CLINICAL STUDY PROTOCOL

A Phase 1b, Open Label Study of Dalantercept plus Sorafenib in Patients with Advanced Hepatocellular Carcinoma

INVESTIGATIONAL PRODUCT:	**Dalantercept**
PROTOCOL NUMBER:	**A041-05**
SPONSOR:	**Acceleron Pharma Inc.** **128 Sidney Street** **Cambridge, MA 02139 USA** **Tel: 617-649-9200** **Fax: 617-649-9988**
MEDICAL MONITOR:	**Matthew Sherman, MD** **Chief Medical Officer**
PROTOCOL DATE:	**08 November 2013**
AMENDMENT 01:	**23 April 2014**
AMENDMENT 02:	**04 November 2016**

Signature Page

Acceleron Pharma Approval

Signature: _____ **Date:** _____

Name (print): _____

Investigator Agreement:

I have read the protocol and agree to conduct the study as outlined in the protocol. The study will be conducted in accordance to current United States Food and Drug Administration (FDA) regulations, International Conference of Harmonization (ICH) Guidelines, Good Clinical Practices (GCP), the Declaration of Helsinki, and local ethical and legal requirements.

Signature: _____ **Date:** _____

Name (print): _____

Institution Name and Address:

_____

_____

_____

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Contact Information
Medical Monitor	Matthew Sherman, MD	Acceleron Pharma Inc. 128 Sidney Street Cambridge, MA 02139 Office Tel: 617-649-9282 Cell Tel: 617-584-5023 Fax: 617-649-9988
Pharmacovigilance	Drug Safety Hotline	Covance Inc. 206 Carnegie Center Princeton, NJ 08540 Tel: 888-724-4908 Fax: 888-887-8097

1. PROTOCOL SYNOPSIS

Name of Sponsor/Company: Acceleron Pharma Inc., 128 Sidney Street, Cambridge, MA 02139

Name of Investigational Product: Dalantercept (also known as ACE-041)

Name of Active Ingredient: Dalantercept is a recombinant fusion protein consisting of the extracellular domain (ECD) of human activin receptor-like kinase 1 (ALK1) linked to the Fc (hinge, CH2 and CH3 domains) portion of human immunoglobulin G1 (IgG1).

Title of Study: A phase 1b, open label study of dalantercept plus sorafenib in patients with advanced hepatocellular carcinoma

Study Center(s): Up to 20 centers

Phase of Development: 1b

Objectives:

Primary:

- Evaluate the safety and tolerability of dalantercept plus sorafenib in patients with advanced hepatocellular carcinoma (HCC) to determine the recommended phase 2 dose level of dalantercept in combination with sorafenib

Secondary:

- Evaluate the pharmacokinetic (PK) profiles of dalantercept and sorafenib when used in combination
- Evaluate the preliminary activity of dalantercept plus sorafenib in patients with advanced HCC as defined by response rates per RECIST v1.1, time to progression (TTP), progression free survival (PFS), disease control rate (DCR), and overall survival (OS)Explore the association of the expression of BMP9/10, ALK1 and/or other relevant pharmacodynamic (PD) markers in archived or recent tumor biopsy with tumor response and/or other assessments of clinical response
- Explore association of serum pharmacodynamic (PD) biomarkers with assessments of response

Study Design, Dosage and Administration:

This is an open label, multi-center phase 1b study to evaluate the safety, tolerability, PK and PD, and preliminary activity of dalantercept plus sorafenib in patients with advanced HCC.

The dose level of dalantercept for the first cohort will be 0.6 mg/kg administered subcutaneously (SC) every 3 weeks (Q3W) plus sorafenib 400 mg orally (PO) once daily (QD).

Dose escalation:

The dose escalation portion will include up to three planned cohorts of a minimum of 3 patients

each to determine the maximum tolerated dose (MTD) of the combination. Patients may require dose modification(s) of dalantercept or sorafenib as indicated per protocol or prescribing information, respectively.

At least three patients must complete the Day 22 visit at each dalantercept dose level with review of data through Day 22 by the Safety Review Team (SRT) prior to escalation to the next higher dose level. The SRT may recommend adding additional patients, for a total of up to 6 patients, to the current dose level for further evaluation, escalating to an intermediate dose level or discontinuing escalation.

The planned dose escalation for dalantercept and sorafenib is outlined below.

Planned Starting Dose Regimen Per Cohort

Dose Cohort	Dalantercept	Sorafenib	Number of Patients
1	0.6 mg/kg Q3W	400 mg QD	3-6
2	0.9 mg/kg Q3W	400 mg QD	3-6
3	0.9 mg/kg Q3W	400 mg BID	3-6
Expansion	TBD	TBD	up to 20
Total (planned)			up to 38

Expansion cohort:

Once the MTD or maximum tested dose level has been determined by the SRT and Sponsor, up to a total of 20 patients may be enrolled at or below the MTD to further evaluate the safety, tolerability, and PK profile of dalantercept plus sorafenib. The SRT will meet after a minimum of 10 patients have been evaluated for a minimum of 21 days after the first dose of dalantercept/sorafenib (Day 22) to review safety data. The SRT may recommend adding up to an additional 10 patients to the current dose level for further evaluation or to an intermediate dose level.

Duration of Treatment:

The total duration of participation in the study will vary between patients. There will be a 14-day screening period, a treatment period lasting for as long as patients are eligible to remain on-study, a final visit approximately 1 month after the last dose of dalantercept and follow-up for 1 year from first dose for patient survival.

If a patient has a positive anti-drug antibody (ADA) result at the last visit, the patient may be asked to return for additional ADA testing every three months, until a negative result is obtained or the result is considered to be stabilized.

Diagnosis and Main Criteria for Eligibility

Inclusion Criteria:

1. Age ≥ 18 years.
2. Histologically confirmed (from either a recent or archival biopsy), locally advanced (no presence of distant metastases, unresectable and not eligible for transplant) or metastatic HCC.
3. Child-Pugh Score A (5-6) (Appendix 1).
4. At least one target lesion that has not been treated with local therapy and is measurable by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Appendix 2). If there is a lesion within the field of local therapy and has shown ≥ 20% in size since post treatment assessment, this can be classified as a target lesion.
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 (Appendix 3).
6. Life expectancy of at least 12 weeks.
7. Able to tolerate oral therapy.
8. Clinical laboratory values that meet the following criteria within 72 hours prior to study day 1:
    - Hematology (in the absence of hematopoietic growth factor support):
        - Absolute neutrophil count (ANC) ≥ 1,000/μL (≥ 1.0 x 10^9/L).
        - Hemoglobin ≥ 9 g/dL (≥ 90 g/L).
        - Platelet count ≥ 60,000 /μL (≥ 60 x 10^9/L) without transfusion support 30 days prior to cycle 1 day 1 unless required for biopsy for study eligibility provided their pre-transfusion platelet count was at least 60,000 /μL.
    - Creatinine ≤ 1.5 x ULN or measured or calculated creatinine clearance, using the Cockcroft-Gault formula, (Appendix 4) ≥ 60 mL/min.
    - Total bilirubin ≤ 1.5 x upper limit of normal (ULN). Patients with known Gilbert's Syndrome may have bilirubin levels up to 3.0 mg/dL.
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 5 x ULN.
    - PT/INR ≤ 1.5 x ULN.
    - Serum albumin ≥ 2.8 g/dL (≥ 28 g/L).
    - Urinary protein < 2+ by urine dipstick or urinalysis. If ≥ 2+, then patient may be enrolled if 24-hour urine protein < 2 g/24hr.
9. Females of child bearing potential (defined as sexually mature women who have not undergone hysterectomy or bilateral oophorectomy, or are not naturally postmenopausal ≥ 24 consecutive months) must have negative urine or blood pregnancy test prior to enrollment and use adequate birth control methods (abstinence, oral contraceptives,

barrier method with spermicide, or surgical sterilization) during study participation. Males must agree to use a latex condom during any sexual contact with females of child-bearing potential while participating in the study and for 12 weeks following the last dose of dalantercept, even if he has undergone a successful vasectomy. Patients must be counseled concerning measures to be used to prevent pregnancy and potential toxicities prior to the first dose of dalantercept.

10. Signed written informed consent.

Exclusion Criteria:

1. Mixed tumor histology (e.g., hepatocellular carcinoma plus cholangiocarcinoma) or fibrolamellar variant tumors.
2. Prior solid organ or allogeneic bone marrow transplantation.
3. Prior systemic therapy for metastatic disease.
4. Adjuvant therapy < 6 months prior to study day 1.
5. Prior treatment with dalantercept or other agent targeting the ALK1 pathway.
6. Prior treatment with sorafenib or other RAF/VEGF targeted therapies.
7. Hepatic radiation, chemoembolization, and radiofrequency ablation < 4 weeks prior to study day 1.
8. Palliative radiation therapy to metastatic sites of disease < 2 weeks prior to study day 1.
9. Interferon therapy < 4 weeks prior to study day 1.
10. Uncontrolled Hepatitis B despite appropriate therapy.
11. Clinically significant pulmonary, endocrine, neurologic, hematologic, gastrointestinal (GI), autoimmune, psychiatric or genitourinary disease unrelated to HCC that in the judgment of the investigator should preclude treatment with dalantercept or sorafenib.
12. Known HIV infection.
13. Clinically significant cardiovascular risk including:
    - Ejection fraction (EF) ≤ 50%.
    - Significant history of congestive heart failure (CHF) defined as New York Heart Association (NYHA) class II-IV (Appendix 5).
    - Hospitalization for CHF (any NYHA class) within 6 months of study day 1.
    - Active coronary artery disease [e.g., myocardial infarction (MI), uncontrolled angina], peripheral vascular disease, cerebrovascular disease [e.g., transient ischemic attack (TIA), stroke], bypass surgery, angioplasty, or vascular stenting within 12 months prior to study day 1. Worsening symptoms attributable to cardiac or vascular disease or new findings on cardiac evaluation (e.g. clinical, stress test, etc.) within 3 months prior to study day 1.
    - Known deep vein thrombosis (DVT) within 6 months of study day 1 (with the

exception of portal vein thrombosis).

- Significant arrhythmia or electrophysiologic disease including placement of implantable cardioverter defibrillator (ICD), atrial fibrillation with uncontrolled rate or prolonged QTc interval > 450 ms.
- Uncontrolled hypertension defined as systolic blood pressure (BP) ≥ 150 mm Hg or diastolic BP ≥ 95 mm Hg. Patients with a history of hypertension must be well-controlled (BP ≤ 150/90 mmHg) upon study entry using a stable regimen of anti-hypertensive therapy.

14. Clinically significant active pulmonary risk including pulmonary hypertension and pulmonary edema within 12 months of study day 1 or pulmonary embolism within 6 months of study day 1.
15. Known CNS metastasis.
16. Known active GI bleeding, as evidenced by hematemesis, hematochezia, or melena within 3 months prior to study day 1 without evidence of resolution documented by endoscopy or colonoscopy.
17. Known bleeding diathesis including clinically significant platelet disorders or active hemoptysis defined as bright red blood of ≥ 1/2 teaspoon (2.5 mL) in any 24 hour period within 6 months prior to study day 1. For clinically significant epistaxis within 4 weeks prior to study day 1, no risk of further bleeding must be clearly documented.
18. Known history of hereditary hemorrhagic telangiectasia (HHT).
19. History of another primary cancer, with the exception of:
    - Curatively resected non-melanoma skin cancer.
    - Curatively treated cervical carcinoma in situ.
    - Other primary solid tumor with no known active disease in the opinion of the investigator that will not affect patient outcome in the setting of current HCC diagnosis.
20. Major surgery within 4 weeks prior to study day 1. Patients must have recovered completely from any previous surgery prior to study day 1.
21. Active infection requiring parenteral antibiotic therapy within 1 month prior to study day 1 or systemic antibiotics within 2 weeks of study day 1.
22. Anti-coagulation therapy (e.g., clopidogrel, dabigatran, warfarin, and heparin) or prophylactic aspirin > 81 mg within one week prior to study day 1. Low dose aspirin (≤ 81 mg) for cardiovascular prophylaxis is permitted unless the investigator deems the patient is at a significant risk for bleeding.
23. Concomitant treatment with potent CYP3A4 inducers (carbamazepine, dexamethasone, felbamate, omeprazole, phenobarbital, phenytoin, amobarbital, nevirapine, primidone, rifabutin, rifampin, St. John's wort) is not allowed and should be discontinued 2 weeks prior to study day 1.

24. Persistent peripheral edema within 2 weeks prior to study day 1.
25. History of recurrent ascites requiring paracentesis within 4 weeks of study day 1.
26. History of severe (defined as ≥ grade 3, using the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 4.0 [NCI-CTCAE] v4 (Appendix 6) current minor version) allergic or anaphylactic reaction or hypersensitivity to recombinant proteins or excipients (10 mM Tris buffered saline) in the investigational agent.
27. Pregnant or lactating female patients.

Assessments for Evaluation:

Safety: Patient safety will be assessed by monitoring AEs using the NCI-CTCAE v4 current minor version, physical examinations, vital signs (including weight), clinical laboratory tests, ECHO, ECG and ADA testing.

