CLINICAL STUDY PROTOCOL

A Phase 2 Randomized, Double-Blind Study of Dalantercept plus Axitinib Compared to Placebo plus Axitinib in Patients with Advanced Renal Cell Carcinoma

INVESTIGATIONAL PRODUCT:	**Dalantercept**
PROTOCOL NUMBER:	**A041-04**
SPONSOR:	**Acceleron Pharma Inc.** **128 Sidney Street** **Cambridge, MA 02139 USA** **Tel: 617-649-9200** **Fax:617-576-0479**
MEDICAL MONITOR:	**Susan Pandya, MD** **Senior Director, Medical Research**
PROTOCOL DATE:	**18 July 2012**
AMENDMENT 01:	**20 March 2013**
AMENDMENT 02:	**07 October 2013**
AMENDMENT 03:	**10 April 2014**
AMENDMENT 04:	**30 October 2014**
AMENDMENT 05:	**19 June 2015**

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:

_____

_____

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PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Contact Information
Medical Monitor	Susan Pandya, MD	Acceleron Pharma Inc. 128 Sidney Street Cambridge, MA 02139 Office Tel: 617-649-9313 Cell Tel: 617-216-7231 Fax: 617-547-1043
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 2 randomized, double-blind study of dalantercept plus axitinib compared to placebo plus axitinib in patients with Advanced Renal Cell Carcinoma

Study Center(s): Approximately 60 centers

Phase of Development: 2

Objectives:

Part 1

Primary:

- Evaluate safety and tolerability of dalantercept plus axitinib in patients with advanced renal cell carcinoma (RCC) to determine the recommended Phase 2 dose level of dalantercept plus axitinib for Part 2

Secondary:

- Evaluate progression free survival (PFS), overall survival (OS), objective response rate (ORR = complete response [CR] + partial response [PR]), duration of response (DR), and disease control rate (DCR includes CR, PR, or stable disease [SD])
- Evaluate the pharmacokinetic (PK) profiles of dalantercept and axitinib when used in combination
- Explore association of the expression of bone morphogenetic protein (BMP) 9/10, ALK1 and/or other relevant pharmacodynamic (PD) markers in archived tumor biopsy with tumor response and/or other assessments of clinical response
- Explore association of serum pharmacodynamic (PD) biomarkers with assessments of response

Part 2

Primary:

- To determine whether treatment with dalantercept plus axitinib prolongs progression free survival (PFS) compared to placebo plus axitinib in patients with advanced RCC

Secondary:

- Determine the PFS for the subgroups of patients who had 2 or more prior lines of

anticancer therapy receiving dalantercept plus axitinib vs. placebo plus axitinib

- Evaluate safety and tolerability of dalantercept plus axitinib
- Evaluate overall survival (OS), objective response rate (ORR), duration of response (DR), and disease control rate (DCR)
- Explore association of the expression of BMP9/10, ALK1 and/or other relevant pharmacodynamic (PD) biomarkers in archived tumor biopsy with tumor response and/or other assessments of clinical response
- Explore association of serum pharmacodynamic (PD) biomarkers with assessments of response

Methodology:

This is a two-part, multi-center, randomized, double-blind, placebo-controlled Phase 2 study to evaluate the safety, tolerability, efficacy, PK and PD of dalantercept plus axitinib in patients with advanced RCC.

Part 1 (dose escalation):

Patients who have signed the informed consent form (ICF) and meet the eligibility criteria will be enrolled in Part 1 of the study. Part 1 will include up to four cohorts (planned dalantercept dose levels: 0.6, 0.9, 1.2 and 1.5 mg/kg) of a minimum of 3 patients each to determine the maximum tolerated dose (MTD) level of dalantercept plus standard dosing of axitinib. Patients will receive dalantercept once every 3 weeks by subcutaneous (SC) injection and continuous dosing of axitinib at a starting dose of 5 mg orally (PO) twice daily (BID), with dose modification of each drug as indicated per protocol or prescribing information, respectively. Treatment will be discontinued for progression of disease, as defined by RECIST (version 1.1, Appendix 1).

At least three patients must complete the Day 29 visit at each dalantercept dose level with full review of data through Day 29 by the Safety Review Team (SRT) prior to escalation to the next higher dose level. The SRT may recommend adding an additional three patients to the current dose level for further evaluation prior to treatment of the next cohort with the planned (higher) dose level, escalating to an intermediate dose level or discontinuing escalation.

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 up to 2 different dose levels at or below the MTD to further evaluate safety, tolerability, and preliminary anti-tumor activity of dalantercept plus axitinib and to determine the recommended Phase 2 dose level for Part 2. The SRT will meet after a minimum of 10 patients have been evaluated for a minimum of 29 days to review safety data and vital signs data to assess safety. Treatment will be discontinued for progression of disease, as defined by RECIST (version 1.1, Appendix 1).

The initiation of Part 2 will be based on evaluation of cumulative safety and clinical activity of dalantercept plus axitinib in Part 1.

Part 2 (randomized, double-blind, placebo-controlled):

Based upon recommendations from the SRT and per sponsor decision, 130 patients will be enrolled and randomized in a 1:1 configuration to receive either the recommended Phase 2 dose level for Part 2 of dalantercept as identified in Part 1, (n=65) or placebo (n=65) plus axitinib. The randomization will be stratified by prior mammalian target of rapamycin (mTOR) inhibitor

therapy and prior immune therapy. Patients will receive dalantercept/placebo once every 3 weeks by SC injection and continuous dosing of axitinib at a starting dose of 5 mg PO BID, with dose modification of each drug as indicated per protocol or prescribing information, respectively. Treatment will be discontinued for progression of disease, as defined by RECIST (version 1.1, Appendix 1) or discontinuation of either dalantercept/placebo or axitinib.

All patients will undergo a final visit approximately 1 month following their last dose of dalantercept or placebo, and begin follow-up for progression of disease and 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.

Number of Patients (planned):

Up to 44 patients will be enrolled in the dose escalation phase of the study (Part 1) and approximately 130 patients will be enrolled in the randomized phase of the study (Part 2) for a total of up to approximately 174 patients. Patients who are not evaluable may be replaced in Part 1 only.

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 or placebo, and follow-up for progression of disease and patient survival. If a patient has a positive 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, advanced, predominantly clear cell renal cell carcinoma (RCC).
3. **Part 1:** Progression of disease following up to three lines of prior therapy, including at least one approved VEGF receptor tyrosine kinase inhibitor (TKI) for RCC. Adjuvant therapy is permitted as one line of prior therapy.

   Part 2: Progression of disease following one VEGF pathwaypathway inhibitor for RCC (sunitinib, pazopanib, sorafenib, bevacizumab, tivozanib, or cabozantinib) inclusive of adjuvant therapy if there was documented disease progression during treatment. Patients may have received one additional line of an approved mTOR kinase inhibitor (everolimus, temsirolimus) Prior exposure to investigational and/or approved anticancer immune therapies is permitted.
4. A minimum of 1 week since the last dose of prior therapy (a minimum of 4 weeks since anticancer immune therapy or bevacizumab +/- interferon).
5. Measurable disease that is evaluable by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Appendix 1).
6. Eastern Cooperative Oncology Group (ECOG) performance status of

0 or 1 (Appendix 2).

7. Life expectancy of at least 12 weeks.
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) ≥ 1,500 /µL (≥ 1.5 x 10^9 /L).
        - Hemoglobin ≥ 9 g/dL (≥ 90 g/L).
        - Platelet count ≥ 100,000 /µL (≥ 100 x 10^9 /L).
    - Measured or calculated creatinine clearance, using the Cockcroft-Gault formula, (Appendix 5) ≥ 40 mL/min.
    - Total bilirubin ≤ 1.2 x upper limit of normal (ULN). Patients with confirmed Gilbert's Syndrome may have bilirubin levels up to 3.0 mg/dL.
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN (≤ 5 x ULN if liver metastases are present).
    - Serum albumin ≥ 3.0 g/dL (≥ 30 g/L).
    - Sodium ≥ 133 mEq/L (≥ 133 mmol/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. Ability to adhere to the study visit schedule, and to understand and comply with protocol requirements.
11. Signed written informed consent.

Exclusion Criteria:

1. Clinically significant pulmonary, endocrine, neurologic, hematologic, gastrointestinal (GI), autoimmune, or genitourinary disease unrelated to RCC that in the judgment of the investigator should preclude treatment with dalantercept or axitinib.
2. Clinically significant cardiovascular risk including:
    - Ejection fraction (EF) ≤ 50% by echocardiogram (ECHO). Multi-gated acquisition scan (MUGA) should be obtained to estimate EF if quality of ECHO is not good.
    - Presence of grade 2 pericardial effusion on baseline ECHO.

- Significant history of congestive heart failure (CHF) defined as New York Heart Association (NYHA) class II-IV (Appendix 3).
- 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 and new findings on cardiac evaluation (e.g., clinical, stress test, etc.) within 3 months prior to study day 1.
- Deep vein thrombosis (DVT) including tumor thrombus within 6 months of study day 1.
- Significant arrhythmia or electrophysiologic disease including placement of implantable cardioverter defibrillator (ICD), atrial fibrillation with uncontrolled rate or prolonged QTc interval > 450 ms for men and > 470 ms for women.[1]
- Patients receiving cardiac medications should be on stable doses for at least 1 week prior to study day 1.
- 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 < 150/95) upon study entry using a stable regimen of anti-hypertensive therapy.

3. Known CNS metastases or leptomeningeal disease:
   - For Part 1, patients with CNS metastases treated with whole brain radiotherapy, gamma knife, and/or surgery who are considered stable by CNS imaging and are not being treated with corticosteroids 6 weeks prior to study day 1 may be enrolled.
   - For Part 2, patients with CNS metastases treated with stereotatic radio-surgery (SRS) and/or surgery who are considered stable by CNS imaging for at least 2 monthss prior to enrollment and are not being treated with corticosteroids to manage their CNS disease within 4 weeks prior to study day 1 may be enrolled.
4. Active GI bleeding, unrelated to cancer, as evidenced by hematemesis, hematochezia, or melena within 3 months prior to study day 1 without evidence of resolution documented by endoscopy or colonoscopy.
5. Any active malignancy, other than RCC, for which chemotherapy or other anti-cancer therapy is indicated. Patients with adequately treated non-melanoma skin cancer or in situ cancer are permitted. Patients with other cancers from which they have been disease-free for at least 3 years will be permitted.
6. Any lesion invading or having encasement ≥ 180 degrees around the wall of a major blood vessel as assessed by computed tomography (CT) scan and/or magnetic resonance imaging (MRI).
7. Radiotherapy within 2 weeks prior to study day 1.
8. Lack of recovery from toxic effects of previous treatment for RCC to ≤ grade 1 with the

exception of alopecia, unless stabilized under adequate medical control.

