatment with Pexa-Vec across all indications which is relatively stable since the prior report of myocardial ischemia (MCN #2017SLU000230)

Close monitoring of clinical trials for any cardiac toxicity including cardiac ischemia/MI will be continued. Further, as outlined in [Section 6.B, Exclusion Criteria](#), patients with significant current or past cardiovascular disease are excluded from the study unless cardiology consultation and clearance has been obtained for study participation. Additionally, patients with symptomatic cardiovascular disease within the preceding 12 months, as well as patients with medical conditions that may predispose them to untoward medical risk in the event of volume load, tachycardia, and/or hypotension during or following Pexa-Vec treatment are excluded from the study. To increase the rigor of cardiology evaluation prior to study entry, independent, central cardiology review will be required for patients who undergo local, pre-study cardiology screening prior to enrollment in studies of Pexa-Vec to ensure a consistent approach to evaluation of potential study candidates.

In the case of a suspected myocardial ischemia, cardiology consultation should be arranged and cardiac work up including angiography, echocardiography, electrocardiogram, and cardiac enzymes (e.g., cardiac troponin) should be performed, as clinically indicated.

- **Portal Vein Thrombosis**

One patient has experienced acute portal vein thrombosis (PVT) in JX594-HEP024. The patient experienced abdominal pain, abdominal distension, headache, and tonsillitis (MCN #2017SLU000212). The patient had significant thrombosis of the portal vein at baseline and was diagnosed with acute PVT 5 days following the second Pexa-Vec injection. The same patient has subsequently developed liver rupture, Grade 3 (PT: tumor rupture, MCN #2017SLU000235) after approximately a 3-week course of sorafenib treatment assessed as related to Pexa-Vec by the Investigator and deemed to be a rapid HCC progression by the Sponsor. Despite compelling alternative etiology, the Investigator concluded that the causal relationship of Pexa-Vec and acute PVT could not be completely ruled out and the Sponsor agreed with that assessment. Notably, PVT is a common finding in patients with advanced HCC which is observed

in ~10–60% of HCC patients according the literature reported data (*Catalano 2010; Quirk 2015; Chan 2016; etc.*).

8.A.3 Risks Linked to IT Injection Procedure

At the tumor or skin injection the following toxicities may be observed (refer to the IB for further details on patient management):

- pain at the injection site,
- general reactions (e.g., vasovagal reaction, hypotension, bradycardia, pyrexia, anxiety, nausea, vomiting, diarrhea),
- anesthetic reactions,
- prolonged bleeding from the injection site or internal bleeding (e.g., subcapsular liver hematoma, hemoperitoneum, hemothorax, hemobilia),
- infection at the injection site that may cause sepsis and other infections (e.g., septicemia peritonitis, perihepatic abscess, pneumonia),
- hepatic encephalopathy,
- ascites,
- puncture of other organs (e.g., pleural effusion, pneumothorax),
- fluctuations of biological parameters: anemia, transient bilirubin and transaminases increases, creatinine increase.

8.A.4 Concomitant Authorized and Contraindicated Treatments

8.A.4.a Definitions and Reporting of Concomitant Medication and Non-Drug Therapy

Concomitant medications or significant non-drug therapies (therapeutic intervention [e.g., surgery, blood transfusion]) will be reported within the month before start of study treatment up to 28 days after the last dose of Pexa-Vec or sorafenib.

All medications (International Nonproprietary Names [INN]), dosage, route of administration, frequency, duration of administration, and the indication will be recorded in the appropriate sections of the eCRF.

Concomitant medications or non-drug therapy used or performed to treat a SAE, an AE related to study treatments or any other significant AE as recommended by the Sponsor, should be recorded beyond the AE reporting period as described in [Section 11](#).

Each time a frequency, dosage, or an indication changes, a new entry must be made in the appropriate section of the eCRF.

8.A.4.b Concomitant Authorized & Contraindicated Treatments

8.A.4.b.1 *Recommended Medications Related to Flu-like Symptoms (mild-to-severe fever, rigors, anorexia, aches/pain, fatigue, headache, and/or nausea) – Arm A*

Pre-Medication for Treatment Day

Patients should receive approximately 1 liter of solute-containing fluids (e.g., normal saline) IV or orally within 12 hours of treatment initiation.

All patients should be pre-medicated with acetaminophen (and/or equivalent, e.g., NSAIDs, unless contraindicated) on each treatment day. For acetaminophen, the following regimen may be used:

- 500–1000 mg 2 hours pre-infusion
- 500–1000 mg at 4 hours post-procedure
- 500–1000 mg every 6 hours thereafter, as needed (the total acetaminophen dose should be carefully assessed to avoid cumulative toxicity)

Acute Post-Treatment Symptom Management

During the observation period post-treatment, patients should receive IV solute-containing fluid and other measures (e.g., vasopressor therapy) per SOC as needed for blood pressure support. Anti-rigor medication (e.g., meperidine) or support medications may be used as needed.

Anti-emetics may be used at the Investigator's discretion for treatment of nausea or vomiting; it is noted, however, that corticosteroids should not be used.

Analgesics, anti-pyretics (e.g., prophylactic acetaminophen), antidepressants, bisphosphonates, EPO growth factors and other supportive care measures may be used at the Investigator's discretion.

8.A.4.b.2 Management of Hypotension and Contraindicated Treatments - Arm A

To mitigate risk of hypotension following Pexa-Vec treatment, the following are required:

- Prehydration with 1 liter of solute-containing fluid (p.o. or IV) prior to each treatment
- Suspension of anti-hypertensive medication for 48 hours prior to and 48 hours after all Pexa-Vec treatments
- Anti-hypertensive medications include, but are not limited to, the following:
 - ❖ Diuretics
 - ❖ Beta-blockers
 - ❖ ACE inhibitors
 - ❖ Aldosterone agonists

8.A.4.b.3 Agents with Potential Inhibitory Activity Against Vaccinia Viruses - Arm A

In the extremely unlikely case of generalized vaccinia virus infection, encephalitis or another clinically-significant, progressive toxicity that, in the opinion of the Investigator could be related to Pexa-Vec replication, Investigators may consider the use of agents with vaccinia inhibitory activity, if available in their country for such clinical use. Such agents may include anti-vaccinia immune globulin (VIG), cidofovir, and/or Arestvyr (USAN tecovirimat; ST-246). In addition, based on limited preclinical data, interferon, ribavirin, and sorafenib may have anti-vaccinia activity. For clarity, none of these agents have been used or approved for this purpose to date. Since these agents have not been used in Pexa-Vec treated patients to date, clinical judgment should be used when determining the optimal regimen and duration of treatment.

The availability of these or similar antiviral products is country-dependent; options will be investigated and a plan for a response to infection-related toxicities will be documented and communicated to study staff prior to initiation of the clinical trial.

8.A.4.b.4 Contraindicated Antiviral Therapy Shown to Inhibit Vaccinia Replication

- Cidofovir (except to treat toxicities potentially related to uncontrolled Pexa-Vec replication)
- Interferon/PEG-interferon, ribavirin (see also Exclusion Criteria 18)

8.A.4.b.5 Other Contraindicated Treatments

- Anti-cancer therapy once a patient has been randomized
- High dose systemic corticosteroids (defined as ≥ 20 mg/day prednisone or equivalent which is ongoing at the time of arm allocation and/or was taken for more than 4 weeks within the preceding 2 months of randomization) or other immunosuppressive medications (Arm A)
- Anti-coagulation or anti-platelet medication that cannot be interrupted prior to IT injections (Arm A), including:
 - ❖ Aspirin that cannot be discontinued for 7 days prior to treatment
 - ❖ Coumadin that cannot be discontinued for 7 days prior to treatment
 - ❖ LMWH that cannot be discontinued >24 hours prior to treatment and UFH that cannot be discontinued >4 hours prior to treatment (LMWH or UFH may be used to transition patients on and off the above anti-coagulants, if deemed appropriate by the treating physician) prior to Pexa-Vec treatments as long as the last dose of LMWH is administered 24 hours prior to treatments and the last dose of UFH is administered >4 hours prior to treatments)
 - ❖ Oral direct thrombin inhibitor (dabigatran) or direct Factor Xa inhibitor (rivaroxaban, apixiban, and endoxaban) that cannot be discontinued for 4 days prior to treatments

8.A.4.b.6 Other Authorized Concomitant Treatments

- thrombopoietin, erythropoietin, G-CSF
- antidepressants
- steroids (**NOTE:** oral or parenteral steroids are not allowed during the Pexa-Vec treatment period, and for 1 week prior to and 2 weeks after Pexa-Vec treatment)
- topical therapies for symptomatic relief of hand-foot skin reaction and rash related to sorafenib
- biphosphonates, vitamin B12 and vitamin D
- Hepatitis B antivirals are ALLOWED as DO NOT inhibit vaccinia virus replication: lamivudine, adefovir (and adefovir dipivoxil prodrug), telbivudine, tenofovir, emtricitabine, clevudine and entecavir. The ability of combinations of these agents to inhibit vaccinia virus

replication has however not been evaluated. Therefore, combination therapy with anti-viral agents should be avoided if at all possible.

NOTES:

- Please contact the Sponsor for any questions regarding management of immunosuppressive, anticoagulant, antihypertensive, or antiviral medications prior to treatments.
- Sites will be notified as additional information regarding allowed and contraindicated antivirals becomes available

8.A.5 Potential Mechanisms of Pexa-Vec Shedding to the Environment, Biodissemination and Prevention of Transmission

8.A.5.a Superficial Skin Pustules

As mentioned in [Section 8.A.1](#), small (<1 cm) superficial skin or oral mucous membrane pustules containing Pexa-Vec may develop after Pexa-Vec treatment. If pustules develop, they do so typically within 1 week after the first administration. These pustules generally resolve within approximately the following 2–3 weeks, a time course that is consistent with the usual course following intentional vaccination with wild-type (non-attenuated) vaccinia vaccine. All pustules to date have been self-limited and resolved without complications or the need for specific anti-viral treatment.

Since these pustules contain Pexa-Vec they should be managed as per the “**Recommendations for Pexa-Vec Handling and Patient Management**” (Appendix B of the IB).

The following steps should be carried out in the event of skin or oral mucosa pustule identification (patient or patient contact, which is unexpected):

1. Record the AE (event term for Pexa-Vec related pustules must be recorded as “papularpustular rash”).
2. Instruct the patient/contact to cover the pustule with non-occlusive dressing (or wear a mask when around other people if oral lesions are present). Refer to the “**Recommendations for Pexa-Vec Handling and Patient Management**” (Appendix B of the IB) for further instructions.

8.A.5.b Urine, Feces, Blood, Throat and/or Saliva

Testing for the presence of Pexa-Vec after patient treatment has been conducted in several clinical studies in throat swabs, urine, feces, and blood samples.

Refer to the current Pexa-Vec IB for available data on shedding and to the “Pexa-Vec Guidelines” for recommendations on the care of Pexa-Vec treated patients. No person-to-person transmission of Pexa-Vec has been reported.

8.A.6 *Expected Toxicities of Sorafenib Treatment*

Per registered SmPC, the most common adverse reactions observed with sorafenib are diarrhea, rash, alopecia and hand-foot syndrome (corresponds to palmar plantar erythrodysesthesia syndrome in Medical Dictionary for Regulatory Activities [MedDRA]).

For further details on sorafenib toxicities, please refer to the registered SmPC.