Preliminary Activity: Response to treatment with dalantercept plus sorafenib will be determined according to RECIST v1.1 evaluating response rates, time to progression (TTP), progression free survival (PFS), disease control rate (DCR), and overall survival (OS). Patients will be assessed for efficacy using data from tumor response assessments as well as evaluation of PD biomarkers in blood and tissue.

Statistical Methods:

Determination of Sample Size: There is no formal sample size calculation for this study. A standard dose escalation of 3-6 patients will be implemented for dose escalation and up to 20 patients may be enrolled in the expansion to further evaluate safety, tolerability, and the PK profile of this combination.

The Safety Analysis Set (SAF) will be used for all safety analyses and will consist of all patients who received any study drug.

The Pharmacokinetics (PK) population will consist of all patients who have received at least 1 dose of dalantercept plus sorafenib and have sufficient PK samples collected and assayed.

Primary Safety Analysis

The safety analyses will be performed on the SAF population. Adverse event incidence rates will be tabulated by System Organ Class and preferred term and without regard to causality. The frequency of occurrence of overall toxicity, categorized by toxicity grades, will be summarized. Shift tables and change from baseline will be summarized by analyte for laboratory panels. Treatment-emergent laboratory findings will be summarized. Change from baseline and shift tables may be presented for vital sign and ECG parameters.

Interim Analysis

There are no planned interim analyses.

2. SCHEDULE OF EVENTS

Schedule of Events[1]														
	Screening[2]	Cycle 1			Cycle 2		Cycle 3		Cycle 4		Cycle 5[4]	Cycle 6[4]	Final Visit[5]	Follow Up[15]
		C1D1[3]	C1D8	C1D15	C2D1[3]	C2D8	C3D1[3]	C3D8	C4D1[3]	C4D8	C5D1[3]	C6D1[3]		
	Day -14	Day 1	Day 8 (± 2d)	Day 15 (± 2d)	Day 22 (± 2d)	Day 29 (± 2d)	Day 43 (± 3d)	Day 50 (± 3d)	Day 64 (± 3d)	Day 71 (± 3d)	Day 85 (± 3d)	Day 106 (± 3d)		
Informed consent[17]	X													
Inclusion/exclusion criteria	X	X												
Medical history	X													
Tumor biopsy	X													
Pregnancy test	X[7]													
Physical examination[12]	X	X	X		X		X		X		X	X	X	
Vital signs (including weight)	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG performance status	X	X					X				X		X	
Hematology/serum chemistry[8]	X[8]	X[8]	X	X	X	X	X	X	X	X	X	X	X	
Coagulation	X[8]	X[8]			X		X		X		X	X	X	
Thyroid Function[9]	X													
Urinalysis and Urine Chemistry[8]	X[8]	X[8]			X		X		X			X[4]	X	
Alpha-fetoprotein (AFP)	X	X					X				X		X	
PD blood biomarkers		X			X	X	X		X		X		X	
PK blood sample collection[16]		X[16]	X	X	X	X[16]	X							
Anti-drug antibody (ADA)		X					X					X[4]	X[10]	X[10]
ECHO scan[6]	X[2]								X				X[6]	
ECG (12-lead)[6]	X								X				X[6]	
Tumor response assessment scan[11]	X[2]						X				X		X[5]	
Monitoring of AEs and concomitant medications	X[13]	X[14]	X	X	X	X	X	X	X	X	X	X	X	
Dalantercept administration		X			X		X		X		X	X		
Sorafenib administration		Continuous daily dosing												
Survival Follow-up														X[15]

[1] All visit day windows should be determined relative to the date of the previous dose of dalantercept except for tumor assessments (see footnote 11). Actual visit days (e.g., day 1, day 8, day 15) may be different than planned due to windows on visits and potential dosing delays.

[2] All screening procedures should be performed within 14 days prior to study day 1. ECHO and tumor response assessment scans obtained for clinical purposes within 28 days prior to study day 1 may be used as the baseline image for this study and do not need to be repeated.

[3] Perform all assessments prior to dosing dalantercept plus sorafenib and review for potential dose modifications. All AEs and abnormal laboratory or other findings that might require modification of dosing (see Section 11.5) should be reviewed prior to dosing to ensure that the patient is still eligible to receive dalantercept. Assessments performed on C1D1 prior to dosing will be considered baseline.

[4] If the patient has stable or responding disease at the end of 6 cycles of treatment, repeat the procedures performed for cycles 5 and 6 until the patient completes cycle 14 (C7D1=C5D1, C8D1=C6D1, etc.). NOTE: after cycle 6, ADA and urinalysis only need to be repeated once every 4 cycles (C10D1, C14D1, etc.). If the patient has stable or responding disease at the end of 14 cycles of treatment, please refer to Section 3. Schedule of Events (Cycle ≥15)

[5] Patients who terminate from the study should complete the Final Visit. The Final Visit should occur approximately 30 days after the last dose of dalantercept ± 10 days. The tumor response assessment at the Final Visit should only be performed to assess progression if progression has not already been confirmed by a previous tumor response assessment scan.

[6] ECHO scans for ejection fraction and presence or absence of pericardial effusion unless additional testing is clinically indicated. ECHO scans may be performed up to 5 days prior to a scheduled visit. A complete cardiac evaluation including ECG and ECHO should be performed if determined to be clinically necessary even if it is an unscheduled time point. Cardiac evaluation should be included at the Final Visit for early termi nation patients if determined to be clinically necessary.

[7] Urine or blood pregnancy test required for patients of child bearing potential only.

[8] Baseline hematology, chemistry, coagulation and urinalysis may be collected up to 72 hours prior to dosing. If the screening visit is within 72 hours prior to study day 1, hematology, chemistry, coagulation and urinalysis do not need to be repeated. This includes the following:
Hematology - complete blood count (CBC) with differential and reticulocyte count; CBC includes red blood cells (RBCs), white blood cells (WBCs), platelets, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC);
Chemistry - albumin, alkaline phosphatase (ALP), ALT, AST, blood urea nitrogen (BUN), calcium, chloride, carbon dioxide (CO_2), creatinine, glucose, lactate dehydrogenase (LDH), serum osmolality, phosphorus, potassium, sodium, total bilirubin, total protein, amylase, and lipase;
Coagulation - PT, INR;
Urine by urinalysis or dipstick analysis - pH, specific gravity, protein, glucose, ketones, blood, leukocyte esterase, and nitrite with microscopic examination if indicated;
Urine Chemistry - osmolality and sodium.

[9] Thyroid function includes the following: free thyroxine (T_4) and thyroid stimulating hormone (TSH).

[10] If the patient has a positive ADA result at their last assessment, the patient may be asked to return approximately every three months for additional testing, until a negative result is obtained or the result is considered stabilized.

[11] Tumor response assessment scans may be performed up to 5 days prior to a scheduled visit (except screening and final visit which have wider windows). Tumor response assessment scans must be reviewed prior to dosing the next cycle of treatment. Tumor response assessment scans should be performed every 6 weeks regardless of dalantercept or sorafenib dosing delays.

[12] A full physical exam [skin (including telangiectasias), head, eyes, ears, nose, throat and neck, lymph nodes, cardiovascular, respiratory, gastrointestinal, musculoskeletal (including edema), and neurological is required at screening, C1D1, C1D8, C2D1, C3D1, C4D1,C5D1,C6D1 and the final visit. A targeted physical exam requiring assessment of the respiratory, cardiovascular and musculoskeletal (including edema) body systems is required at all other time points including beyond cycle 6. If clinically indicated, additional assessment of other body systems should occur.

[13] Concomitant medications taken within 28 days prior to study day 1 will be collected.

[14] Adverse events will be collected after the first dose administration. Non-serious AEs prior to dosing on study day 1 will be collected as medical history.

[15] All patients should be contacted every 3 months (± 2 weeks) for up to 1 year from the date of first dose for survival

[16] PK blood sample collection should be performed pre-dose for dalantercept and sorafenib at all time points. In addition, PK blood samples should be collected between 1-3 hours and 4-6 hours post dalantercept and sorafenib dosing at C1D1 visit and between 1-3 hours and 4-6 hours post sorafenib dosing at C2D8 visit.

[17] Informed consent must be obtained within 28 days prior to C1D1 and prior to any study specific procedures.

3. SCHEDULE OF EVENTS (CYCLES ≥ 15)

Schedule of Events[1]			
	Cycle 15[2]	**Cycle 16[2]**	**Final Visit[4]**
	C15D1[3]	**C16D1[3]**	
	Day 295 (± 3d)	**Day 316 (± 3d)**	
Physical examination[5]	X		X
Vital signs (including weight)	X	X	X
Hematology/serum chemistry[6]	X	X	X
ECHO scan[7]			X
ECG (12-lead)[7]			X
ADA[8]	X[2]		X[8]
Tumor response assessment scan[9]	X[2]		X[4]
Alpha-fetoprotein (AFP)	X[2]		
Monitoring of AEs and concomitant medications	X	X	X
Dalantercept administration	X	X	
Sorafenib administration	Continuous daily dosing		

[1] All visit day windows should be determined relative to the date of the previous dose of dalantercept except for tumor assessments (see footnotes 2 and 9). Actual visit days (e.g., day 1, day 8, day 15) may be different than planned due to windows on visits and potential dosing delays.

[2] If the patient has stable or responding disease at the end of 14 cycles of treatment repeat, the procedures performed for cycles 15 and 16 until the patient is taken off study (C17D1=C15D1, C18D1=C16D1, etc.). NOTE: after cycle 15, tumor assessments, ADA, and AFP only need to be repeated once every 4 cycles (C19D1, C23D1, C27D1, etc.).

[3] Perform all assessments prior to dosing dalantercept plus sorafenib and review for potential dose modifications. All AEs and abnormal laboratory or other findings that might require modification of dosing (see Section 11.5) should be reviewed prior to dosing to ensure that the patient is still eligible to receive dalantercept.

[4] Patients who terminate from the study should complete the final visit. The final visit should occur approximately 30 days after the last dose of dalantercept ± 10 days. The tumor response assessment at the final visit should only be performed to assess progression if progression has not already been confirmed by a previous tumor response assessment scan.

[5] A full physical exam [skin (including telangiectasias), head, eyes, ears, nose, throat and neck, lymph nodes, cardiovascular, respiratory, gastrointestinal, musculoskeletal (including edema), and neurological is required at screening, C1D1, C1D8, C2D1, C3D1, C4D1,C5D1,C6D1 and the final visit. A targeted physical exam requiring assessment of the respiratory, cardiovascular and musculoskeletal (including edema) body systems is required at all other time points including beyond cycle 6. If clinically indicated, additional assessment of other body systems should occur.

[6] **Hematology** - complete blood count (CBC) with differential; CBC includes red blood cells (RBCs), white blood cells (WBCs), platelets, hemoglobin, hematocrit;
Chemistry - albumin, alkaline phosphatase (ALP), ALT, AST, blood urea nitrogen (BUN), chloride, carbon dioxide (CO2), creatinine, glucose, lactate dehydrogenase (LDH), potassium, total bilirubin, total protein, and sodium. Amylase and lipase only if clinically indicated.

[7] A complete cardiac evaluation including ECG and ECHO should be performed if determined to be clinically necessary even if it is an unscheduled time point. Cardiac evaluation should be included at the Final Visit for early termination patients if determined to be clinically necessary..

[8] If the patient has a positive ADA result at their last assessment, the patient may be asked to return approximately every three months for additional testing, until a negative result is obtained or the result is considered stabilized.