9. Systemic steroids or immunosuppressive agents within 1week of study day 1 (with the exception of corticosteroids for CNS disease, see Exclusion #3 or physiologic doses of corticosteroids) or biologic anti-inflammatory immune modulating agents (e.g. infliximab) within 4 weeks of study day 1.
10. Patients undergoing renal dialysis.
11. Major surgery within 4 weeks prior to study day 1 (patients must have recovered completely from any previous surgery prior to study day 1).
12. Any active infection requiring antibiotic therapy within 1 week1 of study day 1.
13. Anti-coagulation therapy. Aspirin, otherother anti-platelet agents, and low molecular weight heparin arepermitted unless the investigator deems the patient is at a significant risk for bleeding.
14. Current use or anticipated inability to avoid strongCYP3A4/5 inhibitors or inducers (please refer to the Inlyta® [axitinib] prescribing informationinformation) during participation in the study.
15. PeripheralP edema requiring medical intervention within 2 weeks prior to study day 1.
16. BMI < 16 kg/m^2.
17. 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.
18. 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.
19. Known history of hereditary hemorrhagic telangiectasia (HHT).
20. Known active hepatitis B virus (HBV) or hepatitis C virus (HCV) infections or positive human immunodeficiency virus (HIV) antibody results. Patients with sustained virologic response to HCV treatment or immunity to HBV from prior infection without cirrhosis may be included.
21. History of severe (defined as ≥ grade 3, using the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 4.0 [NCI-CTCAE] v4 current active minor version) allergic or anaphylactic reaction or hypersensitivity to recombinant proteins or excipients (10 mM Tris buffered saline) in the investigational agent.
22. Any prior treatment with dalantercept or any other agent targeting ALK1 pathway.
23. Any prior treatment with axitinib.
24. A morbidity (per the Inlyta® [axitinib] prescribing information) that would require starting a patient at a reduced dose of axitinib.
25. Treatment with another investigational drug (with the exception of anticancer immune therapy) or device, or approved therapy for investigational use, within 5 times the half-life of the drug or within 3 weeks prior to study day 1 if the half-life is not known.

26. Pregnant or lactating female patients.

Investigational Product, Dosage, and Mode of Administration:

Dalantercept is a frozen liquid formulation at a concentration of 50 mg/mL in 10 mM Tris buffered saline (pH 7.5 ± 0.5). Dalantercept will be administered by subcutaneous (SC) injection(s) once every 3 weeks until progression of disease or unmanageable toxicity occurs. The dose level of dalantercept for the first cohort will be 0.6 mg/kg SC q3 weeks, plus a starting dose level of axitinib 5 mg PO BID. The planned dose escalation for dalantercept is below.

Part 1:

Dose Level Per Cohort

Dose Cohort	Dalantercept Dose Level (mg/kg)	Number of Patients
1	0.6	3-6
2	0.9	3-6
3	1.2	3-6
4	1.5	3-6
Expansion Cohort	TBD	up to 20
Total (planned)		up to 44

Part 2:

Patients will be randomized to receive dalantercept or placebo plus a starting dose of axitinib 5 mg PO BID. Based upon a safety review of the Part 1 data, the recommended Phase 2 dose level of dalantercept was determined to be 0.9 mg/kg in combination with axitinib.

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

Safety Assessment: Dose Escalation

Dose-Limiting Toxicity (DLT) Definition:
A DLT is defined as any of the following events that are considered possibly or probably related to dalantercept.

- Weight gain (due to fluid retention) grade 2 or higher
- Pulmonary edema grade 2 or higher
- Bleeding grade 2 or higher
- Cardiovascular event grade 3 or higher
- Non-hematologic adverse event grade 3 or higher with the exception of grade 3 or higher amylase and lipase in the absence of clinical 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

Part 1:

Safety and Dose Limiting Toxicities (DLTs) will be evaluated by the SRT. In addition, the MTD or maximum tested dose, the number of patients to be enrolled in the expansion cohort and the recommended Phase 2 dose level for Part 2 will be determined 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 study day 29 to assess the safety of a dose level prior to dose escalation. Dose escalation will not occur until the patients in the preceding dose level have been evaluated for a minimum of 29 days.

After a minimum of 3 evaluable patients have been evaluated for a minimum of 29 days, the SRT will consider dose escalation to the next dose level cohort or the addition of 3 additional 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 of 3 patients at a dose level experiences a DLT, 3 additional patients may be enrolled at the current dose level.
    - If there are no further DLTs in the 3 additional patients, dose escalation to the next dose level may proceed.
- If a DLT occurs in ≥ 2 patients in any dose level 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 axitinib at an appropriate dose level as outlined in the Management of Adverse Events table.

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 up to 2 different dose levels at or below the MTD to further evaluate safety, tolerability, and preliminary anti-tumor activity of dalantercept plus axitinib and to determine the recommended Phase 2 dose level for Part 2. The SRT will meet after a minimum of 10 patients have been evaluated for a minimum of 29 days to review safety data and vital signs data to assess safety.

If 4 DLT events occur at any time during the first 29 days in a minimum of 10 patients in the expansion cohort, further enrollment in that expansion cohort will be discontinued. The SRT may decide to cease enrollment if fewer than 4 DLT event(s) occur 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.

Part 2:

The sponsor and an independent data monitoring committee (DMC) are responsible for reviewing safety throughout Part 2 of the study. The DMC will be comprised of a minimum of 3 members (non-Sponsor and non-study investigators) and will review available study data (e.g. serious

adverse events (SAEs), adverse events (AEs), laboratory results (including hematology and chemistry), ECHO, ECG, tumor response assessment scans and vital signs data) on a regular basis to assess the safety of the patients and verify the proper conduct of the trial. The DMC responsibilities, membership, meeting frequency, and procedures will be outlined in a separate DMC charter.

Assessments for Evaluation:

Efficacy: Response to treatment with dalantercept plus axitinib will be determined according to the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1, Appendix 1) for patients with solid tumors. Patients will be assessed for efficacy using data from tumor response assessments (PFS, ORR, DR and DCR) as well as evaluation of OS and PD biomarkers.

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

Statistical Methods:

Sample Size Calculation:

Part 1

There is no formal sample size calculation for Part 1 (dose escalation and expansion).

Part 2

The primary analysis of efficacy will be performed when at least 82 PFS events have been observed and documented. If the median time to PFS is assumed to be 5 months in the placebo plus axitinib control group, then a total of 82 PFS events will provide approximately 80% power to detect a 3 month extension from 5 to 8 months in the dalantercept plus axitinib experimental treatment group when performing a stratified log-rank test of the null hypothesis of no difference between treatment groups using a one-sided 10% significance level.

The projection of power is made under a proportional hazards assumption so that the hazard ratio (HR) for dalantercept plus axitinib relative to placebo plus axitinib is equal to 0.625 under the alternative hypothesis. It is projected that 130 patients will need to be randomized to obtain 82 PFS events. The number of patients to be randomized provides for patient censoring patterns that could occur under the alternative hypothesis in the event the dropout rate is higher than expected in either treatment group.

Analysis Populations:

The **All Treated (AT) Population** includes all patients who received any study drug. The AT is the population that will be used when performing the primary analysis of the primary endpoint and all safety analyses. The AT population will be analyzed according to treatment received.

The **Full Analysis Set (FAS)** includes all randomized patients. The intent-to-treat principle will be used for this study population. The FAS will be used in secondary analyses of the primary endpoint.

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

Statistical Analysis:

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

The primary analysis of PFS will be based on investigator assessment using the AT population. Time to radiographic progression or death is the primary efficacy analysis and will be performed using a stratified (by prior treatment) log-rank test.

A log-rank test stratified by prior mTOR and immune therapy will be used to test the null hypothesis of no difference between dalantercept plus axitinib and placebo plus axitinib using a one-sided 0.10 significance level. Kaplan-Meier curves will be displayed depicting each treatment group. The hazard ratio (dalantercept plus axitinib: placebo plus axitinib) will be estimated using a stratified Cox proportional hazards model along with the 95% confidence intervals.

For the secondary PFS objective in the subgroup of patients who had 2 or more prior lines of anticancer therapy, the stratified log-rank test will be performed at one-sided 0.20 significance level due to a smaller sample size.

Data Monitoring Committee:

A data monitoring committee (DMC), independent from the sponsor, will be established to review unblinded safety data on a regular basis and to make appropriate recommendations regarding the conduct of the trial.

2. SCHEDULE OF EVENTS

Schedule of Events[2]												
	Screening[3]	Cycle 1			Cycle 2		Cycle 3	Cycle 4	Cycle 5[16]	Cycle 6	Final Visit[17]	Follow Up[19]
		C1D1[11]	C1D8	C1D15	C2D1[11]	C2D8	C3D1[11]	C4D1[11]	C5D1[11]	C6D1[11]		
	Day -14	Day 1	Day 8 (± 2d)	Day 15 (± 2d)	Day 22 (± 2d)	Day 29 (± 2d)	Day 43 (± 3d)	Day 64 (± 3d)	Day 85 (± 3d)	Day 106 (± 3d)		
Informed consent[1]	X											
Inclusion/exclusion criteria	X	X										
Medical history	X											
Archived tumor biopsy	X											
Head CT or MRI[4]	X											
Pregnancy test[5]	X	X			X		X	X	X	X		
Physical examination[6]	X	X	X	X	X	X	X	X	X	X	X	
Vital signs (including weight)	X	X	X	X	X	X	X	X	X	X	X	
ECOG and Karnofsky performance status	X[7]	X					X		X		X	
Hematology/serum chemistry[8]	X[8]	X[8]	X	X	X	X	X	X	X	X	X	
Thyroid Function	X[9]	X[9]					X		X[16]			
Urinalysis	X[8]	X[8]			X		X	X	X[16]		X	
PD blood biomarkers		X			X	X	X	X	X[16]		X	
PK blood sample collection[15]		X			X		X					
Anti-drug antibody (ADA)		X					X		X[16]		X[18]	X[18]
ECHO scan[10]	X[3]							X			X[10]	
ECG (12-lead)[10]	X							X			X[10]	
Chest X-ray (CXR)[10]	X[3]											
Tumor response assessment scan[12]	X[3]						X		X[16]		X[17]	X[19]
Monitoring of AEs and concomitant medications	X[13]	X[14]	X	X	X	X	X	X	X	X	X	
Dalantercept/placebo administration		X			X		X	X	X	X		
Axitinib administration		Continuous daily dosing (BID)										
Survival Follow-up												X[19]

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

[2]All visit day windows should be considered relative to the date of the previous dose of dalantercept/placebo. 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.

[3]All screening procedures should be performed within 14 days prior to study day 1. ECHO, CXR 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.

[4]Head CT or MRI is required at screening to exclude any patients with active brain metastasesmetastases. Head 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. Scans do not need to be repeated at subsequent visits unless clinically indicated.

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

[6] A full physical exam [skin (including telangiectasias), head, eyes, ears, nose, throat and neck, lymph nodes, cardiovascular, respiratory, gastrointestinal, and musculoskeletal (including edema)] is required at screening, C1D1, C1D8, C2D1, C3D1, C4D1, C5D1, C6D1 and the final visit. A neurologic exam is required at screening only and only repeated if clinically indicated. At all other timepoints noted and beyond C6, a targeted physical exam of the respiratory, cardiovascular and musculoskeletal (including edema) body systems is required. If clinically indicated, additional assessment of other body systems should occur.