8.B SAFETY, CLINICAL, DEMOGRAPHY, AND DIAGNOSIS ASSESSMENTS

The following parameters will be evaluated during the course of the study:

- Inclusion/Exclusion criteria: patient eligibility by the Investigator by confirming all inclusion/exclusion criteria. Violation of any entry criterion excludes a patient from enrollment into the study. If violation is discovered after enrollment, the patient may be discontinued.
- Demography: Date of birth (in countries where complete date of birth is not permitted, this will be de-identified as required), gender, race, ethnicity, childbearing potential status
- History of studied disease including but not restricted to date of diagnosis and stage at diagnosis, histology and prior HCC therapy
- BCLC and CLIP scoring
- Pre-treatment biopsy if no histological diagnosis is present in medical file
- Occurrence of AEs/SAEs (refer to [Section 11](#))
- Concomitant medications and significant non-drug therapies collection
- Clinical laboratory evaluations:

- ❖ HIV and HCV serology; detection of antigen HBs at Baseline (approximately 15 mL of blood)
- ❖ Standard serum chemistry panel: sodium, potassium, chloride, CO² content, blood urea nitrogen (BUN), creatinine, random glucose, total bilirubin, ALT, AST, calcium, lactate dehydrogenase (LDH), total protein, albumin (approximately 5 mL of blood)
- ❖ Hematology: complete blood count (CBC) with differential and platelet count (approximately 5 mL of blood)
- ❖ Coagulation: partial thromboplastin time (PTT), prothrombin time/international normalized ratio (PT/INR) (approximately 5 mL of blood)
- ❖ CD4 and CD8 counts (approximately 5 mL of blood)
- ❖ AFP (approximately 5 mL of blood)
- ❖ Blood pregnancy test at screening (approximately 5 mL of blood) and urinary pregnancy test at Baseline (for women of childbearing potential)
- ❖ Standard urinalysis (Screening only)
- Physical examinations of the major organ system including skin assessment in Arm A patients (after Pexa-Vec treatment has been initiated), weight and vital signs (blood pressure, pulse and temperature). Height will be collected at Baseline.
- Performance status on the ECOG scale

8.C EFFICACY ASSESSMENTS

8.C.1 *Biomarker/Immune Assessments*

Archival serum sample (10 mL of blood will be collected to prepare the serum sample): further immune analysis including analysis of soluble mediators, cell populations, immunophenotyping, enzyme-linked immunosorbent assay (ELISA), CDC assay may be performed.

8.C.2 *Imaging Data Acquisition and Evaluations*

8.C.2.a Imaging Data Acquisition

All patients (Arm A and Arm B) will undergo imaging of the chest, abdomen, and pelvis using helical/spiral contrast-enhanced CT scanning (preferentially) or MRI with non-contrast CT of the

chest at Screening. Tumors will be numbered with a unique number and identified as Target or Non-Target tumors (refer to the next paragraph for definitions). Tumors should be assigned the next available chronological number wherever possible.

Collection of radiographic imaging scans will then occur at Week 6 (± 2 day window) and continue thereafter every 6 weeks (± 7 days) for as long as the patient remains on sorafenib therapy.

Beyond 12 months of treatment, the evaluations will be performed every 12 weeks.

If a patient discontinues the treatment phase prior to documented radiographic progression (e.g. permanently stops taking the study medication), PFS Follow-up Visits will be performed every 6 weeks for radiology evaluation until documented radiographic progression or until premature study discontinuation.

Imaging studies will continue after radiographic progression has been documented as long as the patient continues to receive sorafenib therapy on-study.

Specific imaging acquisition instructions are provided in the Imaging Manual provided by the core imaging laboratory.

Preferred Modality: Triphasic helical/spiral CT of the abdomen (pre-contrast, arterial phase, and portal venous phase; delayed imaging of the abdomen is optional) and post-contrast helical/spiral CT of the chest and pelvis. All follow-up scans must also be CT. If a CT IV contrast allergy (toxicity) develops after the patient has been randomized, then a DCE MRI of the abdomen and pelvis with gadolinium contrast will be required along with a non-contrast CT of the chest.

Alternative Modality: While triphasic CT remains the preferred modality for the abdomen, if a patient is unable to undergo triphasic CT due to iodinated contrast allergy, then Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE MRI) of the abdomen and pelvis with gadolinium contrast will be required along with a non-contrast CT of the chest. The abdominal MRI will be triphasic in nature, and the pelvic MRI will be performed following MRI of the abdomen. If an MRI is performed at screening, all follow-up scans must also be DCE MRI of the abdomen and pelvis with gadolinium contrast with a non-contrast CT of the chest.

The same method of assessment and the same technique should be used to assess each identified and reported lesion for the radiological baseline (screening CT/MRI) and each follow up scan collected during the study.

8.C.2.b Imaging Data Evaluations

The management of patients is based on RECIST version 1.1 ([Eisenhauer 2009](#)). If the site reader determines that radiographic PD has occurred, the patient will be considered to have progressed radiographically.

In addition, independent central efficacy reads of the images will be performed in a blinded manner with both mRECIST for HCC and RECIST 1.1, by a group of expert radiologists: 2 primary readers and 1 reader who acts as the adjudicator of differences between the 2 primary readers (in the case of a disagreement about the date of progression or overall response).

Modifications to the standard RECIST criteria were proposed for patients with HCC. This is due to a poor correlation between RECIST responses (i.e., based solely on changes in tumor size), to molecularly targeted agents as well as locoregional therapy, and clinical benefit ([Forner 2009](#); [Llovet 2008a](#); [Lencioni 2010](#)). Definitions and methodology indicated hereafter are based on RECIST 1.1. For the central imaging process (exploratory objectives), mRECIST methodology will be described within the Imaging Charter.

Regarding the study objectives, secondary endpoints will be based on central review according to central mRECIST for HCC and exploratory endpoints will be based on measurements according to both local and central RECIST 1.1.

8.C.2.b.1 *Measurability of Tumor*

All measurements should be recorded in metric notation (mm). The radiological baseline will be defined according to the screening CT/MRI and tumor lesions/lymph nodes will be categorized as measurable (Target lesions) or non-measurable (Non-Target lesions). Lymph nodes that have a short axis <10 mm at Baseline are considered non-pathological and should not be recorded or followed. If no measurable lesions are identified at Baseline, the patient will not be allowed to enter the study.

For tumor lesions: the LD in the plane of measurement has to be recorded with a minimum size of 10 mm by CT scan when CT scan slice thickness is no greater than 5 mm.

For nodal lesions: at Baseline and in the follow-up, only the short axis of lymph node will be measured and followed. To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed at Baseline.

8.C.2.b.2 *Non-Measurable Lesions*

Non-measurable lesions are defined as all other lesions present at baseline, including small lesions (longest diameter <10 mm or pathological lymph node with ≥ 10 mm to <15 mm short axis) as well as truly non measurable lesions.

8.C.2.b.3 *Target / Non Target Tumors*

Each lesion reported must be uniquely and sequentially numbered on the eCRF, even if it resides in the same organ, from baseline and throughout the study. For the evaluation of lesions at baseline and throughout the study, the lesions are classified as target and non-target lesions.

Target Tumors: Target tumors should be selected on the basis of their size (tumors with the LD which are able to be reproducibly measured across time points) and are preferred to be within the liver. However, target tumors may be selected outside of the liver. Up to a maximum of 5 tumors total, and a maximum of 2 tumors per organ (except for the liver where 5 tumors can be selected as non-target for the purpose of this trial), representative of all involved organs will be identified as target tumors and will be recorded and measured at baseline by the site reader.

Selection of tumors outside the liver is subject to Sponsor's approval.

All post-baseline measurements must be performed using the same tumors and methods as the baseline assessment.

Response assessments for target tumors are defined as:

- **Complete Response (CR):** Disappearance of all target tumors. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- **Partial Response (PR):** At least 30% decrease in the SLD of target tumors, taking as reference the baseline SLD of target tumors.
- **Progressive Disease (PD):** Radiographic tumor progression for target tumors requires an increases in the SLD of target tumors of at least 20% taking as reference the smallest sum of diameters of target tumors recorded since the treatment started (this includes the baseline sum if that is the smallest on study).
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD, taking as reference the smallest SLD while on study (including Baseline). Contingent upon minimum duration of 6 weeks from enrollment.

- Non-Evaluable (NE): Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline. Rules for selecting non-evaluable include the following:
 1. All target tumors are not evaluable.
 2. Or, if at least 1 target tumor is not evaluable, the target tumor SLD is still calculated using the remaining evaluable/measurable target tumors. The only acceptable assessment in this situation is progressive disease or non-evaluable. If the SLD of target tumor has increased at least 20% from nadir (including Baseline if it is the nadir) then the response is PD. Any other calculated result gives an assessment of non-evaluable.

NOTE: SLD = sum of the LDs of viable enhancing hepatic target tumors plus LDs of any non-nodal extrahepatic target tumors plus the short axis diameters of any nodal target tumors will be calculated.

Non-Target Tumors: All other lesions, including pathological lymph nodes, are considered non-target lesions. Measurements of these lesions are not required and these lesions should be followed as “present”, “absent”, “worsening” or in rare cases “unequivocal progression” (as defined in the below note) throughout the study. Multiple non-target lesions involving the same organ can be assessed as a group and recorded as a single item (i.e., multiple enlarged pelvic lymph nodes). Each non-target lesion identified at Baseline should be assessed at each subsequent evaluation and be recorded in the eCRF.

Furthermore, for the purposes of this trial, special assessments are recommended for the following:

- Malignant portal vein thrombosis should be considered a non-measurable tumor due to the difficulty of performing reliable repeat measurements of a malignant thrombus.
- Porta hepatis lymph node can be considered as malignant if the lymph node short axis is at least 20 mm.
- Ascites, pleural effusion, and pericardial effusion: these may not be used to assess response as non-target tumors, nor may they be selected as evidence of new disease as radiographic progression. They may not be used due to the incidence of therapeutic fluid removal and benign occurrence of these fluid collections which makes them unreliable as a marker of disease evolution.

Response assessments for non-target tumors are defined as:

- Complete Response (CR): Disappearance of all non-target tumors. All lymph nodes must be non-pathological in size (<10 mm short axis).
- Incomplete Response / Stable Disease (SD): Neither CR nor PD
- Progressive Disease (PD): Unequivocal progression of existing non-target tumors
- Non-Evaluable (NE): Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a different method than baseline not allowing a reliable comparison.

Rules for selecting non-evaluable for non-target tumors include the following:

1. All non-target tumors are not evaluable.
2. Or, if at least 1 non-target tumor is not evaluable and no other non-target tumor demonstrates unequivocal progression, the assessment is “NE”
3. If at least 1 non-target tumor is not evaluable and at least 1 other non-target tumor demonstrates unequivocal progression, the assessment is “unequivocal progression.”

NOTE: To achieve “unequivocal progression” on the basis of the non-target disease, there must be an overall level of substantially worsening in non-target disease such that, even in the presence of CR, PR, or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A “modest” increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of progression solely on the basis of change in non-target disease in the face of CR, PR, or SD of target disease will therefore be extremely rare.

8.C.2.b.4 New Tumors:

The appearance of new lesion is always associated with PD. A lesion identified on a follow-up assessment in an anatomical location that was not scanned at baseline is also considered a new lesion. If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If at the next scheduled assessment, PD is confirmed, the date of progression would be the earlier date when PD was suspected.

New Tumor Progressive Disease (PD): If a newly detected lesion is obviously a tumor, progression criteria is met at the current time point. The evaluation of overall response at each assessment is a composite of the target lesions response, non-target lesions response and presence of new lesions as shown below.

**Table 2:
Overall Response Assessment in RECIST 1.1¹**

Target Tumors	Non-Target Tumors	New Tumors	Overall Response
CR	CR	No	CR ²
CR	Non-CR/non-PD	No	PR
CR	Non-PD or not all evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR ²
SD	Non-PD or not all evaluated	No	SD ^{2,3}
Not all evaluated	Non-PD	No	NE ¹
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

¹ Responses for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions

² this overall lesion response also applies when there are no non-target lesions identified at baseline.

³ once confirmed PR is achieved, all these assessments are considered PR.

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = non evaluable

If no non-target lesions are identified at baseline, the non-target lesion response at each assessment will be considered “not applicable” (NA).

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate / biopsy) to confirm CR. It may be sometimes reasonable to incorporate Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) scanning to complement CT in assessment of progression (especially in case of possible “new” lesion) or in case where a residual radiographic abnormality is thought to represent fibrosis or scarring.

For equivocal findings of PD (e.g., very small and uncertain new lesions, cystic changes or necrosis in existing lesions) treatment may continue until the next scheduled assessment.

8.D SYMPTOMATIC AND QUALITY OF LIFE ASSESSMENTS

Patient-Reported Outcomes (PROs), defined as report of the status of patient's health condition that comes directly from the patient, will be recorded to assess HRQoL. HRQoL will take into account the patient's subjective perception of the treatment (Pexa-Vec followed by Sorafenib versus Sorafenib) and the impact of HCC on their life. Generic and disease-specific measures are essential to provide a comprehensive picture of HRQoL in HCC.