[9] Tumor response assessment scans may be performed up to 5 days prior to a scheduled visit (except final visit which have wider windows). Tumor response assessment scans must be reviewed prior to dosing the next cycle of treatment. Tumor response assessment scans should be performed every 12 weeks regardless of dalantercept or sorafenib dosing delays

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5. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Term	Definition
ADA	Anti-drug antibody
AE	Adverse event
AFP	Alpha-fetoprotein
ALK1	Activin receptor-like kinase1
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the curve
BID	Twice per day
BMP	Bone morphogenetic protein
BP	Blood pressure
BUN	Blood urea nitrogen
C1D1	Cycle 1 Day 1
CBC	Complete blood count
CFR	Code of federal regulations
CHF	Congestive heart failure
CL/F	Apparent clearance
C_{max}	Maximum concentration
CNS	Central nervous system
CO_2	Carbon dioxide
CR	Complete response
CRA	Clinical research associate
CRF	Case report form
CRO	Contract research organization
CT scan	Computed tomography scan
DCE-MRI	Dynamic contrast-enhanced magnetic resonance imaging
DCR	Disease control rate

Term	Definition
DLT	Dose limiting toxicity
DVT	Deep venous thrombosis
ECD	Extracellular domain
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EF	Ejection fraction
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FGF	Fibroblast growth factor
GCP	Good Clinical Practice
GI	Gastrointestinal
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HED	Human equivalent dose
HHT	Hereditary hemorrhagic telangiectasia
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
ICD	Implantable cardioverter-defibrillator
IRB	Institutional Review Board
LDH	Lactate dehydrogenase
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MI	Myocardial infarction
MRI	Magnetic resonance imaging

Term	Definition
MTD	Maximum tolerated dose
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NOAEL	No observed adverse effect level
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
OS	Overall survival
PD	Pharmacodynamic
PET-CT	Positron emission tomography-computed tomography
PFS	Progression free survival
PHI	Protected health information
PK	Pharmacokinetic
PO	Orally
PT/INR	Prothrombin time/international normalized ratio
Q3W	Every 3 weeks
QD	Once daily
RAF	Rapidly Accelerated Fibrosarcoma
RBC	Red blood cell
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical analysis plan
SC	Subcutaneous
SCCHN	Squamous cell carcinoma of the head and neck
SD	Stable disease
SDV	Source data verification
SOC	System organ class
SRT	Safety review team
SUSAR	Suspected, unexpected serious adverse reaction

Term	Definition
$T_{1/2}$	Elimination half- life
T_4	Thyroxine
TGF-β	Transforming growth factor β
TK	Toxicokinetic
TKI	Tyrosine kinase inhibitor
T_{max}	Time to maximum concentration
TSH	Thyroid stimulating hormone
TTP	Time to tumor progression
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
Vz/F	Apparent volume of distribution
WBC	White blood cell

6. ETHICS

6.1. Institutional Review Board

The investigator will submit this protocol, any protocol modifications, and the patient informed consent form (ICF) to be used in this study to the appropriate institutional review board (IRB) for review and approval. A letter confirming IRB approval of the protocol and ICF as well as a statement that the IRB is organized and operates according to Good Clinical Practice (GCP) and the applicable laws and regulations, must be forwarded to the sponsor prior to the enrollment of patients into the study. A copy of the approved ICF will also be forwarded to the sponsor. Appropriate reports on the progress of the study will be made to the IRB and the sponsor by the principal investigator in accordance with applicable governmental regulations and in agreement with the policy established by the sponsor.

6.2. Ethical Conduct of the Study

The sponsor and the investigator must comply with all instructions, regulations, and agreements in this protocol and in the applicable International Conference on Harmonisation (ICH) and GCP guidelines, and must also conduct the study in accordance with local regulations.

6.3. Patient Information and Consent

A signed ICF is required from each patient prior to any testing under this protocol, including screening tests and evaluations. The consent form, as specified by the clinical site's IRB, must follow the Protection of Human Patients regulations listed in the Code of Federal Regulations (CFR), Title 21, Part 50.

The background of the proposed study and the benefits and risks of the procedures and study must be explained to the patients. It is the responsibility of the investigator to obtain consent and to provide the patient with a copy of the signed and dated ICF. Confirmation of a patient's informed consent must also be documented in the patient's medical record prior to any testing under this protocol, including screening tests and evaluations.

All ICFs used in this study must be approved by the appropriate IRB and by the sponsor or designee. The ICF must not be altered without the prior agreement of the relevant IRB and the sponsor (or designee).

6.4. Patient Data Protection

Prior to any testing under this protocol, including screening tests and evaluations, patients must authorize the release and use of protected health information (PHI), as required by local law.

The patient will not be identified by name in the case report form (CRF) or in any study reports. These reports will be used for research purposes only. The sponsor, its designee, and various government health agencies may inspect the records of this study. Every effort will be made to keep the patient's personal medical data confidential.

7. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Acceleron Pharma is the sponsor for this trial. The sponsor or designee will serve as the medical monitor for the study. The sponsor or designee will manage the conduct of the trial and provide clinical monitoring, data management, biostatistics, and report writing. Clinical research associates (CRAs) will monitor each study center on a periodic basis and verify source documentation for each patient. The sponsor's regulatory representative will be responsible for timely reporting of serious adverse events (SAEs) to United States regulatory authorities as required.

Prior to trial initiation, the investigator will provide the sponsor with a fully executed and signed Food and Drug Administration (FDA) Form 1572 and a Financial Disclosure Form. Financial Disclosure Forms will also be completed by all sub-investigators listed on the Form 1572 who will be involved directly in the treatment or evaluation of patients enrolled in this trial.

8. INTRODUCTION AND STUDY RATIONALE

Dalantercept (also known as ACE-041) is a novel biologic anti-angiogenesis agent that inhibits signaling through activin receptor-like kinase 1 (ALK1). ALK1 is a type I receptor in the transforming growth factor-β (TGF-β) superfamily that is selectively expressed on the surface of activated endothelial cells during development or in response to injury or disease. ALK1 binds with high affinity to the ligands bone morphogenetic proteins (BMP) 9 and BMP10. Signaling through ALK1 requires binding of ligand and simultaneous engagement of a type II receptor (ActRIIB, ActRIIA or BMPRII) which results in phosphorylation of the intracellular Smad 1/5/8 cascade which activates proangiogenic transcription factors such as Id1 and Id3.[1-3] Endoglin (CD105), an accessory receptor to ALK1 and may facilitate signaling by acting as a ligand chaperone but is not required for ALK1 signaling and has no known intracellular signaling activity. Dalantercept is a recombinant fusion protein consisting of the extracellular domain (ECD) of human ALK1 linked to the Fc (hinge, CH2 and CH3 domains) portion of human immunoglobulin G1 (IgG1) and acts as a ligand trap by binding to BMP9 and BMP10.

Multiple lines of evidence characterize the BMP9/ALK1/SMAD 1/5/8 pathway as playing a pivotal role in the maturation phase of angiogenesis which leads to the development of functional vasculature.[4] The processes involved in vascular maturation include vessel stabilization via incorporation of pericytes and other stromal cells which are commonly downstream of the proliferative stage processes which are driven by vascular endothelial growth factor (VEGF) and other proangiogenic factors. Furthermore, ALK1 expression is normally low in established blood vessels but elevated in neovascular endothelium during tumor growth or wound healing which is in contrast to the VEGF/VEGFR axis which is constitutively expressed in new and established blood vessels and in other tissues.[5] In addition, the BMP9/BMP10/ALK1 pathway regulates development of lymphatic vessels[6], which has implications for metastatic spread of tumor cells through lymphatic vasculature.[7] Thus targeting the ALK1 and VEGF pathways simultaneously may result in more effective angiogenic blockade and delay tumor progression in a variety of cancers.

Dalantercept has demonstrated robust anti-angiogenic activity in tumor model studies, and has demonstrated preliminary anti-tumor activity in a completed Phase 1 study in advanced solid tumor patients. In support of this therapeutic strategy, experiments were conducted in mouse xenograft renal cell carcinoma (RCC) models combining VEGF receptor tyrosine kinase inhibitor (TKI), sunitinib, with dalantercept which demonstrated additive tumor growth delay beyond either agent alone and curtailed sunitinib resistance. In an ongoing randomized Phase 2 study combining axitinib, a VEGF receptor TKI, with dalantercept in patients with advanced RCC, safety and preliminary activity of the combination have been observed in the first two cohorts of patients all of whom had prior VEGF and in some cases mammalian target of rapamycin (mTOR) directed therapies.

In addition to demonstrating efficacy in RCC models, dalantercept was tested in an HCC xenograft model using the human BEL-7402 hepatocellular carcinoma cell line. In mice with established BEL-7402 tumors, treatment with dalantercept as a single agent therapy demonstrated significant inhibition of tumor growth such that treated tumors were 25% the size of vehicle treated control mice ($p \leq 0.001$) after 35 days of treatment. The only targeted agent

currently approved for the treatment of advanced HCC is sorafenib, a VEGF receptor TKI and multi-kinase inhibitor. Therapeutic responses to sorafenib are short lived and few options exist outside of a clinical trial. ALK1 has been detected in the vasculature of many human tumor types including hepatocellular carcinoma (HCC).[8] BMP9 expression occurs predominantly in the liver. Based upon immunohistochemical testing conducted at Acceleron Pharma and published results from the human protein atlas (www.proteinatlas.org), BMP9 expression appears elevated in HCC compared to unaffected liver in human and mouse tissue. In addition to its role in ALK1 mediated angiogenesis, BMP9 has been shown to induce epithelial to mesenchymal transition leading to cell migration and invasiveness in the HCC HepG2 model.[9,10] Furthermore, HepG2 cells produce BMP9 as an autocrine growth factor that directly supports the proliferative and survival capacity of these tumor cells.[10]

In summary, the BMP9/ALK1/SMAD 1/5/8 pathway is a novel target in angiogenesis and may play an important role in the malignant progression of HCC. Given the limited efficacy of sorafenib and growing incidence of HCC, there is a critical need for more effective therapies. We hypothesize dalantercept can be combined safely with sorafenib and will augment the therapeutic response to sorafenib in HCC by enhancing angiogenic blockade and inhibiting BMP9 induced cellular proliferation.

8.1. Overview of Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) most commonly develops in the setting of chronic liver disease and affects a diverse group of patients including those with hereditary and metabolic syndromes, auto-immune disease, viral hepatitis B and C and alcoholism. In 2013, it is estimated there will be 30,640 new cases of HCC diagnosed and 21,670 deaths due to the disease in the US.[11] Moreover, HCC is the 5th leading cause of cancer mortality in US men. Globally, HCC is the 7th leading cause of cancer and the 3rd leading cause of cancer mortality.[12]

Historically, systemic treatment options for patients with advanced HCC remained limited to toxic chemotherapy regimens which were relatively ineffective in prolonging survival. The most active chemotherapy agent in HCC is doxorubicin which is associated with a 4% response rate and survival of approximately 8 months.[13] The exploration of growth factors in HCC has implicated VEGF and angiogenesis as a critical component in the malignant progression of the disease and has encouraged the development and investigation of novel anti-angiogenic agents.[14] Sorafenib is an oral multi-targeted tyrosine kinase inhibitor of VEGFR-1, 2, 3, PDGF, Raf, and other kinases.[15] In the international phase 3 study entitled "Sorafenib HCC Assessment Randomized Protocol" (SHARP trial), 602 subjects with advanced HCC (Child-Pugh Class A cirrhosis) who had received no prior systemic therapy were randomized to sorafenib 400 mg twice daily or placebo. The overall response to sorafenib was only 2%. However, the disease control rate 43% vs. 32% and overall survival 10.7 vs. 7.9 months (hazard ratio: 0.69, $p < 0.001$) were significantly better with sorafenib compared to placebo. The median TTP was 5.5 months with sorafenib and 2.8 months with placebo ($p < 0.001$).[16]

Based upon the modest activity of sorafenib, several clinical studies have been conducted to explore additional VEGF and other targeted agents in comparison to sorafenib or after sorafenib failure. Combinations with sorafenib have also been explored with epidermal growth factor receptor (EGFR) TKI, erlotinib. To date, none of these approaches has resulted in meaningful

improvements in time to progression or overall survival compared to sorafenib monotherapy.[17] Importantly, there is growing interest in targeting the ALK1 pathway in HCC, as shown by recent or ongoing studies with TRC105 (anti-endoglin antibody) and PF-03446962 (anti-ALK1 antibody). There has been clinical activity reported in a completed phase I study with PF-03446962 in patients with HCC who were intolerant to or progressed on sorafenib. Of the 24 patients in this cohort the disease control rate at 12 weeks was 29% and median TTP was 3 months.[18]

8.2. Summary of Nonclinical Studies

8.2.1. Pharmacology Studies

Signaling through the ALK1 receptor is important in vascular development and pathological angiogenesis. Activation of the ALK1 pathway helps regulate endothelial cell sprouting after initiation of angiogenesis by various growth factors.[19] The data from studies designed to evaluate the inhibition of angiogenesis in response to known angiogenic growth factors such as vascular endothelial growth factor (VEGF) or fibroblast growth factor (FGF) demonstrate that blocking signaling through the ALK1 receptor by the use of a soluble receptor [dalantercept or RAP-041 (murine ortholog of dalantercept)] can inhibit angiogenesis initiated by a variety of factors. In oncology models, RAP-041 has demonstrated inhibition of tumor progression in xenograft models of breast cancer (MDA-MB-231, MCF-7), lung cancer (Calu-6) and renal cell carcinoma Cell (A498) head and neck cancer (FaDu, CCL-30), as well as in genetic models of pancreatic cancer (RIP1 Tag2),[20] breast cancer (mouse mammary tumor virus) and multiple myeloma (5T2MM). Dalantercept has also shown efficacy as both a single agent and in combination with sunitinib using renal cell carcinoma xenograft models. In the subcutaneously implanted A498 kidney carcinoma cell line dosing of dalantercept inhibited tumor growth similar to sunitinib treated mice. Importantly combination therapy with both dalantercept and sunitinib inhibited tumor growth to a greater extent than either agent alone. In a second xenograft model, subcutaneously implanted 786-O kidney adenocarcinoma cells were also treated with dalantercept alone or in combination with sunitinib. In this model dalantercept did not demonstrate single agent efficacy. In this model it is known that tumors treated with sunitinib develop rapidly develop resistance and continue to grow. Combination therapy with dalantercept reduced tumor growth to a greater extent than single agent sunitinib and continued to show tumor inhibition even when the tumors treated with sunitinib alone began to develop resistance and progressed further.[21] Overall, these data provide a rationale for the clinical development of dalantercept as an anti-angiogenic therapy in combination with VEGF pathway targeted therapy.