[7]Karnofsky Performance Status only required at Screening.

[8]Assessments performed prior to dosing on C1D1 will be considered baseline. Baseline hematology, chemistry, and urinalysis results must be reviewed prior to dosing on C1D1 but may be collected up to 72 hours prior to dosing. Therefore ifi the screening visit is within 72 hours prior to study day 1, hematology, chemistry and urinalysis do not need to be repeated on C1D1. This includes the following:

Chemistry - albumin, alkaline phosphatase (ALP), ALT, AST, blood urea nitrogen (BUN), calcium, chloride, carbon dioxide (CO_2), creatinine, glucose, lactate dehydrogenase (LDH), phosphorus, potassium, sodium, total bilirubin,amylase, and lipase. After C15, amylase and lipase are not required unless clinically indicated.

Hematology - complete blood count (CBC) with differential; CBC includes RBCs, white blood cells (WBCs), platelets, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC). PT/INR and aPTT should be collected at screening only (within 14 days of study day 1)

Urine by urinalysis or dipstick analysis - pH, specific gravity, protein, glucose, ketones, blood, leukocyte esterase, and nitrite with microscopic examination if indicated.

[9]Baseline thyroid function may be collected up to 72 hours prior to dosing. If the screening visit is within 72 hours of study day 1, thyroid function does not need to be repeated. This includes the following: free thyroxine (T_4) and thyroid stimulating hormone (TSH).

[10] ECHO scans for ejection fraction and presence or absence of pericardial effusion only. MUGA should be performed to estimate EF if quality of ECHO is not good. Additional testing to be done if clinically indicated. ECHO scans may be performed up to 5 days prior to a scheduled visit. A complete cardiac evaluation including CXR, 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.

[11]Perform all assessments prior to dosing dalantercept/placebo and review for potential dose modifications. All AEs and abnormal laboratory or other findings that might require modification of dosing (see Section 10.6) should be reviewed prior to dosing to ensure that the patient is still eligible to receive dalantercept/placebo. Assessments performed on Cycle 1 Day 1 (C1D1) prior to dosing will be considered baseline.

[12]Tumor response assessment scans may be performed up to 5 days prior to a scheduled visit (except screening & final visit which have wider windows). Tumor response assessment scans should be reviewed prior to dosing the next cycle of treatment. Tumor response assessment scans should be performed every 6 weeks regardless of dalantercept/placebo or axitinib dosing delays through C15. After C15 tumor response assessment scans should be performed every 12 weeks regardless of dalantercept/placebo or axitinib dosing delays (e.g. C19D1, C23D1, etc).

[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]PK blood sample collection should be performed pre-dose for dalantercept/placebo and axitinib at C1D1, C2D1 and C3D1. C3D1

[16]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 is taken off study (C7D1=C5D1, C8D1=C6D1, etc.). NOTE: After C5, ADA, urinalysis, thyroid function and PD biomarkers only need to be repeated once every 4 cycles (C9D1, C13D1, etc).

[17]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/placebo ± 10 days. The tumor response assessment scans 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.

[18]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.

[19]All patients should be contacted every 3 months (± 2 weeks) from the date of the final visit for survival. Patients will 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. Patients that discontinue study treatment and initiate a new therapy or continue on axitinib alone, prior to documented radiographic disease progression are not required to return to the clinic every 3 months for tumor response assessment scans.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Term	Definition
aPTT	Activated partial thromboplastin time
ADA	Anti-drug antibody
AE	Adverse event
ALK1	Activin receptor-like kinase1
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AT	All treated
AUC	Area under the curve
BID	Twice daily
BMI	Body mass index
BMP	Bone morphogenetic protein
BP	Blood pressure
BSSR	Blinded sample size re-estimation
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
CO2	Carbon dioxide
CR	Complete response
CRA	Clinical research associate
CRF	Case report form
CRO	Contract research organization

Term	Definition
CT scan	Computed tomography scan
CXR	Chest x-ray
DCE-MRI	Dynamic contrast-enhanced magnetic resonance imaging
DCR	Disease control rate
DLT	Dose limiting toxicity
DMC	Data monitoring committee
DR	Duration of response
DVT	Deep venous thrombosis
ECD	Extracellular domain
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EF	Ejection fraction
FAS	Full Analysis Set
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
HR	Hazard ratio
IB	Investigator's Brochure
IC	Inhibitory concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICD	Implantable cardioverter-defibrillator

Term	Definition
IEC	Institutional Ethics Committee
IgG1	Immunoglobulin G1
IMDC	International Metastatic Renal Cancer Database Consortium
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
LV	Left ventricular
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MI	Myocardial infarction
MRI	Magnetic resonance imaging
MSKCC	Memorial Sloan Kettering Cancer Center
MTD	Maximum tolerated dose
mTOR	Mammalian target of rapamycin
MUGA	Multi-gated acquisition scan
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NE	Non-Evaluable
NOAEL	No observed adverse effect level
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PD	Pharmacodynamic
PET-CT	Positron emission tomography-computed tomography
PFS	Progression free survival
PHI	Protected health information
PlGF	Placental growth factor
PK	Pharmacokinetic
PO	Orally

Term	Definition
PR	Partial response
PT/INR	Prothrombin time/international normalized ratio
RBC	Red blood cell
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
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
SRS	Stereotatic radio-surgery
SRT	Safety review team
SUSAR	Suspected unexpected serious adverse reaction
$T_{1/2}$	Elimination half- life
T_4	Thyroxine
TGFβ	Transforming growth factor β
TIA	Transient ischemic attack
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
VEGFR	Vascular endothelial growth factor receptor
VHL	Von Hippel-Lindau syndrome
Vz/F	Apparent volume of distribution
WBC	White blood cell

5. ETHICS

5.1. 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.

5.2. 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.

5.3. 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).

5.4. 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.

6. 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.

7. INTRODUCTION

Dalantercept (also known as ACE-041) is a recombinant fusion protein consisting of the ECD of human ALK1 linked to the Fc (hinge, CH2 and CH3 domains) portion of human immunoglobulin G1 (IgG1). ALK1 is a type I receptor belonging to the transforming growth factor-beta (TGFβ) superfamily that is selectively expressed on activated endothelial cells during development or in response to injury or disease.[2] ALK1 has been implicated in the maturation phase of angiogenesis and is believed to play a pivotal role in development of functional vasculature.

Dalantercept primarily binds to the ligands bone morphogenetic protein (BMP) 9 and BMP10 and inhibits their interaction with ALK1, thus blocking ALK1-mediated signaling. Dalantercept binding results in the inhibition of vascular endothelial cell maturation and disruption of the process of vascular development.[3] In contrast to other anti-angiogenic agents (e.g., anti-VEGF [Vascular Endothelial Growth Factor] TKIs [tyrosine kinase inhibitors] and bevacizumab) that block the proliferative phase of angiogenesis, dalantercept blocks the maturation phase of angiogenesis, and therefore may represent a novel and effective agent in the treatment of a wide range of malignancies.

With the recent approvals of anti-angiogenic targeted therapies for RCC, progression-free intervals and survival have been significantly extended. However, advanced RCC remains incurable, as patients inevitably progress despite treatment with these newer agents. The treatment algorithm in advanced RCC is not well defined, with patients typically progressing through multiple lines of VEGF-targeted and/or mTOR-targeted anti-angiogenic therapies. The rate of objective response is lower and duration of progression-free survival is shorter with each successive line of therapy. In the Phase 3 study of sunitinib in treatment-naïve advanced RCC patients the median PFS was 10.9 months compared to 5.1 months for the interferon-alfa-treated control group.[4] In the Phase 3 study of axitinib in mRCC patients who had progressed on their first-line VEGF TKI, the median PFS was 4.8 months compared to 3.4 months for the sorafenib-treated control group.[5] Tumor resistance to TKI therapy is thought to be the result of the upregulation of alternate pro-angiogenic signaling pathways, such as placental growth factor (PlGF), fibroblast growth factor (FGF), angiopoietins and other angiogenic factors.[6]

Dalantercept is an ALK1 ligand trap that has demonstrated robust anti-angiogenic activity in tumor model studies, and has demonstrated anti-tumor activity in a completed Phase 1 study in advanced solid tumor patients. By binding the ligands BMP9 and BMP10, dalantercept blocks signaling through the ALK1 receptor. While VEGF, PlGF, FGF and other pro-angiogenic factors are known to drive the initial proliferative stage of angiogenesis[7], the ALK1 pathway is thought to regulate the maturation stage of angiogenesis.[2] Since maturation stage processes, including vessel stabilization via incorporation of pericytes and other stromal cells, are commonly downstream of proliferative stage processes, we hypothesize that ALK1 pathway inhibition could be synergistic when used in combination with anti-VEGF therapy, and may also provide efficacy in VEGF-inhibition-resistant tumors.[3]

7.1. Overview of Renal Cell Carcinoma

Approximately 65,000 people will be diagnosed with and over 13,000 deaths will be attributed to kidney cancers in the United States in 2012.[8] The incidence rates of kidney cancer have been rising by approximately 2% per year over recent decades, and the reason for the increase is unknown. The median age at diagnosis is 65 years.[9] The most common etiologic factors in renal cancer are smoking, obesity, high blood pressure and a family history of Von Hippel-Lindau (VHL) syndrome. Early stage kidney cancer is usually asymptomatic. Patients with tumors that have progressed may have symptoms including hematuria, abdominal or lower back pain, fatigue or weight loss.

Renal cell carcinoma (RCC), which arises from renal epithelium, is the most common form of kidney cancer, accounting for approximately 90% of all cases. Of RCC cases, approximately 85% are clear cell tumors, while the rest are of more rare subtypes including papillary, chromophobe and collecting duct tumors.[10] Localized or locoregional RCC is typically treated with surgical excision, though 20-30% of patients will relapse with median time to relapse of 1-2 years.[11] In addition, approximately one third of patients present with advanced disease, with metastases occurring most commonly in the lung, bone, brain, liver and adrenal gland.

Relapsed or advanced RCC is currently incurable, so for these patients the objective of treatment is palliation and prolongation of life. Until recently, advanced RCC patients were treated with cytokine therapies, including high dose interleukin-2 or interferon-alfa. Since the mid-2000's, a number of targeted therapies have been approved, including VEGF-targeted or mTOR-targeted receptor tyrosine kinase inhibitors, and a VEGF-targeted antibody.[12] These targeted therapies, including Sutent® (sunitinib, Pfizer), Nexavar® (sorafenib, Bayer/Onyx), Votrient® (pazopanib, GlaxoSmithKline), Inlyta® (axitinib, Pfixer), Torisel® (temsirolimus, Wyeth/Pfizer), Afinitor® (everolimus, Novartis), and Avastin® (bevacizumab, Genentech/Roche), have demonstrated significant impact on progression-free survival in randomized, controlled clinical studies.[13]

7.2. Summary of Nonclinical Studies

7.2.1. 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.[14] 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 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)[15], 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.[16] This may indicate that an ALK1 dependent pathway is activated as a consequence of sunitinib resistance leading to better efficacy in a combination therapy. Overall, these data provide a rationale for the clinical development of dalantercept as an anti-angiogenic therapy in sunitinib refractory renal cell carcinoma indications.