The FACT-Hep is a 45-items questionnaire designed to measure HRQoL in patients with HCC. The FACT-Hep consists of 27-items FACT-General (FACT-G), which assesses generic HRQoL concerns using 5 sub-scales, and the 18-items hepatobiliary sub-scale, which assesses specific symptoms of hepatobiliary cancer and side effects of treatment. The disease specific questionnaire, FACT Hepatobiliary Symptom Index 8 (FHSI-8), will be used to assess symptomatic progression. A decrease of 4 points or more from Baseline FHSI-8 is considered as symptomatic progression. ECOG performance status will also be assessed by the Investigator until symptomatic progression occurs; a decrease in ECOG performance status to 4 or death is considered symptomatic progression.

The EQ-5D-3L, a generic, preference-based measure questionnaire will be used for PRO measurement to assess utility (*Herdman 2011; Scalone 2013*).

All questionnaires (except ECOG performance status) should be completed by the patient. Once done, a person (this person is often a nurse in outpatient or inpatient care, e.g., trial nurse or clinical researcher) will check all questions are answered. Patients should not be shown their previous responses. All questionnaires will be completed by the patient at Baseline, at Week 6 and then every 6 weeks until end of treatments. Beyond 12 months of treatment, the questionnaires should be completed every 12 weeks.

8.E PHARMACOECONOMIC ASSESSMENTS

To determine a trial-based economic evaluation, patient-level resource and service-use will be collected to evaluate the comparative cost-effectiveness of Pexa-Vec followed by sorafenib versus sorafenib alone. Detailed costs will be collected during the Phase 3 trial using data entered in eCRF, hospital invoices, pharmacy worksheet data and 2 other questionnaires: “health care resource utilization” and “patient accommodation and transport” derived from CSRI (*Beecham 2001*).

The questionnaire “health care resource utilization” is designed to capture direct-medical costs non-documented neither in the CRF nor in hospital invoices. The questionnaire will be completed by the patient prior to any other visit procedures at Baseline, Week 6, and then every 6 weeks until end of treatment visit. Beyond 12 months of treatment, the questionnaires should be completed every 12 weeks until end of treatment visit.

The “patient accommodation and transport” covers all expenses related to indirect-medical costs. The questionnaire will be completed by the patient prior to any other visit procedures at Baseline, at Week 12, and at the End of Treatment Visit.

Utility values collected throughout the study with EQ5D-3L questionnaire will also be assessed to produce generic measures for economic appraisal.

9 MANAGEMENT OF NON-PATIENT EXPOSURE TO PEXA-VEC

Transmission to patient contact or caregivers has not been documented to date. Nevertheless, the following guidelines should be considered as also noted in the current Pexa-Vec IB and Pexa-Vec Guidelines (Appendix B of the IB), to minimize the risk of potential transmission and to manage infected individuals should an unexpected transmission occur.

9.A EXPOSURE TO PEXA-VEC

If an accidental human exposure to Pexa-Vec occurs, no specific interventions other than local wound care, as needed, and close observation are indicated. Specifically, the following is recommended:

1. Implementation of local, institutional needle stick, or other exposure guidelines.
2. Wash area thoroughly with soap and water.
3. Cover area with non-occlusive dressing until complete resolution.
4. Report the event to the Principal Investigator, the institution's Biosafety Specialist, and/or physician knowledgeable in the care of individuals experienced with vaccinia infection. Record and report the event to the Sponsor by completing and submitting a *Report of Exposure to Infectious Material* form as indicated on the report form.

9.B CONTACTS EXHIBITING SYMPTOMS OF VIRAL INFECTION

If a contact of a patient treated with Pexa-Vec reports symptoms of a possible Pexa-Vec related toxicity:

1. Immediately notify the institution's Biosafety Specialist
2. The individual should be referred to and medically monitored by a physician knowledgeable in the care and treatment of patients with vaccinia infections
3. Report the event to the Sponsor by completing and submitting a *Report of Possible Pexa-Vec Toxicity* form. Follow all instructions on the form regarding avoidance of excluded individuals, consideration (in conjunction with consultation with infectious diseases expert and the Sponsor) of antiviral treatment if warranted (refer to [Section 8.A.3](#)), obtaining clinical samples if applicable, monitoring the individual for response to treatment (if any), and resolution of symptoms.

10 INVESTIGATIONAL PRODUCTS (IP)

Pexa-Vec is in development for an advanced HCC patient population in sequential combination with sorafenib (SOC). Therefore, in this study Pexa-Vec and sorafenib are considered as Investigational Product (IP).

Pexa-Vec and sorafenib are provided free of charge by the Sponsor. The Investigator/Pharmacist will not supply IP to any patient not randomized in the study, nor to any physicians or scientists who are not designated as sub-Investigators. The Investigator must ensure that patients receive IP only from personnel who fully understand the procedures for dosing and administering the drugs.

10.A PEXA-VEC (JX-594)

10.A.1 *Nomenclature of Pexa-Vec*

- Sponsor code designation: Pexa-Vec; VACC-6.25.1
- Synonyms: Recombinant Vaccinia/GM-CSF (VAC-6.25.1 [GM-CSF1]),
VAC GM-CSF
Vaccinia/GM-CSF (Pexa-Vec)
- Generic Name: Recombinant Vaccinia GM-CSF; RAC VAC GM-CSF (thymidine kinase-deactivated plus GM-CSF)

Pexa-Vec is provided with a technical sheet detailing its characteristics.

10.A.2 *Pharmaceutical Form of Pexa-Vec*

Pexa-Vec is a viral suspension supplied in individual 4-mL glass vials. Each vial contains Pexa-Vec diluted in 30 mM Tris 10% Sucrose buffer. The recoverable volume of Pexa-Vec in each vial is 2 mL with an infectious titer of 1×10^9 pfu (9.0 Log pfu). Each vial is intended for single use (i.e., 1 injection to 1 patient).

10.A.3 *Packaging and Labeling of Pexa-Vec*

Each vial is packed in a cardboard box (secondary packaging) which constitutes a Pexa-Vec treatment kit (1-vial treatment kit).

The primary labels on the vials as well as the secondary labels on the cardboard boxes are in the language of countries where the study is to be performed. Labels are compliant with local regulatory requirements and contain information including, but not limited to: Sponsor name, product code, lot number, concentration, volume, storage conditions, route of administration and a cautionary statement in proper language.

10.A.4 Biosafety/Containment Level Classification of Pexa-Vec

Depending on the country, Pexa-Vec is classified a Biosafety/Containment Level 1 or Level 2 infectious substance. All applicable infection control policies should be consulted and followed.

Refer to the current Pexa-Vec IB and Pexa-Vec Guidelines (Appendix B of the IB) for recommendations on handling Pexa-Vec and for management of Arm A patients treated with Pexa-Vec, as well as for any Arm A patients who develop Pexa-Vec-related pustules.

10.A.5 Transport of Pexa-Vec

10.A.5.a Interstate and International Transport

Pexa-Vec is shipped on dry-ice with the official transport designation as a “Biological Substance, Category B” in compliance with International Air Transportation Association and Department of Transportation regulations and other local regulations for air and road transport of infectious substances (UN 3373 regulations).

10.A.5.b Drug Receipt and Approval of Shipment

The supply of Pexa-Vec is managed automatically using an IVRS/IWRS.

Detailed information on drug receipt instructions and approval of shipment process are provided in the Product Handling Manual.

10.A.5.c Transport within the Institution

All transport of Pexa-Vec (in vial, IV bag or syringe containing the dose to be administered) within the institution must be done using a leak-proof container/bag clearly-marked with a biohazard symbol.

10.A.6 Storage of Pexa-Vec

Pexa-Vec must be stored at or below -60°C in an alarmed, temperature-monitored, secure freezer with restricted access. Detailed information on drug storage requirements and temperature excursions management are provided in the Product Handling Manual.

10.A.7 Dispensing of Pexa-Vec

On either the day of Pexa-Vec treatment or the day before, site personnel will access IVRS/IWRS to obtain kit number assignment for Pexa-Vec treatment.

Pexa-Vec will be dispensed only with the written authorization of the Investigator or a sub-Investigator to staff that have been specifically designated and trained for this study.

Please refer to site user guide for IVRS/IWRS and the Product Handling Manual for detailed instructions.

10.A.8 Handling of Pexa-Vec

All applicable institutional policies for preparation, transport, and disposal of viral vectors should be consulted and followed. During all Pexa-Vec manipulations gloves, gown, surgical mask and goggles (or safety glasses with side shields) must be worn. Headgear and overshoes are not mandatory.

In addition, refer to the IB, Pexa-Vec Guidelines (Appendix B to the IB), and supplemental information (as available) for recommendations regarding proper handling during preparation, administration, and disposal of Pexa-Vec.

10.A.8.a Preparation of Pexa-Vec

Preparation of Pexa-Vec will be carried out in accordance with local regulatory requirements for Biosafety/Containment level (Level 1 or Level 2 depending on countries) in a pharmacy or laboratory, according to site's standard operating procedures (SOPs) and all applicable laws and regulations.

Pexa-Vec is suspended in sterile normal saline buffered with sodium bicarbonate. Detailed information on drug preparation is provided in the Pexa-Vec IT Injection Preparation Worksheet.

10.A.8.b Administration of Pexa-Vec

The injection volume (Pexa-Vec and sodium bicarbonate buffered sterile normal saline, when needed) will be approximately 25% of the size of the tumor to be injected (percentage dependent on the size [LD] of the tumor – refer to the IT injection of Pexa-Vec: Procedure Manual for details), not to exceed a specified upper limit. Tumor numbers and measurements will be documented at baseline and before each IT re-treatment and transmitted to the pharmacy for drug preparation purposes and to the study coordinator for eCRF completion. Calculation and preparation instructions are provided in the Pexa-Vec IT Injection Preparation Worksheet.

10.A.8.c Cleaning / Disinfection and Disposal

Standard institutional policies should be followed for cleaning and decontamination while handling vaccinia virus-based products. Hospital-grade chemical disinfectants containing: bleach (with at least 0.6% of active chlorine), alcohols ($\geq 60\%$), aldehydes, hydrogen peroxide (3%), iodophor (75 ppm), phenols or quaternary ammonium compounds are adequate for routine cleaning and disinfection of work areas after Pexa-Vec handling. The manufacturer's instructions should be followed to ensure adequate contact time and confirm the ability of the equipment to withstand the disinfectant used.

All contaminated material (e.g., syringes, catheters, needles, tubing, gloves, used or unused vials, containers, bandages, etc.) should be disposed of in a clearly-marked biomedical waste container and discarded according to regular institution procedure for infectious waste i.e., autoclaving, incineration, or treatment with sodium hypochlorite solution. Biomedical waste will not be left unattended in a public area; autoclaved medical waste must not be disposed of as regular trash.

Textiles and fabrics can be laundered in hot water (71°C) with detergent and hot air drying.

10.A.8.d Spills or Environmental Contamination

In the event of a spill, people in the immediate area will be alerted and other institutional personnel will be notified as required by institutional policies. Refer to the current Pexa-Vec IB and Pexa-Vec Guidelines (Appendix B of the IB) and the Technical Sheet, for detailed instructions.

Spills and accidents that result in overt exposures to infectious material will be reported as required by institutional policies. Refer to [Section 9.A](#).

10.A.8.e Unused Drug Return or Destruction

During the course of the study based on the Sponsor's request and at termination of the study all unused Pexa-Vec patient kits will be destroyed locally or returned to the drug supply provider contracted by the Sponsor.

For local destruction, the Investigator/Pharmacist or delegated person will ensure that destruction is performed according to written instructions available in the Pexa-Vec IB and the Technical Sheet and will not expose humans to any risks from Pexa-Vec. A certificate of destruction will be completed and provided to the Sponsor (copy retained by the site). The drug supply provider contracted by the Sponsor will coordinate the return of all unused Pexa-Vec patient kits. A certificate of return will be completed and provided to the drug supply provider (copy retained by the site).

Upon completion or termination of the study at a site, the monitor will verify that all used Pexa-Vec patient kits have been decontaminated (if applicable) and disposed, all unused Pexa-Vec patient kits have been returned or destroyed, and no IP remains on site.

10.A.9 Drug Accountability

The Investigator/Pharmacist, or delegated person, will maintain a Pexa-Vec accountability log detailing the dates and quantities dispensed for each patient along with kit and vial numbers. Pexa-Vec accountability records will be verified by the monitor during site visits.

All documentation related to Pexa-Vec shipment, receipt, authorization for use, dispensing, destruction, temperature monitoring, etc., must be filed in the Pharmacy Binder and must be available for inspection. A copy of all drug accountability records will be returned to the Sponsor at the end of the study.