8.2.2. Toxicology Studies

Dalantercept has been evaluated in two species, rats and monkeys, for toxicological effects and pharmacokinetic (PK) properties following single and repeated subcutaneous (SC) injections. Single-dose SC injections up to a high dose of 100 mg/kg were well tolerated in both rats and monkeys. Repeat-dose toxicity studies were conducted in both rats and monkeys for 3 months; both studies included male and female animals, a recovery period, and toxicokinetic (TK) evaluations. Dalantercept dose levels were 10, 30 and 100 mg/kg in the rat study, and 3, 10 and 30 mg/kg in the monkey study. Dose administration was weekly, which ensured continuous

exposure to dalantercept, based on serum half-lives of approximately 3 days in rats and approximately 5 days in monkeys.

Subcutaneous administration of dalantercept at ≥ 30 mg/kg resulted in edema and fluid in the thoracic and abdominal cavities that contributed to the death of moribund animals. The most significant findings were observed in the heart. In the 3-month rat study, heart weights were increased at ≥ 30 mg/kg, with histological findings of myocardial degeneration/necrosis, LV hypertrophy, atrial dilation and mononuclear cell infiltration. These effects resolved by the end of the one month recovery period. In the 3-month monkey study, increases in heart weight were observed at 30 mg/kg. By echocardiogram (ECHO) there was increased LV mass in animals dosed at 10 and 30 mg/kg in addition to increased left atrial (LA) area at 30 mg/kg. Both effects were substantially or completely reversed after one month of recovery. The increased heart weight in monkeys did not correlate with any microscopic changes or increases in serum markers of heart muscle damage. Electrocardiography (ECG) and ejection fraction (EF) were normal.

The highest dose level in the 3-month rat toxicity study was 100 mg/kg with a no observed adverse effect level (NOAEL) of 10 mg/kg, while the highest dose level in the 3-month monkey toxicity study was 30 mg/kg with a NOAEL of 10 mg/kg. The two NOAEL values corresponded to a human equivalent dose (HED) of 1.6 mg/kg (rat data) and 3.2 mg/kg (monkey data).

8.3. Summary of Clinical Experience

A Phase 1, open-label, multiple dose, dose escalation study (A041-01)[22] of dalantercept has been conducted in patients with advanced solid tumors or relapsed/refractory multiple myeloma. A total of 37 patients with advanced solid tumors were enrolled. The first 25 patients were enrolled in 7 dose-escalating cohorts (0.1 to 4.8 mg/kg SC with a treatment cycle of 3 weeks), followed by 12 patients who were enrolled in an expansion cohort at a dose of 1.6 mg/kg (11 patients) or 0.8 mg/kg (1 patient). Based on the cumulative safety data observed at the 1.6 mg/kg and higher dose levels, the recommended phase 2 dose was selected as 1.2 mg/kg.

Tumor response was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Patients must have had a baseline and at least one post-treatment tumor response assessment to be evaluable; 29 patients met these criteria for the analysis.

Antitumor activity as evident by partial response or prolonged stable disease was observed in 9 of 29 evaluable patients at dose levels ranging from 0.2 to 4.8 mg/kg; 1 patient with squamous cell carcinoma of the head and neck (SCCHN) involving the base of the tongue had a partial response by Cycle 9 at a dose level of 0.4 mg/kg, and 8 patients had prolonged periods of stable disease (SD) for at least 3 months after the first dose across a range of dose levels (0.2 to 4.8 mg/kg), including 3 patients with non-small cell lung cancer (NSCLC), 1 patient each with neuroendocrine carcinoid, SCCHN, granulosa cell tumor, small bowel mucinous adenocarcinoma, and colorectal adenocarcinoma.

Tumor metabolic activity was evaluated using fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) scan. Tumor metabolic activity decreased from baseline in 17 (63%) of 27 evaluable patients. Seven out of the 8 patients with prolonged stable disease were evaluable for FDG PET-CT. All 7 of these patients had a reduction in metabolic

activity. In addition, the patient with a partial response had a 44% reduction in metabolic activity.

Tumor blood flow was evaluated using dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). Analysis by DCE-MRI found that 71% (10 out of 14) of patients with evaluable DCE-MRI data showed reduced tumor blood flow (K_{trans}) at day 15 compared to baseline. Nine out of 11 patients with evaluable data from both DCE-MRI and RECIST data showed reductions in K_{trans} at day 15 compared to baseline. Six patients with stable disease had evaluable DCE-MRI data and 5 had decreases in K_{trans}. Three patients with prolonged stable disease ($\geq$ 3 months) were evaluable for DCE-MRI and all 3 patients had a reduction in K_{trans}.

A Phase 2, open-label study A041-03 of dalantercept is currently being conducted in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN). The first two patients received 80 mg however, due to the general co-morbidities of this heavily pre-treated patient population, the protocol was amended to a lower weight based dose of 0.6 mg/kg. Thirteen patients were enrolled at this dose level which demonstrated a generally safe toxicity profile. A second amendment increased the dose level to 1.2 mg/kg and an additional 31 patients were enrolled. In total, forty-six patients have been enrolled and enrollment has ended. The primary endpoint in this study is objective response rate.

Study A041-04 is a two-part, multi-center, randomized, placebo-controlled, double-blind, phase 2 study to evaluate safety, tolerability, efficacy, PK and PD of dalantercept in combination with axitinib in patients with advanced RCC. The study will enroll up to 44 patients in the dose escalation, open label phase of the study (Part 1) and approximately 130 patients in the randomized, double-blind, placebo-controlled phase of the study (Part 2) for a total of up to approximately 174 patients. The primary endpoint in this study is progression free survival.

Two additional studies with dalantercept at 1.2 mg/kg as monotherapy in ovarian and endometrial cancer are ongoing under investigator-sponsored IND(s) conducted by the Gynecologic Oncology Group (GOG). Acceleron is responsible for providing dalantercept drug product for these studies.

8.4. Potential Risks of Human Use of Dalantercept

Dalantercept is designed to bind to the protein ligands BMP9 and BMP10 to inhibit their interaction with the ALK1 receptor, thus blocking a cell signaling process involved in angiogenesis. Effects on other organ systems, including erythropoiesis, may also be related to ALK1 or BMP9/10 inhibition.

The most frequently observed AEs ($\geq$ 10% patients) in the dalantercept monotherapy clinical trials (A041-01 and A041-03) as of September 10, 2013 were fatigue, peripheral edema, headache, anemia, dyspnea, nausea, constipation, vomiting, anorexia, pyrexia, abdominal pain, cough, dehydration, epistaxis, hyponatremia, telangiectasia, diarrhea, hypotension, insomnia, arthralgia, back pain, dizziness and pleural effusion.

In the actively accruing two-part Phase 2 RCC A041-04 study with the combination of dalantercept plus axitinib, as of September 10, 2013, the most frequently observed AEs ($\geq$ 20% of patients, n=10) regardless of causality, have included dysphonia, fatigue, diarrhea, arthralgia, constipation, hypertension, blood alkaline phosphatase increased, blood creatinine increased,

chills, cough, dizziness, headache, hyperkalemia, muscle spasm, nausea, thrombocytopenia and vomiting.

In the completed Phase 1 study, serious AEs considered related to dalantercept included congestive heart failure (1 patient at 1.6 mg/kg and 1 patient at 4.8 mg/kg), fluid overload (2 patients at 1.6 mg/kg), fatigue (1 patient at 1.6 mg/kg), and left ventricular dysfunction (1 patient at 0.4 mg/kg). Three of these patients (2 patients with CHF and 1 with LV dysfunction) had a prior history of coronary artery disease. Although dyspnea and other signs typical of heart failure were reported, serial echocardiograms did not show a trend for worsening of LV ejection fraction in the majority of patients receiving dalantercept.

In the Phase 2 SCCHN study (A041-03), dalantercept-related SAEs to date have included 2 events of pleural effusion (1 patient at 0.6 mg/kg, 1 patient at 1.2 mg/kg), one event each of pulmonary edema and tracheal obstruction occurring in one patient receiving 1.2 mg/kg.

In the GOG sponsored endometrial carcinoma study, serious adverse events possibly related to dalantercept reported to date include 2 patients with ascites, 1 patient each with gastric hemorrhage, rectal fistula, pleural effusion, vomiting, anemia and dyspnea. The gastric hemorrhage was a fatal event which occurred in a patient with a prior history of small bowel obstruction and radiation fibrosis.

In the GOG sponsored ovarian carcinoma study, serious adverse events possibly related to dalantercept reported to date occurred in 1 patient and include hypokalemia, anorexia, dehydration, and creatinine increase.

Across studies, peripheral edema and weight gain events have responded to diuretic therapy. A possible explanation of these events may be the effect of dalantercept on capillary or lymphatic vessels which may lead to fluid leakage and result in fluid overload. Serial ECHO data from the completed phase 1 and ongoing studies do not show a trend for a decline in LV ejection fraction in the majority of patients treated with dalantercept.

In summary, the safety data to date suggest that patients with significant bleeding and/or cardiovascular risks should be excluded from participating in studies with dalantercept. The volume-related events such as peripheral edema, weight gain, pleural effusion, and pulmonary edema, across the studies appear to be least common when dalantercept is administered at doses $\leq$ 1.6 mg/kg.

The effects of dalantercept on reproduction and development are not fully known. Although no histopathological effects were seen in reproductive organs in 3-month toxicology studies in monkeys and rats, use of adequate birth control measures should be required in dalantercept studies and dalantercept should not be administered to pregnant or nursing women.

As with all biologics, there is the potential for the development of anti-drug antibodies that can be associated with altered drug clearance and/or hypersensitivity reactions. No specific anti-drug antibodies were detected in the Phase 1 study. Anti-drug antibody formation should be monitored in selected clinical studies.

A comprehensive review of dalantercept, as well as details regarding the information summarized above, is provided in the Investigator's Brochure (IB). The most recent version of the dalantercept IB should be reviewed prior to initiating the study.

8.5. Potential Risks of Human Use of Sorafenib

The most common side effects observed in at least 20% of patients which were considered related to sorafenib include fatigue, weight loss, rash/desquamation, hand-foot skin reaction, alopecia, diarrhea, anorexia, nausea and abdominal pain. For additional risks associated with patients taking sorafenib, please refer to the sorafenib prescribing information (see Nexavar® [sorafenib] prescribing information, *Warnings and Precautions*).

9. TRIAL OBJECTIVES

Primary:

- Evaluate the safety and tolerability of dalantercept plus sorafenib in patients with advanced hepatocellular carcinoma (HCC) to determine the recommended phase 2 dose level of dalantercept in combination with sorafenib

Secondary:

- Evaluate the pharmacokinetic (PK) profiles of dalantercept and sorafenib when used in combination
- Evaluate the preliminary activity of dalantercept plus sorafenib in patients with advanced HCC as defined by response rates per RECIST v1.1, time to progression (TTP), progression free survival (PFS), disease control rate (DCR), and overall survival (OS). Explore the association of the expression of BMP9/10, ALK1 and/or other relevant pharmacodynamic (PD) markers in archived or recent tumor biopsy with tumor response and/or other assessments of clinical response
- Explore association of serum pharmacodynamic (PD) biomarkers with assessments of response

10. OVERALL STUDY DESIGN AND PLAN

10.1. Study Design

This is an open label, multi-center phase 1b study to evaluate the safety, tolerability, PK and PD, and preliminary activity of dalantercept plus sorafenib in patients with advanced HCC.

The dose level of dalantercept for the first cohort will be 0.6 mg/kg administered subcutaneously (SC) every 3 weeks (Q3W) plus sorafenib 400 mg orally (PO) once daily (QD).

Dose Escalation

The dose escalation portion will include up to three planned cohorts of a minimum of 3 patients each to determine the maximum tolerated dose (MTD) of the combination. Patients may require dose modification(s) of dalantercept or sorafenib as indicated per protocol or prescribing information, respectively.

At least three patients must complete the Day 22 visit at each dalantercept dose level with review of data through Day 22 by the Safety Review Team (SRT) prior to escalation to the next higher dose level. The SRT may recommend adding additional patients, for a total of up to 6 patients, to the current dose level for further evaluation, escalating to an intermediate dose level or discontinuing escalation. The following general dose escalation rules will apply:

1. Dalantercept starting dose level is 0.6 mg/kg in combination with sorafenib starting dose level of 400 mg QD.
2. Dalantercept will be escalated to a maximum dose level of 0.9 mg/kg plus sorafenib 400 mg QD.
3. Once the maximum tolerated dose level of dalantercept is determined, sorafenib will be escalated to 400 mg BID.
4. After the MTD level of the combination is determined in the dose escalation portion, an additional 10-20 patients will be added in the expansion portion.
5. If the dalantercept starting dose level of 0.6 mg/kg is not tolerated, there will be one dose level de-escalation to 0.4 mg/kg.

The planned dose escalation for dalantercept and sorafenib is outlined below in Table 2.