7.2.2. Toxicology Studies

Dalantercept has been evaluated in rats and monkeys following single and repeated subcutaneous (SC) injections, for assessment of its toxicological effects and pharmacokinetic (PK) properties following single and repeated subcutaneous (SC) injections. Single-dose SC injections up to a dose of 100 mg/kg were well tolerated in both rats and monkeys. Repeat-dose toxicity studies of 3 months duration were conducted in rats and monkeys; 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 was intended to provide continuous exposure to dalantercept, based on serum half-lives of approximately 3 days in rats and approximately 6 days in monkeys.

Subcutaneous administration of dalantercept at ≥ 30 mg/kg in rats 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 degeneration/necrosis, hypertrophy, 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 in animals at 30 mg/kg. By echocardiogram (ECHO) there was increased LV mass in animals dosed at 10 and 30 mg/kg dose groups in addition to increased left atrial 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 and 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).

7.3. Summary of Clinical Experience

Dalantercept was evaluated in a phase 1, open-label, multiple-dose, dose escalation study (A041-01) in patients with advanced solid tumors or multiple myeloma. The primary objective of the study was to evaluate the safety and tolerability of dalantercept in these populations. Secondary objectives of the study were to identify the maximum tolerated dose (MTD), examine the PK profile, and evaluate the preliminary antitumor activity and effect of dalantercept on

pharmacodynamic (PD) biomarkers. Preliminary data from Study A041-01 as of July 2011 are summarized below.

A total of 37 patients were enrolled. The first 25 patients were enrolled in 7 dose-escalating cohorts (0.1 to 4.8 mg/kg SC every 3 weeks) followed by an additional 12 patients who were enrolled in an expansion cohort at 1.6 mg/kg. The mean (standard deviation) age was 61.0 (11.7) years and the primary tumor types included colorectal cancer (n=7), non-small cell lung cancer (NSCLC, n=6), sarcoma (various, n=5), ovarian cancer (n=3), pancreatic cancer (n=3) and squamous cell carcinoma of the head and neck (n=3). There were no patients with renal cell carcinoma enrolled.

A preliminary analysis of PK data demonstrated a linear relationship to dose level for maximum concentration (C_{max}) and area under the curve ($AUC_{0\text{-}21d}$). The median time to maximum concentration (t_{max}) was 4-7 days and the mean elimination half-life ($t_{½}$) was approximately 10-15 days.

Tumor response was evaluated in 29 patients using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. One patient with SCCHN had a partial response (PR) by Cycle 10 at a dose of 0.4 mg/kg, with 32.5% maximum shrinkage of the target lesion. Eight patients had prolonged periods of stable disease ([SD] ≥ 12 weeks) across the dose range (0.2 to 4.8 mg/kg).

Tumor metabolic activity (change in standard uptake value), as measured by fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) scan, decreased from baseline in 19 of 33 evaluable patients. Tumor blood flow as measured by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) decreased from baseline in 8 of 12 evaluable patients.

Subcutaneous administration of dalantercept once every 3 weeks in this study was generally well tolerated. Treatment-related SAEs occurred in 5 patients including 3 patients with fluid overload and/or congestive heart failure (CHF), 1 patient with LV dysfunction, and 1 patient with fatigue. Adverse events (AEs) observed with increased frequency at higher dose levels included peripheral edema, anemia, epistaxis, and telangiectasia. The AEs of epistaxis and telangiectasia may be related to the mechanism of action of dalantercept on angiogenesis, leading to dilated vessels in the skin. Dose-dependent fluid retention manifested as peripheral edema, dyspnea, and weight gain, responded to diuretic therapy. Dalantercept treatment resulted in a dose-dependent decrease in red blood cells (RBC) and hemoglobin levels, with no evidence of hemolysis or hemorrhage. No significant, dose-related events of hypertension, GI perforation, or proteinuria have been observed in the study to date, indicating a safety profile that appears distinct from VEGF-inhibitors. Due to toxicities observed at higher doses, patients in the dose expansion cohort were treated with 1.6 mg/kg.

Dalantercept is also being evaluated in an on-going Phase 2, open-label study in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN, A041-03) who have been previously treated with at least one platinum-containing regimen. The primary objective is to estimate the objective response rate (ORR) in this population. Secondary objectives include safety and tolerability and pharmacokinetic (PK) profile of dalantercept as well as evaluate progression free survival (PFS), overall survival (OS), time to tumor progression (TTP), duration of response, and rate of disease control (ORR + stable disease [SD]). In addition, the study will explore association of the expression of BMP9/10, ALK1 and/or other

relevant markers in tumor tissue and blood with tumor response and/or other assessments of clinical response and pharmacodynamic (PD) biomarkers. The dalantercept IB should be reviewed prior to initiating the study for the most current information.

7.4. 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 (≥ 10% patients) in the dalantercept monotherapy clinical trials (A041-01, 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.

As of September 10, 2013, the most frequently observed AEs (> 20% of patients, n=10) in this study with the combination of dalantercept plus axitinib, regardless of causality, have included dysphonia, fatigue, diarrhea, arthralgia, constipation, hypertension, blood alkaline phosphatase increased, blood creatinine increased, chills, cough, dizziness, headache, hyperkalemia, muscle spasms, nausea, thrombocytopenia and vomiting.

On the basis of toxicology data in rats and monkeys and the preliminary clinical data, patients with significant cardiac risk will be excluded from participating in dalantercept studies and eligible patients will undergo comprehensive cardiac assessments which include, but are not limited to ECHO, electrocardiogram (ECG), laboratory testing, vital signs, and clinical evaluation.

Other potential risks associated with inhibition of ALK1 signaling may be inferred from the phenotypic findings in humans deficient in ALK1 expression. In humans, inactivating mutations in one copy of the ALK1 gene leads to a form of hereditary hemorrhagic telangiectasia (HHT). Hereditary hemorrhagic telangiectasia is characterized by recurrent epistaxis and telangiectasia, and in more severe cases, arteriovenous malformations (AVMs).[17,18] To date, telangiectasia and epistaxis have been reported in the Phase 1 clinical study (A041-01); however, AVMs have not been reported in that study, nor were AVMs observed in toxicology studies with dalantercept. As a precaution, patients with a significant bleeding risk will be excluded from participating in dalantercept studies.

Previous experience with other anti-angiogenesis agents suggests that the following toxicities may be encountered: hypersensitivity reactions, impaired wound healing, hypertension, GI perforations, and cardiovascular thromboembolic events. It is unknown if dalantercept will have any of these toxicities.

Effects of dalantercept on reproduction and development are unknown. Reproductive toxicology studies of dalantercept in animals have not been conducted. However, no effects were observed on the ovaries or testes and no histopathological effects were seen in reproductive organs in 3-month toxicology studies in monkeys and rats. The use of adequate birth control measures will continue to be required in clinical studies with dalantercept.

As with all biologics, there is the potential for the development of anti-drug antibodies (ADA) that can be associated with increased drug clearance and hypersensitivity reactions. Antidrug antibody formation will be monitored in early phase 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.

7.5. Potential Risks of Human Use of Axitinib

The most common side effects observed in more than 20% of patients who have taken axitinib include diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, palmar-plantar erythrodysesthesia (hand-foot) syndrome, weight decreased, vomiting, asthenia, and constipation. For additional risks associated with patients taking axitinib, please refer to the axitinib prescribing information (see Inlyta® [axitinib] prescribing information, *Warnings and Precautions*).

8. TRIAL OBJECTIVES

Part 1

Primary

- Evaluate safety and tolerability of dalantercept plus axitinib in patients with advanced renal cell carcinoma (RCC) to determine the recommended Phase 2 dose level of dalantercept plus axitinib for Part 2

Secondary

- Evaluate progression free survival (PFS), overall survival (OS), objective response rate (ORR = complete response [CR] + partial response [PR]), duration of response (DR), and disease control rate (DCR includes CR, PR, or stable disease [SD])
- Evaluate the pharmacokinetic (PK) profiles of dalantercept and axitinib when used in combination
- Explore association of the expression of BMP9/10, ALK1 and/or other relevant pharmacodynamic (PD) markers in archived tumor biopsy with tumor response and/or other assessments of clinical response
- Explore association of serum pharmacodynamic (PD) biomarkers with assessments of response

Part 2

Primary

- To determine whether treatment with dalantercept plus axitinib prolongs progression free survival (PFS) compared to placebo plus axitinib in patients with advanced RCC

Secondary

- Determine the PFS for the subgroups of patients who had 2 or more prior lines of anticancer therapy receiving dalantercept plus axitinib vs. placebo plus axitinib
- Evaluate safety and tolerability of dalantercept plus axitinib
- Evaluate overall survival (OS), objective response rate (ORR), duration of response (DR), and disease control rate (DCR)
- Explore association of the expression of BMP9/10, ALK1 and/or other relevant pharmacodynamic (PD) biomarkers in archived tumor biopsy with tumor response and/or other assessments of clinical response
- Explore association of serum pharmacodynamic (PD) biomarkers with assessments of response

9. OVERALL STUDY DESIGN AND PLAN: DESCRIPTION

9.1. Study Design

This is a two-part, multi-center, randomized, double-blind, placebo-controlled Phase 2 study to evaluate the safety, tolerability, efficacy, PK and PD of dalantercept plus axitinib in patients with advanced RCC.

Part 1 (dose escalation):

Patients who have signed the informed consent form (ICF) and meet the eligibility criteria will be enrolled in Part 1 of the study. Part 1 will include up to four cohorts (planned dalantercept dose levels: 0.6, 0.9, 1.2 and 1.5 mg/kg) of a minimum of 3 patients each to determine the maximum tolerated dose (MTD) level of dalantercept plus standard dosing of axitinib. Patients will receive dalantercept once every 3 weeks by subcutaneous (SC) injection and continuous dosing of axitinib at a starting dose of 5 mg orally (PO) twice daily (BID), with dose modification of each drug as indicated per protocol or prescribing information, respectively. Treatment will be discontinued for progression of disease, as defined by RECIST (version 1.1, Appendix 1).

At least three patients must complete the Day 29 visit at each dalantercept dose level with full review of data through Day 29 by the Safety Review Team (SRT) prior to escalation to the next higher dose level. The SRT may recommend adding an additional three patients to the current dose level for further evaluation prior to treatment of the next cohort with the planned (higher) dose level, escalating to an intermediate dose level or discontinuing escalation.