10.B SORAFENIB

10.B.1 Nomenclature

Sorafenib 200 mg film-coated tablets.

Sorafenib is provided with its registered SmPC.

10.B.2 Pharmaceutical Form of Sorafenib

Sorafenib is provided as film-coated tablets for oral administration. Each tablet contains 200 mg of sorafenib.

10.B.3 Packaging and Labeling of Sorafenib

Sorafenib is supplied in a study-specific secondary packaging with a study-specific label for study identification and use. The study-specific secondary packaging is a cardboard box that contains 1 blister pack of 4 × 7 tablets (i.e., 28 tablets in total), that constitutes a sorafenib treatment kit.

10.B.4 Transport of Sorafenib

10.B.4.a Transport Conditions

Sorafenib is shipped per manufacturer instructions.

10.B.4.b Drug Receipt and Approval of Shipment

The supply of sorafenib is managed automatically using an IVRS/IWRS.

Detailed information on drug receipt instructions and approval of shipment process are provided in the *Product Handling Manual*.

10.B.4.c Transport within the Institution

No specific instructions.

10.B.5 Storage of Sorafenib

Sorafenib must be stored according to the manufacturer instructions (refer to the registered SmPC and *Product Handling Manual*).

10.B.6 Drug Dispensing of Sorafenib

Site personnel will access IVRS/IWRS to obtain kit number assignment for sorafenib treatment.

Sorafenib will be dispensed only with the written authorization of the Investigator or a sub-Investigator to staff that have been specifically designated and trained for this study.

Please refer to site user guide for IVRS/IWRS and the *Product Handling Manual* for detailed instructions.

10.B.7 Handling of Sorafenib

10.B.7.a Posology

Per registered SmPC, the recommended dose of sorafenib in adults is 400 mg (2 tablets of 200 mg) twice daily (equivalent to a total daily dose of 800 mg).

Sorafenib is allowed as long as the patient is clinically benefiting from the treatment and at least until progression or until unacceptable toxicity occurs.

10.B.7.b Method of Administration

Sorafenib has to be administered according manufacturer instructions (refer to the registered SmPC).

For oral use, it is recommended that sorafenib is administered without food or with a low or moderate fat meal. If the patient intends to have a high-fat meal, sorafenib tablets should be taken at least 1 hour before or 2 hours after the meal. The tablets should be swallowed with a glass of water.

10.B.7.c Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

10.B.7.d Unused Drug Return or Destruction

During the course of the study based on the Sponsor's request and at termination of the study all unused sorafenib will be destroyed locally or returned to the drug supply provider contracted by the Sponsor.

For local destruction, the Investigator/Pharmacist or delegated person will ensure that destruction is performed according to local requirements. A certificate of destruction will be completed and provided to the Sponsor (copy retained by the site).

The drug supply provider contracted by the Sponsor will coordinate the return of all unused sorafenib patient kits. A certificate of return will be completed and provided to the drug supply provider (copy retained by the site).

Upon completion or termination of the study at a site, the monitor will verify that all used sorafenib patient kits have been disposed, and all unused sorafenib patient kits have been returned or destroyed.

10.B.8 Drug Accountability

The Investigator/Pharmacist or delegated person will maintain a sorafenib accountability log detailing the dates and quantities dispensed for each patient along with kit numbers. Sorafenib accountability records will be verified by the monitor during site visits.

All documentation related to sorafenib shipment, receipt, authorization for use, dispensing, destruction, temperature monitoring, etc., must be filed in the Pharmacy Binder and must be available for inspection. A copy of all drug accountability records will be returned to the Sponsor at the end of the study.

11 SAFETY REPORTING

The condition of the patient will be monitored throughout the study.

11.A DEFINITIONS

Adverse Event (AE): An AE for the purposes of this protocol is a medical occurrence or deterioration of a pre-existing medical condition occurring after first dosing with either study drug, and even if the event is not considered to be related to the study treatment(s). Prior to first on-study treatment, only SAEs caused by a protocol-required procedure (e.g., SAEs related to invasive procedures such as biopsies) will be collected and reported to the Sponsor as specified in [Section 11.E](#).

Examples of AEs include:

1. Pre-existing conditions (any sign, symptom, physical examination finding or laboratory result) that worsens in nature, severity, or frequency compared to Day 1, before the first administration of the IP. A pre-existing condition is one that is present prior to the first administration of the IP and is reported at Baseline or Day 1.
2. Clinical laboratory abnormality, vital signs measurements, physical examinations or ECG findings should be reported as an AE only if it is considered clinically significant (i.e., with clinical manifestations or receiving treatment or clinical management) by the Investigator.
3. All Grade 3 and Grade 4 clinical laboratory results that represent an increase in severity from Baseline will be reported as AEs.
4. Leukocytosis will not be reported as an AE; however, any clinical signs or symptoms resulting from leukocytosis will be recorded as an AE.
5. All reactions from IP, including those occurring as a result of an overdose, abuse, withdrawal phenomena, sensitivity, or toxicity to the IP.
6. Concurrent illness.
7. Injury or accident.

Adverse Drug Reaction (ADR): All noxious and unintended responses to the IP related to any dose or to a study specific procedure as determined by the Investigator or the Sponsor.

Laboratory Abnormality: A laboratory abnormality is reported as an AE if it is out of range and considered by the Investigator as clinically significant (i.e., with clinical manifestations or requiring treatment or clinical management).

Other Significant AEs: Any AE and any laboratory abnormality, other than those reported as SAEs, that are considered by the Investigator or the Sponsor to be of special interest because of clinical importance whether or not they lead to an intervention, including:

- withdrawal,
- modification of the schedule of administration of Pexa-Vec,
- modification of the schedule of administration or the dose of sorafenib,
- addition of significant concomitant therapy.

Serious Adverse Event (SAE): Any untoward medical occurrence that at any dose fulfills one or more of the following criteria:

- Results in death; the death of a patient is not per se an AE but an outcome. “Death” should be considered as a SAE only in case of “unexplained death” when no cause is identified. The event that resulted in a fatal outcome should be determined and reported as a SAE.
- Is life threatening; this term refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization; the hospitalization is an action taken to treat the event. It should not be reported as a SAE, but the AE leading to hospitalization.
- Results in persistent or significant disability/incapacity; the disability is a substantial disruption of a person’s ability to conduct normal life functions.
- Is a congenital anomaly/birth defect; a “congenital anomaly/birth defect” relates to events occurring to babies born after their mother and/or father have taken the IP at the time of pregnancy confirmation or during pregnancy.

- Is a medically significant defined as an event that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

NOTE: Medical and scientific judgment should be exercised in deciding whether some events should be considered as serious because their quick reporting to the Sponsor or its representative may be of interest for the overall conduct of the study.

NOTE ABOUT HOSPITALIZATION:

Planned hospitalization for the purpose of administering the study treatment and monitoring the patient per protocol will not be considered a SAE.

It will not be considered an SAE if patients are hospitalized or their hospitalization is prolonged post-treatment for observation of Grade 1 or 2 flu-like symptoms, provided the hospitalization or prolongation of hospitalization does not last longer than 24 hours.

Hospitalization planned before or during the study should not be considered as a SAE in case it occurs for:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition;
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened in an unexpected way since signing informed consent;
- Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission;
- Social reasons and respite care in the absence of any deterioration in the patient's general condition.

Suspected Unexpected Serious Adverse Drug Reaction (SUSAR): Any unexpected SAE considered as related to the IP or to a study specific procedure.

Overdose: An overdose is an administration of the IP at a higher dose than the highest dose already tested in clinical studies or higher than known therapeutic doses or higher than the dose planned according to the schedule of administration.

Overdose is not be considered an AE. However, if the patient experiences an AE/SAE related to this overdose, it should be reported as such.

11.B INTENSITY, RELATIONSHIP AND OUTCOME EVALUATION

11.B.1 Intensity

The intensity of AEs/SAEs will be graded according to the NCI-CTCAE version 4.03 (dated 14 June 2010).

Should an event be missing in the CTCAE, the following 5-point scale is to be used:

- Mild: Discomfort noticed, but no disruption of normal daily activity
- Moderate: Discomfort sufficient to affect normal daily activity
- Severe: Inability to work or perform normal daily activity
- Life-threatening: Risk of death at the time of the event
- Fatal: The patient died

The correspondence between the 2 scales is as follows:

CTCAE	5 point scale
1	Mild
2	Moderate
3	Severe
4	Life threatening
5	Death

11.B.2 Relationship to the IP

The relationship to the IP of each AE/SAE will be evaluated by the Investigator with the “global introspection” method using the following levels:

- **Not related:** The temporal relationship of the clinical event to the administration of the IP makes a causal relationship unlikely; and other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.
- **Related:** The temporal relationship of the clinical event to the administration of the IP makes a causal relationship possible; and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event. A clear-cut temporal association with improvement on cessation of the study drug or recurrence upon rechallenge may also be observed.

11.B.3 Outcome

The outcome is rated as follows:

- recovered,
- not recovered,
- recovered with sequelae,
- fatal,
- unknown.

NOTE ON "FATAL": this outcome is to be used only for the event leading to death. The outcome of all other events at the time of the death must be reported; if ongoing at the time of death, the outcome of those other events should be reported as "not recovered".

11.C TIME PERIOD FOR COLLECTION

From the date of signature of the informed consent form and up to prior to initiation of IP administration, only SAEs caused by a protocol-required procedure (e.g., SAEs related to invasive procedures such as biopsies) will be collected and reported to the Sponsor as specified in [Section 11.E](#).

After the initiation of IP and up to 28 days after the last dose of IP, all AEs and SAEs should be collected and recorded on the eCRFs as described in [Section 11.D](#) and SAE reported to the Sponsor as specified in [Section 11.E](#).

Post-study SAEs (i.e., occurring more than 28 days after the last dose of IP), and evaluated by the Investigator as related to the IP should be collected and reported to the Sponsor indefinitely even after study closure as specified in [Section 11.E](#). These would however not be reported in the eCRF.

11.D ADVERSE EVENT MANAGEMENT

11.D.1 Reporting

Any AE/SAE directly observed (physical examination, laboratory test, or other assessments), mentioned by the patient or reported by the patient upon non-directive questioning at each visit during the study, will be reported by the Investigator on the “Adverse Events” page of the eCRF as follows:

- AE term (i.e., the nature of the event with self-explanatory and concise medical terminology [indicate a diagnosis or syndrome instead of symptoms]),
- date of onset and date of end (i.e., actual dates when the event starts and is resolved rather than dates when the Investigator is informed),
- outcome,
- intensity,
- relation to Pexa-Vec, sorafenib or study procedure (e.g., IT injection)
- action taken regarding Pexa-Vec, sorafenib
- action taken regarding the event,
- evaluation of seriousness.

AE requiring therapy must be treated with recognized standards of medical care to protect the health and wellbeing of the patient. Any treatment given will be reported on the page "Concomitant medication" of the eCRF.

The Sponsor or its representative reserves the right to ask for further information on any AE/SAE that may be considered of interest or when the event is not previously documented in the IB (new occurrence) and is thought to be related to Pexa-Vec, sorafenib, the combination or a study specific procedure.

11.D.2 Follow-up

AE must be followed until resolution or the last visit planned by the protocol.

The AE listed below must be followed until they are resolved or stable or returned to Baseline status, which may occur after the last visit planned by the protocol:

- AE evaluated as related to Pexa-Vec and/or sorafenib or to a study specific procedure,
- SAEs,
- any other significant AE as recommended by the Sponsor.

11.D.3 Documentation

AE will be reported in the source document with at least the nature of the event, the start and end date, the relationship to the IP and the treatment (if applicable) of the event.

11.E SERIOUS ADVERSE EVENT MANAGEMENT

11.E.1 Reporting

SAE occurring during the course of a study, irrespective of the treatment received by the patient MUST be reported by the Investigator to the Sponsor or its representative within 24 hours of occurrence or knowledge of the event. The Investigator will also complete the "SAE Form" to be provided to the Sponsor or its representative as specified in the SAE reporting guidelines located in the Investigator site file. SAE related documentation, if any, must be kept at the study site in the Investigator site file.

11.E.2 Follow-Up

Follow-up information (e.g., complications or progression of the initial SAE) must be notified as soon as possible to the Sponsor or its representative using a new SAE form with the box "follow-up" ticked. New information must be sent to the Sponsor or its representative within 24 hours of knowledge as specified in the Investigator site file. The Sponsor or its representative may request further information as needed.