Table 2: Planned Starting Dose Regimen Per Cohort

Dose Cohort	Dalantercept	Sorafenib	Number of Patients
1	0.6 mg/kg Q3W	400 mg QD	3-6
2	0.9 mg/kg Q3W	400 mg QD	3-6
3	0.9 mg/kg Q3W	400 mg BID	3-6
Expansion	TBD	TBD	up to 20
Total (planned)			up to 38

Expansion Cohort

Once the MTD or maximum tested dose level has been determined by the SRT and Sponsor, up to a total of 20 patients may be enrolled at or below the MTD to further evaluate the safety, tolerability, and PK profile of dalantercept plus sorafenib. The SRT will meet after a minimum of 10 patients have been evaluated for a minimum of 21 days after the first dose of dalantercept/sorafenib (Day 22) to review safety data. The SRT may recommend adding up to an additional 10 patients to the current dose level for further evaluation or to an intermediate dose level.

Duration of Treatment

The total duration of participation in the study will vary for each patient. There will be a 14-day screening period, a treatment period lasting for as long as patients are eligible to remain on-study, a final visit approximately 1 month after the last dose of dalantercept and follow-up for for 1 year from first dose for patient survival.

If a patient has a positive anti-drug antibody (ADA) result at the last visit, the patient may be asked to return for additional ADA testing every three months, until a negative result is obtained or the result is considered to be stabilized.

10.2. Discussion of Study Design

Dalantercept is a novel anti-angiogenic agent that inhibits the BMP9/ALK1/Smad 1/5/8 signaling cascade involved in blood vessel maturation and stabilization. In addition to its role in angiogenesis, BMP9 may directly stimulate HCC cellular proliferation based on in vitro data. In an Acceleron mouse xenograft study using the human BEL-7402 HCC cell line, single agent therapy with dalantercept significantly inhibited tumor growth when dosed at 15 mg/kg three times per week for 5 weeks. Preclinical, Phase 1 and early Phase 2 clinical data support the development of dalantercept in combination with VEGF pathway inhibitors to maximize growth inhibition in tumors that are sensitive to anti-angiogenic agents. Importantly, the dalantercept side effect profile to date is mostly non-overlapping with the toxicity profiles of VEGF TKI therapies including sorafenib. Ongoing studies targeting the ALK1 pathway in HCC are underway and support further development of combination approaches in this challenging and underserved disease. Thus we propose to investigate the safety, tolerability, and PK profile of the novel combination of dalantercept with sorafenib, a VEGF and multi-kinase TKI, in the treatment of patients with newly diagnosed advanced HCC utilizing a dose escalation of sorafenib and dalantercept followed by an expansion.

10.3. Selection of Study Population

10.3.1. Inclusion Criteria

1. Age ≥ 18 years.
2. Histologically confirmed (from either a recent or archival biopsy), locally advanced (no presence of distant metastases, unresectable and not eligible for transplant) or metastatic HCC.
3. Child-Pugh Score A (5-6) (Appendix 1).

4. At least one target lesion that has not been treated with local therapy and is measurable by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Appendix 2). If there is a lesion within the field of local therapy and has shown ≥ 20% in size since post treatment assessment, this can be classified as a target lesion.
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 (Appendix 3).
6. Life expectancy of at least 12 weeks.
7. Able to tolerate oral therapy.
8. Clinical laboratory values that meet the following criteria within 72 hours prior to study day 1:
    - Hematology (in the absence of hematopoietic growth factor support):
        - Absolute neutrophil count (ANC) ≥ 1,000/µL (≥ 1.0 x 10^9/L).
        - Hemoglobin ≥ 9 g/dL (≥ 90 g/L).
        - Platelet count ≥ 60,000 /µL (≥ 60 x 10^9/L) without transfusion support 30 days prior to cycle 1 day 1 unless required for biopsy for study eligibility provided their pre-transfusion platelet count was at least 60,000 /µL.
    - Creatinine ≤ 1.5 x ULN or measured or calculated creatinine clearance, using the Cockcroft-Gault formula, (Appendix 4) ≥ 60 mL/min.
    - Total bilirubin ≤ 1.5 x upper limit of normal (ULN). Patients with known Gilbert's Syndrome may have bilirubin levels up to 3.0 mg/dL.
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 5 x ULN.
    - PT/INR ≤ 1.5 x ULN.
    - Serum albumin ≥ 2.8 g/dL (≥ 28 g/L).
    - Urinary protein < 2+ by urine dipstick or urinalysis. If ≥ 2+, then patient may be enrolled if 24-hour urine protein < 2 g/24hr.
9. Females of child bearing potential (defined as sexually mature women who have not undergone hysterectomy or bilateral oophorectomy, or are not naturally postmenopausal ≥ 24 consecutive months) must have negative urine or blood pregnancy test prior to enrollment and use adequate birth control methods (abstinence, oral contraceptives, barrier method with spermicide, or surgical sterilization) during study participation. Males must agree to use a latex condom during any sexual contact with females of child-bearing potential while participating in the study and for 12 weeks following the last dose of dalantercept, even if he has undergone a successful vasectomy. Patients must be counseled concerning measures to be used to prevent pregnancy and potential toxicities prior to the first dose of dalantercept.
10. Signed written informed consent.

10.3.2. Exclusion Criteria

1. Mixed tumor histology (e.g. hepatocellular carcinoma plus cholangiocarcinoma) or fibrolamellar variant tumors.
2. Prior solid organ or allogeneic bone marrow transplantation.
3. Prior systemic therapy for metastatic disease.
4. Adjuvant therapy < 6 months prior to study day 1.
5. Prior treatment with dalantercept or other agent targeting the ALK1 pathway.
6. Prior treatment with sorafenib or other RAF/VEGF targeted therapies.
7. Hepatic radiation, chemoembolization, and radiofrequency ablation < 4 weeks prior to study day 1.
8. Palliative radiation therapy to metastatic sites of disease < 2 weeks prior to study day 1.
9. Interferon therapy < 4 weeks prior to study day 1.
10. Uncontrolled Hepatitis B despite appropriate therapy.
11. Clinically significant pulmonary, endocrine, neurologic, hematologic, gastrointestinal (GI), autoimmune, psychiatric or genitourinary disease unrelated to HCC that in the judgment of the investigator should preclude treatment with dalantercept or sorafenib.
12. Known HIV infection.
13. Clinically significant cardiovascular risk including:
    - Ejection fraction (EF) ≤ 50%.
    - Significant history of congestive heart failure (CHF) defined as New York Heart Association (NYHA) class II-IV (Appendix 5).
    - Hospitalization for CHF (any NYHA class) within 6 months of study day 1.
    - Active coronary artery disease [e.g., myocardial infarction (MI), uncontrolled angina], peripheral vascular disease, cerebrovascular disease [e.g., transient ischemic attack (TIA), stroke], bypass surgery, angioplasty, or vascular stenting within 12 months prior to study day 1. Worsening symptoms attributable to cardiac or vascular disease or new findings on cardiac evaluation (e.g. clinical, stress test, etc.) within 3 months prior to study day 1.
    - Known deep vein thrombosis (DVT) within 6 months of study day 1 (with the exception of portal vein thrombosis).
    - Significant arrhythmia or electrophysiologic disease including placement of implantable cardioverter defibrillator (ICD), atrial fibrillation with uncontrolled rate or prolonged QTc interval > 450 ms.
    - Uncontrolled hypertension defined as systolic blood pressure (BP) ≥ 150 mm Hg or diastolic BP ≥ 95 mm Hg. Patients with a history of hypertension must be

well-controlled (BP ≤ 150/90 mmHg) upon study entry using a stable regimen of anti-hypertensive therapy.

14. Clinically significant active pulmonary risk including pulmonary hypertension and pulmonary edema within 12 months of study day 1 or pulmonary embolism within 6 months of study day 1.
15. Known CNS metastasis.
16. Known active GI bleeding, as evidenced by hematemesis, hematochezia, or melena within 3 months prior to study day 1 without evidence of resolution documented by endoscopy or colonoscopy.
17. Known bleeding diathesis including clinically significant platelet disorders or active hemoptysis defined as bright red blood of ≥ 1/2 teaspoon (2.5 mL) in any 24 hour period within 6 months prior to study day 1. For clinically significant epistaxis within 4 weeks prior to study day 1, no risk of further bleeding must be clearly documented.
18. Known history of hereditary hemorrhagic telangiectasia (HHT).
19. History of another primary cancer, with the exception of:
    - Curatively resected non-melanoma skin cancer.
    - Curatively treated cervical carcinoma in situ.
    - Other primary solid tumor with no known active disease in the opinion of the investigator that will not affect patient outcome in the setting of current HCC diagnosis.
20. Major surgery within 4 weeks prior to study day 1. Patients must have recovered completely from any previous surgery prior to study day 1.
21. Active infection requiring parenteral antibiotic therapy within 1 month prior to study day 1 or systemic antibiotics within 2 weeks of study day 1.
22. Anti-coagulation therapy (e.g., clopidogrel, dabigatran, warfarin, and heparin) or prophylactic aspirin > 81 mg within one week prior to study day 1. Low dose aspirin (≤ 81 mg) for cardiovascular prophylaxis is permitted unless the investigator deems the patient is at a significant risk for bleeding.
23. Concomitant treatment with potent CYP3A4 inducers (carbamazepine, dexamethasone, felbamate, omeprazole, phenobarbital, phenytoin, amobarbital, nevirapine, primidone, rifabutin, rifampin, St. John's wort) is not allowed and should be discontinued 2 weeks prior to study day 1.
24. Persistent peripheral edema within 2 weeks prior to study day 1.
25. History of recurrent ascites requiring paracentesis within 4 weeks of study day 1.
26. History of severe (defined as ≥ grade 3, using the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 4.0 [NCI-CTCAE] v4 (Appendix 6) current minor version) allergic or anaphylactic reaction or hypersensitivity to recombinant proteins or excipients (10 mM Tris buffered saline) in the investigational agent.

27. Pregnant or lactating female patients.

10.4. Patient Withdrawal Criteria

Patients will be informed that they have the right to withdraw from study treatment or from the study at any time for any reason without prejudice to their medical care.

Patients may be withdrawn from study treatment for any of the following reasons:

- Patient's request
- Patient's unwillingness or inability to comply with the protocol
- Withdrawal of consent
- Pregnancy
- Progression of disease
- Use of prohibited medications
- Medical reason, at the discretion of the investigator and/or the medical monitor
- At the discretion of the sponsor (i.e. discontinuation of the study)

In addition, patients may be withdrawn from the study for any of the following reasons:

- Death
- Lost to follow-up
- Withdrawal of consent
- At the discretion of the sponsor (i.e. discontinuation of the study)

The reasons for withdrawal must be recorded in the patient's CRF. The investigator must notify the sponsor, the medical monitor and the contract research organization (CRO) immediately when a patient has been discontinued/withdrawn due to an Adverse Event (AE).

The investigator must notify the sponsor and the CRO when a patient has been discontinued/withdrawn for reasons unrelated to the study or study drug (i.e., withdrawn consent, lost to follow-up).

10.5. Patient Replacement Criteria

Patients who discontinue prematurely from the study for reasons unrelated to the study or dalantercept (e.g., withdrawn consent) and prior to C2D1 may be replaced at the Sponsor's discretion as required for the study to meet its objectives. Data from the patients who are replaced will continue to be evaluated for safety.

11. TREATMENT OF PATIENTS

11.1. Treatments Administered

Once a patient is assigned to a cohort, the appropriate dose of dalantercept will be administered on study day 1 with the starting dose of sorafenib. Subsequent dalantercept doses will be administered once every 3 weeks with safety follow-up visits after each dose as outlined in the Schedule of Events (Section 2). Patients should be observed for a minimum of 30 minutes following treatment with dalantercept.

Patients will administer daily dosing of sorafenib, dispensed as per prescribing information (see Nexavar® [sorafenib] prescribing information, *Dosage and Administration*).

Dose reductions for dalantercept or sorafenib may be required (see Section 11.5, Dose Modifications).

11.1.1. Continuation of Treatment

11.1.2. Progressive Disease

Accumulating evidence indicates that the emergence of objective responses to anti-angiogenesis agents may follow delayed kinetics of weeks or months, and may be preceded by initial apparent radiological progression. It is thus reasonable, in the absence of clinical deterioration, to continue to treat these patients until radiologic progression is both confirmed and found to have worsened at a subsequent imaging evaluation.[23]

The initial tumor response assessment for all patients will occur prior to the C3D1 dosing visit. The decision to treat a patient with additional cycles of sorafenib plus dalantercept will be based on tumor response evaluation performed every 2 treatment cycles, prior to Day 1 of the next cycle. After cycle 14, tumor response evaluation will be performed every 4 treatment cycles. Patients with PD per RECIST v1.1 should be managed as follows:

- PD at the end of Cycle 2: At the discretion of the treating physician in consultation with the sponsor medical monitor, the patient may continue dosing with the combination in the absence of clinical progression and the lack of any new measurable disease.
- PD at the end of Cycle 4 or later: If there is worsening PD (e.g., increase in target lesions, increase in non-target lesions, development of new lesions) in comparison to the end of Cycle 2 imaging, treatment will be discontinued and the patient will complete the final visit and enter follow-up.

11.2. Concomitant Medications

During screening and throughout the study, patients may take stable doses of medications for chronic conditions that are not specifically excluded by the protocol (see Section 10.3.1, Inclusion Criteria and Section 10.3.2, Exclusion Criteria). Concomitant medications will be documented at all study visits beginning at screening and will include all medications taken within 28 days prior to study day 1.