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 up to 2 different dose levels at or below the MTD to further evaluate safety, tolerability, and preliminary anti-tumor activity of dalantercept plus axitinib and to determine the recommended Phase 2 dose level for Part 2. The SRT will meet after a minimum of 10 patients have been evaluated for a minimum of 29 days to review safety data and vital signs data to assess safety. Treatment will be discontinued for progression of disease, as defined by RECIST (version 1.1, Appendix 1).

The initiation of Part 2 will be based on evaluation of cumulative safety and clinical activity of dalantercept plus axitinib in Part 1.

Part 2 (randomized, double-blind, placebo-controlled):

Based upon recommendations from the SRT and per sponsor decision, 130 patients will be enrolled and randomized in a 1:1 configuration to receive either the recommended Phase 2 dose level for Part 2 of dalantercept as identified in Part 1, (n=65) or placebo (n=65) plus axitinib. Patients will receive dalantercept/placebo once every 3 weeks by SC injection and continuous dosing of axitinib at a starting dose of 5 mg PO BID, with dose modification of each drug as indicated per protocol or prescribing information, respectively. Treatment will be discontinued for progression of disease, as defined by RECIST (version 1.1, Appendix 1) or discontinuation of either dalantercept/placebo or axitinib.

All patients will undergo a final visit approximately 1 month following their last dose of dalantercept or placebo and begin follow-up for progression of disease and patient survival. If a patient has a positive 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.

9.2. Discussion of Study Design

9.2.1. Study Design Rationale

Dalantercept was tested in the A498 and the 786-O RCC mouse tumor models, both as monotherapy and in combination with sunitinib. In the monotherapy studies, dalantercept showed anti-tumor activity in the A498 model, but not in the 786-O tumor line. However, in the combination therapy studies, dalantercept plus sunitinib slowed tumor growth to a greater extent than either agent alone or untreated tumors in both models.[16] The data demonstrate that blocking ligand signaling through the endogenous ALK1 receptor, either alone or in combination with other anti-angiogenic therapies, is a valid strategy for treatment of renal cell carcinoma.

Dalantercept was tested in a Phase 1 study in advanced, refractory cancer patients, and was well tolerated at dose levels up to 1.6 mg/kg Q3W.[19] Though no RCC patients were included in the Phase 1 study, one solid tumor patient had a partial response and eight patients had prolonged periods of stable disease. The dose-limiting toxicity was fluid overload, and the most frequently reported treatment-emergent adverse event (TEAEs) were fatigue, peripheral edema, nausea, anorexia, anemia, dyspnea, headache, vomiting, pyrexia, constipation, dehydration, and epistaxis. Importantly, the dalantercept side effect profile appeared largely non-overlapping with the toxicity profiles of the TKI therapies approved for the treatment of RCC. In addition in a phase one study of an anti ALK-1 antibody, a patient with RCC had a partial response.[20] Based on its mechanism of action, the robust pharmacology model data set, and the initial safety and activity profile from the Phase 1 clinical trial, we propose to study dalantercept in combination with VEGF TKI therapy in patients with renal cell carcinoma.

9.2.2. Endpoints Rationale

Progression Free Survival is an accepted endpoint for evaluating antitumor activity in Phase 2 studies. Evaluation of ORR, OS, DR, and DCR are also important secondary endpoints to support the primary endpoint.

9.2.3. Dose and Regimen Rationale

Part 1: Significant inhibition of ALK1 is expected at dose levels above 0.2 mg/kg based on the half maximal inhibitory concentration (IC_{50}) of dalantercept (150 ng/mL) in cell-based potency assays. Preliminary analysis of PK data from the phase 1 clinical study (A041-01) demonstrated a linear relationship to dose level for C_{max} and $AUC_{(0\text{-}21d)}$. The median t_{max} was 4-7 days and the mean $t_{½}$ was approximately 14-18 days. These data support a dose administration frequency of once every 3 weeks. An analysis of the relationship of dose level to AE risk supports the starting dose of 0.6 mg/kg in combination with axitinib followed by dose escalation.

Part 2: Based on the safety data from the dose escalation and expansion cohorts in Part 1 of the study, the recommended Phase 2 dose level of dalantercept was determined to be 0.9 mg/kg.

Patients will be randomized to receive 0.9 mg/kg of dalantercept or placebo plus a starting dose of axitinib 5 mg PO BID.

9.3. Selection of Study Population

9.3.1. Inclusion Criteria

Eligible patients must meet **all** of the following criteria.

1. Age ≥ 18 years.
2. Histologically confirmed, advanced, predominantly clear cell renal cell carcinoma (RCC).
3. **Part 1:** Progression of disease following up to three lines of prior therapy, including at least one approved VEGF receptor tyrosine kinase inhibitor (TKI) for RCC. Adjuvant therapy is permitted as one line of prior therapy.

   Part 2: Progression of disease following one VEGF pathwaypathway inhibitor for RCC (sunitinib, pazopanib, sorafenib, bevacizumab, tivozanib, or cabozantinib) inclusive of adjuvant therapy if there was documented disease progression during treatment. Patients may have received one additional line of an approved mTOR kinase inhibitor (everolimus, temsirolimus). Prior exposure to investigational and/or approved anticancer immune therapies is permitted.
4. A minimum of 1 week since the last dose of prior therapy (a minimum of 4 weeks since anticancer immune therapy or bevacizumab +/- interferon).
5. Measurable disease that is evaluable by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Appendix 1).
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1(Appendix 2).
7. Life expectancy of at least 12 weeks.
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) ≥ 1,500 /µL (≥ 1.5 x 10^9 /L).
     - Hemoglobin ≥ 9 g/dL (≥ 90 g/L).
     - Platelet count ≥ 100,000 /µL (≥ 100 x 10^9 /L).
   - Measured or calculated creatinine clearance, using the Cockcroft-Gault formula, (Appendix 5) ≥ 40 mL/min.
   - Total bilirubin ≤ 1.2 x upper limit of normal (ULN). Patients with confirmed Gilbert's Syndrome may have bilirubin levels up to 3.0 mg/dL.
   - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN (≤ 5 x ULN if liver metastases are present).
   - Serum albumin ≥ 3.0 g/dL (≥ 30 g/L).

- Sodium ≥ 133 mEq/L (≥ 133 mmol/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. Ability to adhere to the study visit schedule, and to understand and comply with protocol requirements.
11. Signed written informed consent.

9.3.2. Exclusion Criteria

1. Clinically significant pulmonary, endocrine, neurologic, hematologic, gastrointestinal (GI), autoimmune, or genitourinary disease unrelated to RCC that in the judgment of the investigator should preclude treatment with dalantercept or axitinib.
2. Clinically significant cardiovascular risk including:
    - Ejection fraction (EF) ≤ 50% by echocardiogram (ECHO). Multi-gated acquisition scan (MUGA) should be obtained to estimate EF if quality of ECHO is not good.
    - Presence of grade 2 pericardial effusion on baseline ECHO.
    - Significant history of congestive heart failure (CHF) defined as New York Heart Association (NYHA) class II-IV (Appendix 3).
    - 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 and new findings on cardiac evaluation (e.g., clinical, stress test, etc.) within 3 months prior to study day 1.
    - Deep vein thrombosis (DVT) including tumor thrombus within 6 months of study day 1.
    - Significant arrhythmia or electrophysiologic disease including placement of implantable cardioverter defibrillator (ICD), atrial fibrillation with uncontrolled rate or prolonged QTc interval > 450 ms for men and > 470 ms for women.

- Patients receiving cardiac medications should be on stable doses for at least 1 week prior to study day 1.
- 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 < 150/95) upon study entry using a stable regimen of anti-hypertensive therapy.

3. Known CNS metastases or leptomeningeal disease:
    - For Part 1, patients with CNS metastases treated with whole brain radiotherapy, gamma knife, and/or surgery who are considered stable by CNS imaging and are not being treated with corticosteroids 6 weeks prior to study day 1 may be enrolled.
    - For Part 2, patients with CNS metastases treated with stereotatic radio-surgery (SRS), and/or surgery who are considered stable by CNS imaging for at least 2 months prior to enrollment and are not being treated with corticosteroids to manage their CNS disease within 4weeks prior to study day 1 may be enrolled.
4. Active GI bleeding, unrelated to cancer, as evidenced by hematemesis, hematochezia, or melena within 3 months prior to study day 1 without evidence of resolution documented by endoscopy or colonoscopy.
5. Any active malignancy, other than RCC, for which chemotherapy or other anti-cancer therapy is indicated. Patients with adequately treated non-melanoma skin cancer or in situ cancer are permitted. Patients with other cancers from which they have been disease-free for at least 3 years will be permitted.
6. Any lesion invading or having encasement ≥ 180 degrees around the wall of a major blood vessel as assessed by computed tomography (CT) scan and/or magnetic resonance imaging (MRI).
7. Radiotherapy within 2 weeks prior to study day 1.
8. Lack of recovery from toxic effects of previous treatment for RCC to ≤ grade 1 with the exception of alopecia, unless stabilized under adequate medical control.
9. Systemic steroids or immunosuppressive agents within 1 week of study day 1 (with the exception of corticosteroids for CNS disease, see Exclusion #3 or physiologic doses of corticosteroids) or biologic anti-inflammatory immune modulating agents (e.g. infliximab) within 4 weeks of study day 1.
10. Patients undergoing renal dialysis.
11. Major surgery within 4 weeks prior to study day 1 (patients must have recovered completely from any previous surgery prior to study day 1).
12. Any active infection requiring antibiotic therapy within 1 week of study day 1.
13. Anti-coagulation therapy. Aspirin, other anti-platelet agents, and low molecular weight heparin areare permitted unless the investigator deems the patient is at a significant risk for bleeding.

14. Current use or anticipated inability to avoid strong CYP3A4/5 inhibitors or inducers (please refer to the Inlyta® [axitinib] prescribing informationinformation) during participation in the study.
15. PeripheralP edema requiring medical intervention within 2 weeks prior to study day 1.
16. BMI < 16 kg/m^2.
17. 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.
18. 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.
19. Known history of hereditary hemorrhagic telangiectasia (HHT).
20. Known active hepatitis B virus (HBV) or hepatitis C virus (HCV) infections or positive human immunodeficiency virus (HIV) antibody results. Patients with sustained virologic response to HCV treatment or immunity to HBV from prior infection without cirrhosis may be included.
21. History of severe (defined as ≥ grade 3, using the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 4.0 [NCI-CTCAE] v4 current active minor version) allergic or anaphylactic reaction or hypersensitivity to recombinant proteins or excipients (10 mM Tris buffered saline) in the investigational agent.
22. Any prior treatment with dalantercept or any other agent targeting ALK1 pathway.
23. Any prior treatment with axitinib.
24. A morbidity (per the Inlyta® [axitinib] prescribing information) that would require starting a patient at a reduced dose of axitinib.
25. Treatment with another investigational drug (with the exception of anticancer immune therapy) or device, or approved therapy for investigational use, within 5 times the half-life of the drug or within 3 weeks prior to study day 1 if the half-life is not known.
26. Pregnant or lactating female patients.