All SAEs will be followed until the final outcome is known.

11.E.3 Notifications

The Sponsor or its representative will be responsible for reporting SUSARs and any follow-up information to Regulatory Authorities and to central Ethics Committees (ECs) as per local regulation. In case of a SUSAR, the Sponsor or its representative will inform all Investigators involved in any study with Pexa-Vec that such an event occurred.

The Sponsor or its representatives will provide copies of all safety reports submitted to regulatory authorities to the Investigator for inclusion in the Investigator site file.

The Investigator is responsible for informing local Institutional Review Boards (IRBs) / Institutional Ethics Committee (IECs) / Research Ethics Boards (REBs), Institutional Biosafety Committees (IBCs), and other required institutional committees of SUSARs and any follow-up information as per local regulations.

11.F SPECIAL SITUATIONS

11.F.1 Post-Study SAE

Any SAE occurring more than 28 days after the last IP administration **and** that is considered by the Investigator to be related to the IP must be reported to the Sponsor or its representative, documented and followed-up as described in [Section 11.E](#).

11.F.2 Pregnancy

A patient's treatment (Pexa-Vec or sorafenib) must be discontinued immediately if she becomes pregnant.

If a patient or their partner becomes pregnant during the active study participation phase and up to 6-weeks of last Pexa-Vec dose or sorafenib dose, the Investigator must report the pregnancy to the Sponsor or its representative, using a "Pregnancy form" within 24 hours of the site's awareness of the pregnancy.

NOTE: If a patient's partner becomes pregnant, the Sponsor or its representatives will make every effort to obtain consent from the partner to collect data on the pregnancy.

Pregnancies have to be followed by the Investigator up to the completion or termination of the pregnancy, collecting information about the pregnancy, the new-born medical status follow up on the status of the infant until 8–12 weeks of age.

Pregnancy itself is not considered as an AE. However, any problem met during the pregnancy and its outcome should be reported as an AE or a SAE. Spontaneous or induced abortions as well as ectopic pregnancy should be considered as serious. Any problem concerning the newborn should also be reported as an AE or SAE.

All pregnancies starting from the first IP administration and up to 6 weeks after the last IP administration must be reported.

11.F.3 Overdose

Any overdose should be reported to the Sponsor's representative and documented and followed-up using an "Overdose form". In addition, any associated symptoms should be reported as an AE or SAE as per instructions in [Section 11.D](#) and [Section 11.E](#), respectively.

11.F.4 Death

Death of a study patient occurring during the active study participation phase must be reported to the Sponsor or its representative by phone and email or fax within 24 hours of the site's awareness of the event as per the instructions in [Section 11.E](#).

Deaths that occur outside of this reporting period but that are the outcome of an unresolved AE or SAE will also be reported to the Sponsor or its representative on a dedicated eCRF page.

In addition, if the patient's death occurred within 28 days of the most recent dose of Pexa-Vec, or death was >28 days after the most recent dose of Pexa-Vec but was due to an unresolved potentially related AE or SAE, the Sponsor may also request formalin-fixed and flash frozen tissue specimens from normal organs examined as well as from as many tumor site(s) as possible to assess the biodistribution and safety of Pexa-Vec in humans. Special histopathology stains for Pexa-Vec replication and gene expression, virus-induced cytopathic effects, and inflammatory infiltration (characterize immune cells in tissues) may be performed. Tissue specimens may be retained by the Sponsor for up to 2 years after sampling for these purposes.

A copy of the death certificate should be obtained.

If an autopsy is performed, a copy of the autopsy report should be obtained by the site and provided to the Sponsor or its representative.

12 STATISTICAL CONSIDERATIONS

12.A OVERVIEW

The primary objective of this study is to determine and compare overall survival (time to death) based on a stratified re-randomization test, for patients receiving Pexa-Vec followed by sorafenib (Arm A) versus those receiving sorafenib (Arm B) in patients with advanced HCC without prior systemic therapy.

Secondary objectives are to determine and compare TTP, PFS, ORR, DCR, and to determine patient TSP, QoL, safety and tolerability of Pexa-Vec followed by sorafenib (Arm A) compared to sorafenib (Arm B).

Other objectives include TIR, DoR and tumor size evolution over time. In addition, overall survival, PFS and TTP will be analyzed in patients exhibiting tumor response or in subgroups of patients.

Details of the statistical analyses will be specified prospectively in a SAP.

12.B SAMPLE SIZE DETERMINATION

Efficacy will be evaluated comparing the overall survival in the Pexa-Vec arm (Arm A, Pexa-Vec followed by sorafenib) with the sorafenib arm (Arm B).

Unlike chemotherapy, cancer immunotherapies exert their effects on the immune system and demonstrate new kinetics that involve building a cellular immune response, followed by changes in tumor burden or patient survival. Thus, a design anticipating a 6-month delayed separation of the Kaplan-Meier curves was applied. The hazard ratios are described as a function of time recognizing differences before and after separation of curves.

It is assumed that Pexa-Vec does not reduce the hazard of overall survival during the first 6 months of treatment (HR = 1.00 for the first 6 months), while it reduces the hazard by 40% thereafter (HR = 0.6 after 6 months). The median overall survival in the control arm is expected to be approximately 11 months.

Based on the aforementioned assumptions, and assuming a 1:1 randomization a total of 474 events of death should be observed to reject the null hypothesis of no Pexa-Vec effect with a power of 86% (assuming that HR = 1 for the first 6 months and 0.6 thereafter) using a stratified log-rank test at a 1-sided cumulative 2.5% level of significance. This corresponds to a HR smaller than or equal to 0.83 at the final analysis to declare a significant treatment benefit. For this analysis, the

p-value of the re-randomization test (based on the stratified log-rank test) will be computed and compared to the threshold defined as 0.021 (if the analysis is performed at 474 events exactly) due to the alpha adjustment induced by the interim analysis for efficacy (using an α -spending function due to Lan-DeMets (*Gordon 1983*) with O'Brien-Fleming type (*O'Brien 1979*) stopping boundary as presented below). If the p-value is lower than this boundary, the treatment will be considered as effective.

A first interim analysis for futility will be performed when 190 deaths (40% of the required events for final analysis) are documented in the ITT population with a stopping boundary defined as HR = 1.1. The p-value of the re-randomization test (based on the stratified log-rank test) will be computed and compared to the threshold corresponding to HR = 1.1. If exactly 190 events are considered in this analysis, the boundary for the p-value is defined as 0.744. If the p-value computed is higher than this threshold, the futility boundary will have been crossed.

A second interim analysis for efficacy will be performed when 379 deaths (80% of the required events for final analysis) are documented in the ITT population. An α -spending function due to Lan-DeMets with O'Brien-Fleming type stopping boundary (as implemented in EAST® 6.3) will be used for the interim efficacy analysis. If the interim analysis is performed after exactly 379 events, the O'Brien-Fleming boundary for efficacy consists in using a significance level equal to 0.012 (corresponding to a HR equal to 0.79). If the p-value of the re-randomization test (based on the stratified log-rank test) is lower than this threshold, the efficacy boundary will have been crossed.

The nominal p-values and critical values used to declare statistical significance at the time of interim and final analyses may be slightly different as based on the actual number of deaths that have been documented at the time of analysis.

Assuming a non-uniform enrolment and about 5% lost to follow-up or withdrawal of consent rate, a total of 600 patients should be recruited in 19 months. It is estimated that the required 190 deaths and 379 deaths for both interim analyses will be observed approximately 21 months and 34 months respectively after starting the trial. Likewise, it is estimated that the required 474 events for final analysis will be observed approximately 29 months after the inclusion of the last patient.

12.C ANALYSIS POPULATIONS

The ITT population will comprise all randomized patients. Following the intent-to-treat principle, patients will be analyzed according to the treatment and stratum that they were assigned to at

randomization. The ITT population will be the primary population for efficacy analyses and for summaries of demographic and Baseline variables.

The safety population will comprise all patients who receive at least one dose of any one component of the study treatment (Pexa-Vec or sorafenib). The occurrence of death also constitutes a valid safety assessment. Patients will be analyzed according to the treatment they actually received. The safety population will be the population for safety and drug exposure analyses.

Patients with no post-baseline assessments will be listed.

The PP population will comprise all patients from the ITT population without any major protocol deviations who have completed a minimum exposure requirement. In Arm A, the minimum exposure is at least one Pexa-Vec injection and in Arm B, the minimum exposure consists in at least 2 weeks of sorafenib. However, if a patient progressed as per Investigator radiology data, discontinued for AE, or died before the minimum exposure requirement could be met, that patient will still be included in the PP population.

12.D METHODS OF ANALYSIS

12.D.1 General Considerations

Statistical summaries will be produced using SAS[®] software version 9.2 or higher.

Continuous variables will be described using the number of observations (N), arithmetic mean (Mean), standard deviation, minimum (MIN), median (Median), and maximum (MAX). Categorical variables will be summarized by frequency (N) and percentage (%). Proportions will be estimated with their exact (binomial) 95% CIs when appropriate.

12.D.2 Disposition of Patients

The number of screening failure patients and reasons for screening failure will be summarized. A patient listing will be provided with the reason of screening failure.

The disposition data will be presented by patient and treatment arm in data listings and the following items will be presented by treatment arm in a summary table on the ITT population:

- The number of patients randomized
- The number of patients included in each population

- The number of patients excluded from the populations and reasons for exclusion
- The number of patients who are still on treatment (Pexa-Vec or sorafenib)
- The number of patients who have completed:
 - ❖ The end of treatment visit
 - ❖ The safety follow-up visit
- The number of patients who discontinued Pexa-Vec and reasons for discontinuation Pexa-Vec
- The number of patients who discontinued sorafenib and reasons for discontinuation the sorafenib
- The number of patients who discontinued sorafenib before or after progression
- The number of patients who were followed for overall survival after end of study treatments
- The number of patients who discontinued the study during the survival follow-up for overall survival and reasons for discontinuation during this follow-up (lost to follow-up, withdrawal of consent)

12.D.3 Demographic and Baseline Characteristics

Baseline demographics and disease characteristics data will be listed and summarized by treatment arm.

Qualitative data (e.g., gender, ethnic origin, PS) will be summarized by means of contingency tables for each treatment arm, and quantitative data (e.g., age and body weight) will be summarized by appropriate descriptive statistics (mean, standard deviation, median, minimum, and maximum) for each treatment arm.

The numbers and percentage of patients with relevant medical history/current medical conditions will be presented by treatment arm, system organ class and preferred term.

12.D.4 Treatments (Study Treatment, Concomitant Therapies)

The safety population will be used for all summaries and listings about treatments.

12.D.4.a Study Treatments (Pexa-Vec and Sorafenib)

Exposure to Pexa-Vec will be provided by summarizing the dose received during each treatment session (in pfu, corrected if not complete) and the cumulative dose (sum of doses received during each injection). In addition, number of Pexa-Vec doses received (partial doses will be counted as one dose) will be categorized (0, 1, 2 or 3) and summarized.

Exposure of Sorafenib will be provided by summarizing the duration of exposure, the dose (in mg/day), and the information about dose reduction by treatment arm. Number of patients who received the planned dose and who had a dose reduction during the study will be summarized.

In addition, total duration of study treatment (including Pexa-Vec and Sorafenib) will be listed and summarized by treatment arm.

Sorafenib compliance will be summarized for each treatment arm. This will be based on the number of tablets dispensed and used as reported in the eCRF.

12.D.4.b Concomitant Medications

Medications and/or non-drug therapies will be collected as described in [Section 8](#).

The concomitant medications (i.e., ongoing at the start of study treatment or taken during the course of the study) will be coded using the WHO Drug Dictionary and will be listed and summarized by active ingredient and treatment arm by means of frequency counts and percentages.

Any prior medications or significant non-drug therapies starting and ending within the month before start of study treatment will be listed.

12.D.5 Efficacy

12.D.5.a Primary Efficacy Analysis: Overall Survival

Overall survival is defined as the time from randomization until death from any cause. For patients not known to have died at the time of the analysis, overall survival will be censored on the date they were last known to be alive. If a patient withdraws early, overall survival will not be censored at the date of withdrawal unless this is the date they were last known to be alive. Date of death will be obtained from the death certificate (preferable) or from a written statement from the primary care or attending physician, or from death registry data.