- During the course of the study, concurrent therapy with any new prescription medication or dosage may be administered at the discretion of the investigator based upon clinical need. If a patient requires treatment with any new medications that are specifically excluded by the eligibility criteria (Section 10.3.1, 10.3.2) or the sorafenib prescribing label (e.g., therapeutic anticoagulation medication, strong CYP3A4/5 inhibitors, strong CYP3A4/5 inducers, and any anti-cancer treatment other than dalantercept or sorafenib), the patient will be discontinued from the study. These patients should complete the final visit procedures and enter the follow-up period of the study. The investigator should consult the medical monitor regarding any questions about whether a new medication or the dosage of an existing medication would require the patient to discontinue from the study. Note that treatment with diuretics is expected for some patients during this study and such use should not be used to determine grading of hypertension.

11.3. Randomization

This is an open-label dose escalation study that does not require randomization.

11.4. Treatment Compliance

Each dose of dalantercept will be administered by SC injection(s) at the clinical site by the study staff and will be documented in the study record.

Daily dosing of sorafenib will be the responsibility of each patient. Drug accountability will be performed at each study visit by the study staff and recorded in the patient's study record.

11.5. Dose Modifications

11.5.1. Dose Modifications of Dalantercept

Patients will continue to receive the same dose level of dalantercept as they were assigned at study entry unless a dose modification is required to manage AEs. Patients who experience dalantercept related AEs may continue treatment with dalantercept, provided that the AE can be managed (see below).

Table 3 describes the management of related AEs and required dose modifications for dalantercept. For any AE, including AEs not specifically mentioned in the table below, the investigator may decide to delay dosing or modify the dose level of dalantercept based on their clinical judgment. If possible, these decisions should be discussed with the sponsor medical monitor prior to implementation. If more than 1 AE occurs that would require a dose modification, upon resolution of all AEs to baseline or grade 1, dalantercept should be reduced two dose levels, or the patient should discontinue treatment. If a patient has a repeating AE or an AE of similar nature that would require a dose modification, the patient should be dose reduced to the next dose level or the patient should discontinue treatment depending upon the nature of the AE and patient status. The guidelines for management of AEs described in Table 3 are applicable to all scheduled visits as well as any unscheduled visits. Refer to Table 4, Dalantercept Dose Level Modifications, for dose level reductions.

A dose delay of up to 3 weeks for dalantercept will be allowed for all AEs as outlined in Table 3. Adverse events must resolve as outlined in Table 3 prior to further dosing. If a dose is delayed, the patient should resume the study with the next scheduled dosing cycle.

If administration of dalantercept cannot be resumed within 3 weeks after the scheduled start of the next treatment cycle, the patient must be discontinued from the study and should complete the Final Visit. Exemptions may be considered for those patients who are determined by the investigator to have received clinical benefit from treatment.

For individual patients judged by the investigator to be at an unacceptable risk, despite not meeting the protocol-defined conditions for a dose modification, the investigator should consult with the sponsor's medical monitor to decide whether to continue dosing at the same dose level, reduce the dose level, or discontinue the patient's treatment with dalantercept.

Table 3: Management of Adverse Events Related to Dalantercept

Adverse Event or Abnormal Finding	Action	Dalantercept Dose Modification
Weight/Peripheral Edema Events[a] – If there is weight gain due to fluid retention or edema follow the weight management guidelines below. If a weight event occurs that is related to ascites, follow management of ascites guidelines below. Weight gain due to improvement in health, is not considered an adverse event or abnormal finding.		
1. ≥ 3 to < 5% increase in weight from baseline or grade 1 peripheral edema	• Administer therapy[a] as needed to maintain approximate baseline weight or to reduce edema • Hold dalantercept treatment until weight returns to baseline (< 3% increase) or edema resolves	1. Upon normalization of weight or resolution of edema, dalantercept should be restarted at the same dose level.
2. ≥ 5 to < 10% increase in weight from baseline (Grade 1) or grade 2 peripheral edema		2. Upon normalization of weight or resolution of edema, dalantercept should be reduced one dose level.
3. ≥ 10% increase in weight from baseline (≥ Grade 2) or grade 3 peripheral edema	• Administer therapy[a] as needed to maintain approximate baseline weight or to reduce edema • Hold dalantercept treatment until weight returns to baseline (< 3% increase) or edema resolves • A complete cardiac evaluation including ECG, ECHO and any applicable laboratory tests should be performed if determined to be clinically indicated.	3. Upon normalization of weight or normalization of edema, dalantercept should be reduced two dose levels.
Pulmonary Events		
1. A new onset of signs or symptoms of pulmonary edema (Grade 1). Signs and symptoms include but are not limited to shortness of breath, coughing up blood, end-inspiratory crackles, etc.	• Administer therapy[a] as needed. • Hold dalantercept treatment until resolution of AE(s).	1. Upon resolution of AE(s), dalantercept should be reduced one dose level.
2. ≥ Grade 2 pulmonary edema	• Administer therapy[a] as needed. • Hold dalantercept treatment until resolution of AE(s). • A complete cardiac evaluation including, ECG, ECHO and any applicable laboratory tests should be performed if determined to be clinically necessary.	2. Upon resolution of AE(s), dalantercept should be reduced two dose levels.
3. Grade 1 pleural effusion	• Administer therapy as needed.	3. Reduce dalantercept one dose level.
4. ≥ Grade 2 pleural effusion	• Administer therapy as needed. • Hold dalantercept treatment until resolution of AE to ≤ Grade 1.	4. Upon resolution of AE, dalantercept should be reduced two dose levels.
Cardiovascular Events		
1. Grade 2 ejection fraction decreased	• Administer therapy as needed. • Hold dalantercept treatment until resolution of AE(s) or improvement of EF > 50%. • A cardiac evaluation including ECHO should be performed prior to starting next cycle.	1. Upon resolution of AE(s) or improvement of EF > 50% dalantercept should be reduced one dose level and continue to follow repeat ECHO if determined to be clinically necessary.

Adverse Event or Abnormal Finding	Action	Dalantercept Dose Modification
2. Grade 2 pericardial effusion detected on imaging	• Administer therapy as needed. • Hold dalantercept treatment and repeat ECHO in three weeks.	2. If stable or resolved on repeat ECHO, reduce dalantercept one dose level. If worsened, discontinue dalantercept.
3. ≥ Grade 3 cardiovascular event[b] including grade 3 pericardial effusion detected on ECHO	• Discontinue further dalantercept treatment.	
Other Events		
1. ≥ Grade 2 bleeding event, with the exception of Grade 2 epistaxis	• Discontinue further dalantercept treatment.	
2. Any other event ≥ Grade 3 with the exception of ≥ Grade 3 amylase and/or lipase or Grade 3 hyponatremia in the absence of clinical symptoms	• Hold dalantercept treatment until resolution of AE(s).	2. Upon resolution of AE(s) to grade 1 or baseline, dalantercept should be reduced one dose level.
3. Grade 2 ascites: symptomatic, medical intervention indicated	• If first occurrence of ascites, proceed with paracentesis at the discretion of the investigator.	3. Upon resolution to at least grade 1, continue current dose of dalantercept.
	• If second occurrence of ascites, proceed with paracentesis at investigator discretion.	3. Upon resolution to at least grade 1, dalantercept should be reduced one dose level.
	• > 2 occurrences, proceed with paracentesis at investigator discretion.	3. Upon resolution to at least grade 1, reduce dalantercept one dose level with each additional occurrence.
4. Grade 3 ascites	• If first occurrence of ascites, proceed with paracentesis.	4. Upon resolution to at least grade 1, reduce dalantercept one dose level.
	• If second occurrence of ascites, proceed with paracentesis.	4. Upon resolution to at least grade 1, dalantercept should be reduced two dose levels.
	• > 2 occurrences, proceed with paracentesis.	4. Discontinue further dalantercept treatment.

[a] Investigators can administer fluid management therapy as described in Section 11.5.3
[b] Note that treatment with diuretics is expected for some patients during this study and should not be used to determine grading of hypertension.

Patients are allowed up to 3 dose modifications of approximately 25% each (Table 4) due to AEs.

Table 4: Dalantercept Dose Level Modifications[1]

Dose Modification[a]	Cohort 1 (mg/kg)	Cohorts 2 and 3 (mg/kg)
Starting dose level	0.6 mg/kg	0.9 mg/kg
First dose reduction level	0.45 mg/kg	0.65 mg/kg
Second dose reduction level	0.35 mg/kg	0.50 mg/kg
Third dose reduction level	0.25 mg/kg	0.40 mg/kg
Fourth dose reduction level	Discontinue dalantercept treatment	

[a] If the starting dose level is de-escalated to 0.4 mg/kg, the dose modification levels will be 0.3 mg/kg, 0.2 mg/kg and 0.15 mg/kg.

11.5.2. Dose Modifications of Sorafenib

Patients enrolled in cohort 1 and 2 may have their dose of sorafenib increased to 400 mg BID, after the sponsor and the principal investigator have conducted a complete review of the individual patient's safety data through Day 43 and the first on-study tumor assessment is evaluated.

Over the course of treatment and at the discretion of the investigator, management of some adverse events such as hypertension, venous or arterial thromboembolic events, hemorrhage, gastric perforation or fistula, and proteinuria may require temporary dose interruption or permanent discontinuation and/or dose reduction of sorafenib (see Nexavar® [sorafenib] prescribing information, *Warnings and Precautions*). If dose reduction from 400 mg BID is required, the recommended reduced dose is 400 mg QD or QOD. Please refer to the labeling guidelines on the management of sorafenib related hand-foot skin reaction.

In the event of a Grade 3 or greater toxicity, if it is deemed at the investigator's discretion to be related to sorafenib, then sorafenib may be held or dose reduced until resolution of the toxicity or return to Grade 1 or baseline in keeping with the current labeling guidelines.

Patients who require permanent discontinuation of sorafenib due to an adverse event related only to sorafenib may continue to receive treatment with dalantercept. If patients requiring discontinuation of sorafenib have received < 2 doses of dalantercept plus sorafenib, they may be replaced (see Section 10.5). The patients remaining on dalantercept not in combination with sorafenib will continue to follow the regular schedule of events (Section 2).

11.5.3. Fluid Management Therapy

11.5.3.1. Diuretics

Use of diuretics is allowed to maintain approximate baseline weight in the instance of weight gain related to fluid events as described in Table 3. Note that treatment with diuretics is expected for some patients during this study and such use should not be used to determine

grading of hypertension. For ascites events that are deemed to be related to dalantercept, follow Table 3 outlining management of ascites.

11.6. Safety Review Team (SRT)

11.6.1. Dose-Limiting Toxicity (DLT) Definition

A DLT is defined as any of the following events that are considered possibly or probably related to dalantercept and occur within 21 days after the first dose of dalantercept/sorafenib (Day 22):

- Recurrent Grade 3 ascites event in a single patient despite optimal management of first event
- Pulmonary edema grade 2 or higher
- Bleeding grade 2 or higher with the exception of grade 2 epistaxis
- Non-hematologic adverse event grade 3 or higher with the exception of grade 3 or higher amylase, lipase or grade 3 hyponatremia without symptoms, and grade 3 nausea, vomiting, or diarrhea in the absence of appropriate prophylaxis
- Grade 3 thrombocytopenia with associated bleeding
- Grade 4 anemia or thrombocytopenia
- Grade 4 neutropenia with fever

Safety and DLTs will be evaluated by the SRT. The SRT, which is comprised of a minimum of one study investigator, a Sponsor medical monitor, and a clinical investigator not participating in this study, will review safety data including AEs and serious adverse events (SAEs), laboratory results (including hematology and chemistry), and vital signs data through the Day 22 visit to assess the safety of a dose level prior to dose escalation.

After a minimum of 3 patients have been evaluated for a minimum of 21 days after the first dose of dalantercept/sorafenib (Day 22), the SRT will consider dose escalation to the next dose cohort or adding additional patients, for a total of up to 6 patients, to the current dose cohort based in part upon the following dose escalation criteria:

- If there are no DLTs, dose escalation to the subsequent dose level may proceed.
- If 1 patient at a dose level experiences a DLT, additional patients may be enrolled at the current dose level for a total of up to 6 patients in the cohort.
    - If there are no further DLTs in the additional patients, dose escalation to the next dose level may proceed.
- If a DLT occurs in ≥ 2 patients in any dose cohort of 3-6 patients, no further dose escalation will occur and a previous or lower intermediate dose level will be defined as the MTD. Patients enrolled in this dose level cohort may continue to receive additional doses of dalantercept plus sorafenib at an appropriate dose level as outlined in Table 2.

11.6.2. Expansion Cohort

Once the MTD or maximum tested dose level has been determined by the SRT and Sponsor, up to a total of 20 patients may be enrolled at or below the MTD to further evaluate the safety, tolerability, and PK profile of dalantercept plus sorafenib. The SRT will meet after a minimum of 10 patients have been evaluated for a minimum of 21 days after the first dose of dalantercept/sorafenib (Day 22) to review safety data. The SRT may recommend adding up to an additional 10 patients to the current dose level for further evaluation or to an intermediate dose level.