9.4. 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
- 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)

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) 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).

9.5. Patient Replacement Criteria

Patients participating in Part 1 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 in Part 1 who are replaced will continue to be evaluated for safety.

10. TREATMENT OF PATIENTS

10.1. Dosing for Each Patient

Part 1: The starting dose level of dalantercept will be 0.6 mg/kg SC q3 weeks, plus a starting dose of axitinib 5 mg PO BID. The planned doses of dalantercept that will be administered are outlined below in Table 2.

Table 2: Part 1 Dose Level Per Cohort

Cohort Level	Dose Level (mg/kg)	Number of Patients Dalantercept + Axitinib
1	0.6	3-6
2	0.9	3-6
3	1.2	3-6
4	1.5	3-6
Expansion Cohort	TBD	up to 20
Total (planned)		up to 44

Part 2: Patients will be randomized to receive dalantercept or placebo plus a starting dose of axitinib 5 mg PO BID. Based upon a safety review of the Part 1 data, the recommended Phase 2 dose level of dalantercept was determined to be 0.9 mg/kg in combination with axitinib.

Dose reductions for dalantercept/placebo may be required (see Section 10.6, Dose Modifications).

10.2. 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 9.3.1, Inclusion Criteria and Section 9.3.2, 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 prolonged treatment with any new medications that are specifically excluded by the eligibility criteria (Section 9.3.1, 9.3.2) or the Inlyta® (axitinib) prescribing information (e.g., therapeutic anticoagulation medication, strong CYP3A4/5 inhibitors, strong CYP3A4/5 inducers), and any anticancer treatment other than dalantercept or axitinib, the patient will be discontinued from the study, 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.

10.3. Randomization and Blinding

Part 1: This is an open-label dose escalation that does not require randomization.

Part 2: Patients will be randomized to receive 0.9 mg/kg of dalantercept or placebo plus axitinib 5 mg PO BID. Randomization assignments will be generated through a computerized system, provided by an Interactive Web Response System (IWRS). Patients who have signed informed consent and met all eligibility criteria will be stratified according to prior mTOR therapy and prior immune therapies. Patients will then be randomly assigned to dalantercept or placebo plus axitinib within each stratum.

Only the pharmacist or his/her designee who prepares the study drug (dalantercept or placebo) and an unblinded clinical research associate at the CRO will be unblinded to the patient treatment assignments. All other study personnel, including but not limited to Investigators, study coordinators, nursing staff, clinical monitors, the Sponsor, and the Sponsor's representatives, will remain blinded to the study treatment assignments.

In the event of a medical emergency for an individual patient in which knowledge of the study drug is critical to the patient's medical management, the investigator may break the blind for that patient. However, prior to breaking the blind, every effort must be made by the investigator to first discuss the need to break the blind with the medical monitor. Further, it must be determined by the investigator that breaking the treatment blind is necessary information for the medical management of that patient. If the blind is broken, investigator discretion, in consultation with the medical monitor as needed, should be used to determine if the patient should continue on treatment or be discontinued from the study.

10.4. Treatment Compliance

Each dose of dalantercept or placebo 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 axitinib 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.

10.5. Treatments Administered

Patients will be enrolled and will receive dalantercept or placebo on study day 1 of each 3 week cycle, with safety follow-up visitsas outlined in the Schedule of Events (Section 2). Patients should be observed for a minimum of 30 minutes following treatment with dalantercept or placebo.

Patients will receive continuous dosing of axitinib at a starting dose of 5 mg PO BID, as per prescribing information (see Inlyta® [axitinib] prescribing information, *Dosage and Administration*).

Patients may be discontinued from treatment for reasons outlined in Section 9.4.

10.6. Dose Modifications and Delays

10.6.1. Dose Modifications of dalantercept

Patients will continue to receive the same dose level of dalantercept or placebo as they were assigned at study entry unless a dose modification is required. In general dose delays for reasons other than management of AEs are discouraged. A dose delay of up to 3 weeks for dalantercept/placebo will be allowed at the discretion of the investigator in consultation with the medical monitor for reasons including management of AEs and for mitigating circumstances (e.g. planned procedures and patient request). Palliative radiation to pre-existing non-target lesions per RECIST v1.1 that have not demonstrated unequivocal radiographic progression will be allowed provided dalantercept/placebo dosing does not occur within 1 week pre- and post-radiation completion. Axitinib should be held 2 days before and resumed 2 days after completion of radiation. If administration of dalantercept/placebo cannot be resumed within 3 weeks after the scheduled start of the next treatment cycle, the patient should 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. If a dose is delayed, the patient should resume the study at the planned dosing cycle (e.g. if the patient missed a dose at C4D1, then they would resume dosing at C4D1 and not skip to C5D1).

Patients who experience dalantercept/placebo related AEs may continue treatment with dalantercept/placebo, provided that the AE can be managed (see below).

Table 3 describes the management of related AEs and required dose modifications for dalantercept/placebo. 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/placebo based on their clinical judgment. If possible, these decisions should be discussed with the 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/placebo 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 the patient status. The rules for management of AEs described in Table 3 are applicable to all scheduled visits as well as any unscheduled visits. Refer to Table 4 and Table 5, Dose Level Modifications, for dose level reductions.

Adverse events must resolve as outlined in Table 3 prior to further dosing. 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 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/placebo.

Table 3: Management of Adverse Events Related to Dalantercept/Placebo

Adverse Event or Abnormal Finding	Action	Dalantercept Dose Modification
Weight/peripheral edema Events[a] - Weight gain (not due to fluid retention or edema) due to improvement in health would not be 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/placebo treatment until weight returns to baseline (< 3% increase) or edema resolves.	1. Upon normalization of weight or resolution of edema, dalantercept/placebo 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/placebo 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/placebo treatment until weight returns to baseline (< 3% increase) or edema resolves. • A complete cardiac evaluation including chest x-ray (CXR), ECG, ECHO, troponin, and BNP should be performed if determined to be clinically necessary.	3. Upon normalization of weight or resolution of edema, dalantercept/placebo 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/placebo treatment until resolution of AE(s). • A complete cardiac evaluation including CXR, ECG, ECHO, troponin, and BNP should be performed if determined to be clinically necessary.	1. Upon resolution of AE(s), dalantercept/placebo should be reduced one dose level.
2. ≥ Grade 2 pulmonary edema	• Administer therapy[a] as needed. • Hold dalantercept/placebo treatment until resolution of AE(s). • A complete cardiac evaluation including CXR, ECG, ECHO, troponin, and BNP should be performed if determined to be clinically necessary.	2. Upon resolution of AE(s), dalantercept/placebo should be reduced two dose levels.
3. Grade 1 pleural effusion	• Administer therapy as needed	3. Reduce dalantercept/placebo one dose level
4. ≥ Grade 2 pleural effusion	• Administer therapy as needed • Hold dalantercept/placebo treatment until resolution of AE to ≤ Grade 1	4. Upon resolution of AE, dalantercept/placebo should be reduced two dose levels.

Adverse Event or Abnormal Finding	Action	Dalantercept Dose Modification
Cardiovascular Events		
1. Grade 2 ejection fraction decreased	• Administer therapy as needed • Hold dalantercept/placebo treatment until resolution of AE(s) or improvement of EF > 50%. • A cardiac evaluation including ECHO should be performed prior to starting next cycle. • Consider holding or modifying dose of axitinib.	1. Upon resolution of AE(s) or improvement of EF > 50% dalantercept/placebo should be reduced one dose level and continue to follow repeat ECHO every 6-12 weeks throughout study duration. 2. Consider axitinib dose modification.if determined to be clinically necessary.
2. Grade 2 pericardial effusion detected on imaging	• Administer therapy as needed • Hold dalantercept/placebo treatment and repeat ECHO prior to starting next cycle. in three weeks	3. If stable or resolved on repeat ECHO, reduce dalantercept/placebo one dose level. Repeat ECHO as clinically indicated. If worsened, discontinue dalantercept/placebo.
3. ≥ Grade 3 cardiovascular event[b] including grade 3 pericardial effusion detected on ECHO	• Discontinue further dalantercept/placebo treatment.	
Other Events		
1. ≥ Grade 2 bleeding event with the exception of grade 2 epistaxis	• Discontinue further dalantercept/placebo treatment.	
2. Any other event ≥ Grade 3 [e.g., hyponatremia (< 130 mmol/L)] with the exception of ≥ Grade 3 amylase and/or lipase in the absence of clinical symptoms.	• Hold dalantercept/placebo treatment until resolution of AE(s). • Work up as appropriate (e.g., serum and urine osmolality, serum and urine sodium, etc.).	2. Upon resolution of AE(s) to grade 1 or baseline, dalantercept/placebo should be reduced one dose level.

[a] Investigators can administer fluid management therapy as described in Section 10.6.3 (Fluid Management Therapy).
[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 (Table 3) due to AEs (e.g., from 0.9 mg/kg to 0.68 mg/kg, from 0.68 mg/kg to 0.51 mg/kg, and from 0.51 mg/kg to 0.38 mg/kg).

Table 4: Dalantercept Dose Level Modifications (Part 1)

Dose Modification	Cohort 1	Cohort 2	Cohort 3	Group 4
Starting dose level	0.6 mg/kg	0.9 mg/kg	1.2 mg/kg	1.5 mg/kg
First dose reduction level	0.45 mg/kg	0.68 mg/kg	0.9 mg/kg	1.13 mg/kg
Second dose reduction level	0.34 mg/kg	0.51 mg/kg	0.68 mg/kg	0.85 mg/kg
Third dose reduction level	0.26 mg/kg	0.38 mg/kg	0.51 mg/kg	0.64 mg/kg
Fourth dose reduction level	Discontinue dalantercept treatment			

Table 5: Dalantercept/Placebo Dose Level Modifications (Part 2)

Dose Modification	Patients Randomized in Part 2
Starting dose level	0.9 mg/kg
First dose reduction level	0.68 mg/kg
Second dose reduction level	0.51 mg/kg
Third dose reduction level	0.38 mg/kg
Fourth dose reduction level	Discontinue dalantercept/placebo treatment

10.6.2. Dose Modifications of Axitinib

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 axitinib (see Inlyta® [axitinib] prescribing information, *Warnings and Precautions*). If dose reduction from 5 mg BID is required, the recommended reduced dose is 3 mg BID. If additional dose reduction is required, the recommended reduced dose is 2 mg BID.

Asymptomatic changes in ejection fraction and CHF events have been documented with the class of VEGFR TKIs and therefore, investigators may consider holding or reducing the dose of axitinib in the event of these adverse events.[21]

In the event of a Grade 3 or greater toxicity, if it is deemed at the investigator's discretion to be related to axitinib, then axitinib 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 axitinib due to an adverse event related only to axitinib may continue to receive treatment with dalantercept in Part 1 only. Patients who require permanent discontinuation of axitinib due to an adverse event related only to axitinib in Part 2 should be discontinued from study treatment and should complete the final visit. If patients requiring discontinuation of axitinib have received < 2 doses of dalantercept plus axitinib, they may be replaced, in Part 1 only (see Section 9.5). The patients remaining on

dalantercept not in combination with axitinib will continue to follow the regular schedule of events (Section 2).