The primary analysis will be a comparison of overall survival between Arm A and Arm B using a stratified re-randomization test using stratified log rank test stratified by region at the one-sided 2.5% level in the ITT population with etiology, extrahepatic disease, vascular invasion, performance status and AFP levels as covariates in the model.

Overall survival will be presented descriptively for each treatment arm using Kaplan-Meier curves. Summary statistics from the Kaplan-Meier distribution will be determined, including median overall survival and 25% and 75% quartiles with corresponding 95% CIs. The proportions of patients alive at 6, 12, 18, and 24 months, along with corresponding 95% CIs, will also be provided by treatment arm.

12.D.5.a.1 Supportive Analysis

Estimates of the HRs (Arm A over Arm B) with 95% CIs will be obtained from a proportional hazard (PH) model stratified by stratification factor (i.e., region) with etiology, extrahepatic disease, vascular invasion, performance status and AFP levels as covariates in the model. In order to take the delayed effect into account, the model will allow for a time dependent treatment effect. In particular, it is expected that the Pexa-Vec effect can only be seen after about 6 months since the beginning of treatment. An interaction test will be conducted to check the statistical significance of the interaction.

Sensitivity Analysis

- An unstratified re-randomization test will be performed to assess the robustness of the results.
- In addition, a stratified and an unstratified log-rank test will be performed. HR (together with associated 95% CI) resulting from an unstratified Cox model will also be presented.

Following the ITT principle, patients will be analyzed according to the treatment arm and strata they were assigned to at randomization.

The Kaplan-Meier curves, re-randomization test, log-rank test and the Cox model analyses will also be repeated on the PP set.

12.D.5.b Secondary Efficacy Analyses

A hierarchical testing strategy will be adopted, TTP will be compared between the 2 treatment arms if the primary endpoint overall survival is statistically significant. If TTP is statistically

significant (i.e., $p < 0.025$) then PFS will be compared between the treatment groups and finally ORR will be analyzed.

The analyses of the secondary efficacy endpoints will be performed on the ITT population and a subset will be repeated on the PP population.

12.D.5.b.1 Time to Tumor Progression (TTP)

- Time to Tumor Progression (TTP) is defined as the time from randomization to the date of first documented radiographic tumor progression; TTP does not include deaths. If a patient has not had a TTP event at the cut-off date for analysis, TTP will be censored at the date of last evaluable tumor assessment before the cut-off.

If a progression is observed after 2 or more missing or non-evaluable tumor assessments, then the date of progression will be censored at the latest occurring evaluable tumor assessment before missing; for a progression observed after a single missing or non-evaluable tumor assessment, the actual date of disease progression will be used.

A re-randomization test using stratified log rank test stratified for region will be performed at the one-sided 2.5% level to compare the 2 treatment arms. HR (together with associated 95% CI) resulting from the stratified Cox model will also be presented.

TTP will be presented descriptively for each treatment arm separately using Kaplan Meier curves. Summary statistics from the Kaplan Meier distributions will be determined, including median TTP and 25% and 75% quartiles with corresponding 95% CIs. The proportions of patients remaining progression free at 3, 6, and 9 months, along with 95% CIs will also be provided by treatment arm.

Sensitivity Analyses:

- Analyses will be repeated in the same way except that unstratified re-randomization test will be used. HR (together with associated 95% CI) resulting from an unstratified Cox model will also be presented. In addition, a stratified and an unstratified log-rank test will be performed.
- Analyses will be repeated in the same way except that TTP will not be censored if a progression is observed after 2 or more missing or non-evaluable tumor assessments.

Analyses will be performed based on local assessments using mRECIST for HCC and will be repeated both locally and centrally using RECIST 1.1 criteria as exploratory analyses.

12.D.5.b.2 Progression Free Survival (PFS)

Progression free survival (PFS) is defined as the time from randomization to the date of first documented radiographic tumor progression or death due to any cause, whichever occurs first. If a patient has not had a PFS event at the cut-off date for analysis, PFS will be censored at the date of last evaluable tumor assessment before the cut-off.

If a progression is observed after 2 or more missing or non-evaluable tumor assessments, then the date of progression will be censored at the latest occurring evaluable tumor assessment before missing; for a progression observed after a single missing or non-evaluable tumor assessment, the actual date of disease progression will be used.

A re-randomization test using stratified log rank test stratified for region will be performed at the one-sided 2.5% level to compare the 2 treatment arms. HR (together with associated 95% CI) resulting from the stratified Cox model will also be presented.

PFS will be presented descriptively for each treatment arm separately using Kaplan-Meier curves. Summary statistics from the Kaplan-Meier distributions will be determined, including median PFS and 25% and 75% quartiles with corresponding 95% CIs. The proportions of patients remaining progression-free at 3, 6, and 9 months, along with 95% CIs will also be provided by treatment arm.

Sensitivity Analyses:

- Analyses will be repeated in the same way except that unstratified re-randomization test will be used. HR (together with associated 95% CI) resulting from an unstratified Cox model will also be presented. In addition, a stratified and an unstratified log-rank test will be performed.
- Analyses will be repeated in the same way except that TTP will not be censored if a progression is observed after 2 or more missing or non-evaluable tumor assessments.

Secondary endpoint analyses will be performed based on central assessments using mRECIST for HCC and will be repeated both locally and centrally using RECIST 1.1 criteria as exploratory analyses.

12.D.5.b.3 Overall Response Rate (ORR)

Overall response rate (ORR) is defined as the proportion of patients whose best overall response is either CR or PR. The best overall response is the best response recorded from the randomization until disease progression.

Proportions of patients with a best overall response of CR or PR will be presented by treatment arm along with exact 95% CIs. The Chi-square test will be used to compare the 2 treatment arms with respect to the ORR at a 1-sided 2.5% level of significance. As a sensitive analysis, a two-sided 95% CI for the difference in proportion of patients whose best overall response is either CR or PR, stratified by stratification factor, will be computed by using the method of Yan and Su ([Yan 2010](#)).

Secondary endpoint analyses will be performed based on central assessments using mRECIST for HCC and will be repeated both locally and centrally using RECIST 1.1 criteria as exploratory analyses.

12.D.5.b.4 Disease Control Rate (DCR)

Disease control rate (DCR) is defined as the proportion of patients whose best overall response is either CR, PR, or SD.

Proportions of patients with a best overall response of CR, PR, or SD will be presented by treatment arm along with exact 95% CIs. The Chi-square test will be used to compare the 2 treatment arms with respect to the DCR at a 1-sided 2.5% level of significance. As a sensitive analysis, a two-sided 95% CI for the difference in proportion of patients whose best overall response is either CR, PR or SD, stratified by stratification factor, will be computed by using the method of Yan and Su ([Yan 2010](#)).

Secondary endpoint analyses will be performed based on central assessments using mRECIST for HCC and will be repeated both locally and centrally using RECIST 1.1 criteria as exploratory analyses.

12.D.5.b.5 Time to Symptomatic Progression (TSP)

Time to symptomatic progression (TSP) is defined as the time from randomization until the first documented event of symptomatic progression defined as a decrease of 4 points or more from baseline in the FHSI-8 questionnaire or a decrease in ECOG performance status to 4, or death. If

a patient has not had a TSP event at the cut-off date for analysis, TSP will be censored at the date of last evaluable tumor assessment before the cut-off.

If a progression is observed after 2 or more missing or non-evaluable FHSI-8 or ECOG assessments, then the date of progression will be censored at the latest occurring FHSI-8 or ECOG assessment before missing; for a progression observed after a single missing or non-evaluable FHSI-8 or ECOG assessment, the actual date of symptomatic progression will be used.

A log-rank test stratified for region will be performed at the one-sided 2.5% level to compare the 2 treatment arms. HR (together with associated 95% CI) resulting from the stratified Cox model will also be presented.

TSP will be presented descriptively for each treatment arm separately using Kaplan-Meier curves. Summary statistics from the Kaplan-Meier distributions will be determined, including median TSP and 25% and 75% quartiles with corresponding 95% CIs. The proportions of patients remaining progression-free at 3, 6, and 9 months, along with 95% CIs will also be provided by treatment arm.

Sensitivity Analyses:

- Analyses will be repeated in the same way except that unstratified log-rank test will be used. HR (together with associated 95% CI) resulting from an unstratified Cox model will also be presented.

12.D.5.c Exploratory Efficacy Analysis

As mentioned in the secondary endpoints paragraph, TPP, PFS, ORR, and DCR will be assessed both locally and centrally using RECIST 1.1. In addition, the following endpoints will be assessed:

12.D.5.c.1 Time to Initial Response (TIR)

The Time to Initial Response (TIR) is defined as the time from randomization until the first documented response (CR or PR). Patients who did not achieve a response will be censored at last adequate tumor assessment date otherwise.

A Kaplan-Meier curve will be constructed for each treatment arm. Median TIR and 25% and 75% quartiles will be presented along with 95% CIs for each treatment arm. In addition, the Kaplan-Meier estimates with 95% CIs at 3, 6, and 9 months will be presented by treatment arm.

Analyses will be performed based on central assessments using mRECIST for HCC and will be repeated using both local and central RECIST 1.1 criteria.

12.D.5.c.2 Duration of Response (DoR)

Duration of response (DoR) applies only to patients whose best overall response is CR or PR. The DoR is defined as the time from the first documented response (CR or PR) until the event defined as first documented disease progression. If a patient has not had a DoR event at the cut-off date for analysis, DoR will be censored at the date of last evaluable tumor assessment before the cut-off.

If a progression is observed after 2 or more missing or non-evaluable tumor assessments, then the date of progression will be censored at the latest occurring evaluable tumor assessment before missing assessments; for a progression observed after a single missing or non-evaluable tumor assessment, the actual date of disease progression will be used.

DoR will be summarized by treatment arm. A Kaplan-Meier curve will be constructed for each treatment arm. Median DoR and 25% and 75% quartiles will be presented along with 95% CIs for each treatment arm. In addition, the Kaplan-Meier estimates with 95% CIs at 3, 6, and 9 months will be presented by treatment arm.

Analyses will be performed based on central assessments using mRECIST for HCC and will be repeated using both local and central RECIST 1.1 criteria.

12.D.5.c.3 Tumor Size Over Time

The effect of Pexa-Vec on tumor size over time will be studied. Tumor size is defined as the SLD for target lesions as identified during Screening for baseline determination when the same method of evaluation is used. For each time point, tumor size will be calculated along with the relative change from Baseline. A repeated measurements analysis model will be used to compare the 2 treatment arms with respect to changes in the tumor size longitudinally over time.

Analyses will be performed based on central assessments using mRECIST for HCC and will be repeated using both local and central RECIST 1.1 criteria.

12.D.5.c.4 Efficacy in Subgroups of Patients

Efficacy of Pexa-Vec will be evaluated with respect to overall survival, PFS and TTP in subgroups of patients (if the number of patients is sufficient) according to minimization criteria and other criteria described in the SAP.

Efficacy of Pexa-Vec will also be evaluated with respect to overall survival, PFS and TTP in patients subdivided according to the presence or not of an objective response (CR or PR), if the number of patients with CR or PR is sufficient. These analyses will be interpreted with due caution.

Analyses based on radiological endpoints will be performed based on central assessments using mRECIST for HCC and will be repeated using both local and central RECIST 1.1 criteria.

12.D.5.c.5 Efficacy with the Date of Introduction of Sorafenib as a Reference

Efficacy of Pexa-Vec will be evaluated with respect to overall survival by reference to the date of introduction of sorafenib (instead of the date of randomization).

A Kaplan-Meier curve will be constructed for each treatment arm. Median overall survival, PFS, or TTP and 25% and 75% quartiles will be presented along with 95% CIs for each treatment arm. In addition, the Kaplan-Meier estimates with 95% CIs at 3, 6, and 9 months will be presented by treatment arm.

12.D.5.c.6 Biomarkers Evaluation

Descriptive statistics will be used to summarize baseline clinical and immune parameters, as well as changes over time. Exploratory analyses will be conducted to correlate baseline parameters with patient outcome and response to treatments.

12.D.6 Safety

Safety is a secondary endpoint of the study.

Analyses will be based on the safety population. The safety summary tables will include all safety assessments collected from the start of treatment with Pexa-Vec or sorafenib up to 28 days after the last treatment dose of Pexa-Vec or sorafenib. All safety data will be listed and those collected before the first Pexa-Vec injection and later than 28 days after the last treatment dose will be flagged in the listings.