If 4 out of 10 patients in the expansion cohort experience a DLT at any time during the first 21 days after the first dose of dalantercept/sorafenib (Day 22) further enrollment in that expansion cohort will be discontinued. The SRT may decide to cease enrollment if fewer than 4 out of 10 patients experience a DLT if the nature of the event(s) is deemed a significant risk to patients for that dose level. The next lower or an intermediate dose level may be recommended to enroll up to an additional 10 patients for assessment of safety following the same stopping rules.

12. STUDY PROCEDURES

Please refer to Section 2, Schedule of Events for the schedule of procedures required for each visit.

12.1. Written Informed Consent

Patients will be required to sign an IRB/Independent Ethics Committee (IEC)-approved ICF prior to any study related procedures, including screening evaluations.

12.2. Safety Assessments

12.2.1. Clinical Laboratory Tests

- Chemistry: Albumin, alkaline phosphatase (ALP), ALT, AST, blood urea nitrogen (BUN), calcium, chloride, carbon dioxide (CO_2), creatinine, glucose, lactate dehydrogenase (LDH), serum osmolality, phosphorus, potassium, sodium, total bilirubin, total protein, amylase, and lipase.
- Hematology: Complete blood count (CBC) with differential and reticulocyte count; CBC includes red blood cells (RBCs), white blood cells (WBCs), platelets, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).
- Coagulation: PT, INR
- Thyroid Function: Free thyroxine (T_4) and thyroid stimulating hormone (TSH).
- Urine tests by dipstick or urinalysis: pH, specific gravity, protein, glucose, ketones, blood, leukocyte esterase, and nitrite with microscopic examination if indicated. Urine Chemistry to include osmolality and sodium.
- Alpha-fetoprotein (AFP)

12.2.2. Other Safety Assessments

Specific details regarding any testing to be performed by a central laboratory for this study will be located in the Study Reference Guide.

- Physical examination: Full exam [skin (including telangiectasias, head, eyes, ears, nose, throat and neck, lymph nodes, cardiovascular, respiratory, gastrointestinal, musculoskeletal (including edema), and neurological] required at screening, Cycle 1 Day 1 (C1D1), C1D8, C2D1, C3D1, C4D1, C5D1, C6D1, and the final visit. A targeted exam [respiratory, cardiovascular and musculoskeletal (including edema) body systems] is required at all other visits beyond cycle 6 unless additional assessments are clinically indicated. Findings at screening will be recorded on the medical history form. Findings after C1D1 dosing will be recorded as AEs.
- Vital signs: Including height, weight, systolic and diastolic BP, heart rate. Height will be collected at screening only.

- Cardiac function testing: 12-lead ECG and ECHO scan (Ejection Fraction and presence or absence of pericardial effusion).
- Anti-drug antibody and neutralizing antibody testing: As indicated.

12.3. Pharmacokinetic, Pharmacodynamic Assessments and Biopsies

Specific details regarding these assessments will be located in the Study Reference Guide.

12.3.1. Pharmacokinetic Assessments

Blood will be collected as outlined in the Schedule of Events (Section 2) to assess serum levels of dalantercept and sorafenib.

12.3.2. Pharmacodynamic Blood Biomarkers

Blood will be collected as outlined in the Schedule of Events (Section 2) to assess blood levels of PD biomarkers.

12.3.3. Tumor Biopsy

Patients will provide a sample of recent or archived biopsy of tumor tissue. These recent or archived biopsies will be analyzed for expression of BMP9/10, ALK1 and other relevant markers.

12.4. Tumor Response Assessment

12.4.1. Tumor Assessments

CT or MRI scans will be read at the investigational site and treatment response and disease progression will be assessed using RECIST v1.1 (Appendix 2). Using local investigator assessments, it should be determined that a patient has not progressed before the next cycle study treatment is given unless continued treatment through first radiographic progression is justified (see Section 11.1.2).

13. STUDY SCHEDULE

Please refer to Section 2, Schedule of Events for the schedule of procedures required for each visit. All visit day windows should be determined relative to the date of the previous dose of dalantercept. Actual visit days (e.g., day 1, day 8, day 15) may be different than planned due to windows on visits and potential dosing delays.

13.1. Screening

Signature of the current IRB-approved ICF should occur within 28 days prior to study day 1 and prior to initiation of any study-specific screening procedures.

- All screening procedures should be performed within 14 days prior to study day 1. Echocardiogram and tumor response assessment scans obtained for clinical purposes within 28 days prior to study day 1 may be used as the baseline image for this study and do not need to be repeated.
- The urine or blood pregnancy test is only required for patients of child-bearing potential.
- Archived or recent tumor tissue sample(s) should be sent as soon as possible to the designated tissue sample vendor.
- Concomitant medications taken within 28 days prior to study day 1 will be documented in CRF.
- Screen failure information will be maintained to document specific information, including but not limited to, reason for failure.

13.2. Dosing Days and Interim Visits

- All screening and study day 1 procedure results required to confirm eligibility must be obtained and reviewed prior to dalantercept and sorafenib administration. Patient eligibility for inclusion/exclusion criteria must be confirmed from these results, as applicable.
- Baseline hematology, chemistry, coagulation and urinalysis may be collected up to 72 hours prior to dosing. If the screening visit occurs within 72 hours of study day 1, the hematology, chemistry, coagulation and urinalysis testing do not need to be repeated.
- Any non-serious AEs that occur prior to dalantercept and sorafenib dosing on study day 1 should be recorded in the medical history CRF.
- All AEs that occur after dalantercept and sorafenib dosing on study day 1 should be recorded in the AE CRF.
- On subsequent dosing days, all AEs and abnormal laboratory or other findings that might require modification of dosing (see Section 11.5) should be reviewed prior to dosing to ensure that the patient is still eligible to receive additional doses of dalantercept or sorafenib.

- ECHO scans may be performed up to 5 days prior to a scheduled visit.
- Tumor response assessment scans may be performed up to 5 days prior to a scheduled visit (except screening and final visit which have wider windows). Tumor response assessment scans must be reviewed prior to dosing the next cycle of treatment. Tumor response assessment scans should be performed every 6 weeks regardless of dalantercept or sorafenib dosing delays.
- PK blood sample collection should be performed pre-dose for dalantercept and sorafenib at all time points. In addition, PK blood samples should be collected between 1-3 hours and 4-6 hours post dalantercept and sorafenib dosing at C1D1 and between 1-3 hours and 4-6 hours post sorafenib dosing at C2D8 visit.
- The schedule of events outlines procedures through C6D1. If patients have stable or responding disease and are able to continue beyond 6 cycles of treatment, the procedures outlined for cycle 5 and 6 should be repeated until the patient completes cycle 14 (i.e. C7D1=C5D1, C8D1=C6D1, etc.). The only exception is that after cycle 6, ADA and urinalysis are required once every 4 cycles instead of once every 2 cycles (i.e., C10D1, C14D1, etc.).
- If the patient has stable or responding disease at the end of 14 cycles of treatment, the procedures outlined for cycles 15 and 16 should be repeated until the patient comes off study. Note: ADA collection continues on a schedule of once every 4 cycles starting at cycle 6 and tumor response scans only need to be repeated once every 4 cycles (C19D1, C23D1, C27D1 etc.) starting at cycle 15.

13.2.1. Final Visit

- The final visit should occur when a patient discontinues from the study within 30 days after the last dose of dalantercept (± 10 days).
- The tumor response assessment scan does not need to be repeated at the final visit to assess progression if progression of disease was confirmed by a previous tumor response assessment scan.
- If the patient has a positive ADA result at their last assessment, the patient may be asked to return approximately every 3 months for additional testing until a negative result is obtained, or the result is considered stabilized.

13.2.2. Follow-up

- After the final visit, patients will be contacted by phone or other appropriate method of communication approximately every 3 months (±2 weeks) for up to 1 year from date of first dose for survival.
- Patients may also be asked to return to the clinic approximately once every 3 months for tumor response assessment scans if progression of disease has not previously been documented and/or every 3 months for additional ADA testing until a negative/stable result is obtained.

13.3. Discontinuation of Study

The sponsor may terminate this study or a dose level after consultation with the investigator, the SRT, or at any time for safety or administrative reasons. The sponsor will terminate the study if the occurrence of SAEs or other findings suggests unacceptable risk to the health of the patients.

14. STUDY DRUG MATERIALS AND MANAGEMENT

14.1. Study Drug

Dalantercept is a recombinant fusion protein consisting of the extracellular domain (ECD) of human activin receptor-like kinase 1 (ALK1) linked to the Fc (hinge, CH2 and CH3 domains) portion of human immunoglobulin G1 (IgG1).

14.2. Study Drug Packaging and Labeling

Dalantercept is supplied as a frozen liquid formulation at a concentration of 50 mg/mL in 10 mM Tris buffered saline (pH 7.5 ± 0.5) in 2 mL clear glass vials containing 1 mL of dalantercept.

Please refer to the Nexavar® (sorafenib) prescribing information, *Dosage and Administration*, for how sorafenib is supplied.

14.3. Study Drug Storage

Dalantercept should be stored at ≤ -65°C.

Sorafenib should be stored at 25°C (77°F) in a dry place; excursions permitted to 15-30°C (59-86°F).

14.4. Study Drug Preparation

Please refer to the Study Reference Guide for detailed dalantercept drug handling, administration, and storage instructions.

There is no preparation needed for sorafenib.

14.5. Administration

Dalantercept is to be administered by SC injection. Each injection will not exceed 1.5 mL; multiple injections may be required to administer the required dose. Each injection should be administered in alternating patterns in the upper and lower extremity regions. Please refer to the Study Reference Guide for detailed dalantercept drug handling, administration, and storage instructions.

Sorafenib is to be administered PO and is available in a 200 mg tablet formulation. Please refer to the Nexavar® (sorafenib) prescribing information, *Dosage and Administration*, for additional sorafenib administration information.

14.6. Study Drug Accountability

Accountability for dalantercept and sorafenib is the responsibility of the investigator.

Investigational clinical supplies must be received by a designated person at the clinical site and kept in a secured location. The investigational site must maintain accurate records demonstrating dates and amounts of dalantercept received, to whom it was dispensed (patient-by-patient accounting), and accounts of any dalantercept accidentally or deliberately destroyed or returned.

When possible all vials of dalantercept, both used and unused, should be saved for drug accountability purposes. The used vials may be discarded, per the institution's standard practice, after drug accountability assessment has been completed by the monitor. If this method of drug accountability does not follow the institution's standard practice, then the plans for performing accurate drug accountability should be documented and followed per institution. The investigational site must maintain accurate records documenting sorafenib accountability.

14.7. Study Drug Handling and Disposal

Please refer to the Study Reference Guide for detailed dalantercept drug handling, administration, storage, and disposal instructions.

Please refer to the prescribing information for Nexavar® (sorafenib), *How Supplied/Storage and Handling* for detailed drug handling, administration, storage, and disposal instructions.

15. ASSESSMENT OF SAFETY

15.1. Adverse Event Definitions

Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a study drug, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug whether or not it is considered related to the study drug.

Abnormal laboratory and other abnormal investigational findings (i.e., physical exam, ECG) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation or are otherwise considered clinically relevant by the investigator. In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself. In case of a fatality, the cause of death is considered as the AE, and the death is considered as its outcome.

Unexpected Adverse Events

An unexpected AE is an AE that is not described in nature or severity in the IB.

Events Not to Be Considered as Adverse Events

Pre-existing medical conditions/signs/symptoms present before the screening period that do not worsen in severity or frequency during the study are defined as baseline medical conditions, and are not to be considered AEs.

Serious Adverse Event

A SAE is any AE, occurring at any dose level/regimen and regardless of causality that:

- Results in death.
- Is life-threatening: life-threatening means that the patient was at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form).
- Requires inpatient hospitalization or prolongation of existing hospitalization; however a hospitalization for an elective procedure will not be considered a SAE.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is an important medical event: an important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at

home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events Not to Be Considered as Serious Adverse Events

Elective hospitalizations to administer or to simplify study treatment or procedures are not considered as SAEs.

15.2. Pregnancy and In Utero Drug Exposure

The investigator will attempt to collect pregnancy information if a female patient or a male patient's female partner becomes pregnant while the patient is participating in this study. The pregnancy information will be recorded on the appropriate form and must be submitted to the sponsor within 2 weeks of learning of the pregnancy. The patient or partner will be followed for the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor or designee. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

15.3. Severity

Investigators must evaluate the severity/intensity of AEs according to the NCI-CTCAE v4 current minor version, preferentially using the graded scales. If a particular AE's severity/intensity is not specifically graded, the investigator should apply the general guidelines for determination of Grade 1 through Grade 5 as listed in the NCI-CTCAE v4 current minor version, cover page (reproduced below), using their best medical judgment:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

15.4. Relationship to Study Drug

Investigators must also assess the causal relationship of each AE to dalantercept and sorafenib. Factors for the assessment of causal relationship include, but are not limited to, temporal relationship between the AE and the administration of dalantercept or sorafenib, known side effects of dalantercept or sorafenib, medical history, concomitant therapy, course of the underlying disease and pertinent study procedures.