Patients who tolerate axitinib for at least four consecutive weeks with no axitinib-related adverse reactions > Grade 2 (according to the NCI-CTCAE v4 current active minor version), no dose reductions to axitinib, and stable BP ≤ 150/90 mm Hg, on ≤ 2 concurrent anti-hypertensive medications, may have their dose increased from 5 mg BID to 7 mg BID, and subsequently from 7 mg BID to 10 mg BID using the same criteria.[22] Patients participating in Part 1 of the study should not have their dose level of axitinib increased before study day 29 (C2D8).

10.6.3. Fluid Management Therapy

10.6.3.1. Diuretics

Use of diuretics is allowed to maintain approximate baseline weight in the instance a weight or other fluid event occurs 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.

10.7. Safety Review Team (SRT)/Data Monitoring Committee (DMC)

Dose-Limiting Toxicity (DLT) Definition

A DLT is defined as any of the following events that are considered possibly or probably related to dalantercept.

- Weight gain (due to fluid retention) grade 2 or higher
- Pulmonary edema grade 2 or higher
- Bleeding grade 2 or higher
- Cardiovascular event grade 3 or higher
- Non-hematologic adverse event grade 3 or higher with the exception of grade 3 or higher amylase and lipase without clinical 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

Part 1

Safety and Dose Limiting Toxicities (DLTs) will be evaluated by the SRT. In addition, the MTD or maximum tested dose, the number of patients to be enrolled in the expansion cohort and the recommended Phase 2 dose level for Part 2 will be determined 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 study day 29 to assess the safety of a dose level prior to dose escalation. Dose

escalation will not occur until the patients in the preceding dose level have been evaluated for a minimum of 29 days.

After a minimum of 3 evaluable patients have been evaluated for a minimum of 29 days, the SRT will consider dose escalation to the next dose cohort or the addition of 3 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 of 3 patients at a dose level experiences a DLT, 3 additional patients may be enrolled at the current dose level.
    - If there are no further DLTs in the 3 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 axitinib at an appropriate dose level as outlined in the Management of Adverse Events table.

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 up to 2 different dose levels at or below the MTD to further evaluate safety, tolerability, and preliminary anti-tumor activity of dalantercept plus axitinib and to determine the recommended Phase 2 dose level for Part 2. The SRT will meet after a minimum of 10 patients have been evaluated for a minimum of 29 days to review safety data and vital signs data to assess safety.

If 4 DLT events occur at any time during the first 29 days in a minimum of 10 patients in the expansion cohort, further enrollment in that expansion cohort will be discontinued. The SRT may decide to cease enrollment if fewer than 4 DLT event(s) occur 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.

Part 2

A data monitoring committee (DMC), independent from the sponsor, will be established to review unblinded safety data on a regular basis and to make appropriate recommendations regarding the conduct of the trial.

The first DMC safety review will occur when 25 patients arerandomized. Thereafter, DMC review meetings will be performed at approximately 6 month intervals until the end of the study. If agreed by the DMC and Acceleron, this schedule may be modified based on the rate of patient accrual and findings from DMC reviews. A detailed charter will outline all activities of the DMC (including, but not limited to, type of data to be reviewed, DMC responsibilities, communication paths, and frequency of meetings).

The unblinded safety analyses will be generated for the DMC by an independent statistician.

In order to evaluate study assumptions for the primary endpoint of PFS, a blinded sample size re-estimation (BSSR) will be performed after 85 patients have been recruited. Based on the

results of the BSSR, the DMC will recommend either to continue enrollment to the original planned sample size (n=130) or to increase the sample size to a specified number. The BSSR will be performed from the pooled treatment group survival data[23]. Details will be provided in the Statistical Analysis Plan and the DMC charter. Since the treatments will remain blinded and no inference will be performed during this analysis, the type I error rate for the final analysis will be preserved. Enrollment will continue during the BSSR.

11. STUDY PROCEDURES

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

11.1. 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.

11.2. Safety Assessments

11.2.1. Clinical Safety Laboratory Tests

- Hematology: Complete blood count (CBC) with differential; CBC includes RBCs, white blood cells (WBCs), platelets, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC).
    - Screening visit only (within 14 days prior to study day 1): PT/INR and aPTT should be included in addition to the standard hematology panel outlined above.
- Serum chemistry: Albumin, alkaline phosphatase (ALP), ALT, AST, blood urea nitrogen (BUN), calcium, chloride, carbon dioxide (CO_2), creatinine, glucose, lactate dehydrogenase (LDH), phosphorus, potassium, sodium, total bilirubin,amylase, and lipase. Note: after C15, amylase and lipase are not required unless clinically indicated.
- Thyroid Function: Free thyroxine (T_4) and thyroid stimulating hormone (TSH).
- Urine by urinalysis or dipstick analysis: pH, specific gravity, protein, glucose, ketones, blood, leukocyte esterase, and nitrite with microscopic examination if indicated.

11.2.2. 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, and musculoskeletal (including edema)] required at screening, Cycle 1 Day 1 (C1D1), C1D8, C2D1, C3D1, C4D1, C5D1, C6D1 and the final visit. A neurologic exam is required at screening and repeated only if clinically indicated. At all other timepoints noted and beyond C6, a targeted exam of the respiratory, cardiovascular and musculoskeletal (including edema) is required. If clinically indicated, additional assessment of other body systems should occur. Findings at screening and prior to dosing on C1D1 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, temperature (documented in degrees Celsius), respiration rate, and 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). MUGA should be performed to estimate EF if quality of ECHO is not good.
- Anti-drug antibody and neutralizing antibody testing: As indicated.

11.3. Pharmacokinetic, Pharmacodynamic Assessments and Biopsies

The PK and PD assessments and archived biopsies that are planned for this study are outlined below. Specific details regarding these assessments will be located in the Study Reference Guide.

11.3.1. Pharmacokinetic Assessments

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

11.3.2. Pharmacodynamic Blood Biomarkers

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

11.3.3. Archived Biopsy

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

11.4. Tumor Response Assessment

11.4.1. Tumor Assessments

CT or MRI scans assessing treatment response and disease progression will be read at the investigational site for the primary analysis. It should be determined that a patient has not progressed before the next cycle study treatment is given, using local investigator assessments.

11.4.2. Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1)

RECIST, version 1.1 (Appendix 1) will be used to determine objective response (usually based on CT or MRI scan data). Please see the complete RECIST, version 1.1, guidelines for additional details regarding tumor response assessment.

12. STUDY SCHEDULE

Please refer to Section 2, Schedule of Events for the schedule of procedures required for each visit. Note that all windows on visits should be determined relative to the date of the previous dose of dalantercept/placebo. 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.

12.1. Screening

- Signature of the current IRB-approved ICF should occur within 28 days prior to C1D1 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, CXR 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.
- Head CT or MRI is required at screening to exclude any patients with active brain metastases. This does not need to be repeated at subsequent visits unless clinically indicated.
- Archived 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 the medical history CRF.
- Screen failure information will be maintained to document specific information, including but not limited to, reason for failure.

12.2. Dosing Days and Interim Visits

- All screening and study day 1 procedure results required to confirm eligibility must be obtained and reviewed prior to study drug administration. Patient eligibility for inclusion/exclusion criteria must be confirmed from these results, as applicable. Ideally, patients should be randomized within 48 hours of C1D1.
- Baseline hematology, chemistry, and urinalysis results must be reviewed prior to dosing on C1D1 but may be collected up to 72 hours prior to dosing. Baseline thyroid function may also be collected up to 72 hours prior to dosing. Therefore if the screening visit occurs within 72 hours of study day 1, the hematology, chemistry, thyroid function and urinalysis testing do not need to be repeated.
- Any non-serious AEs that occur prior to dosing in cycle 1 should be recorded in the medical history section of the CRF.
- All AEs that occur after dosing in cycle 1 should be recorded in the AE page of the CRF.

- On subsequent dosing days, all AEs and abnormal laboratory or other findings that might require modification of dosing (see Section 10.6) should be reviewed prior to dosing to ensure that the patient is still eligible to receive additional doses of dalantercept/placebo. Please note that there is an extended window of up to 5 days for the ECHO and tumor response assessment scan, when required.
- PK blood sample collection should be performed pre-dose for dalantercept/placebo and axitinib at C1D1, C2D1 and C3D1.
- Tumor response assessment scans should be performed every 6 weeks regardless of dalantercept/placebo or axitinib dosing delays through C15. After C15 tumor response assessment scans should be performed every 12 weeks regardless of dalantercept/placebo or axitinib dosing delays (e.g. C19D1, C23D1, etc.).
- 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 comes off study (i.e. C7D1=C5D1, C8D1=C6D1, etc.). The only exception is that after cycle 5, ADA, urinalysis, thyroid function and PD biomarkers are required once every 4 cycles instead of once every 2 cycles (i.e., C9D1, C13D1, etc.).

12.2.1. Final Visit

- The final visit should occur when a patient discontinues from the study within 30 days after the last dose of dalantercept/placebo (± 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.

12.2.2. 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 survival.
- Patients will be asked to return to the clinic approximately every 3 months for tumor response assessment scans if progression of disease has not previously been documented. Patients that discontinue study treatment and initiate a new therapy or continue on axitinib alone, prior to documented radiographic disease progression are not required to return to the clinic every 3 months for tumor response assessment scans.
- Patients may also be asked to return to the clinic approximately additional ADA testing until a negative/stable result is obtained.

12.3. Discontinuation of Study

The sponsor may terminate this study or a dose level after consultation with the investigator, the SRT, or DMC, 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.

13. STUDY DRUG MATERIALS AND MANAGEMENT

13.1. Study Drug

Dalantercept is a recombinant fusion protein consisting of the ECD of human ALK1 linked to the Fc (hinge, CH2 and CH3 domains) portion of human IgG1.

13.2. 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.

The placebo (control agent) to be used in this study will be sterile normal saline (0.9% Sodium Chloride for Injection) administered as an SC injection. Sterile normal saline will be supplied by the investigational site's pharmacist. The manufacturer's directions for saline storage and handling are to be followed, as are standard clinical practices for ensuring sterility.

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

13.3. Study Drug Storage

Dalantercept should be stored at ≤ -65°C.

Axitinib should be stored at 20°C to 25°C (68°F to 77°F).

13.4. Study Drug Preparation

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

There is no preparation needed for axitinib.

13.5. Administration

Dalantercept/placebo is to be administered by SC injection once every 3 weeks. Each injection will not exceed 1.0 mL; multiple injections may be required to administer the required dose. Please refer to the Study Reference Guide for detailed dalantercept drug handling, administration, and storage instructions.

The starting dose of axitinib is 5 mg PO BID. Please refer to the Inlyta® (axitinib) prescribing information, *Dosage and Administration*, for additional axitinib administration information.

13.6. Study Drug Accountability

Accountability for dalantercept/placebo and axitinib 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 axitinib accountability.

13.7. 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 Inlyta® (axitinib), *How Supplied/Storage and Handling*) for detailed drug handling, administration, storage, and disposal instructions.

14. ASSESSMENT OF SAFETY

14.1. 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.
Any death occurring greater than 30 days after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours only if it is possibly, probably, or definitely related to the investigational agent/intervention.

14.2. 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.

14.3. Severity

Investigators must evaluate the severity/intensity of AEs according to the NCI-CTCAE v4 current active 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 active 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.

14.4. Relationship to Study Drug

Investigators must also assess the causal relationship of each AE to dalantercept/placebo and axitinib. Factors for the assessment of causal relationship include, but are not limited to, temporal relationship between the AE and the administration of dalantercept/placebo or axitinib, known side effects of dalantercept/placebo or axitinib, 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/placebo or axitinib 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/placebo or axitinib.

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.

14.5. 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 14.1, are considered AEs and must be recorded on the AE CRF. AEs are to be followed for resolution as described in Section 14.6.

It is important that each AE report include a description of the event, duration (onset and resolution dates), severity, relationship with dalantercept/placebo, relationship with axitinib, any other potential causal factors, any treatment given or other action taken (including dose modification or discontinuation of dalantercept or axitinib) 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 14.5.1.

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

14.5.1. 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 14.7 (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.

14.6. 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.

14.7. 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.

For Part 1, 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. For Part 2, requests for follow-up will be made by the CRO Pharmacovigilance representative who may contact the investigator directly to obtain clarification on a particularly critical event.

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

The sponsor will send appropriate blinded or unblinded (as applicable) 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.

15. STATISTICS

Statistical Methods:

Study Design Overview

A dose escalation plus expansion cohort design to evaluate the safety of dalantercept plus axitinib will be implemented to determine the recommended Phase 2 dose level of dalantercept for Part 2 of the trial.

Part 2 is a randomized placebo-controlled trial in previously treated advanced RCC patients. The randomization will be stratified by prior mTOR therapy and prior immune therapy. The primary endpoint for statistical analysis is PFS defined as the time from randomization to documented progression or death based on the investigator assessment.

Analysis Populations:

The **All Treated (AT) Population** includes all patients who received any study drug. The AT is the population that will be used when performing the primary analysis of the primary endpoint and all safety analyses. The AT population will be analyzed according to treatment received.

The **Full Analysis Set (FAS)** includes all randomized patients. The intent-to-treat principle will be used for this study population. The FAS will be used in secondary analyses of the primary endpoint.

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

15.1. Statistical Analysis Plan

Details regarding the final data analysis will be discussed in a separate Statistical Analysis Plan (SAP). The study data from Part 1 and Part 2 of the trial will be analyzed separately.

15.2. Determination of Sample Size

Part 1

There is no formal sample size calculation for Part 1 (dose escalation and expansion).

Part 2

The primary analysis of efficacy will be performed when at least 82 PFS events have been observed and documented. If the median time to PFS is assumed to be 5 months in the placebo plus axitinib control group, then a total of 82 PFS events will provide approximately 80% power to detect a 3 month extension from 5 to 8 months in the dalantercept plus axitinib experimental treatment group when performing a stratified log-rank test of the null hypothesis of no difference between treatment groups using a one-sided 10% significance level.

The projection of power is made under a proportional hazards assumption so that the hazard ratio (HR) for dalantercept plus axitinib relative to placebo plus axitinib is equal to 0.625 under the alternative hypothesis. It is projected that 130 patients will need to be randomized to obtain 82 PFS events. The number of patients to be randomized provides for patient censoring patterns that could occur under the alternative hypothesis in the event the dropout rate is higher than expected in either treatment group.

15.3. Part 1 – Safety and Tolerability Analyses

The assessment of safety will be based mainly on the frequency of adverse events (overall, related, and SAE) and on the frequency of clinically meaningful abnormal laboratory values. Other safety data (e.g., vital signs, ECHO, ECG) will be summarized as changes from baseline and frequency counts as appropriate. All safety data will be listed. The primary study population will be the AT population.

PFS, OS, ORR, duration of response, disease control rate, and PD biomarker studies will be analyzed in a similar manner as described in Part 2.

15.4. Part 2 – Efficacy and Safety

15.4.1. Primary Endpoint

Progression free survival: PFS is the primary endpoint in Part 2 and will be defined as the date of radiographic (also called documented) tumor progression (per RECISTv1.1) or death from any cause, whichever is earliest, minus date of randomization (or first date of dosing in Part 1 as will be implied throughout) plus one day. The term "on-study" will refer to the period from randomization until 28 days after last dose of study medication. Patients will be censored (i.e., those patients not exhibiting radiographic tumor progression or death) on the date of the last tumor assessment on-study and includes:

- Those patients discontinuing study medication due to any reason and having at least 1 radiographic tumor assessment before or on the date of discontinuation
- Those patients in whom radiographic tumor progression or death occurs following ≥ 2 consecutive scheduled missing radiographic tumor assessments
- Those patients given non-study antitumor medication or treatment prior to documentation of radiographic tumor progression

Patients missing baseline radiographic tumor assessments will be censored on the date of randomization. Patients with missing post-randomization radiographic tumor assessments will be censored on the date of randomization unless death occurred prior to the first and second scheduled radiographic tumor assessment, whereby death is the event.

Primary Efficacy Analysis

Primary Efficacy Analysis of PFS

The primary analysis of PFS will be based on investigator assessment using the AT population. Time to radiographic progression or death is the primary efficacy analysis and will be performed using a stratified (by prior treatment) log-rank test.

A log-rank test stratified by prior mTOR therapy and prior immune therapy will be used to test the null hypothesis of no difference between dalantercept plus axitinib and placebo plus axitinib using a one-sided 0.10 significance level. Kaplan-Meier curves will be displayed depicting each treatment group. The hazard ratio (dalantercept plus axitinib: placebo plus axitinib) will be estimated using a stratified Cox proportional hazards model along with the 95% confidence intervals. Multiple sensitivity analyses will be outlined in the SAP. Each sensitivity analysis will be analyzed using the same statistical analyses; however, the PFS definition may differ. One such sensitivity analysis will include patients going off-study for symptomatic progression,

change in cancer treatment, or decreasing performance status which will be considered as PFS events at that known date.

The mode of radiologic assessment should be the same across visits within each patient. Screening/Baseline tumor assessments must be performed prior to randomization and within the screening period. When multiple radiographic tumor assessments are performed prior to randomization, the closest assessment prior to that date will be designated as baseline.

Missing Radiological Assessments and Non-evaluable (NE) Designation
If all lesions cannot be evaluated due to missing data or poor image quality the patient is not evaluable (NE) at that time point. If only a subset of lesions can be evaluated at an assessment, the visit is also considered NE.

Assessment of Potential Influential Prognostic Factors of PFS and OS

In addition to the analyses described above, the following pre-specified prognostic variables will be examined for their influence alone and in combination with the treatment effect on the analysis of PFS.

- Number of sites of metastatic disease;
- Prior nephrectomy;
- ECOG performance status 0 or 1, and
- International Metastatic Renal Cancer Database Consortium (IMDC) and Memorial Sloan Kettering Cancer Center (MSKCC) risk groups both categorized as favorable, intermediate, or poor.[19,24-26]

15.4.2. Secondary Endpoints

Secondary endpoint: PFS in the subgroup of the patients who had 2 or more prior lines of anticancer therapy will be analyzed similarly as the primary PFS analysis. Due to the size of the subgroup, the comparison will be tested at one-sided 0.20 significant level.

If the hazard ratio is 0.625, the same as the PFS hypothesis for overall population, the power to claim statistical significance will be 80% if the subgroup has 52 events and 70% with 34 events.

Safety Analysis: The safety analyses will be performed on the AT population. Adverse event incidence rates will be tabulated by System Organ Class (SOC) 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.

Overall Survival (OS): Another key secondary endpoint that will be estimated is OS. OS is defined as the time from randomization to death. If the trial is concluded and there is no evidence that the patient died, then the patient will be censored at the last follow-up contact visit for which the patient is documented as being alive. If the patient is lost to follow-up, all reasonable effort will be made to ascertain the patient status. Patients who discontinue from the treatment phase of the study will be followed for at least two years from randomization for OS. Median survival along with quartiles and confidence intervals will be calculated.

A Kaplan-Meier curve for survival will be displayed and 95% confidence intervals for median survival computed for each treatment arm. A stratified log-rank will be used to test the difference in OS between the two treatment arms. The hazard ratio for the OS treatment effect will be estimated using a stratified Cox model.

Objective Response Rate (ORR): Patients will be evaluable for ORR if they have at least one measurable lesion at baseline and at least one radiographic disease assessment after baseline. The Best Overall response rate will be estimated based on the proportion of patients evaluable for response. Exact 95% confidence intervals will be calculated.

Duration of Response (DR): Duration of response is defined as the time from the first radiographic tumor response of CR or PR to the date of radiographic tumor progression or death, whichever is earliest.

Disease Control Rate (DCR): Disease control rate will be estimated as the proportion of patients evaluable for response who meet the criteria for CR, PR, or SD. The 95% confidence intervals of disease control rate will be calculated.

PD Biomarkers (Exploratory): Levels of BMP9/10, ALK1 and other relevant markers in tumor tissue and blood will be summarized, and analyzed for correlation with efficacy outcome measures.

15.5. 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 in Part 1 and Part 2. Additional analyses will be performed to assess possible drug-drug interactions, exposure/response, and exposure/toxicity relationships. For all PK analyses, the PK population will be used.

15.6. 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.

16. SOURCE DOCUMENTATION AND INVESTIGATOR FILES

16.1. 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).

16.2. 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.

17. QUALITY CONTROL AND QUALITY ASSURANCE

17.1. Data Quality Control and Quality Assurance

17.1.1. 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.

17.1.2. 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.

18. 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.

19. 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.

20. 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.

21. DATA HANDLING AND RECORDKEEPING

21.1. 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.

21.2. 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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23. APPENDICES

23.1. Appendix 1: RECIST v. 1.1[27]

RECIST Criteria-Response Evaluation

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 normalisation of tumour 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 tumour 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 v. 1.1.

23.2. Appendix 2: ECOG Performance Status[28]

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.

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 selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

23.3. Appendix 3: New York Heart Association - Classification of heart failure[29]

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.

23.4. Appendix 4: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

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

23.5. Appendix 5: Cockcroft-Gault formula for Estimation of Creatinine Clearance[30]

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

23.6. Appendix 6: Karnofsky Performance Status Criteria[31]

Karnofsky Performance Scale	
Percent	**Description**
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity, minor signs or symptoms of disease.
80	Normal activity with effort, some signs or symptoms of disease.
70	Cares for self. Unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization is indicated although death not imminent.
20	Hospitalization necessary, very sick, active supportive treatment necessary.
10	Moribund, fatal processes progressing rapidly.
0	Dead.