The assessment of safety will be based mainly on the frequency of AEs and on the number of laboratory values that fall outside of predetermined ranges. Other safety data (e.g., ECG, vital signs) will be considered as well and reported as AEs.

Overall incidence of AEs and SAEs will be evaluated for each arm of treatment and for the study as a whole.

AEs will be coded and tabulated using the MedDRA classification scheme and based on NCI CTCAE v4.03: 14 June 2010. All AEs, AEs leading to discontinuation, and SAEs recorded during the study will be listed and summarized by body system organ class and preferred terms, severity (grade), relationship to each study treatment component (Pexa-Vec and sorafenib) and treatment arm. AEs related to study procedure will be also listed.

AEs will be summarized by presenting the number and percentage of patients having at least one AE. Data will be presented by system organ class, preferred term and maximum grade. A patient with multiple occurrence of an AE will be counted only once in the AE category.

Laboratory Abnormalities

The summaries will include all laboratory assessments collected no later than 28 days after study treatment discontinuation. All laboratory assessments will be listed and those collected during 28 days after study treatment discontinuation will be flagged in the listings.

All laboratory values will be converted into SI units and the severity grade calculated using appropriate common terminology criteria for AEs (NCI CTCAE, version 4.03). A listing of laboratory values will be provided by laboratory parameter, patient, and treatment arm. A separate listing will display notable laboratory abnormalities (i.e., newly occurring CTCAE Grade 3 or Grade 4 laboratory toxicities). The frequency of laboratory abnormalities will be displayed by parameter and treatment arm.

12.D.7 Quality of Life (QoL)

Quality of life (QoL) will be measured with the validated cancer-specific patient reported outcomes instrument to evaluate the differences over time between the 2 treatment arms.

The number of patients with QoL data and the number of patients missing or expected to have QoL assessments will be summarized by each treatment arm for scheduled assessment time points.

Descriptive statistics will be used to summarize the individual item and scored sub scale scores of QoL data at each scheduled assessment time point. Patients will be included if they completed at least one questionnaire item at each scheduled assessment time point.

Additionally, change from baseline in the domain scores at the time of each assessment will be summarized. Patients with an evaluable baseline score and at least one evaluable post baseline score during the treatment period will be included in the change from baseline analyses (assessments after disease progression will be excluded). A general linear model that includes treatment and the baseline stratification factor in the model will be used to compare the actual and change from baseline in the sub-scale scores at each scheduled time point of assessment. Additionally, a repeated measurements analysis model, (implemented via SAS PROC MIXED) that includes terms for treatment, baseline stratification factor, baseline value and time of visit by treatment group will be used to compare the 2 treatment groups with respect to changes in the QoL domain scores longitudinally over time.

Time to definitive deterioration in the global health status / QoL scale, and in each of the secondary scales, will be compared between the 2 treatment arms in the ITT using the stratified log-rank test and at one-sided type I error rate as of 2.5%. The distributions will be presented descriptively using Kaplan-Meier curves. Summary statistics from the Kaplan-Meier distributions will be determined, including the median time to definitive 5% deterioration and the proportions of patients without definitive 5% deterioration at 3 and 6 months. Both point estimates and 95% CIs will be presented.

12.D.8 Pharmacoeconomic Methods

Analysis of pharmacoeconomic data and production of a final pharmacoeconomic report will be handled separately from the final clinical report of this study. Information obtained from the collection of medical care utilization data in this study may be combined with other data such as cost data or other clinical parameters in the production of a final report.

Health Resources Utilization

An appropriate approach for pharmacoeconomic analysis is to record Health Resources Utilization under alternative treatment strategies according a 2-stage process. The first is to measure resource use in physical units as used by trials patients. The second stage is to add costs to these resources using prices or unit costs. Costs will be assessed according to countries specificity and from a societal perspective.

The collected data of Health Care Resource will be aggregated in a pharmacoeconomic model to perform cost-utility and cost-effectiveness analysis. Thus, a Markov model will be built to evaluate the cost-effectiveness and cost-utility of Pexa-Vec plus sorafenib versus sorafenib alone. The course of the disease will be divided into distinct states and transition probabilities will be assigned for movement between them over a discrete time period. Six health states will be chosen to represent the natural history of the disease:

- First-line treatment with Pexa-Vec,
- First-line treatment with sorafenib following Pexa-Vec, non-progressive advanced disease,
- First-line treatment with sorafenib following Pexa-Vec, progressive advanced disease,
- BSC,
- Palliative Care,
- Death.

Sensitivity analysis to test the robustness of the model to changes in values for input variables will be performed. Thus, in order to assess the overall impact of uncertainty on the model results, we will apply probabilistic sensitivity analysis. The outcomes of probabilistic sensitivity analysis are going to be:

- An acceptability curve to provide the probability of Pexa-Vec to be more cost efficient than Sorafenib for the possible range of “willingness-to-pay” values given the uncertainty of the input model parameters.
- A cost-effectiveness plan

The markov model will be able to adapt to any required sub-group analysis by changing the input parameters of the model (clinical parameters, utilities and costs adaptations). Additionally, the model will support any desired country adaptation by performing input parameterization.

Cost-effectiveness will be expressed as incremental cost-effectiveness ration per life-years gained. Cost-utility will be expressed in terms of the additional cost-effectiveness ration (ICER) per quality-adjusted life-year (QALY) gained. Individual patient-level data will be used to quantify costs during the study and quality of life referred as utility will be assessed by the EuroQol-5D (EQ5D-3L) questionnaire. The health outcome should be quality-adjusted life-year (QALY) based on EQ5D-3L but the results of specific HRQoL questionnaire (FACT-G) might be presented for

information as an additional study in case EQ5D-3L is not sensitive or specific enough. A specific algorithm will be used to map FACT-G data into EQ5D-3L.

The cost-effectiveness and cost-utility analysis will adopt a time-horizon over which the costs and benefits of alternative treatments may vary.

13 ETHICAL REQUIREMENTS

All parties involved with this clinical trial, including Sponsor, representatives of the Sponsor, and the Investigators, will conduct the study in compliance with the protocol and according to the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practices (E6), the Declaration of Helsinki, and all regulatory and institutional requirements, including those for patient privacy, informed consent, IRB/IEC/REB review and approval, source documentation, and record retention and including any local regulation.

13.A PATIENT PRIVACY

Patient medical information obtained for the purposes of this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial prior written permission. Upon the patient's request and written permission, medical information may be given to his/her personal physician or other appropriate medical personnel responsible for the patient's welfare.

Patient confidentiality requirements of the region(s) where the trial is conducted will be met.

However, data generated for this study, with full access, must be available for inspection upon request to representatives of the Food and Drug Administration (FDA) or other national or local health authorities; the Sponsor or its representatives; the associated IRB/IEC/REB and other institutional committees, as required; and/or as required by law.

Patients will be identified only by unique patient's number. However, release of research results or data that reveal patient names or other identifiers, such as photographs, audio or videotapes, must be carried out in accordance with the Department of Health and Human Services proposed Standards for Privacy of Individual Health information, 45 CFR 164.508, and all applicable laws or other country-specific regulations. Written authorization must be obtained from the patient and IRB/IEC/REB (or other institutional committee delegated to represent patient privacy considerations) prior to the release of such information. Identifiable patient data may not be used for purposes of promoting the IP.

In the US, a written Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed by the study participant before participating in the study to permit the use and disclosure of his/her personal health information as stated in the written authorization. Any other applicable laws and other country-specific regulations must also be followed.

13.B IRB/IEC/REB

This study must have the approval of a properly-constituted IRB/IEC/REB. Before the IP may be used to treat patients, the Investigator will provide the Sponsor or its representatives with a copy of the IRB/IEC/REB approval letter stating that the study protocol and ICF have been reviewed and approved. A copy of the approved ICF and other documents, as requested, will be provided to the Sponsor or its representatives.

13.C INSTITUTIONAL BIOSAFETY COMMITTEE (IBC)

In the US, this study must have the approval of an IBC, which has been created under the guidance of the National Institutes of Health (NIH) to ensure proper monitoring and conduct of gene transfer protocols. In other countries, other requirements for biosafety or infection control may apply and will be followed, as applicable.

13.D INFORMED CONSENT

Written consent will be obtained from the patient before he/she can participate in the study. The content and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

Prior to the initiation of any procedures relating to the study, a patient's consent shall be documented by the use of a consent form written in the patient's native language that has been approved by the IRB/IEC/REB and that is signed and personally dated by the patient at the time of consent. The person who conducted the informed consent discussion shall sign and personally date the consent form. A copy of the signed and dated informed consent will be given to the patient. The Investigator must keep each patient's original, signed and dated consent form on file for inspection by a regulatory authority or authorized party at any time.

Depending on national regulations, an authorized person other than the Investigator may inform the patient, sign and date the consent form.

During the patient's participation in the trial, whenever important new information becomes available that may be relevant to the patient's consent, the consent form will be updated accordingly for IRB/IEC/REB approval. The patient should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented. The approved revised consent form will be signed and dated by the patient.

13.E REVIEW COMMITTEE

13.E.1 Data Monitoring Committee (DMC)

The DMC will conduct periodic safety and efficacy reviews (every 4 months) and review the data from both interim analyses. The role, process and constitution of the DMC will be specified in a separate DMC Charter. Its main mission will be to evaluate the benefit versus risk, to ensure the integrity of the data are respected at all times throughout the study and to give recommendations on its further conduct.

13.E.2 Steering Committee

A Steering Committee will be implemented to lead the design and the conduct of the study. Members of the Steering Committee will be experts in leading the conduct of clinical studies in HCC and will consist of Investigators involved in the study. Meetings of the Steering Committee will be held approximately every 6 months and the Sponsor's representatives will attend each meeting. The Steering Committee will be responsible for ensuring the study is being conducted with the highest scientific and ethical standards and will provide input to the study protocol and potential modifications of the protocol. The Steering Committee will review reports relevant to the conduct of the study and may attend the open session of the DMC meeting.

14 STUDY ADMINISTRATION

14.A DOCUMENTS

14.A.1 Investigator's Brochure

The Investigator will review the current version of the Pexa-Vec IB, including Appendix B: Pexa-Vec Guidelines, which contains detailed information regarding warnings, precautions, contraindications, AEs, recommendations for managing the potential for virus transmission to health care workers and patient contacts, and other significant data pertaining to the IP. It is obligatory that the Investigator be familiar with all sections of this document, and ensures adequate training of relevant study personnel, prior to initiation of the study. New information between Pexa-Vec IB updates will be communicated in the form of an IB Attachment or letter.

14.A.2 Protocol Amendments

The Sponsor will initiate any significant changes to this protocol in writing as a protocol amendment. The amendment must be submitted to National Health Authorities and the IRB/IEC/REB with a revised ICF, if necessary and as locally requested. Written documentation of IRB/IEC/REB approval must be received before the amendment may take effect.

14.A.3 Case Report Forms

Clinical data will be recorded on eCRFs provided by the Sponsor or its representatives. All data recorded in the eCRFs must be substantiated by data contained within the patients' original source documents. The electronic system should allow all corrections to the eCRFs to be dated and traceable to the individual making the correction. The Investigator will ensure that all eCRFs are completed accurately. A copy (electronic or paper) of all eCRFs will be retained by the site as part of the study documents.

14.B QUALITY CONTROL AND QUALITY ASSURANCE

14.B.1 Study Monitoring

The Sponsor or its representatives will monitor the site at appropriate intervals to ensure protocol and Good Clinical Practice (GCP) compliance and accurate data recording. The frequency of monitoring may vary depending on enrollment rate and the quality of data collected. The Investigator and staff are expected to cooperate and provide all relevant study documentation upon

request. Each site will also be routinely monitored by phone or email to keep abreast of patient status and to answer questions.

In addition to routine monitoring visits, direct access to all study-related records must also be granted at any time for inspection by FDA or other national or local health authorities, the Sponsor or its representatives, the associated IRB/IEC/REB and other institutional committees, as required, and/or as required by law.

14.B.2 Audit and Inspection

After appropriate notification, the Investigator will make all study-related source data and documents available to a quality assurance auditor mandated by the Sponsor or legal representative, or to domestic or foreign regulatory inspectors. The main purposes of an audit or inspection are to confirm that the rights and well-being of the patients have been adequately protected, and that all data relevant for the study have been processed and reported in compliance with GCP and applicable regulatory requirements.

14.C RECORD RETENTION

The Investigator must retain the following: protocols; amendments; IRB/IEC/REB approvals; IBC approvals (if applicable); copies of the Form FDA 1572; completed, signed, dated consent forms; patient medical records and original source documents; eCRFs; drug accountability records; all study-related correspondence; and any other documents pertaining to the conduct of the study.

According to ICH (E6), essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained.

14.D STUDY TERMINATION

The Sponsor retains the right to terminate the study or terminate a study site and remove all the study materials from the study site at any time. Specific instances that may precipitate such termination are as follows:

- Completion of the study at an investigational site
- Unanticipated adverse medical experiences in this or other studies indicating a potential health hazard caused by the investigational drug
- Significant protocol deviation and/or lack of compliance and cooperation on the part of the Investigator, including but not limited to: failure to obtain signed ICF prior to initiating study related procedures; unsatisfactory patient enrollment with regard to quality or quantity; deviation from protocol requirements without prior approval from the Sponsor; or inaccurate and/or incomplete data recording on a recurrent basis
- Investigator withdrawal from participation in study
- Lack of patient recruitment at an investigational site
- Withdrawal of investigational drug from investigational use
- Termination of this study by the Sponsor or Health Authority
- In the event of premature termination of the study or a site, the Sponsor will work with the Investigator(s) to arrange safety follow-up for all patients exposed to Pexa-Vec. The Follow-Up plan will be communicated to the IRB/IEC/REB, IBC (as applicable), and Regulatory authorities.

14.E PUBLICATION AND PRESENTATION POLICY

The results of this study may be published or presented at scientific meetings. If this is envisaged, the co-authors agree to submit all manuscripts or abstracts to the Sponsor prior to scientific meeting or journal submission allowing for reasonable time to review, consistent with SillaJen policy. This allows the Sponsor to protect proprietary information and to provide medical/scientific review. For intellectual property protection purposes, SillaJen can request the coauthors to delay publication or presentation of results.

Consistent with Good Publication Practices (*Graf 2009*), authorship is to follow the criteria outlined by the International Committee of Medical Journal Editors, and/or follow the policies outlined by the journal or scientific congress. Financial support for medical writing assistance or travel provided to the authors is also to be acknowledged.

In accordance with consistent editorial practice, the Sponsor supports the publication of primary study results from multicenter studies in their entirety prior to any secondary analyses. Publication of individual center data unless ancillary study/data is discouraged. A publication in which the

contribution of the Sponsor's personnel exceeded that of conventional monitoring will be considered for co-authorship provided all other criteria of International Committee of Medical Journal Editors are met.

14.F ARCHIVING

14.F.1 Investigator Site File

In accordance with the ICH GCP standards, the Investigator is responsible for on-site storage and maintenance of all records pertaining to the study for the maximum period of time required by local requirements.

No study site document may be destroyed without prior written agreement between the Investigator and the Sponsor. The Sponsor must be notified if the Investigator assigns the study documentation to another party or moves it to another location.

14.F.2 Trial Master File

The Sponsor, or representative will archive the trial master file in accordance with GCP and applicable regulatory requirements and will inform the Investigator when the archiving of the study documentation is no longer required.

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**APPENDIX A:
SCHEDULE OF ACTIVITIES**

JX594-HEP024 Schedule of Activities Arm A Patients (Pexa-Vec f/b sorafenib)	Screening	Randomi- zation	Baseline	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Long-Term Follow-Up Visits		End of Treatment Visit	Safety Follow-up	PFS Follow- up Visit ²²	Overall Survival
	Within 21 days of D1		Baseline	D1	Pre-W2 (Pre-D15)	W2 (D15)	Pre-W4 (Pre-D29)	W4 (D29)	W6 (D43)	Q3 weeks	Q6 weeks	End of Treatment (Pexa-Vec or sorafenib)		Q6 weeks	Q4 weeks
Visit Description	Determine eligibility		Establish baseline	Pexa-Vec IT#1	Confirm eligibility	Pexa-Vec IT#2	Confirm eligibility	Pexa-Vec IT#3	Radiographic assessment/ Sorafenib initiation	Clinical status assessments	Radiographic status assessments		At least 28 days after last treatment intake (and no later than 2 months after)		Patient &/or next of kin contact
Informed Consent Signed (visit window does not apply)	X														
IVRS (Interactive Voice Response System)	X	X			X		X		X	X	X				
Medical, surgical and cancer history	X			X ¹											
Complete Physical exam (including weight) ²	X		X	X	X	X	X	X	X		X	X	X		
Histological diagnosis (or biopsy if previous histology not available)	X														
ECOG	X		X						X		X	X			
BCLC and CLIP (including Child-Pugh) scoring	X														
Vital signs (BP, temp, pulse)	X ¹³		X	X ¹	X	X ²	X	X ³	X			X	X		
Cardiac function (ECG)	X											X			
TREATMENTS															
Pexa-Vec IT Injection				X		X ⁴		X ⁵							
Counsel patient on sorafenib									X						
Sorafenib dispensation									X	X	X			X	
CENTRAL LABORATORY TESTS (all sites)															
Hematology (CBC with differential and platelet count)	X		X		X		X		X	X	X	X	X		
Chemistry Panel	X		X		X		X		X	X	X	X	X		
Coagulation (PTT, PT/INR)	X		X		X		X		X		X	X	X		
CD4, CD8 counts	X								X		X	X	X		
AFP	X								X		X	X	X		
Pregnancy test (women of childbearing potential) ¹¹	X		X												
Urinalysis	X										X	X	X		
HLA typing (select sites)			X												
Hepatitis B and C panels, HIV Test	X														
SAMPLES ARCHIVING FOR IMMUNE ANALYSIS															
Serum			X	8h post IT					X			X			
IMAGING STUDIES															
Triphasic CT (Abdominal) and post-contrast CT (Chest & Pelvis) OR dynamic MRI (Abdomen and Pelvis) and non-contrast CT (Chest & Pelvis)	X								X		X ⁶	X			X ⁶
Baseline ultrasound (optional/as needed for image-guided injections)			X	X		X		X							
OTHER															
AE collection ⁸ and concomitant medication reporting ⁹	X ⁷		X ⁷	X ⁷	X	X	X	X	X	X	X	X	X	X	
Anti-cancer therapies reporting															X
FACT-Hep questionnaire (including FHSI-B)			X						X		X ¹⁰	X			
EQSD-3L questionnaire			X						X		X ¹⁰	X			X ¹⁰
Health Care Resource Utilization questionnaire ¹⁰			X						X		X ¹⁰	X			
Patient Accommodation and Transport questionnaire ¹⁰			X								only at W12	X			
Patient Contact Log update			X			X			X	X	X	X			
Survival															X

FOOTNOTES:
 1) All visit dates and visit windows will be counted from "Day 1", the date of first Pexa-Vec IT.
 2) Complete physical exam should include assessment for presence of skin pustules. At screening, height will be collected.
 3) Pexa-Vec IT: Vital signs will be taken up to 60 min prior to injection (establish baseline), within 15 minutes of procedure completion (time = 0) (+/- 5 min), then every hour through 8 hours (+/- 15 min).
 4) Patients must meet re-treatment eligibility to be re-treated. If eligibility is initially not met, each of these treatments may be delayed up to 1 week (e.g. until Day 22 for IT#2 and D36 for IT#3) from the originally planned Treatment Visit date.
 5) AEs will continue to be collected and recorded through 28 days after last study treatment.
 6) Concomitant medications will continue to be collected through 28 days after last study treatment.
 7) From the date of signature of the ICF and up to initiation of ITs, only SAEs caused by a protocol-required procedure will be collected and reported to the sponsor.
 8) Beyond 12 months of treatment, this should be performed every 12 weeks until end of treatments.
 9) Medical and surgical history should be updated with any AEs/SAEs that would have occurred from the signature of the informed consent form (before IT).
 10) At selected sites only.
 11) Blood test at screening and urinary test at baseline. If positive, an ultrasound for pregnancy confirmation should be confirmed.
 12) Applicable to patients who discontinue active treatment phase prior to progression.
 13) Oxymetry performed in addition at screening only.

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JX594-HEP024 Schedule of Activities Arm B Patients (sorafenib)	Screening	Randomi- zation	Baseline	Visit 1	Visit 2	Visit 3	Visit 4	Long-Term Follow-Up Visits		End of Treatment Visit	Safety Follow-Up Visit	PFS Follow- up Visit ¹⁰	Overall Survival
	Within 21 days of Day 1		Baseline	Day 1	W2 (Day 15)	W4 (Day 29)	W6 (Day 43)	Q 3 weeks	Q 6 weeks	End of Sorafenib		Q 6 weeks	Q 4 weeks
Window	- 21 days	Upon eligibility	Up to 4 days before Day 1	n/a	+/- 3 days	+/- 3 days	+/- 2 days	+/- 4 days	+/- 7 days		At least 28 days after last treatment intake (and no later than 2 months after)		
Visit Description	Determine eligibility		Establish baseline	Initiation of sorafenib	Follow-up	Follow-up	Radiographic status assessment	Clinical status assessment	Radiographic status assessment				Patient &/or next of kin contact
Informed Consent Signed (visit window does not apply)	X												
IVRS (Interactive Voice Response System)	X	X		X	X	X	X	X	X				
Medical, surgical and cancer history	X			X ¹¹									
Complete Physical exam (including weight) ²	X		X	X	X	X	X		X	X	X		
Histological diagnosis (or biopsy if previous histology not available)	X												
ECOG	X		X				X		X	X			
BCLC and CLIP (including Child-Pugh) scoring	X												
Vital signs (blood pressure, temperature, pulse rate)	X ^{3,7}		X	X	X	X	X			X	X		
Cardiac function (ECG)	X									X			
TREATMENTS													
Counsel patient on sorafenib				X									
Sorafenib dispensation				X	X	X	X	X	X				
CENTRAL LABORATORY TESTS (all sites)													
Hematology (CBC with differential and platelet count)	X		X		X	X	X	X	X	X	X		
Chemistry Panel	X		X		X	X	X	X	X	X	X	X	
Coagulation (PTT, PT/INR)	X		X		X	X	X			X			
CD4, CD8 counts	X						X			X			
AFP	X						X		X	X			
Pregnancy test (women of childbearing potential) ⁹	X		X										
Urinalysis	X												
HLA Typing (select sites)			X										
Hepatitis B and C panels	X												
HIV test	X												
SAMPLES ARCHIVING FOR IMMUNE ANALYSIS													
Serum			X				X			X			
IMAGING STUDIES													
Triphasic CT (Abdominal) and post-contrast CT (Chest & Pelvis) OR dynamic MRI (Abdomin and Pelvis) and non-contrast CT (Chest & Pelvis)	X						X		X ⁶	X		X ⁶	
OTHER													
AE collection ⁵ and concomitant medication reporting ⁴	X ^{5,11}		X ^{5,11}	X ¹¹	X	X	X	X	X	X	X		
Anti-cancer therapies reporting											X		X
FACT-Hep questionnaire (including FHSI-8)			X				X		X ⁸	X			
EQSD-3L questionnaire			X				X		X ⁸	X			X ⁸
Health Care Resource Utilization questionnaire ⁸			X				X		X ⁸	X			
Patient Accommodation and Transport questionnaire ⁸			X						only at W12	X			
Patient Contact Log update			X		X		X	X	X	X	X		
Survival													X

1) All visit dates and visit windows will be counted from "Day 1", the date of first sorafenib intake
 2) At Screening, height will be collected.
 3) AEs will continue to be collected and recorded through 28 days after last study treatment.
 4) Concomitant medications will continue to be collected until 28 days after last study treatment administration.
 5) From the date of signature of the ICF and up to initiation of IP, only SAEs caused by a protocol-required procedure will be collected and reported to the sponsor.
 6) Beyond 12 months of treatment, these evaluations should be completed every 12 weeks until end of treatments
 7) Medical and surgical history should be updated with any AEs/SAEs that would have occurred from the signature of the informed consent form
 8) At selected sites only
 9) Blood test at screening and urinary test at baseline. If positive, an ultrasound for pregnancy confirmation should be confirmed.
 10) Applicable to patients who discontinue active treatment phase prior to progression
 11) Medical and surgical history should be updated with any AEs/SAEs that would have occurred from the signature of the informed consent form (before IT)
 12) Oxymetry performed in addition at screening only