Probably: A causal relationship is clinically/biologically highly plausible and there is a plausible time sequence between onset of the AE and administration of dalantercept or sorafenib and there is a reasonable response on withdrawal.

Possibly: A causal relationship is clinically/biologically plausible and there is a plausible time sequence between onset of the AE and administration of dalantercept or sorafenib.

Unlikely: A causal relationship is improbable and another documented cause of the AE is most plausible.

Not Related: A causal relationship can be definitively excluded and another documented cause of the AE is most plausible.

15.5. Documentation and Methods of Reporting of Adverse Events by Investigator

Patients will be evaluated and questioned generally for AEs during the course of the study, starting at the signing of the informed consent. All non-serious AEs occurring after signing of the ICF until a patient is dosed on C1D1 are to be documented on the medical history CRF. All AEs occurring after the C1D1 dose through 30 days after the last study drug administration (final visit) are to be documented on the AE CRF.

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded on the AE CRF. Any clinically relevant changes in laboratory assessments, or other clinical findings as described in Section 15.1, are considered AEs and must be recorded on the AE CRF. AEs are to be followed for resolution as described in Section 15.6.

It is important that each AE report include a description of the event, duration (onset and resolution dates), severity, relationship with dalantercept, relationship with sorafenib, any other potential causal factors, any treatment given or other action taken (including dose modification or discontinuation of dalantercept or sorafenib) and outcome. In addition, SAEs should be identified and the appropriate seriousness criteria documented. Adverse events categorized as SAEs must also be documented using an SAE Report Form as described in Section 15.5.1.

Specific guidance can be found in the CRF Completion Guidelines provided by the sponsor or designee.

15.5.1. Documentation of Serious Adverse Events

All SAEs that occur after the first study drug administration on C1D1 until 30 days (final visit) after the last study drug administration are to be documented on the AE CRF. SAEs should not be reported for patients who are considered screen failures unless the event is deemed due to a protocol required procedure. For all SAEs, an SAE form must be completed with as much information as possible and submitted within the time frame described in Section 15.7 (Notification about Serious Adverse Events).

When new significant information is obtained as well as when the outcome of an event is known, the investigator should record the information on a new SAE form.

If the patient was hospitalized, a copy of the discharge summary must be included as part of the patient medical file. In all instances, the investigator should follow-up with patients until the outcome of the SAE is known.

15.6. Reporting Period and Monitoring of Patients with Adverse Events

All patients who took at least one dose of study drug should complete the final visit procedures. All AEs will be followed until clinical database lock (or stabilization/resolution if it occurs before database lock). All SAEs will undergo active follow-up until resolved or the event becomes chronic or stable. Follow-up data for SAEs obtained after clinical database lock will be incorporated into the dalantercept safety database.

15.7. Notification about Serious Adverse Events

If an SAE occurs during the reporting period, the investigator must immediately (i.e. within a maximum 24 hours after becoming aware of the event) inform the sponsor via the CRO by telephone, by fax or by e-mail.

All written reports should be transmitted using the study specific SAE Report Form, which must be completed by the investigator following specific completion instructions. Names, addresses, telephone and fax numbers for SAE reporting are located on the SAE Report Form and in the completion instructions provided in the Study Reference Manual. When an SAE (or follow-up information) is reported by telephone, a written report must be sent immediately thereafter by fax or e-mail. Reporting procedures and timelines for follow-up information are the same as for the initially reported SAE.

Relevant pages from the CRF may be provided in parallel (i.e., medical history, concomitant therapy). In all cases, the information provided in the SAE Report Form must be consistent with the data that are recorded in the corresponding sections of the CRF.

The investigator/reporter must respond to any request for follow-up information or to any question the sponsor or designee may have on the SAE within the same timelines as described for initial reports. This is necessary to permit a prompt assessment of the event by the sponsor and (as applicable) to allow the sponsor to meet regulatory timelines associated with expedited reporting obligations.

Requests for follow-up will usually be made by the responsible CRA or Medical Monitor, or in exceptional circumstances by the Acceleron or CRO Pharmacovigilance representative who may contact the investigator directly to obtain clarification on a particularly critical event.

15.7.1. Safety Reporting to Health Authorities, Independent Ethics Committees Institutional Review Boards and Investigators

The sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The investigator must comply with any applicable site-specific requirements related to the reporting of SAEs involving his/her patients to the IEC/IRB that approved the study.

In accordance with ICH/GCP guidelines, the sponsor will inform the investigator of "findings that could adversely affect the safety of patients, impact the conduct of the study, or alter the IRB's approval/favorable opinion to continue the study."

The sponsor will inform the investigator of AEs that are both serious and unexpected and are considered to be related to dalantercept ("suspected unexpected serious adverse reactions" or SUSARs). The investigator should place copies of these Safety Reports in the Investigator Site File. National regulations with regard to Safety Report notifications to investigators will be followed.

When specifically required by regulations and guidelines, the sponsor will provide appropriate Safety Reports directly to each site who is responsible for notifying their IRB and will maintain records of these notifications. When direct reporting by the sponsor is not clearly defined by national or site-specific regulations, the investigator will be responsible for promptly notifying the concerned IRB of any Safety Reports and for filing copies of all related correspondence in the Investigator Site File.

For studies covered by the European Union Clinical Trials Directive 2001/20/EC, the sponsor's responsibilities regarding the reporting of SAEs/SUSARs will be carried out in accordance with that Directive and with the related Detailed Guidances.

16. STATISTICS

16.1. Analysis Populations

The Safety Analysis Set (SAF) will be used for all safety analyses and will consist of all patients who received any study drug.

The Pharmacokinetics (PK) population will consist of all patients who have received at least 1 dose of dalantercept plus sorafenib and have sufficient PK samples collected and assayed.

16.2. Statistical Plan

Details regarding the final data analysis will be discussed in a separate Statistical Analysis Plan (SAP).

16.3. Safety Analysis

The safety analyses will be performed on the SAF population. Adverse event incidence rates will be tabulated by System Organ Class and preferred term and without regard to causality. The frequency of occurrence of overall toxicity, categorized by toxicity grades, will be summarized. Shift tables and change from baseline will be summarized by analyte for laboratory panels. Treatment-emergent laboratory findings will be summarized. Change from baseline and shift tables may be presented for vital sign and ECG parameters.

16.4. Activity Analysis

Response to treatment with dalantercept plus sorafenib will be determined according to RECIST v1.1 (Appendix 2) evaluating response rates, time to progression (TTP), progression free survival (PFS), disease control rate (DCR), and overall survival (OS). Patients will be assessed for efficacy using data from tumor response assessments as well as evaluation of PD biomarkers in tissue and blood.

16.5. Pharmacokinetics Analysis

PK parameters, including but not limited to AUC, maximum concentration (C_{max}), time to maximum concentration (t_{max}), elimination half-life ($t_{½}$), apparent clearance (CL/F), and volume of distribution (Vz/F) will be assessed. Additional analyses to explore the exposure/safety relationship of this combination may be performed. For all PK analysis, the PK population will be used.

16.6. Determination of Sample Size

There is no formal sample size calculation for this study. A standard dose escalation of 3-6 patients will be implemented for dose escalation and up to 20 patients may be enrolled in the expansion to further evaluate safety, tolerability, and PK profile of the combination of dalantercept and sorafenib based on clinical considerations.

16.7. Interim Analysis

There are no planned interim analyses.

16.8. Deviation from Original Analysis Plan

A formal SAP for the analysis and presentation of data from this study will be prepared before database lock. Deviations from the statistical analyses outlined in this protocol will be indicated in this plan; any further modifications will be noted in the final clinical study report.

17. SOURCE DOCUMENTATION AND INVESTIGATOR FILES

17.1. Study Monitoring

The CRA will arrange to visit the investigator sites at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational sites and their facilities. During these visits, CRFs and other data related to the study will be reviewed and any discrepancies or omissions will be resolved. The CRA will be given access to study relevant source documents (including medical records) for purposes of source data verification (SDV).

17.2. Audits and Inspections

The investigators and clinical sites will permit trial-related monitoring, audits, IRB review, and regulatory inspections as requested by FDA and the sponsor or designee. In addition to CRFs, the clinical site will permit direct access to source data/documents (i.e., original medical records, laboratory reports, hospital documents, progress reports, signed ICFs, etc.). During and/or after completion of the study, quality assurance officers named by the sponsor or the regulatory authorities may wish to perform on-site audits. The investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

18. QUALITY CONTROL AND QUALITY ASSURANCE

18.1. Data Quality Control and Quality Assurance

18.1.1. Investigator Responsibility

The investigator is responsible for ensuring the study is conducted according to the protocol, CFRs, GCP, and applicable regulatory requirements. The investigator's responsibilities are outlined in these documents and must include the responsibility to obtain a signed informed consent prior to patient participation in the study.

18.1.2. Protocol Modifications

The investigator should not modify the protocol without agreement from the sponsor and prior review or approval by the IRB, unless an emergency situation requires protocol modification to ensure the safety of patients. Any deviations from the protocol should be documented by the investigator or designee.

19. CONFIDENTIALITY

To maintain patient privacy, all CRFs, study drug accountability records, study reports and communications will identify the patient by the assigned patient identification number. The investigator will grant monitor(s) and auditor(s) from the sponsor or designee and regulatory authorities access to the patient's original medical records for verification of data gathered on the CRFs and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available. The patient's medical information will only be released to the extent permitted by the applicable laws and regulations.

All information regarding the investigational product supplied by the sponsor to the investigator is privileged and confidential information. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the sponsor. It is understood that there is an obligation to provide the sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of the investigational product and may be disclosed to regulatory authorities, other investigators, corporate partners, or consultants as required.

20. PUBLICATION POLICY

All information concerning dalantercept is considered confidential and shall remain the sole property of the sponsor. The investigator agrees to use this information only in conducting the study and shall not use it for any other purposes without the sponsor's written approval. The investigator agrees not to disclose the sponsor's confidential information to anyone except to persons involved in the study that need such information to assist in conducting the study, and then only on like terms of confidentiality and non-use.

It is understood by the investigator that the information developed from this clinical study will be used by the sponsor in connection with the development of dalantercept, and therefore may be disclosed as required to regulatory agencies. To allow for the use of the information derived from clinical studies, it is understood that there is an obligation to provide the sponsor with complete test results and all data developed in the study.

No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between the sponsor and the investigator.

21. PROTOCOL AMENDMENTS

Protocol amendments that impact patient safety, change the scope of the investigation, or affect the scientific quality of the study must be approved by the IRB and submitted to the appropriate regulatory authorities before implementation.

In the event that the protocol needs to be modified immediately to eliminate an apparent hazard to a patient, the sponsor will implement the protocol change and subsequently amend the protocol and notify the regulatory authorities and/or the IRB, as appropriate.

22. DATA HANDLING AND RECORDKEEPING

22.1. Case Report Form Completion

Case report forms will be completed for each enrolled patient. It is the investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the patient's CRF. Source documentation supporting the CRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, and patient status.

Investigators will maintain copies of the CRFs at the clinical site. For patients who discontinue or terminate from the study, the CRFs will be completed as much as possible, and the reason for the discontinuation or termination clearly and concisely specified on the appropriate CRF.

22.2. Retention of Records

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirements. Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product, or according to applicable regulatory requirements. If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The sponsor must be notified in writing if a custodial change occurs.

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24. APPENDICES

24.1. Appendix 1: Child-Pugh Classification of Severity of Liver Disease

Parameter	Points Assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	< 2	2 to 3	> 3
Albumin (g/dL)	> 3.5	2.8 to 3.5	< 2.8
Prothrombin Time: seconds above control	1 to 3 INR: < 1.7	4 to 6 INR: 1.7 to 2.3	> 6 INR: > 2.3
Encephalopathy	None	Grade 1 or 2	Grade 3 or 4

Total score of 5 to 6 is considered Grade A (well-compensated disease); 7 to 9 is Grade B (significant functional compromise); and 10 to 15 is Grade C (decompensated disease).[24- 25]

24.2. Appendix 2: RECIST v1.1

RECIST Criteria-Response Evaluation[26]

Evaluation of target lesions	
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
Progressive Disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
Evaluation of non-target lesions	
Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10mm short axis).
Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD):	Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Please refer to the Study Reference Guide for details on RECIST v1.1.

24.3. Appendix 3: ECOG Performance Status

The ECOG scale is used to assess a patient's quality of life in an evaluation by a health professional of the daily activities and how the activities are affected by the disease of the patient.[27]

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

24.4. Appendix 4: Cockcroft-Gault formula for Estimation of Creatinine Clearance

$$e\mathrm{C_{cr}} = \frac{(140 - \mathrm{Age}) \times \mathrm{Mass\ (kg)} \times (0.85\ \textit{if Female})}{72 \times \mathrm{Serum\ Creatinine\ (mg/dL)}}$$

Reference[28]

24.5. Appendix 5: New York Heart Association - Classification of Heart Failure

Class 1 – Class 1 heart failure – patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
Class 2 – Class 2 heart failure – patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
Class 3 – Class 3 heart failure – patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
Class 4 – Class 4 heart failure – patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

Reference[29]

24.6. Appendix 6: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

See http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE