A Multi-center, Open Label, Randomized Phase 2 Study of AGS-16C3F vs. Axitinib in Metastatic Renal Cell Carcinoma

ISN/Protocol AGS-16C3F-15-3

Version 6.0

Incorporating Substantial Amendment 5

12 August 2020

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Sponsor:

Astellas Pharma Global Development, Inc. (APGD)
1 Astellas Way
Northbrook, IL 60062

Protocol History:
Version 1.0: 16 Sep 2015
Version 2.0: 22 Jan 2016 (Amendment 1)
Version 3.0: 27 May 2016 (Amendment 2)
Version 4.0: 18 Jul 2017 (Amendment 3)
Version 5.0: 09 Feb 2018 (Amendment 4)

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I. INVESTIGATOR'S SIGNATURE

Protocol AGS-16C3F-15-3

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I have read all pages of this clinical study protocol for which Astellas is the Sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with ICH GCP guidelines and applicable local regulations. I will also ensure that sub-investigator(s) and other relevant members of my staff have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

Signature: _____

Date (DD Mmm YYYY)

Printed Name: _____

Address: _____

_____

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

24h-Contact for Serious Adverse Events (SAEs) See Section 5.7.5	**24h Quintiles Medical Emergency Contact Center:** **1-973-659-6677** **1-570-819-8565** **Please fax the SAE Worksheet to:** **Astellas Pharma Global Development, Inc.** **Medical Safety Pharmacovigilance** **Fax number: 1-888-396-3750** **Email: Safety-US@astellas.com**
Clinical Research Contacts	PPD PPD , Medical and Development
Medical Monitor/Medical Expert:	PPD

III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

Abbreviations	Description of abbreviations
ADA	Anti-drug Antibody
ADC	Antibody drug conjugate
AE	Adverse event
AGS-16C3F	Antibody Drug Conjugate derived from CHO cell line
AGS-16M8F	Antibody Drug Conjugate derived from hybridoma cell line
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase (GPT)
ANC	Absolute Neutrophil Count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase (GOT)
ATP	Adenosine Triphosphate
AUC	Area under the concentration-time curve
BCVA	Best corrected visual acuity
BUN	Blood urea nitrogen
C1D1	Cycle 1 Day 1
CBC	Complete blood count
ccRCC	Clear cell renal cell carcinoma
C_{EOI}	Concentration at the end of infusion
CHO	Chinese hamster ovary
CI	Confidence interval
C_{max}	Maximum concentration
CR	Complete response
CRO	Contract Research Organization
CRP	C-Reactive protein
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
Cys-mcMMAF	Active metabolite resulting from the catabolism of AGS-16C3F
DILI	Drug-induced Liver Injury
DLT	Dose limiting toxicity
DVT	Deep Venous (Vein) Thrombosis
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
ENPP	ectonucleotide phosphodiesterases-pyrophosphatase
EOI	End of infusion
EOM	Extraocular movement
ESQ	Eye Symptom Questionnaire
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

Abbreviations	Description of abbreviations
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IHC	Immunohistochemical
IND	Investigational New Drug application
INR	International normalized ratio
IOP	Intraocular pressure
IRB	Institutional Review Board
IRT	Interactive response technology
IV	Intravenous
LA-CRF	Liver Abnormality Case Report form
LDH	Lactate dehydrogenase
LFT	Liver function tests
mAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
MMAF	Monomethyl auristatin F
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
mTOR	Mammalian target of rapamycin
NOAEL	No Observed Adverse Effect Level
PD	Progressive Disease
PE	Pulmonary Embolism
PFS	Progression Free Survival
PK	Pharmacokinetics
PKAS	Pharmacokinetic analysis set
PPS	Per protocol set
PR	Partial response
PRN	as needed
PT	Prothrombin time
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
RCC	Renal cell carcinoma
SAE	Serious adverse event
SPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Apparent terminal elimination half-life
TBL	Total bilirubin
TEAE	Treatment Emergent Adverse Event
TK	Toxicokinetic
t_{max}	Time after dosing when C_{max} occurs
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
uPCR	Urine protein to creatinine ratio
VA	Visual acuity
VEGF	Vascular endothelial growth factor
VHL	von Hippel-Lindau
V_{ss}	Volume of Distribution at Steady State

Definition of Key Study Terms

Terms	Definition of terms
Baseline	Observed values/findings which are regarded observed starting point for comparison.
Enroll	To register or enter into a clinical trial. NOTE: For this study, a subject is considered enrolled once they have been randomized
Intervention	The drug, therapy or process under investigation in a clinical study that is believed to have an effect on outcomes of interest in a study. (e.g., health-related quality of life, efficacy, safety, pharmacoeconomics).
Prescreening period	Period of time after a subject signs the prescreening consent, lasting until the subject signs the main consent
Randomization	The process of assigning trial subjects to treatment or control groups using an element of chance to determine assignments in order to reduce bias.
Screening period	Period of time before entering the treatment period, usually from the time of a subject signing main consent until just before the test drug or comparative drug is given to a subject.
Screening	A process of active consideration of potential subjects for enrollment in a trial.
Screen failure	Potential subject who did not meet one or more criteria required for participation in a trial.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

IV. SYNOPSIS

Date and Version # of Protocol Synopsis:	12 August 2020, Version 6.0
Sponsor: Astellas Pharma Global Development Inc (APGD)	**Protocol Number:** AGS-16C3F-15-3
Name of Study Drug: AGS-16C3F	**Phase of Development:** 2
Title of Study: A Multi-center, Open Label, Randomized Phase 2 Study of AGS-16C3F vs. Axitinib in Metastatic Renal Cell Carcinoma	
Planned Study Period: From 2Q2016 to 3Q2020	
Study Objective(s)**:** **Primary Objective** To evaluate the Progression Free Survival (PFS), based on investigator radiologic review, of AGS-16C3F compared to axitinib in subjects with metastatic renal cell carcinoma (RCC) **Secondary Objectives** • To evaluate the following for AGS-16C3F compared against axitinib: o PFS per RECIST v1.1 by blinded central radiology assessment o Objective Response Rate (ORR) based on the investigator's radiographic assessment o Duration of Response (DOR) based on the investigator's radiographic assessment o Overall Survival (OS) o Disease Control Rate (DCR) based on the investigator's radiographic assessment o Safety • To evaluate the pharmacokinetics of AGS-16C3F • To evaluate the incidence of antidrug antibody formation to human native antibody (AGS-16C3) and antibody drug conjugate (AGS-16C3F)	
Planned Total Number of Study Centers and Location(s): Approximately 30 centers US, Canada	
Study Population: Subjects with metastatic RCC of any histology, who have evidence of progression on or after the last regimen received: • Clear cell histology subjects must have received at least 2 prior systemic regimens, one of which is an anti-VEGF agent. • Non-clear cell histology subjects must have received at least 1 prior anti-VEGF regimen and also screen positive by immunohistochemical (IHC) for ENPP3	
Number of Subjects to be Enrolled/Randomized: Approximately 134 subjects in total randomized 1:1 (the number of subjects with non-clear cell histology is limited to 26 total).	

Study Design Overview:

This multi-center, open-label, randomized study will enroll subjects with metastatic RCC of all histologies who have evidence of progression on or after the last regimen received and have also received at least 2 prior systemic regimens, 1 of which is an anti-VEGF agent (clear cell subjects).

Non-clear cell RCC is a heterogeneous group of tumors typically not driven by von Hippel-Lindau (VHL) gene and sensitivity to anti-VEGF treatments differ from that shown in clear cell RCC. Hence, subjects with non-clear cell histology are only required to have progressed on or after at least one anti-VEGF regimen.

Subjects with non-clear cell histology must also have ENPP3 positive IHC staining at prescreening. Positivity is defined as an IHC H-score ≥ 15. Non-clear cell subjects whose tissue has an IHC H-score of ≥ 15 will qualify to screen for the study.

Clear cell subjects are not required to be screened for ENPP3 to qualify the study, but subjects must submit tissue during the study for retrospective target expression assessment by IHC.

Subjects will be randomized at 1:1 ratio to either AGS-16C3F or axitinib. Randomization will be stratified according to Eastern Cooperative Oncology Group (ECOG) Performance Status (0 or 1), the number of prior systemic RCC regimens (2 or > 2) and RCC histology (clear cell or non-clear cell).

For stratification purpose:

- Non-clear cell subjects who have progressed after only one prior anti-VEGF regimen will be regarded the same as those clear cell subjects who have progressed after 2 prior systemic RCC regimens.
- Non-clear cell subjects who have progressed after > 1 prior systemic RCC regimens will be regarded the same as those clear cell subjects who have progressed after > 2 prior systemic RCC regimens.

Stratification Categories for Randomization Process (see Table 3 below)

Prior Systemic RCC Regimen Stratum	Clear Cell Subjects	Non-Clear Cell Subjects
2	2 prior systemic RCC regimens	1 prior systemic RCC regimen
> 2	> 2 prior systemic RCC regimens	> 1 prior systemic RCC regimens

The RCC histology categorization is defined as the following:

- Clear cell group:
  - Clear cell
  - Clear cell component
  - Mixed clear cell
- Non-clear cell group:
  - Papillary and everything else*
    * everything else: chromophobe, collecting duct, renal medullary, etc., not so common but possible other RCC histologies

Subjects will be eligible to continue receiving treatment on study until disease progression per RECIST v.1.1, unacceptable toxicity, investigator's decision, or study withdrawal. Subjects will also be discontinued from treatment if a significant non-compliance occurs (e.g., those that compromise study objectives or subject safety), or if a subject is lost to follow-up.

All subjects will be required to have a Safety Follow-Up visit at least 28 days (+ 7 days) after the last dose (Refer to Section 5.2.7).

All subjects will be followed for survival approximately every 8 weeks from the Safety Follow-Up visit. This will be done by telephone, until death or study closure, whichever occurs first. A standard of care clinic visit can be used in lieu of a telephone call, if the subject is already coming to clinic.

Those subjects who discontinued the study for reasons other than objective disease progression by RECIST v.1.1 will continue to have disease assessments every 8 weeks (± 7 days) counting from C1D1. This will continue until subject has radiologically confirmed progression, initiates a new therapy, study closure or subject dies.

The primary endpoint is PFS based on investigator assessment utilizing RECIST v.1.1. Secondary endpoints include PFS per blinded central review, and DCR, ORR, DOR (each of the 3 based on investigator review), OS, Safety, and PK.

The study will have an Independent Data-Monitoring Committee (IDMC).

Treatment Plan:

Subjects randomized to AGS-16C3F will be administered at 1.8 mg/kg as a single 60-minute intravenous (IV) infusion once every 3 weeks. Therapy may be interrupted and/or dose adjusted in case of toxicity. Dose changes must be discussed with the Medical Monitor.

These subjects must also use 1% prednisolone acetate ophthalmic suspension prophylactically (prophylaxis steroid drops) starting from Day (-1) of each treatment cycle (Refer to Table 5 in Section 5.1.3.1). Prophylaxis steroid drops will be applied to both eyes, 1 drop to each eye, 6 times daily while awake for the first 7 days of each cycle (starting at Day [-1]), then 4 times daily while awake for an additional 7 days, and then stopped. This will be repeated in each treatment cycle. Should the subsequent dose be delayed, the "no prophylaxis steroid eye drop use" period will extend. The study will not provide the prophylaxis steroid drops (i.e., each site to supply); but the cost will be reimbursed.

Subjects randomized to axitinib will all have a starting dose of 5 mg, administered twice daily continuously, by mouth. This dose may be adjusted during the study as needed, as defined in the product label and local institutional guidelines, in doses ranging from 2 to 10 mg, administered twice daily continuously, by mouth. Axitinib dose changes may be discussed with the Medical Monitor at the discretion of the Investigator.

For both treatment arms, subjects will have disease assessments every 8 weeks (± 7 days) counting from C1D1, irrespective of any treatment hiatus.

- Subject may continue therapy if the disease status is at least Stable Disease (SD) per RECIST v.1.1.
- If the treatment hiatus will be longer than 5 weeks, each case must be discussed with the Medical Monitor.

Treatment Re-challenge:

The Medical Monitor must be consulted for all AGS-16C3F toxicities that may require adjustment in treatment schedule and/or dose. AGS-16C3F dose modifications and/or treatment schedule modifications must be discussed and agreed to in writing by the Medical Monitor on a case-by-case basis before any adjustment is made.

In case of a therapy hiatus longer than 5 weeks, the plan for resuming therapy must be discussed with the Medical Monitor.

Disease Assessment:

A disease assessment (CT or MRI) will be performed every 8 weeks (± 7 days) counting from C1D1, irrespective of any treatment delays.

Inclusion/Exclusion Criteria:

Inclusion:

1. Is at least 18 years of age
2. Histologically confirmed diagnosis of RCC
    a. Non-clear subjects must be ENPP3 positive, defined as IHC H-score ≥15
3. Has evidence of progression on or after the last regimen received:
    a. Clear cell subject: must have received at least 2 prior systemic regimens, one of which is an anti-VEGF agent.
    b. Non-clear cell subject: must have received at least one prior anti-VEGF regimen
4. Has measurable disease according to Response Criteria for Solid Tumors (RECIST v.1.1)
5. Has ECOG Performance Status of 0 or 1
6. Has archive tumor tissue from primary tumor or metastatic site (excluding bone), for which the source and availability have been confirmed.
    a. If no archive tissue is available, the subject may elect to have a biopsy performed to obtain tissue.
7. Has adequate organ function including:
    a. Hematopoietic function as follows:
        i. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
        ii. Platelet count ≥ 100 x 10^9/L
        iii. Hemoglobin ≥ 9 g/dL (transfusions are allowed)
    b. Renal Function as follows:
        i. Creatinine ≤ 1.5 x ULN, or calculated GFR > 40 mL/min (Cockcroft-Gault) if creatinine > 1.5 x ULN
    c. Hepatic function, as follows:
        i. Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) ≤ 2.5 x ULN or ≤ 5 x ULN if known liver metastases
        ii. Total bilirubin ≤ 1.5 x ULN
8. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) levels ≤1.5 x ULN. If institution does not report PT value, the INR must be ≤ ULN.
    a. If subject is receiving Coumadin (warfarin), a stable international normalization ratio (INR) of 2-3 is required.
9. No clinical symptoms of hypothyroidism
10. Urine Protein to Creatinine Ratio (uPCR) < 2.0
    a. If uPCR ≥ 2.0 then a 24-hour urine collection can be performed to qualify. If this is performed to qualify, the protein result must be < 2 g per 24 hours.
11. Female subject must either:
    a. Be of non-childbearing potential:
        i. post-menopausal (defined as at least 1 year without any menses) prior to Screening, or
        ii. documented surgically sterile
    b. Or, if of childbearing potential,
        i. Agree not to try to become pregnant during the study and for 6 months after the final study drug administration
        ii. And have a negative serum pregnancy test ≤ 10 days of C1D1
        iii. And, if heterosexually active, agree to consistently use 2 forms of highly effective birth control* (at least one of which must be a barrier method) starting at Screening and throughout the study period and for 6 months after the final study drug administration.

12. Female subject must agree not to breastfeed starting at Screening and throughout the study period, and for 6 months after the final study drug administration.
13. Female subject must not donate ova starting at Screening and throughout the study period, and for 6 months after the final study drug administration.
14. Male subject and their female spouse/partners who are of childbearing potential must be using highly effective contraception* consisting of 2 forms of birth control (at least one of which must be a barrier method) starting at Screening and continue throughout the study period, and for 6 months after the final study drug administration
15. Male subject must not donate sperm starting at Screening and throughout the study period and, for 6 months after the final study drug administration
16. Is competent to comprehend, sign, and date an independent ethics committee/institutional review board (IEC/IRB) approved informed consent form, as evaluated and documented by the investigator.

    Note: *Highly effective forms of birth control include:

    - Consistent and correct usage of established oral contraception.
    - Established intrauterine device (IUD) or intrauterine system (IUS).
    - Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository

Waivers to the inclusion criteria will **NOT** be allowed.

Exclusion:

1. Has previously been treated with axitinib, AGS-16C3F, or AGS-16M8F
2. Has untreated brain metastasis. In the case of a solitary brain metastasis which has been resected, there must be evidence of a disease-free interval of at least 3 months post-surgery. For brain metastases treated with whole brain or stereotactic radiation therapy, brain imaging must be stable > 3 months. All subjects previously treated for brain metastases must be stable off corticosteroid therapy for at least 28 days prior to C1D1.
3. Has uncontrolled hypertension defined as blood pressure > 150/90 on medication(s) by 2 blood pressure readings taken at least 1 hour apart.
4. Has gastrointestinal abnormalities including:
    a. inability to take oral medication;
    b. requirement for intravenous alimentation;
    c. prior surgical procedures affecting absorption including total gastric resection;
    d. active gastrointestinal bleeding, unrelated to cancer, as evidenced by hematemesis, hematochezia or melena in the past 3 months without evidence of resolution documented by endoscopy or colonoscopy;
    e. malabsorption syndromes such as celiac disease, cystic fibrosis, inflammatory bowel disease, systemic sclerosis, and carcinoid syndrome
5. Has ocular conditions such as:
    a. Active infection or corneal ulcer
    b. Monocularity
    c. Visual acuity of 20/70 or worse in both eyes
    d. History of corneal transplantation
    e. Contact lens dependent (if using contact lens, must be able to switch to glasses during the entire study duration)
    f. Uncontrolled glaucoma (topical medications allowed)
    g. Uncontrolled or active ocular problems (e.g., retinopathy, macular edema, active uveitis, wet macular degeneration) requiring surgery, laser treatment, or intravitreal injections
    h. Papilledema or other active optic nerve disorder

6. Has used any investigational drug (including marketed drugs not approved for this indication) ≤ 14 days of C1D1. No time limit applies to the use of marketed drugs approved for this indication provided that the subject has progressed on the treatment and all toxicities attributable to the drug have resolved, returned to baseline or stabilized.
7. Has known sensitivity to any of the ingredients of:
    a. investigational product AGS-16C3F (Refer to IB for list of ingredients) and/or,
    b. Inlyta® (axitinib) (Refer to product package insert) and/or,
    c. 1% prednisolone acetate ophthalmic suspension (Refer to Product package insert) and any other corticosteroids.
8. Is currently using (i.e., within 14-days prior to first dose) drugs that are known strong CYP3A4/5 inhibitors/inducers (See Appendix 12.1 for list of excluded drugs).
9. Thromboembolic event (e.g., DVT and PE) ≤ 4 weeks of C1D1.
    a. Subjects who had a thromboembolic event ≤ 4 weeks of C1D1 must be receiving adequate anticoagulation treatment for at least 2 weeks before C1D1 and must continue as clinically indicated post first dose.
10. Has history of bleeding disorders (e.g., pulmonary hemorrhage, significant hemoptysis, menometrorrhagia not responding to hormonal treatment) ≤ 2 months before C1D1
11. Has active angina or Class III or IV Congestive Heart Failure (New York Heart Association CHF Functional Classification System) or clinically significant cardiac disease within 6 months of study enrollment, including myocardial infarction, unstable angina, Grade 2 or greater peripheral vascular disease, congestive heart failure, or arrhythmias not controlled by medication.
12. Had major surgery ≤ 4 weeks of C1D1
13. Is pregnant (confirmed by positive serum pregnancy test) or lactating
14. Has active infection requiring treatment with systemic (intravenous or oral) anti-infectives (antibiotic, antifungal, or antiviral agent) ≤ 10 days of C1D1
15. Is unwilling or unable to comply with study requirements
16. Has any medical or psychiatric disorder that compromises the ability of the subject to give written informed consent, and/or comply with the study procedures as evidenced and documented by the investigator.

Waivers to the exclusion criteria will **NOT** be allowed

Investigational Product(s):

AGS-16C3F is a fully human monoclonal antibody conjugated to a microtubule disrupting agent Monomethyl auristatin F (MMAF) targeting ENPP3 (company code name AGS-16).

Each vial of AGS-16C3F Drug Product (DP) is supplied as a single-use, sterile, preservative-free, lyophilized product (30 mg) in 20 mL glass vials that need to be stored refrigerated (2-8°C).

Reconstitute each vial with 5.1 mL sterile water for injection (USP grade), before use. The resulting final formulation contains AGS-16C3F at 6 mg/mL in CCI trehalose dihydrate, CCI Histidine, and CCI Polysorbate 20 at pH 5.2. After reconstitution, AGS-16C3F should be diluted, prior to infusion, with CCI dextrose injection (USP grade) supplied by the site. Depending on the total dose of AGS-16C3F (i.e., reconstituted volume), the investigational product may also be administered undiluted. Refer to Pharmacy Guide for details.

Dose(s):

Each subject will receive AGS-16C3F every 3 weeks at 1.8 mg/kg. The 21-day dosing cycle time will reset at each dosing date (i.e., determine the next dosing date from the current actual dosing date). If for logistical reasons (e.g., public holidays, clinic scheduling, etc.) the next dose cannot be given 21 days from the last dose, a -2 day and a +7 day dosing window is allowed. This window is intended to accommodate occasional scheduling conflicts and is not intended for routine use. The Medical Monitor must be consulted for any dose delays that are due to toxicity and for dose intervals that exceed 5 weeks. Refer to Sections 5.1.2, 5.1.1.3. The dose of AGS-16C3F will be calculated based on the subject's actual body weight in kilograms obtained predose C1D1 (baseline weight). The same dose will be used throughout the study unless the subject's baseline weight changes by ≥ 10%. The dose of AGS-16C3F will then be administered based on the weight change and this will become the new baseline weight.

Mode of Administration:

AGS-16C3F will be administered as an IV infusion (via an infusion pump). The total prescribed dose should be administered over 60 minutes, including time required to flush the line. Refer to Pharmacy Guide for details.

Comparator Drug(s):

Axitinib (Inlyta®, manufacturer Pfizer) is an oral kinase inhibitor indicated for the treatment of advanced RCC after failure of one prior systemic therapy. The Sponsor will provide axitinib for the study.

Dose(s):

Axitinib will be administered at a starting dose of 5 mg, twice daily continuously, by mouth. This dose may be adjusted during the study as needed, as defined in the product label and local institutional guidelines, in doses ranging from 2 to 10 mg, administered twice daily continuously, by mouth. Drug to be used without further modification.

Axitinib subjects will return to clinic every 21 days for clinical assessment and additional axitinib dispensing. If for logistical reasons (e.g., public holidays, clinic scheduling, etc.) the next clinic visit cannot occur 21 days from the last visit, a -2 day and a +7 day visit window is allowed. This window is intended to accommodate occasional scheduling conflicts and is not intended for routine use. The Medical Monitor must be consulted for any study visit delays that are due to toxicity and for treatment hiatus that exceeds 5 weeks. Refer to Section 5.1.1.3.

Mode of Administration:

Oral

Concomitant Medication Restrictions or Requirements:

The investigator may prescribe any medication necessary to ensure the safety and wellbeing of the subject during the study. Please refer to Section 5.1.3.2. If however, the investigator determines that any of the following medications are necessary to provide adequate medical support to the subject, the subject must be withdrawn from further study drug administration. Protocol prohibited medications that are needed temporarily to treat an AE is permitted at investigator's discretion (e.g., dexamethasone used to treat nausea).

1. Chemotherapy, radiotherapy, immunotherapy, monocolonal antibody therapy or other medications intended for antitumor activity (palliative radiation is permitted provided it does not interfere with subject safety and efficacy of the study drug being administered. Palliative radiation cannot be administered to any target lesion)
2. Investigational products or therapy other than AGS-16C3F
3. For subjects randomized to axitinib only: Drugs that are known strong CYP3A4/5 inducers (Refer to Section 5.1.3.2 and Appendix 12.1 for list of excluded drugs).

Duration of Treatment:

Subjects will be eligible to continue receiving treatment on study until disease progression per RECIST v.1.1, unacceptable toxicity, investigator's decision, or study withdrawal. Subjects will also be discontinued from treatment if a significant non-compliance occurs (e.g., those that compromise study objectives or subject safety), or if a subject is lost to follow-up.

Prescreening

Subjects with RCC of non-clear cell histology must sign the prescreening ICF and be prescreened for ENPP3 expression prior to undergoing screening procedures for the main study. Tumor tissue, from a primary or metastatic site (excluding bone), will be submitted to the Sponsor-designated CLIA certified laboratory for ENPP3 determination by IHC. An IHC H-score of ≥ 15 is required for non-clear cell subjects to qualify for study screening. IHC H-scores for ENPP3 eligibility will not expire for the duration of the study (i.e., there is no time limit from prescreen qualification to screening start). Every effort will be made to report the IHC H-score to the investigator ≤ 72 hours of sample receipt at the Sponsor-designated CLIA certified laboratory provided that the specimens were received in good condition along with all required documents fully completed.

Clear cell histology subjects are not required to be screened for target expression to qualify for the study but must provide tissue during the study. Consent to provide tissue is included in the main study informed consent form. Clear cell histology subjects' specimens will be batch assayed during the study. The IHC H-score will be reported back to the investigator for information only when the data become available.

Procedures

Schedule of Assessment and Procedures by study week and days are outlined in Table 1 and Section 5.2.

Ocular Toxicities

A complete eye exam will be done during screening. Subjects randomized to AGS-16C3F, will have a complete eye exam done after the Cycle 2 Day 1 dose but before the Cycle 3 Day 1 dose, after the Cycle 5 Day 1 dose but before the Cycle 6 Day 1 dose, and as clinically indicated. Subjects randomized to axitinib will have a complete eye exam done post baseline as clinically indicated. The frequency of ophthalmology follow-ups outside of protocol requirement is at the discretion of the Investigator and ophthalmologist.

Ocular symptoms reported by the subject during clinic visits will be graded per CTCAE v4.03 (i.e., symptom based assessment) and this will guide the treatment decision for that visit and the necessity for a follow up ophthalmology consult.

An Eye Symptom Questionnaire (ESQ) will be administered at every visit in the oncology clinic. Please see the Study Guide for the form and for complete instructions.

If a subject develops ocular toxicity, the following guidelines may be used:

Subject Reported Symptom Based Ocular AE (i.e., per CTCAE v4.03) (see Table 10 below)

Grade	Study Treatment Action	Ophthalmology Referral
1	Continue per dose and schedule (i.e., AGS-16C3F 1.8 mg/kg q3w or axitinib 5 mg, twice daily)	May be done at Investigator discretion
2	May continue treatment per dose and schedule at Investigator discretion	Required; must occur prior to the subsequent cycle.
3	Hold treatment	Required; must occur prior to the subsequent cycle.

Clinical Ocular AEs are objective findings (e.g., keratitis, macular edema, retinal degeneration) from the ophthalmology evaluation. Clinical Ocular AE grading will be determined based on visual acuity (VA) change from screening (baseline).

The process for grading Clinical Ocular AEs is outlined in Section 5.6.5.2.

Corneal Clinical Ocular AEs

- If Clinical Ocular AE is Grade 3, Medical Monitor will be consulted for treatment decision.
- If Clinical Ocular AE is Grade 4, subject will be permanently discontinued from study treatment.

Non-corneal related clinical ocular AEs

- Clinical Ocular AEs other than ocular surface disease/keratopathy in nature, **irrespective of the grade, must be discussed with the Medical Monitor before the subsequent dose (per axitinib product label, patients treated with this product experienced both retinal artery and retinal vein occlusions. Please see product label for details)**.

The ophthalmology report along with the completed study provided cover form will be forwarded to the Investigator in a timely manner. The investigator will review the ophthalmology report to guide further treatment decisions.

The redacted ophthalmology report will be forwarded to the Sponsor in a timely manner.

Thrombocytopenia Adverse Events:

For thrombocytopenia without signs and symptoms of bleeding that the investigator considers clinically significant, the following AGS-16C3F dosing guidelines will be used (see Table 9 below):

Grade	Description	Action
2	Present, without signs and symptoms of bleeding.	The dose may be administered or held at investigator discretion
	Persistent (i.e., lasting for ≥ 5 weeks), without signs and symptoms of bleeding, and without documented bone marrow suppression.	The subject may be considered for a dose reduction to 1.2 mg/kg. Dose reduction must be discussed with and approved in writing by the Medical Monitor.
	Persistent (i.e., lasting for ≥ 5 weeks), without signs and symptoms of bleeding, and with documented bone marrow suppression.	The subject will be discussed with the Medical Monitor. The possible need for permanent discontinuation will be considered based on clinical benefit of treatment as well as review of overall patient profile (concomitant medication and medical history review, presence or absence of mucosal bleed, other AEs, etc.).
3	Present, without signs and symptoms of bleeding.	The dose will be held until platelet count improves to at least Grade 2 (≥ 50 x 10^9/L)
	Present, without signs and symptoms of bleeding, and has not recovered to at least Grade 2 (≥ 50 x 10^9/L) ≤ 5 weeks.	The subject will either be permanently discontinued or may be considered for a dose reduction to 1.2 mg/kg. Dose reduction must be discussed with and approved in writing by the Medical Monitor.
4	Present, without signs and symptoms of bleeding, and platelet count is confirmed with a repeat lab performed ≤ 72 hours.	Subject will be permanently discontinued.
	Present, without signs and symptoms of bleeding, and isolated (i.e., not confirmed with a repeat lab ≤ 72 hours after first assessment).	Dose will be held until platelet count improves to at least Grade 2 (≥ 50 x 10^9/L)
	Present, without signs and symptoms of bleeding, isolated (i.e., not confirmed with a repeat lab ≤ 72 hours after first assessment), and has not recovered to at least Grade 2 (≥ 50 x 10^9/L) ≤ 5 weeks.	The subject will either be permanently discontinued or may be considered for a dose reduction to 1.2 mg/kg. Dose reduction must be discussed with and approved in writing by the Medical Monitor.

Beginning at Cycle 5 Day 1 and for all subsequent cycles, a bone marrow study or hematology consult, is strongly encouraged for all AGS-16C3F subjects whose predose platelet count is < 75 x 10^9/L at any 2 timepoints. If a hematology consult and/or bone marrow study is/are performed, the redacted report(s) will be timely submitted to the Sponsor.

Adverse Events of Possible Hepatic Origin

See Appendix 12.2 for detailed information on the monitoring and assessment of liver abnormalities, if the AE for a subject enrolled in a study and receiving study drug is accompanied by increases in liver function testing (LFT, e.g.: AST, ALT, bilirubin, etc.) or is suspected to be due to hepatic dysfunction.

Subjects with AEs of hepatic origin accompanied by Liver Function Test (LFT) abnormalities should be carefully monitored.

Other Adverse Events

Subjects who experience a Grade 4 toxicity other than those related to the eye, liver, and thrombocytopenia, as described in Sections 5.6.5, 5.6.2.1.2, 5.6.2.1.1 will be permanently discontinued from AGS-16C3F treatment. Laboratory AEs with a Grade 4 value, must be confirmed with a repeat analysis ≤ 72 hours before discontinuing subject from treatment.

Formal Stopping Rules

The subject will be discontinued from treatment if any of the following occurs:

- Subject develops disease progression per RECIST v.1.1 criteria based on investigator assessment.
- Subject develops clinical progression (if objective disease progression is not evaluated).
- Subject develops a Grade 4 or unacceptable AE as assessed by the Investigator (Refer also to Section 5.6.2.1.3 and Section 5.6.5.2.1)
- Investigator decides that it is in the subject's best interest to discontinue.
- Subject declines further study participation (i.e., study withdrawal).
- A significant protocol violation or non-compliance occurs with a subject that compromises study objectives or subject safety.
- Subject is lost to follow-up despite reasonable efforts by the Investigator to locate the subject.
- The study is terminated by the Sponsor.

The Medical Monitor must be contacted before a subject is discontinued from study treatment for reasons other than objective disease progression per RECIST v.1.1.

Endpoints for Evaluation

Primary Endpoint:

To evaluate the progression-free survival (PFS) of AGS-16C3F compared against axitinib (Investigator radiology assessment per RECIST v.1.1).

PFS is defined as the time from the date of randomization to the earliest of documented disease progression as defined by RECIST v.1.1 or death from any cause.

Secondary Endpoints:

To evaluate the following for AGS-16C3F compared against axitinib:

- PFS calculated based on blinded central radiology assessment per RECIST v.1.1
- Objective Response Rate (ORR); based on the investigator's radiographic assessment
  - Objective response rate (ORR) is defined as the proportion of subjects who have a best overall response of complete response (CR) or partial response (PR).
- Duration of Response (DOR); based on the investigator's radiographic assessment
- Duration of objective response (DOR) is defined as the time from the date of the first response of CR/PR (whichever is first recorded) to the first date of documented progressive disease or death due to any cause.
- Overall Survival (OS)
  - Overall survival, defined as the time from the date of randomization until the date of death from any cause.
- Disease control rate (DCR); based on the investigator's radiographic assessment
  - Disease control rate (DCR) is defined as the proportion of subjects who have a best overall response of CR, PR, or at least 6 months Stable Disease (SD).
- Safety
  - Incidence of AEs (including Grade 3 and 4 AEs, treatment-related AEs, SAEs (serious adverse events), and AEs requiring discontinuation of study drug), laboratory changes and vital signs

Statistical Methods:

The primary efficacy endpoint is progression-free survival (PFS), defined as the time from the date of randomization to the earliest of documented disease progression as defined by RECIST v 1.1 per investigator radiology review, or death from any cause. Disease assessment will continue until disease progression, even after the originally assigned treatment is discontinued.

The primary analysis of investigator assessed PFS will be performed in accordance with the intention-to-treat (ITT) principle. All subjects who undergo randomization will be included in the primary analysis. Subjects will be grouped according to the treatment groups assigned by randomization.

For the primary analysis of PFS, the difference in treatment effect between treatment groups will be tested using the stratified log rank test (on ECOG Performance Status and the number of prior systemic RCC regimens) at a one-sided 0.1 significance level. Histology will not be used as a stratification variable in inferential comparison because a limited number of non-clear cell subjects is expected to be enrolled in the study (no more than 26 non-clear cell histology).

Estimation of the hazard ratio for treatment and its corresponding one-sided 90% CI will be determined using a stratified Cox proportional hazards model (on ECOG Performance Status and the number of prior systemic RCC regimens), without any other covariate. A two-sided 95% CI will also be reported in the clinical study report. Homogeneity in the hazard ratios between strata will be examined by Wald's test. The corresponding results without stratification will be reported as supplemental analyses. The adequacy of the model will be evaluated, including an assessment of the proportional hazards assumption (Therneau, 2000). Exploratory subgroup analyses may be conducted to assess potential heterogeneity of treatment effects across levels of baseline characteristics.

For the primary analysis, PFS will be right-censored for subjects who meet one or more of the following conditions:

- Subjects with no post-baseline disease assessments unless death occurred prior to the first planned assessment (in which case death will be considered a PFS event)
- Subjects who initiate subsequent anti-cancer therapy or intervention in the absence of documented progression
- Subjects who die or have disease progression after missing 2 or more consecutively scheduled disease assessment visits
- Subjects who are last known to be alive and progression-free on or before the data cut-off date

For such subjects, PFS will be right-censored based on the May 2007 FDA Guidance for Industry "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics". Sensitivity analyses will be performed to evaluate the robustness of the PFS results derived under the primary analysis (Bhattacharya, 2009; Carroll, 2007; Stone, 2011).

Progression-free survival by blinded central radiology review and overall survival, defined as the number of months from the date of randomization until the date of death from any cause, will be evaluated as secondary endpoints. They will be analyzed using the same methodology as described for the primary endpoint.

Disease control rate (DCR) will be estimated for each treatment group based on the crude proportion of subjects who have a best overall response of CR, PR or SD. For DCR, SD with a minimum duration of 6 months from the date of randomization is required. Objective response rate (ORR) will be estimated for each treatment group based on the crude proportion of subjects who have a best overall response of CR or PR. The inferential comparison between treatment groups for both DCR and ORR by investigator and central review will be made using the stratified Cochran-Mantel-Haenszel chi-square test at a two-sided significance level of 0.05.

Duration of objective response (DOR) is defined as the time from the date of the first response of CR or PR (whichever is first recorded), and subsequently confirmed, to the first date of documented progressive disease or death due to any cause. Duration of response will be summarized for subjects who have best overall response of CR or PR.

Safety will be evaluated based on the incidence of AEs (including Grade 3 and 4 AEs, treatment-related adverse events, serious adverse events, and AEs requiring discontinuation of study treatment), electrocardiogram (ECG) and laboratory changes and vital signs. AEs will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grading scale, version 4.03. Ocular toxicities based on ophthalmology exams reported on the Eye Exam eCRFs will be graded using the study specific ocular criteria and these will be separately tabulated.

Descriptive statistics will be provided for the PK parameter estimates and subject concentration plots over time may be generated. Please refer to Section 7.6

Descriptive statistics for the incidence of human native antibody (AGS-16C3) and antibody drug conjugate (AGS-16C3F) antibody formation will be provided by treatment group.

Sample size justification:

For subjects with metastatic RCC who have progressed after at least 2 prior lines of therapy, a median PFS of 4 months is anticipated for the control agent. It is hypothesized that AGS-16C3F will improve median PFS in such subjects by 2 months (i.e., 4 vs 6 months). Under the assumption of exponential distribution of PFS, such an improvement corresponds to a hypothesized hazard ratio of 0.667. If this hypothesized hazard ratio is true, 110 PFS events provide 80% power to achieve a one-sided p-value of 0.1 or smaller. Such a result will be achieved when the observed hazard ratio is 0.783 or smaller; and the observed difference in median PFS is 1.1 months or larger (assuming observed median PFS for the control arm is 4 months). Assuming accrual of approximately 7 subjects per month for 18 months, 110 PFS events are projected 24 months after the date the first subject is randomized. Approximately 134 subjects may be enrolled to accommodate for up to 10% of subjects who may become lost to follow-up.

Efficacy:

PFS is defined as the time from the date of randomization to the earliest of documented disease progression as defined by RECIST v.1.1 or death from any cause. Disease assessment will continue until disease progression, even after the originally assigned treatment is discontinued.

PFS will be summarized descriptively using the Kaplan-Meier method with 95% confidence intervals calculated about the median using Greenwood's formula. For the primary analysis of PFS, the difference in treatment effect between treatment groups will be tested using the stratified log rank test (on ECOG Performance Status and the number of prior systemic RCC regimens) at a one-sided 0.1 significance level.

Pharmacokinetics:

The PK data for ADC and MMAF will be analyzed using the noncompartmental method. Parameters to be assessed will include concentrations at the end of infusion or maximum observed concentration (C_{EOI} or C_{max}), concentrations at trough (C_{trough}), time to maximum observed concentration (T_{max}), partial area under the concentration time curve ($AUC\tau$) for Cycle 1 and 4, and either terminal or apparent terminal half-life ($t_{1/2}$) as appropriate. Additionally, clearance (CL) and volume of distribution at steady state (V_{ss}) will be included as appropriate. Descriptive statistics will be provided for the PK parameter estimates and subject concentration plots over time may be generated.

Pharmacodynamics:

N/A. A pharmacodynamic marker has not yet been established for this target.

Safety:

Safety will be evaluated based on the incidence of AEs (including Grade 3 and 4 AEs, treatment-related adverse events, serious adverse events, and AEs requiring discontinuation of study treatment), ECG and laboratory changes and vital signs. AEs will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grading scale, version 4.03. Ocular toxicities based on ophthalmology exams reported on the Eye Exam eCRFs will be graded using the study specific ocular criteria and these will be separately tabulated.

Interim Safety Review:

The study will have an Independent Data-Monitoring Committee (IDMC) overseeing the study. The IDMC will conduct safety reviews at prespecified times during the study to make a recommendation for continuation of recruitment, protocol modification or study discontinuation for safety reasons.

The IDMC will operate under the Study's IDMC Charter.

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

Figure 1 Flow Chart

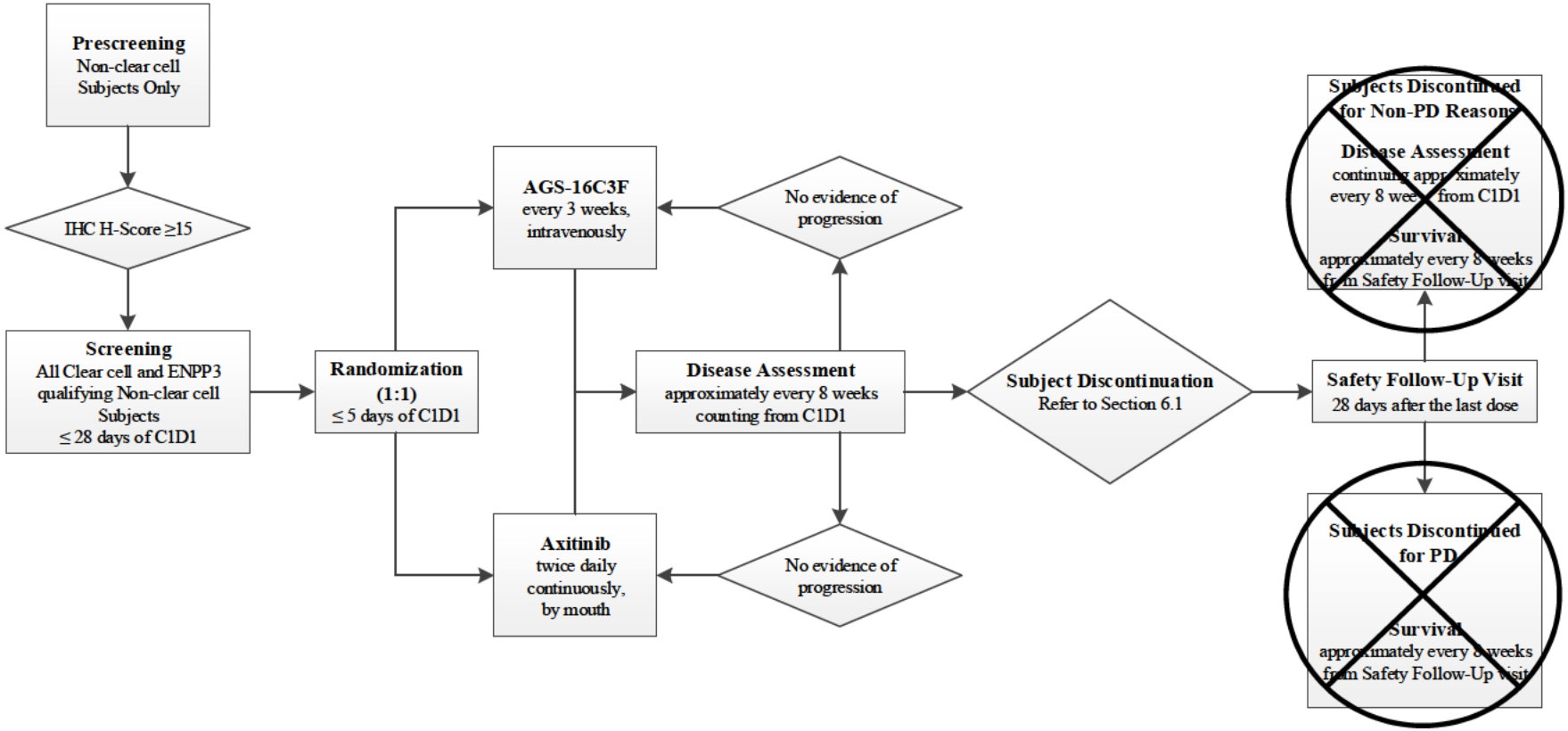

Table 1 Schedule of Assessments

			Cycle 1[t]				Cycles 2-4[t]							C5[t]	C6[t]	Treatment Period beginning Cycle 7[t]	Safety F/U [s]
Procedures	**Screen[a]**	**Cycle**	**1**				**2**	**3**		**4**				**5**	**6**		
		Week	**1**	**1**	**1**	**3**	**4**	**7**	**8-9**	**10**	**10**	**10**	**12**	**13**	**16**		
		Day	**1**	**2**	**4**	**15**	**22**	**43**	**50-57**	**64**	**65**	**67**	**78**	**85**	**106**		
Prescreen Informed Consent (Non-clear Subjects Only)	**X[b]**																
Informed Consent	**X[c]**																
Medical History	**X**																
ECOG [d]	**X**		**X**				**X**	**X**		**X**				**X**	**X**	**Q3W**	**X**
Physical Exam	**X**		**X**				**X**	**X**		**X**				**X**	**X**	**Q3W**	**X**
Weight	**X**		**X**				**X**	**X**		**X**				**X**	**X**	**Q3W**	**X**
Vital Signs [e]	**X**		**X**				**X**	**X**		**X**				**X**	**X**	**Q3W**	**X**
Laboratory [f]	**X[g]**		**X**				**X**	**X**		**X**				**X[f]**	**X[f]**	**Q3W[f]**	**X**
CRP	**X[g]**		**X**				**X**	**X**		**X**				**X**	**X**	**Q3W**	**X**
PT/aPTT	**X[g]**		**X**				**X**	**X**		**X**				**X**	**X**	**Q3W**	**X**
uPCR	**X**		**X**					**X**						**X**		**Every Odd Cycle**	**X**
Thyroid Function Test	**X**		**X**					**X**						**X**		**Every Odd Cycle**	**X**
ECG [h]	**X[g]**		**X[h]**														**X**
Serum Pregnancy Test [i]	**X[g]**																
Adverse Events [j]			<---------- **PRN** ---------->														
Concomitant Medications [j]			<---------- **PRN** ---------->														
Full Eye Exam [k]	**X**		<---------- **PRN** ---------->					**X**	<---------- **PRN** ---------->						**X**	**PRN**	**PRN**
Eye Symptom Questionnaire [u]	**X**		**X**	**X[u]**	**X[u]**	**X[u]**	**X**	**X**	**X**	**X**	**X[u]**	**X[u]**	**X[u]**	**X**	**X**	**Q3W**	**X**
Randomization [l]	**X**																
PK [m] (AGS-16C3F Subjects Only)			**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**		**X**		
anti-AGS-16C3F antibody formation [n] (AGS-16C3F Subjects Only)			**X**							**X**					**X**		
Disease Assessment [o]	**X**		<---------- **Q8W from C1D1** ---------->														
Bone Imaging [p]	**X**		<---------- **Q12W from C1D1[p]** ---------->														
Brain Imaging [p]	**X**																
AGS-16C3F Administration [q] (AGS-16C3F Subjects Only)			**X**				**X**	**X**		**X**				**X**	**X**	**Q3W**	

Table continued on next page

			Cycle 1[t]	Cycles 2-4[t]	C5[t]	C6[t]	Treatment Period beginning Cycle 7[t]	Safety F/U [s]
Axitinib Administration (Axitinib Subjects Only)			<----------Twice Daily Continuously----------					
Tumor Tissue [r]	X							

[a] All screening procedures are to occur ≤ 28 days of C1D1, unless otherwise specified

[b] Non-clear cell subjects will sign at any time prior to screening for the main study. An mmunohistochemical (IHC) H-score of ≥ 15 is required for non-clear cell subjects to qualify for study screening. IHC H-scores for ENPP3 eligibility do not expire for the duration of the study (i.e., there is no time limit from prescreen qualification to screening start).

[c] Clear cell and IHC qualifying Non-clear cell subjects will sign ≤ 28 days of C1D1

[d] Refer to Appendix 12.5

[e] At Screening, vitals will be taken once. Subjects randomized to AGS-16C3F, on the days of study drug administration, vital signs will be taken predose, and approximately 30 minutes after administration of study drug (i.e., end of infusion). Subjects randomized to axitinib, vital signs will be taken once at each clinic visit.

[f] Laboratory assessments include hematology and chemistry (refer to Section 5.2.6). All safety labs (all analytes listed in Section 5.6.3) are performed locally. Starting from Cycle 5 Day 1 and for all subsequent cycles: A bone marrow study or hematology consult is strongly encouraged for all AGS-16C3F subjects whose predose platelet count is < 75 x 10^9/L at any 2 timepoints

[g] To be performed ≤ 10 days of C1D1

[h] All ECGs performed on study must be done in triplicate (3-5 min apart), and subjects must be in the same position for every reading. At Screening, ECGs will be taken in triplicate once. Subjects randomized to AGS-16C3F, at C1D1, ECGs will be taken predose (anytime predose on actual dosing day) and 2 hours after the end of infusion, when the total prescribed dose has been administered (e.g., 2 h after the end of infusion). Subjects randomized to axitinib, at C1D1, ECGs will be taken predose (anytime predose on actual dosing day) only. Refer to Section 5.6.4

[i] Women of childbearing potential only

[j] All AEs and Concomitant Medications to be documented throughout the study.

[k] A complete eye exam will be done during screening. Subjects randomized to AGS-16C3F, will have a complete eye exam done after the Cycle 2 Day 1 dose but before the Cycle 3 Day 1 dose, after the Cycle 5 Day 1 dose but before the Cycle 6 Day 1 dose, and as clinically indicated. Subjects randomized to axitinib, will have a complete eye exam done post baseline as clinically indicated. At the screening (baseline) ophthalmology visit, the complete eye exam will consist of Visual Acuity with Snellen Chart, best corrected visual acuity (BCVA), intraocular pressure (IOP), extraocular movement (EOM), pupils, external exam, slit lamp exam, and dilated fundoscopic exam. For post baseline ophthalmology visits, the complete eye exam will be the same as the baseline visit, but the dilated fundoscopic exam may be deferred if not clinically indicated (i.e., if there is no change in vision or if the vision change can be explained as a non-retinal event). If deferred, an undilated fundoscopic exam is still required as part of the full eye exam. Schirmer's test (with and without anesthetic) is optional if subject has dry eyes at screening (baseline).

[l] Randomization will occur after all screening procedures have been completed and ≤ 5 days of C1D1

[m] Refer to PK sampling schema Table 2 for sample collection dates and times

[n] Where applicable, must be collected on the same day as PK sample collection. Beyond Cycle 6, samples will be collected every 12 weeks. If result is positive, samples will continue to be collected for immunogenicity testing every 12 weeks until it returns to negative or baseline value.

Footnotes continued on next page

[o] Disease assessments (CT and/or MRI; refer to Section 5.5) will be done every 8 weeks (± 7 days) counting from C1D1.

[p] Required only if clinically indicated. Post screening bone imaging will be done only for subjects with bone disease at screening. The imaging method will be any imaging modality per local or institutional standard of care (SOC) (e.g., NaF PET, MRI Bone, Tc-99 Bone Scan, etc.)

[q] Subjects randomized to AGS-16C3F must use 1% prednisolone acetate ophthalmic suspension prophylactically (prophylaxis steroid drops) starting from Day (-1) of each treatment cycle. Refer to Section 5.1.3.1.

[r] Paraffin-embedded tumor tissue from primary or metastasis (excluding bone), for immunohistochemical studies to be conducted at a Sponsor specified CLIA certified laboratory. This is required for all non-clear cell histology subjects before Screening. Clear cell histology subjects must also provide tissue but at any point during the study. If no archive tissue is available; a biopsy may be performed to obtain tissue.

[s] Subjects are required to have a safety follow-up visit; refer to Section 5.2.7.

[t] Physical exam, laboratory assesssments, and ECOG assessment may be performed ≤ 4 days in advance of the subsequent Cycle Day 1.

[u] An Eye Symptom Questionnaire (ESQ) will be administered at every visit. Only subjects randomized to AGS-16C3F will have the ESQ done on PK only days. Refer to Section 5.6.5.1

VI. PK SAMPLING COLLECTION SCHEMA

Table 2 AGS-16C3F PK Sampling Time Points

Cycle	Study Day	Time	Window
1	1	Predose	Anytime Predose *
		EOI	Within 2 min after EOI
		4 h†	± 15 min
	2	24 h from Day 1†	± 4 h
	4	72 h from Day 1†	± 1 day
	15	336 h from Day 1†	± 4 h
2	22	Predose	Anytime Predose §
3	43	Predose	Anytime Predose §
4	64	Predose	Anytime Predose §
		EOI	Within 2 min after EOI
		4 h†	± 15 min
	65	24 h from day 64†	± 4 h
	67	72 h from day 64†	± 1 day
	78	336 h from day 64†	± 4 h
6	106	Predose	Anytime Predose §
Q12W (starting at C6)		Predose	Anytime Predose §

* May be performed ≤ 4 days in advance of C1D1

† timepoints are from end of infusion, when the total prescribed dose has been administered (e.g., 4 h after the end of infusion)

§ Anytime predose on the actual day of AGS-16C3F administration

1 INTRODUCTION

1.1 Background

1.1.1 Disease

Renal cell carcinoma (RCC) accounts for 2% to 3% of all malignant diseases in adults. It is the seventh most common cancer in men and the ninth most common in women.

Historically, treatment has focused primarily on nephrectomy, followed by nonspecific immunotherapy, and sometimes radiation therapy. Nonspecific immunotherapy includes treatment with the cytokines interleukin-2 or interferon-2α, as either single agents or in combination (Belldegrun et al, 2008). After surgical excision, 20-30% of patients will develop metastatic disease within 1-3 years, often in the lung (Motzer, 2011). Median survival for patients with metastatic disease is approximately 13 months (Ljungberg et al, 2010).

Since 2005, 10 agents have been approved in the United States and other world regions for the treatment of advanced RCC: sorafenib (Nexavar®), sunitinib (Sutent®), temsirolimus (Torisel®), everolimus (Affinitor®), bevacizumab (Avastin® in combination with interferon alpha), pazopanib (Votrient®), axitinib (Inlyta®), cabozantinib (Cabometyx®), lenvatinib (Lenvima® in combination with everolimus), and nivolumab (Opdivo®). These drugs target specific pathways important in RCC, including angiogenesis and mTOR signaling, or act as a checkpoint inhibitor, allowing the immune system to fight the cancer. Their use was shown mostly to affect response rate and/or duration.

While these drugs which either block the vascular endothelial growth factor (VEGF) pathway, inhibit mammalian target of rapamycin (mTOR), or block the signal that prevents activated T cells from attacking the cancer have significantly increased both treatment options and improved outcomes for patients with advanced RCC, the vast majority still relapse.

The recent advances in treatment options mainly affected patients with clear cell histology, while no real progress has been made in those with other histologies.

A novel mechanism of action drug to treat advanced RCC of all histologies with a different treatment approach is much desired.

1.1.2 Agensys Antibody Drug Conjugate against Renal Cell Carcinoma

AGS-16C3F, an antibody drug conjugate (ADC) developed by Agensys, is comprised of a chinese hamster ovary (CHO) cell line-derived antibody against ENPP3, conjugated to monomethyl auristatin F (MMAF), a microtubule disruptive agent. A Phase 1 study was conducted to evaluate the pharmacokinetics and safety of AGS-16C3F administered monotherapy in metastatic RCC subjects. This Astellas Phase 2 study is planned based on the results of the Phase 1 study. Results from the Phase 1 study are pending full data analysis.

1.1.3 ENPP3 Antigen Target and Expression in Cancer

The antigen target, ENPP3 (referred to as AGS-16), was cloned from a patient renal carcinoma specimen and identified as an 875 amino acid type II single transmembrane

antigen that is upregulated in the majority of renal and in a subset of hepatocellular cancers. Sequencing of AGS-16 identified it as ENPP3 (CD203c), one of 7 members of a family of cell surface ectonucleotide phosphodiesterases-pyrophosphatases (PDEs), ENPP1-7 (Deissler et al, 1995; Jin-Hua et al, 1997; Buhring et al, 2001; Goding et al, 2003; Stefan et al, 2005). The physiological substrate of ENPP3 is unknown, but studies have suggested that the enzyme catalyzes extracellular nucleotides (e.g., ATP; Goding et al, 2003).

Immunohistochemical (IHC) and tissue cross reactivity studies have shown restricted expression of ENPP3 in normal tissues predominantly in a subset of cells in the kidney cortex. Low levels of staining were also observed in the epithelium of the fallopian tube, a subset of cells within gastrointestinal tract epithelium, in uterine endometrium, parotid gland, and the cortex of the thymus. Flow cytometric analysis has also shown that ENPP3 is expressed on activated basophils and mast cells (Buhring, 1999). ENPP3 is highly expressed in approximately 90% renal clear cell carcinoma; 69% papillary RCC and 27% hepatocellular carcinoma as determined at Agensys by staining tissue microarrays with an immunohistochemistry antibody specific for ENPP3.

1.2 Non-clinical and Clinical Data

1.2.1 Antibody Drug Conjugate AGS-16C3F Non-clinical Pharmacology

AGS-16C3F is comprised of a fully human $IgG2_k$ mAb, following conjugation with the cytotoxic drug MMAF via a non-cleavable maleimidocaproyl (mc) linker. MMAF is a synthetic analog of the naturally occurring tubulin-binding drug, dolastatin 10, that was modified to contain a charged C-terminal phenylalanine residue (Doronina et al, 2006; Pettit, 1987). Conjugation takes place on cysteine residues that comprise the interchain disulfide bonds of the antibody to yield a product with a target drug to antibody ratio of 4.0 + 0.5.

AGS-16C3F binds specifically to ENPP3 (AGS-16) expressed on the surface of renal, hepatocellular and chronic myelogenous leukemia (CML) cells with high affinity (Kd = 0.54 nM). Following binding to cell surface ENPP3, AGS-16C3F is internalized and trafficked through the endocytic pathway to the lysosomes where catabolism results in release of cysteine adducts of mcMMAF that subsequently bind to and inhibit microtubules (Sutherland et al, 2006).

The mechanism of action and catabolism of AGS-16C3F is similar to that of other mAbs conjugated with non-cleavable linkers (Polson et al, 2009; Oflazoglu et al, 2008; Erickson et al, 2006). These ADCs have the potential to yield an excellent therapeutic index due to increased stability of the non-cleavable linker in circulation and impaired cellular access of the charged metabolic products produced intracellularly (Alley et al, 2009; Doronina et al, 2006). The pharmacologic data collected for AGS-16C3F demonstrate that it binds with high affinity to both human and cynomolgus monkey ENPP3 and that it does not cross react with other ENPP family members. Moreover, treatment with AGS-16C3F produces potent cellular cytotoxicity in vitro and regression or long term growth inhibition of well-established tumors in vivo.

AGS-16C3F inhibited tumor growth in 3 different ccRCC xenograft models. While AGS-16M8F, the hybridoma cell line-derived version of the same ADC studied earlier, was shown to bind to basophils from human and monkey, *in vitro* experiments showed no histamine release upon incubation of human or cynomolgus monkey blood with AGS-16M8F. Moreover, there were no signs of allergic reactions to AGS-16M8F in cynomolgus monkeys treated with doses up to 6 mg/kg/week for 4 weeks. Likewise, no overt kidney toxicities were observed.

Please refer to the confidential AGS-16C3F Investigator's Brochure for further details.

1.2.2 AGS-16C3F Non-clinical Toxicology and Pharmacokinetics

A comprehensive non-clinical safety assessment package was conducted for AGS-16M8F, the fully human hybridoma-derived monoclonal antibody conjugated to MMAF. A summary of findings from these studies can be found in the Investigator Brochure.

Based on biological characterization and analytical testing of the CHO-derived product, AGS-16C3F, it was shown to be similar to AGS-16M8F. To supplement these results, a non-clinical bridging study was conducted in primates comparing the pharmacokinetic and toxicology properties of AGS-16M8F and AGS-16C3F at a dose level of 6 mg/kg (established NOAEL dose for AGS-16M8F in the non-human primate study).

Administration of AGS-16C3F by once-weekly intravenous (IV) infusion for 4 weeks was well tolerated in cynomolgus monkeys at levels of 6 mg/kg/week. There were no differences noted between AGS-16M8F and AGS-16C3F for in-life toxicology parameters assessed in this study.

There were AGS-16C3F-related changes in a number of hematology (decreased platelets and increased monocytes) and clinical chemistry parameters (increased ALT, AST, LDH, ALP, GGT (Gamma Glutamyl Transferase), globulin, and total protein and decreased albumin and A:G ratio). In general, the magnitude of these changes was similar for AGS-16M8F and AGS-16C3F treated male and female animals. The changes returned to baseline following recovery and did not correlate with clinical signs or histopathology, and were therefore not considered adverse.

Toxicokinetic data for AGS-16C3F and AGS-16M8F were considered similar based on the pre-specified comparability criteria.

Microscopic findings related to AGS-16C3F at terminal sacrifice were present in the liver and seminal vesicle, and microscopic findings related to AGS-16M8F and AGS-16C3F were present in the uterus. None of these changes were present in recovery animals. In the liver of AGS-16C3F males, minimal to moderate focal to multifocal dilation of the hepatic sinusoids was present, and correlated with increased liver weight, but the biological significance was unknown since there were no clinical or clinical pathology correlates. A mild increase in cellular apoptosis and mitotic figures was present in the seminal vesicle of the only sexually mature male dosed with AGS-16C3F. Minimal to moderate increases in cellular apoptosis and/or mitotic figures were present in the uterus (endometrial glandular epithelium) of most females treated with AGS-16M8F or AGS-16C3F. The increase in cellular apoptosis and

mitotic figures was an expected effect based on the intended activity of the drug payload (MMAF) to inhibit microtubule formation.

Overall, the toxicity and TK characteristics of AGS-16M8F and AGS-16C3F when given at a comparable dose by IV infusion once weekly for 4 weeks to cynomolgus monkeys were comparable.

1.2.3 Nonclinical Summary of mcMMAF

The safety of the primary metabolite of AGS-16C3F, Cys-mcMMAF, was evaluated in several studies described in the AGS-16C3F Investigator's Brochure. Cys-mcMMAF was not found to be genotoxic in a standard battery of assays; however, no embryo-fetal toxicity data is currently available. MMAF is a tubulin inhibitor and has the same mechanism of action as monomethyl auristatin E (MMAE), which has been shown to be genotoxic and embryotoxic.

As a precautionary measure, it is recommended that males and females continue to use contraception for 6 months after taking the last dose of AGS-16C3F and avoid pregnancy, breastfeeding and donating ova/sperm.

Please refer to the confidential AGS-16C3F Investigator's Brochure for further details.

1.3 Summary of Key Safety Information for Study Drugs

1.3.1 Investigational Drug - AGS-16C3F

1.3.1.1 Development History and Background

One Phase 1 AGS-16C3F-12-2 study evaluated the safety and pharmacokinetics of AGS-16C3F given by IV infusion over 60 minutes every 3 weeks to subjects with metastatic RCC of either clear cell or papillary histology. The study started at a bridging dose identified from an earlier metastatic RCC Phase 1 study in which the target antibody (AGS-16M8F) was manufactured from a hybridoma cell line. AGS-16M8F and AGS-16C3F demonstrated highly similar analytical results, comparable biological characteristics, and similar pharmacologic, pharmacokinetic, and toxicological profiles. The AGS-16M8F Phase 1 study closed for enrollment without reaching the maximum tolerated dose (MTD) to transition the compound development to AGS-16C3F. The highest dose tested in the AGS-16M8F study was 4.8 mg/kg, which was the starting dose for protocol AGS-16C3F-12-2.

1.3.1.2 AGS-16C3F Phase 1 Study (Protocol AGS-16C3F-12-2)

Overall, 34 subjects were treated in protocol AGS-16C3F-12-2 in 4 dose cohorts and the dose that was determined to be the recommended Phase 2 dose was 1.8 mg/kg.

The study is complete, and the safety information is as follows.

All subjects in the study experienced at least 1 treatment emergent adverse event (TEAE), many of which were attributable to the underlying disease. Three (3) dose limiting toxicities (DLT) were observed at the 4.8 and 3.6 mg/kg dose levels. Two (2) subjects at 4.8 mg/kg experienced a DLT of Grade 3 keratitis, and Grade 2 leukoencephalopathy and Grade 3 fall. One (1) subject at 3.6 mg/kg had a Grade 4 thrombocytopenia DLT.

The most frequently reported TEAEs across all dose levels and irrespective of severity, seriousness or causal attribution were: fatigue (71%), nausea (56%), dry eye (50%), vision blurred and decreased appetite (with individual frequency of 44% each), vomiting (38%), thrombocytopenia (35%), and keratitis and headache (with individual frequency of 32% each). Eight (8) subjects (24%) experienced infusion related reactions.

At the 1.8 mg/kg dose level, the most frequently reported TEAEs were: fatigue (85%), nausea (69%), dry eye, headache, and constipation (with individual frequency of 54% each), vision blurred and decreased appetite (with individual frequency of 46% each), epistaxis and vomiting (with individual frequency of 39% each), and dyspnea and anemia and diarrhea and insomnia (with individual frequency of 31% each).

Eighteen (18) subjects experienced serious adverse events (SAEs) across all doses. Of these, 6 subjects had SAEs that were judged as at least possibly related to the investigational product. One (1) of these drug related SAEs occurred in a subject treated at the 1.8 mg/kg dose level.

Two (2) subjects at dose level 2.7 mg/kg died on study: 1 due to peritoneal hemorrhage and 1 due to cardiac arrest. Both fatal events were judged unrelated to the investigational product.

Please refer to the confidential AGS-16C3F Investigator's Brochure for further details.

1.3.2 Comparator Drug - Axitinib (Inlyta®)

Axitinib is an oral kinase inhibitor which has the chemical name *N*-methyl-2-[3-((*E*)2-pyridin-2-yl-vinyl)-1*H*-indazol-6-ylsulfanyl]-benzamide. Axitinib has been shown to inhibit receptor tyrosine kinases including vascular endothelial growth factor receptors (VEGFR)-1, VEGFR-2, and VEGFR-3 at therapeutic plasma concentrations. These receptors are implicated in pathologic angiogenesis, tumor growth, and cancer progression. VEGF-mediated endothelial cell proliferation and survival were inhibited by axitinib *in vitro* and in mouse models. Axitinib was shown to inhibit tumor growth and phosphorylation of VEGFR-2 in tumor xenograft mouse models [Axitinib U.S. Package Insert (Pfizer Labs), Aug 2014].

Most frequent adverse reactions from a pooled dataset of 672 patients who received axitinib in clinical studies for the treatment of RCC were as follows: diarrhea (55%), hypertension (51%), fatigue (45%), decreased appetite (39%), nausea, weight decrease and dysphonia (33% each), hand-foot syndrome (32%), hemorrhage (26%), hypothyroidism (25%), vomiting (24%), proteinuria (21%),constipation and cough (20% each).

Detailed information on the toxicity associated with axitinib can be found within the Package Insert, Summary of Product Characteristics (SPC) or local product information. Please note the prescribing warnings and precautions for use in patients with cardiac failure, hypertension, thyroid dysfunction, arterial and venous embolic/thrombotic events, elevation of hemoglobin/hematocrit, hemorrhage, gastrointestinal perforation, wound healing complications, posterior reversible encephalopathy syndrome, proteinuria, and liver-related adverse reactions/hepatic impairment.

1.3.3 Class Effects

Monoclonal antibodies and ADCs are known to carry the risk of hypersensitivity and/or infusion related toxicity. As a reference, infusion related reactions occurred in about 10% of subjects enrolled in the Phase 1 and 2 Studies of brentuximab vedotin, 15-21% of those who received cetuximab and about 40% of those who received trastuzumab (Hong et al, 2012, Younes et al, 2012, Younes et al, 2010, Schwartzberg et al, 2009). Mild-to-moderate infusion reactions may include pruritus, rash, bronchospasm, fever and chills. More severe infusion related reactions might include hypotension and shock.

Hematopoietic toxicity, predominantly expressed as neutropenia, is a common complication of several ADCs, including vedotin- (Younes et al, 2012, Younes et al, 2010), emtansine- (Burris et al, 2011) and ozogamicin-conjugates (Advani et al, 2010, Larson et al, 2005). ADCs are also reported to cause isolated thrombocytopenia as reported as a DLT by trastuzumab-DM1. The pathogenesis is unknown (Krop et al, 2010).

Neuropathy is described as a complication of most tubulin inhibitor-based ADCs (Younes et al, 2012, Burris et al, 2011, Younes et al, 2010, Swain et al, 2008) although it has not emerged so far in the ongoing Phase 1 study using AGS-16C3F.

Monoclonal antibodies and ADCs can also be associated with the development of antibodies (Hughes, 2010, Lambert et al, 2005).

Finally, corneal lesions are an emerging toxicity, reported in subjects treated with auristatin F- or DM4 –conjugated ADC (Coiffier et al, 2011).

1.4 Risk-Benefit Assessment

The recommended Phase 2 dose from the completed Study AGS-16C3F-12-2 was 1.8 mg/kg administered once every 3 weeks. Thirteen (13) subjects were enrolled at this dose level.

At this dose and frequency, durable anti-tumor effects (Partial Response [PR] and Stable Disease [SD]) were observed. Three (3) subjects achieved durable PR (3/13, 23%), 9/13 subjects had SD (69%), and 1/13 subject had PD (8%).

The median treatment duration for the 13 subjects who were enrolled at 1.8 mg/kg is 17.7 weeks (9.3-143.1 weeks).

The compound's primary unique toxicity is ocular toxicities. At the 1.8 mg/kg dose level, reversible ocular toxicities were reported from all but one subject (12/13, 92%) but only 2 subjects (15%) experienced Grade 3 events. No Grade 4 ocular toxicities were reported.

Another common toxicity of this compound is thrombocytopenia. One subject (7.7%) at the 1.8 mg/kg dose level experienced a Grade 3 thrombocytopenia.

Refer to Section 1.3.1.2 for other frequently reported AEs from Study AGS-16C3F-12-2.

2 STUDY OBJECTIVE(S), DESIGN AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary

To evaluate the Progression Free Survival (PFS), based on investigator radiologic review, of AGS-16C3F compared to axitinib in subjects with metastatic RCC

2.1.2 Secondary

- To evaluate the following for AGS-16C3F compared against axitinib:
    - PFS per RECIST v1.1 by blinded central radiology assessment
    - Objective Response Rate (ORR) based on the investigator's radiographic assessment
    - Duration of Response (DOR) based on the investigator's radiographic assessment
    - Overall Survival (OS)
    - Disease Control Rate (DCR) based on the investigator's radiographic assessment
    - Safety
- To evaluate the pharmacokinetics of AGS-16C3F
- To evaluate the incidence of antidrug antibody formation to human native antibody (AGS-16C3) and antibody drug conjugate (AGS-16C3F).

2.2 Study Design and Dose Rationale

2.2.1 Study Design

This multi-center, open-label, randomized study will enroll subjects with metastatic RCC of all histologies who have evidence of progression on or after the last regimen received and have also received at least 2 prior systemic regimens 1 of which is an anti-VEGF agent (clear cell subjects).

Non-clear cell RCC is a heterogeneous group of tumors typically not driven by von Hippel-Lindau (VHL) gene and sensitivity to anti-VEGF treatments differ from that shown in clear cell RCC. Hence, subjects with non-clear cell histology are only required to have progressed on or after only at least one anti-VEGF regimen.

Subjects with non-clear cell histology must also have ENPP3 positive immunohistochemical (IHC) staining at prescreening. Positivity is defined as an IHC H-score ≥ 15. Non-clear cell subjects whose tissue has an IHC H-score of ≥ 15 will qualify to screen for the study.

Clear cell subjects are not required to be screened for ENPP3 to qualify for the study, but subjects must submit tissue during the study for retrospective target expression assessment by IHC.

Subjects will be randomized at 1:1 ratio to either AGS-16C3F or axitinib. Randomization will be stratified according to Eastern Cooperative Oncology Group (ECOG) Performance

Status (0 or 1), the number of prior systemic RCC regimens (2 or > 2), and RCC histology (clear cell or non-clear cell).

For stratification purpose:

- Non-clear cell subjects who have progressed after only one prior anti-VEGF regimen will be regarded the same as those clear cell subjects who have progressed after 2 prior systemic RCC regimens.
- Non-clear cell subjects who have progressed after > 1 prior systemic RCC regimens will be regarded the same as those clear cell subjects who have progressed after > 2 prior systemic RCC regimens.

AGS-16C3F will be administered at 1.8 mg/kg as a single 60-minute IV infusion once every 3 weeks.

Axitinib is a commercial product and will be administered as defined in its product label. Axitinib will have a starting dose of 5 mg, twice daily continuously, by mouth. Axitinib dose may be adjusted during the study as needed as defined in the product label and local institutional guidelines, in doses ranging from 2 to 10 mg, twice daily continuously, by mouth.

Subjects will be eligible to continue receiving treatment on study until disease progression per RECIST v.1.1, unacceptable toxicity, investigator's decision, or study withdrawal. Subjects will also be discontinued from treatment if a significant non-compliance occurs (e.g., those that compromise study objectives or subject safety), or if a subject is lost to follow-up. The study may also be terminated by the Sponsor for any reason. Refer to Section 6 for details.

Disease assessments will be performed every 8 weeks (± 7 days) counting from C1D1. Bone imaging will be performed every 12 weeks (± 7 days) counting from C1D1 (only subjects with bone disease at screening).

Those subjects who discontinued the study for reasons other than objective disease progression by RECIST v.1.1 will continue to have disease assessments every 8 weeks (± 7 days) counting from C1D1. This will continue until subject has radiologically confirmed progression, initiates a new therapy, study closure or subject dies.

The study will have an Independent Data Monitoring Committee (IDMC) overseeing the study. The IDMC will conduct safety reviews at predetermined times during the study to make a recommendation for continuation of recruitment, protocol modification or study discontinuation for safety reasons.

A separate IDMC Charter will specify the governance and conduct of the IDMC. Refer to Section 7.8 for IDMC composition and additional details.

2.2.2 Number of Centers/World Regions

Approximately 30 sites (United States and Canada) are planned to participate in this study. Each site is expected to enroll at least 4 subjects in this study. Sites that do not enroll a subject ≤ 3 months from the study initiation visit date may be terminated and replaced.

2.2.3 Number of Subjects

Participants in this clinical investigation shall be referred to as "subjects". This study will enroll approximately 134 subjects total. Within this total (i.e., 134), the number of subjects with non-clear cell histology is limited to 26 total.

2.2.4 Estimated Study Duration

The study duration, up to the study's primary endpoint assessment, is approximately 24 months.

2.2.5 Dose Rationale

In the Phase 1 study, AGS-16C3F-12-2, 4 dose levels were tested; 4.8, 3.6, 2.7, and 1.8 mg/kg administered via IV every 3 weeks. The 3 higher dose levels were not tolerated in multiple doses. Thirteen (13) subjects were enrolled at the 1.8 mg/kg and 5 subjects were dose reduced to 1.8 mg/kg from 2.7 mg/kg. The 1.8 mg/kg dose level was tolerated in multiple doses administered every 3 weeks and determined to be the recommended Phase 2 dose.

Axitinib is a commercial product and will be administered as defined in its product label. Axitinib will be administered at a starting dose of 5 mg, twice daily continuously, by mouth. Axitinib dose may be adjusted during the study as needed as defined in the product label and local institutional guidelines, in doses ranging from 2 to 10 mg, twice daily continuously, by mouth.

2.3 Endpoints

2.3.1 Primary Endpoints

To evaluate the PFS of AGS-16C3F compared against axitinib (Investigator radiology assessment per RECIST v.1.1).

PFS is defined as the time from the date of randomization to the earliest of documented disease progression as defined by RECIST v.1.1 or death from any cause.

2.3.2 Secondary Endpoints

To evaluate the following for AGS-16C3F compared against axitinib:

- PFS calculated based on blinded central radiology assessment per RECIST v.1.1
- Objective Response Rate (ORR); based on the investigator's radiographic assessment
    - Objective response rate (ORR) is defined as the proportion of subjects who have a best overall response of Complete Response (CR) or Partial Response (PR).

- Duration of Response (DOR); based on the investigator's radiographic assessment
    - Duration of objective response (DOR) is defined as the time from the date of the first response of CR/PR (whichever is first recorded) to the first date of documented progressive disease or death due to any cause.
- Overall Survival (OS)
    - Overall survival, defined as the time from the date of randomization until the date of death from any cause.
- Disease control rate (DCR); based on the investigator's radiographic assessment
    - Disease control rate (DCR) is defined as the proportion of subjects who have a best overall response of Complete Response (CR), Partial Response (PR), or at least 6 months Stable Disease (SD).
- Safety
    - Incidence of AEs (including grade 3 and 4 AEs, treatment-related AEs, SAEs, and AEs requiring discontinuation of study drug), laboratory changes and vital signs.

3 STUDY POPULATION

3.1 Selection of Study Population

Subjects with metastatic RCC of any histology, who have evidence of progression on or after the last regimen received:

- Clear cell histology subjects must have received at least 2 prior systemic regimens, one of which is an anti-VEGF agent.
- Non-clear histology subjects must have received at least 1 prior anti-VEGF regimen and also screen positive by IHC for ENPP3.

3.1.1 Prescreening

Subjects with RCC of non-clear cell histology must sign the prescreening ICF and be prescreened for ENPP3 expression prior to undergoing screening procedures for the main study. Refer to Section 5.2.2 for details.

Clear cell histology subjects are not required to be prescreened for target expression to qualify for the study but must provide tissue during the study for ENPP3 determination by IHC.

3.2 Inclusion Criteria

1. Is at least 18 years of age
2. Histologically confirmed diagnosis of RCC
    a. Non-clear subjects must be ENPP3 positive, defined as IHC H-score ≥ 15
3. Has evidence of progression on or after the last regimen received:

a. Clear cell subject: must have received at least 2 prior systemic regimens, one of which is an anti-VEGF agent.

b. Non-clear cell subject: must have received at least one prior anti-VEGF regimen

4. Has measurable disease according to Response Criteria for Solid Tumors (RECIST v.1.1)
5. Has ECOG Performance Status of 0 or 1
6. Has archive tumor tissue from primary tumor or metastatic site (excluding bone), for which the source and availability have been confirmed.
    a. If no archive tissue is available, the subject may elect to have a biopsy performed to obtain tissue.
7. Has adequate organ function including:
    a. Hematopoietic function as follows:
        i. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
        ii. Platelet count $\geq 100 \times 10^9$/L
        iii. Hemoglobin ≥ 9 g/dL (transfusions are allowed)
    b. Renal Function as follows:
        i. Creatinine $\leq$ 1.5 x ULN, or calculated GFR > 40 mL/min (Cockcroft-Gault) if creatinine > 1.5x ULN
    c. Hepatic function, as follows:
        i. Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) $\leq$ 2.5 x ULN or $\leq$ 5x ULN if known liver metastases
        ii. Total bilirubin $\leq$ 1.5 x ULN
8. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) levels $\leq$1.5 x ULN. If institution does not report PT value, the INR must be $\leq$ ULN
    a. If subject is receiving Coumadin (warfarin), a stable international normalization ratio (INR) of 2-3 is required.
9. No clinical symptoms of hypothyroidism
10. Urine Protein to Creatinine Ratio (uPCR) < 2.0
    a. If uPCR $\geq$ 2.0 then a 24-hour urine collection can be performed to qualify. If this is performed to qualify, the protein result must be < 2 g per 24 hours.
11. Female subject must either:
    a. Be of non-childbearing potential:
        i. post-menopausal (defined as at least 1 year without any menses) prior to Screening, or
        ii. documented surgically sterile

b. Or, if of childbearing potential,

   i. Agree not to try to become pregnant during the study and for 6 months after the final study drug administration

   ii. And have a negative serum pregnancy test ≤ 10 days of C1D1

   iii. And, if heterosexually active, agree to consistently use 2 forms of highly effective birth control* (at least one of which must be a barrier method) starting at Screening and throughout the study period and for 6 months after the final study drug administration.

12. Female subject must agree not to breastfeed starting at Screening and throughout the study period, and for 6 months after the final study drug administration.
13. Female subject must not donate ova starting at Screening and throughout the study period, and for 6 months after the final study drug administration.
14. Male subject and their female spouse/partners who are of childbearing potential must be using highly effective contraception* consisting of 2 forms of birth control (at least one of which must be a barrier method) starting at Screening and continue throughout the study period, and for 6 months after the final study drug administration
15. Male subject must not donate sperm starting at Screening and throughout the study period and, for 6 months after the final study drug administration
16. Is competent to comprehend, sign, and date an independent ethics committee/institutional review board (IEC/IRB) approved informed consent form, as evaluated and documented by the investigator.

    Note: *Highly effective forms of birth control include:

    - Consistent and correct usage of established oral contraception.
    - Established intrauterine device (IUD) or intrauterine system (IUS).Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository

Waivers to the inclusion criteria will **NOT** be allowed.

3.3 Exclusion Criteria

1. Has previously been treated with axitinib, AGS-16C3F, or AGS-16M8F
2. Has untreated brain metastasis. In the case of a solitary brain metastasis which has been resected, there must be evidence of a disease-free interval of at least 3 months post-surgery. For brain metastases treated with whole brain or stereotactic radiation therapy, brain imaging must be stable > 3 months. All subjects previously treated for brain metastases must be stable off corticosteroid therapy for at least 28 days prior to C1D1.
3. Has uncontrolled hypertension defined as blood pressure > 150/90 on medication(s) by 2 blood pressure readings taken at least 1 hour apart.

4. Has gastrointestinal abnormalities including:
    a. inability to take oral medication;
    b. requirement for intravenous alimentation;
    c. prior surgical procedures affecting absorption including total gastric resection;
    d. active gastrointestinal bleeding, unrelated to cancer, as evidenced by hematemesis, hematochezia or melena in the past 3 months without evidence of resolution documented by endoscopy or colonoscopy;
    e. malabsorption syndromes such as celiac disease, cystic fibrosis, inflammatory bowel disease, systemic sclerosis, and carcinoid syndrome
5. Has ocular conditions such as:
    a. Active infection or corneal ulcer
    b. Monocularity
    c. Visual acuity of 20/70 or worse in both eyes
    d. History of corneal transplantation
    e. Contact lens dependent (if using contact lens, must be able to switch to glasses during the entire study duration)
    f. Uncontrolled glaucoma (topical medications allowed)
    g. Uncontrolled or active ocular problems (e.g., retinopathy, macular edema, active uveitis, wet macular degeneration) requiring surgery, laser treatment, or intravitreal injections
    h. Papilledema or other active optic nerve disorder
6. Has used any investigational drug (including marketed drugs not approved for this indication) ≤ 14 days of C1D1. No time limit applies to the use of marketed drugs approved for this indication provided that the subject has progressed on the treatment and all toxicities attributable to the drug have resolved, returned to baseline or stabilized.
7. Has known sensitivity to any of the ingredients of:
    a. investigational product AGS-16C3F (Refer to IB for list of ingredients) and/or,
    b. Inlyta® (axitinib) (Refer to product package insert) and/or,
    c. 1% prednisolone acetate ophthalmic suspension (Refer to Product package insert) and any other corticosteroids.
8. Is currently using (i.e., within 14-days prior to first dose) drugs that are known strong CYP3A4/5 inhibitors/inducers (See Appendix 12.1 for list of excluded drugs).
9. Thromboembolic event (e.g., DVT and PE) ≤ 4 weeks of C1D1.
    a. Subjects who had a thromboembolic event ≤ 4 weeks of C1D1 must be receiving adequate anticoagulation treatment for at least 2 weeks before C1D1 and must continue as clinically indicated post first dose.

10. Has history bleeding disorders (e.g., pulmonary hemorrhage, significant hemoptysis, menometrorrhagia not responding to hormonal treatment) ≤ 2 months before C1D1
11. Has active angina or Class III or IV Congestive Heart Failure (New York Heart Association CHF Functional Classification System) or clinically significant cardiac disease within 6 months of randomization, including myocardial infarction, unstable angina, Grade 2 or greater peripheral vascular disease, congestive heart failure, or arrhythmias not controlled by medication.
12. Had major surgery ≤ 4 weeks of C1D1
13. Is pregnant (confirmed by positive serum pregnancy test) or lactating
14. Has active infection requiring treatment with systemic (intravenous or oral) anti-infectives (antibiotic, antifungal, or antiviral agent) ≤ 10 days of C1D1
15. Is unwilling or unable to comply with study requirements
16. Has any medical or psychiatric disorder that compromises the ability of the subject to give written informed consent, and/or comply with the study procedures as supported by subject records and/or documented by the investigator.

Waivers to the exclusion criteria will **NOT** be allowed.

4 TREATMENT(S)

4.1 Identification of Investigational Product(s)

4.1.1 Investigational Drug – AGS-16C3F

AGS-16C3F is a fully human monoclonal antibody conjugated to a cytotoxic agent MMAF targeting ENPP3 (company code name AGS-16). Subjects randomized to AGS-16C3F will receive AGS-16C3F at 1.8 mg/kg via IV infusion.

AGS-16C3F will be reconstituted with sterile water for injection (USP grade) and diluted in pyrogen-free CCI dextrose solution (USP grade). Depending on the total dose of AGS-16C3F (i.e., reconstituted volume), the investigational product may also be administered undiluted. If diluted, the protein concentration must be ≥ 0.3 mg/mL.

AGS-16C3F will be administered via an infusion pump. The total prescribed dose should be administered over 60 minutes, including time required to flush the line. Supplies necessary for infusion preparation will be supplied by the site pharmacy.

Refer to the Study Pharmacy Guide for reconstitution and infusion preparation instructions.

4.1.2 Comparator Drug – Axitinib (Inlyta®)

Inlyta® (axitinib, manufacturer Pfizer) is an oral kinase inhibitor indicated for the treatment of advanced RCC after failure of one prior systemic therapy. Axitinib is a commercial product and will be administered as defined in its product label. The Sponsor will provide axitinib for the study.

Subjects randomized to axitinib will all have a starting dose of 5 mg, twice daily continuously, by mouth. This dose may be adjusted during the study as needed as defined in the product label and local institutional guidelines, in doses ranging from 2 to 10 mg, twice daily continuously, by mouth. Drug to be used without further modification.

4.2 Packaging and Labeling

Each vial of AGS-16C3F Drug Product (DP) is supplied as a single-use, sterile, preservative-free, lyophilized product (30 mg) in 20 mL glass vials to be stored refrigerated (2-8 °C). Six (6) individually labeled vials will be packaged in a labeled carton for this study. AGS-16C3F will be supplied to site pharmacy in the necessary quantity as a site supply (i.e., supply is not subject specific).

Axitinib will be provided to subjects for the study in its original packaging with a study label affixed. Axitinib will be dispensed in a whole bottle unit to each subject. Axitinib should be stored at room temperature (20-25 °C).

Refer to separate Pharmacy Guide for details.

4.3 Study Drug Handling

For this protocol, the term "study drug" refers to both AGS-16C3F and axitinib, unless otherwise specified.

Current ICH GCP Guidelines require the investigator to ensure that study drug deliveries from the Sponsor are received by the investigator and

- that such deliveries are recorded,
- that study drug is handled and stored according to labeled storage conditions,
- that study drug has an appropriate expiry date and is only dispensed to study subjects in accordance with the protocol, and
- that any unused study drug is destroyed per local pharmacy SOP with appropriate destruction documentation or returned to the Sponsor designated vendor.

Drug inventory and accountability records for the study drugs will be kept by the investigator. Study drug accountability throughout the study must be documented and reconciled. The following guidelines are therefore pertinent:

- The investigator agrees not to supply study drugs to any persons except the eligible subjects in this study in accordance with the protocol.
- The investigator will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these test drugs.
- A study drug inventory will be maintained by the investigator. The inventory will include details of material received and a clear record of when they were dispensed and to which subject.

- At the conclusion or termination of this study, the investigator agrees to conduct a final drug supply inventory and to record the results of this inventory on the Drug Accountability Record. It must be possible to reconcile delivery records with those of used and/or destroyed/returned medication. Any discrepancies must be accounted for and documented. Appropriate forms of deliveries and returns must be signed by the site staff delegated this responsibility.
- At the end of the study or after product expiry, with Sponsor approval, the site will destroy unused study drugs per local pharmacy SOP with appropriate destruction documentation. If local destruction is not possible, contact the Sponsor for alternate destruction arrangements.

Refer to Pharmacy Guide for details.

4.4 Assignment and Allocation

Randomization will be performed via Interactive Response Technology (IRT). After the subject has completed screening and the eligibility worksheet process, the site staff will access the study's IRT system for subject randomization ≤ 5 days before C1D1. The IRT system will not allow randomization to occur if it has been more than 28 days since the main ICF has been signed. Specific procedures for randomization through the IRT are described in the study's IRT manual.

Subjects will be randomized at 1:1 ratio to either AGS-16C3F or axitinib. Randomization will be stratified according to ECOG Performance Status (0 or 1), the number of prior systemic RCC regimens (2 or > 2) and RCC histology (clear cell or non-clear cell).

The RCC histology categorization is defined as the following:

- Clear cell group:
  - Clear cell
  - Clear cell component
  - Mixed clear cell
- Non-clear cell group:
  - Papillary and everything else*
    * everything else: chromophobe, collecting duct, renal medullary, etc., not so common but possible other RCC histologies

Table 3 Stratification Categories for Randomization Process

Prior Systemic RCC Regimen Stratum	Clear Cell Subjects	Non-Clear Cell Subjects
2	2 prior systemic RCC regimens	1 prior systemic RCC regimen
> 2	> 2 prior systemic RCC regimens	> 1 prior systemic RCC regimens

Subject must start study treatment ≤ 5 days of randomization.

5 TREATMENTS AND EVALUATION

5.1 Dosing and Administration of Study Drug(s) and Other Medication(s)

5.1.1 Dose/Dose Regimen and Administration Period

5.1.1.1 AGS-16C3F

The dose of AGS-16C3F will be calculated based on the subject's actual body weight in kilograms obtained predose C1D1 (baseline weight). The same dose will be used throughout the study unless the subject's baseline weight changes by ≥ 10%. The dose of AGS-16C3F will then be administered based on the weight change and this will become the new baseline weight.

The effects of overdose of this product are not known.

Each subject will receive AGS-16C3F every 3 weeks at 1.8 mg/kg through an IV infusion. The 21-day dosing cycle time will reset at each dosing date (i.e., determine the next dosing date from the current actual dosing date). If for logistical reasons (e.g., public holidays, clinic scheduling, etc.) the next dose cannot be given 21 days from the last dose, a -2 day and a +7 day dosing window is allowed. This window is intended to accommodate occasional scheduling conflicts and is not intended for routine use. The Medical Monitor must be consulted for any dose delays that are due to toxicity and for dose intervals that exceed 5 weeks. Refer to Sections 5.1.2 and 5.1.1.3.

5.1.1.1.1 AGS-16C3F Infusion Related Adverse Events

Of the 34 subjects in the Phase 1 study (AGS-16C3F-12-2), 7/34 (20.6%) experienced an infusion related reaction; all were mild in severity (Grade 1/2). At the 1.8 mg/kg dose, 3/13 (23.1%) reported an infusion related reaction; 2 were Grade 1 and 1 was Grade 2. All infusion related reactions were effectively managed with medication and no subject discontinued study due to infusion reaction.

The antibody moiety of this ADC is fully human and immune problems (e.g., anaphylactoid reactions) with ADCs of such type are rare.

5.1.1.1.2 AGS-16C3F Infusion Related Adverse Event Treatment Guidelines

The initial infusion should be administered, without premedication and the total prescribed dose should be administered over 60 minutes, including flush of the line. After completion of the infusion, subjects should be observed for signs of toxicity as necessary and appropriate. It is recommended that each subject be observed for 1 hour after the first infusion. Observation time for subsequent infusions should be determined at Investigator discretion.

The following guidelines are recommended courses of action that the investigator should consider in an event of an infusion related reaction with AGS-16C3F administration. Investigator may, in addition, follow his/her own institutional or local infusion reaction management guidelines:

Table 4 Recommended Guidelines for Infusion Related Adverse Event

Grade/ Severity	Description	Action
Grade 1 or 2	Mild fever, rash, pruritus, urticaria and wheezing; the subject is hemodynamically stable with no clinically significant changes in vital signs (i.e., temperature, pulse or heart rate, respiratory rate, or blood pressure)	May be treated with acetaminophen, diphenhydramine hydrochloride, H2 blocker (e.g., ranitidine) and/or steroids (e.g., methylprednisolone) as clinically appropriate. The investigator may complete the remaining infusion with watchful monitoring at 50% decreased infusion rate.
Grade > 2	Anaphylaxis or anaphylactoid signs or symptoms; the subject has clinically significant changes in vital signs (i.e., temperature, pulse or heart rate, blood pressure or respiratory rate)	May be treated with steroids and/or epinephrine in addition to diphenhydramine, H2 blocker or acetaminophen as clinically indicated. Terminate AGS-16C3F infusion in subjects experiencing severe infusion reactions with severe hemodynamic instability or respiratory distress. Subject should be discontinued from further treatment.

A subject who experienced an infusion related reaction should be provided similar prophylactic treatment in subsequent infusions. Infusion rate should be determined based on severity of prior infusion reaction(s) and how the subject tolerated the remainder of the infusion (i.e., after medical management of event).

Recurrent Grade 2 and 3 infusion reactions, in spite of optimum medical management, must be discussed with the Medical Monitor. Study treatment discontinuation should be considered for recurrent Grade 3 events.

5.1.1.2 Axitinib

Axitinib will have a starting dose of 5 mg, administered twice daily continuously, by mouth. Refer to product label for details. Axitinib subjects will return to clinic every 21 days for clinical assessment and additional axitinib dispensing. If for logistical reasons (e.g., public holidays, clinic scheduling, etc.) the next clinic visit cannot occur 21 days from the last visit, a -2 day and a + 7 day visit window is allowed. This window is intended to accommodate occasional scheduling conflicts and is not intended for routine use. The Medical Monitor must be consulted for any study visit delays that are due to toxicity and for treatment hiatus that exceeds 5 weeks. Refer to Section 5.1.1.3.

5.1.1.3 Treatment Hiatus

For both treatment arms, subjects will have disease assessments every 8 weeks (± 7 days) counting from C1D1, irrespective of any treatment hiatus.

- Subject may stay on study if the disease status is at least Stable Disease (SD) per RECIST v.1.1.
- If the treatment hiatus will be longer than 5 weeks, each case must be discussed with the Medical Monitor.

5.1.2 Increase or Reduction in Dose of the Study Drug(s)

The Medical Monitor must be consulted for all AGS-16C3F toxicities that may require adjustment in treatment schedule and/or dose. AGS-16C3F dose modifications and/or treatment schedule modifications must be discussed and agreed to in writing by the Medical Monitor on a case-by-case basis before any adjustment is made.

Axitinib dose may be adjusted during the study as needed as defined in the product label and local institutional guidelines, in doses ranging from 2 to 10 mg, twice daily continuously, by mouth.

5.1.3 Previous and Concomitant Treatment (Medication and Non-Medication Therapy)

All medications and concomitant treatments administered from date of ICF signature through the last formal follow-up observational period must be recorded in the eDC system.

5.1.3.1 Prophylactic Steroid Eye Drop Use (AGS-16C3F Subjects Only)

Subjects randomized to AGS-16C3F must use 1% prednisolone acetate ophthalmic suspension prophylactically (prophylaxis steroid drops) starting from Day (-1) of each treatment cycle. Prophylaxis steroid drops will be applied to both eyes, 1 drop to each eye, 6 times daily while awake for the first 7 days of each cycle (starting at Day [-1]), then 4 times daily while awake for an additional 7 days, and then stopped. This will be repeated in each treatment cycle. Refer to Table 5 below.

Should the subsequent dose be delayed, the "no prophylaxis steroid eye drop use" period will extend. The study will not provide the prophylaxis steroid drops (i.e., each site to supply); but the cost will be reimbursed.

Table 5 Sample Schedule for Prophylactic Steroid Eye Drop

Sun	Mon	Tues	Wed	Thu	Fri	Sat
Cycle X, Day (-1)	Cycle X, Day 1	Cycle X, Day 2	Cycle X, Day 3	Cycle X, Day 4	Cycle X, Day 5	Cycle X, Day 6
< --- --- --- --- --- --- --- --- --- --- --- --- ---- Drops 6x Daily ---- --- --- --- --- --- --- --- --- --- --- >						
Cycle X, Day 7	Cycle X, Day 8	Cycle X, Day 9	Cycle X, Day 10	Cycle X, Day 11	Cycle X, Day 12	Cycle X, Day 13
< --- --- --- --- --- --- --- --- --- --- --- --- ---- Drops 4x Daily ---- --- --- --- --- --- --- --- --- --- --- >						
Cycle X, Day 14	Cycle X, Day 15	Cycle X, Day 16	Cycle X, Day 17	Cycle X, Day 18	Cycle X, Day 19	Cycle X, Day 20
< --- --- --- --- --- --- --- --- No Prophylaxis Steroid Eye Drop Use --- --- --- --- --- --- --- --- >						
Cycle X, Day 21	Cycle Y, Day 1	Cycle Y, Day 2	Cycle Y, Day 3	Cycle Y, Day 4	Cycle Y, Day 5	Cycle Y, Day 6
< --- --- --- --- --- --- --- --- --- --- --- --- ---- Drops 6x Daily ---- --- --- --- --- --- --- --- --- --- --- >						
Cycle Y, Day 7	Cycle Y, Day 8	Cycle Y, Day 9	Cycle Y, Day 10	Cycle Y, Day 11	Cycle Y, Day 12	Cycle Y, Day 13
< --- --- --- --- --- --- --- --- --- --- --- --- ---- Drops 4x Daily ---- --- --- --- --- --- --- --- --- --- --- >						
Cycle Y, Day 14	Cycle Y, Day 15	Cycle Y, Day 16	Cycle Y, Day 17	Cycle Y, Day 18	Cycle Y, Day 19	Cycle Y, Day 20
< --- --- --- --- --- --- --- --- No Prophylaxis Steroid Eye Drop Use --- --- ------ --- --- --- --- >						

5.1.3.2 Prohibited Concomitant Medications

The investigator may prescribe any medication necessary to ensure the safety and wellbeing of the subject during the study. Please refer to Appendix 12.1 for additional information.

Protocol prohibited medications that are needed temporarily to treat an AE are permitted (e.g., dexamethasone used to treat nausea).

5.1.3.2.1 Subjects Randomized to AGS-16C3F

The following medications are likely to influence evaluation of the safety, pharmacokinetics or efficacy of AGS-16C3F. If the investigator determines that any of the following medications are necessary to provide adequate medical support, the subject must be withdrawn from further study drug administration:

Table 6 Prohibited Medications for Subjects Randomized to AGS-16C3F

	Prohibited Medication	Reason to Exclude
1	Chemotherapy, radiotherapy, immunotherapy, monocolonal antibody therapy or other medications intended for antitumor activity[1]	Likely affect efficacy, safety or pharmacokinetics of AGS-16C3F
2	Investigational products or therapy other than AGS-16C3F	

[1] Palliative radiation is permitted provided it does not interfere with subject safety and efficacy of the study drug being administered. Palliative radiation cannot be administered to any target lesion. Medications used to treat bone metastases (e.g., zoledronic acid, denosumab, etc.) are allowed provided they are not initiated at the same time as Cycle 1 Day 1.

5.1.3.2.2 Subjects Randomized to Axitinib

The following medications are likely to influence evaluation of the safety, pharmacokinetics or efficacy of axitinib. If the investigator determines that any of the following medications are necessary to provide adequate medical support, the subject must be withdrawn from further study drug administration:

Table 7 Prohibited Medications for Subjects Randomized to Axitinib

	Prohibited Medication	Reason to Exclude
1	Chemotherapy, radiotherapy, immunotherapy, monocolonal antibody therapy or other medications intended for antitumor activity other than axitinib[1]	Likely affect efficacy, safety or pharmacokinetics of AGS-16C3F
2	Investigational products or therapy	
3	Strong CYP3A4/5 inducers (e.g., rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentin, phenobarbital, and St. John's wort)[2]	Axitinib is a substrate of CYP3A4/5

[1] Palliative radiation is permitted provided it does not interfere with subject safety and efficacy of the study drug being administered. Palliative radiation cannot be administered to any target lesion. Medications used to treat bone metastases (e.g., zoledronic acid, denosumab, etc.) are allowed provided they are not initiated at the same time as Cycle 1 Day 1.

[2] The drugs defined as CYP Substrates with Narrow Therapeutic Range by FDA's guidance - Guidance for Industry Drug Interaction Studies - Study Design, Data analysis, and Implications for Dosing and Labeling): http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf)

The use of the following medications and foods should be avoided or used with caution and closely monitored:

Table 8 Medications/Food to be Avoided or Used with Caution for Subjects Randomized to Axitinib

	Medications/Food to be Avoided or Used with Caution[1]	Reason to be Cautious
1	Moderate CYP3A4/5 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, and nafcillin)[2]	Axitinib is a substrate of CYP3A4/5
2	Strong CYP3A4/5 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, erythromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin); Grapefruit or grapefruit juice[2]	

1 Please refer to the product label for additional guidance

2 The drugs defined as CYP Substrates with Narrow Therapeutic Range by FDA's guidance - Guidance for Industry Drug Interaction Studies - Study Design, Data analysis, and Implications for Dosing and Labeling): http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf)

5.1.4 Treatment Compliance

5.1.4.1 AGS-16C3F

For the purpose of this study, an overdose will be defined as any dose exceeding the prescribed dose by greater than 20%. In the event of an overdose, refer to Section 5.7.9.

Compliance for prophylaxis steroid eye drop use will be qualitatively assessed at each visit through the study coordinator/nurse administered ESQ.

5.1.4.2 Axitinib

Study subjects are expected to adhere to the investigator's prescribing instructions. The investigator will ensure that subjects are following the prescribing instructions throughout the study. This will be assessed by accounting for the total number of tablets dispensed and returned at each visit and documenting it in the subject's medical records.If the subject is not adequately following the prescribing instructions, the investigator will counsel the subject and ensure steps are taken for improvement.

Subjects randomized to the axitinib arm must bring their axitinib bottles (including empty bottles), to each clinic visit.

In the event of an overdose, refer to Section 5.7.9.

5.2 Study Assessments and Procedures

5.2.1 Tissue for Target Expression IHC Testing

All subjects are required to submit tumor tissue for target expression assessment by IHC in the study. At least 5 tumor tissue sections (4 microns thick) or a tumor block must be provided for the assay. If no archive tissue is available, the subject may elect to have a biopsy performed to obtain tissue.

Non-Clear Cell Subjects

Tumor tissue, from primary or metastatic site (excluding bone), will be submitted to the Sponsor-designated CLIA certified laboratory for ENPP3 determination by IHC. An IHC H-score of ≥ 15 is required for non-clear cell subjects to qualify for study screening. IHC H-scores for ENPP3 eligibility will not expire for the duration of the study (i.e., there is no time limit from prescreen qualification to screening start).

Every effort will be made to report the IHC H-score to the investigator ≤ 72 hours of sample receipt at the Sponsor-designated CLIA certified laboratory provided that the specimens were received in good condition along with all required documents fully completed. Refer to Study Guide for details.

Clear Cell Subjects

Clear cell histology subjects are not required to be screened for target expression to qualify for the study, however, the source and availability of archive tissue must be confirmed to meet study eligibility criteria (Inclusion #6). Tissue should be submitted for IHC testing < 3 months from main study consent form signature date. Consent to provide tissue is

included in the main study informed consent form. Clear cell histology subjects' specimens will be batch assayed during the study. The IHC H-score will be reported back to the investigator for information only when the data become available.

5.2.2 Prescreening Period

Prescreening of target expression testing is only required for non-clear cell subjects. Refer to details in Section 5.2.1. Non-clear cell subjects must sign a prescreening informed consent form to obtain and submit tissue for the study and be prescreened for ENPP3 expression prior to undergoing screening procedures for the main study. Only those with an IHC H-score ≥ 15 qualify to proceed with screening. A copy of all signed and dated informed consent forms must be given to the subject before any study specific procedure is performed.

5.2.3 Screening Period

All subjects with RCC of clear cell histology and subjects with RCC of non-clear cell histology who have received an IHC H-score of ≥ 15 are eligible for screening.

All subjects who are eligible to screen will sign the main study ICF ≤ 28 days of C1D1. A copy of all signed and dated informed consent forms must be given to the subject before any study specific procedure is performed. Subjects may undergo study screening procedures prior to giving informed consent provided they are considered standard of care.

The following screening procedures must be performed ≤ 28 days of the C1D1 date, unless otherwise noted.

- Medical history, including previous renal cancer therapies; refer to Section 5.3.2
- Physical Examination including vital signs (blood pressure, heart rate, and respiration rate) and weight
- ECOG Performance Status score; refer to Appendix 12.5
- Hematology, chemistry, CRP, and PT/aPTT evaluations (≤ 10 days of the C1D1; refer to Section 5.6.3)
- Thyroid Function Tests; refer to Section 5.6.3
- uPCR
- Serum pregnancy test (women of childbearing potential; ≤ 10 days of the C1D1)
- Electrocardiogram (ECG) (in triplicate, approximately 3-5 minutes in between ECGs); ≤ 10 days of the C1D1; refer to Section 5.6.4
- Disease assessment; refer to Section 5.5
    - CT scan of the chest, abdomen, and pelvis (Magnetic Resonance Imaging (MRI) is acceptable to assess disease extent if used throughout the study).
    - Imaging of the brain (e.g., MRI or CT), if clinically indicated
    - Bone imaging, if clinically indicated. The imaging method will be any imaging modality per local or institutional standard of care (SOC) (e.g., NaF PET, MRI Bone, Tc-99 Bone Scan, etc.)

- Complete eye exam for all subjects; refer to Section 5.6.5
- Complete ESQ for both Cancer Treatment History and Screening sections; refer to Section 5.6.5.1
- Randomization; refer to Section 5.2.5 for additional details
- Tumor Tissue; refer to Section 5.2.1
- Complete and submit an eligibility worksheet for review. Please see the Study Guide for the form and for complete instructions

Subjects who do not meet the eligibility criteria may be re-screened at the discretion of the Investigator.

5.2.4 Enrollment

In this study, subjects are considered enrolled once randomized.

5.2.5 Randomization

See Section 4.4 and the separate relevant study manuals for details. Randomization will occur after screening has been completed and must be done ≤ 5 days of C1D1. Randomized subjects will not be replaced, whether or not, the subject receives study treatment.

5.2.6 Treatment Period

On C1D1, all procedures, other than post-infusion specific procedures, must be performed BEFORE first dose of study drug is administered and meet all inclusion and exclusion criteria.

During the treatment period, subjects who have a standard of care tumor biopsy or surgery, will have the opportunity to submit part of the sample for ENPP3 analysis. The subject will indicate their choice in the informed consent form.

5.2.6.1 Cycles 1 – 4

All predose procedures below may be performed ≤ 4 days in advance of the actual dosing day, with the exception of the following which must be done on the dosing day:

- Vital signs
- ECG (C1D1 Only)
- Predose PK sample collection for AGS-16C3F subjects on Cycles 2-4. Predose PK sample for Cycles 2-4 must be collected anytime before AGS-16C3F drug administration on the day of infusion.
- Physical exam and body weight
- Vital signs; refer to Section 5.6.1
    - For AGS-16C3F Subjects: On the days of study drug administration, vital signs will be taken predose, and approximately 30 minutes after administration of study drug

  - For axitinib Subjects: Vital signs will be taken once at each clinic visit

- ECG (C1D1 only); refer to Section 5.6.4
  - For AGS-16C3F Subjects: It will be done predose (anytime predose on actual dosing day) and 2 hours after the end of infusion, when the total prescribed dose has been administered (e.g., 2 h after the end of infusion), both in triplicate (approximately 3-5 minutes in between ECGs). Ensure that the subject is in the same position for every reading
  - For axitinib Subjects: ECG will be taken in triplicate (approximately 3-5 minutes in between ECGs) predose (anytime predose on actual dosing day). Ensure that the subject is in the same position for every reading
- ECOG Performance Status; refer to Appendix 12.5
- Hematology, chemistry, CRP, and PT/aPTT; refer to Section 5.6.3
- Thyroid Function Test, every odd cycle (e.g., Cycle 1, Cycle 3, etc.); refer to Section 5.6.3
- uPCR, every odd cycle (e.g., Cycle 1, Cycle 3, etc.); refer to Section 5.6.3
- Complete eye exam for AGS-16C3F subjects only will be done after the Cycle 2 Day 1 dose but before the Cycle 3 Day 1 dose, and as clinically indicated; refer to Section 5.6.5
- Complete ESQ at every scheduled and unscheduled visit; refer to Section 5.6.5.1
- PK and ADA blood samples will be collected for AGS-16C3F subjects only; refer to Table 1 and Table 2
- Disease assessment; refer to Section 5.5

5.2.6.2 Cycles 5 and Beyond

Procedures below will be done starting at Cycle 5 and every 3 weeks thereafter, unless otherwise specified. All predose procedures below may be performed ≤ 4 days in advance of the actual dosing day, with the exception of the following which must be done on the dosing day:

a. Vital signs

- Physical exam and body weight
- Vital signs; refer to Section 5.6.1
  - For AGS-16C3F Subjects: On the days of study drug administration, vital signs will be taken predose, and approximately 30 minutes after administration of study drug
  - For axitinib Subjects: Vital signs will be taken once at each clinic visit
- ECOG Performance Status; refer to Appendix 12.5
- Hematology, chemistry, CRP, and PT/aPTT; refer to Section 5.6.3

- Thyroid Function Test, every odd cycle (e.g., Cycle 5, Cycle 7, etc.); refer to Section 5.6.3
- uPCR, every odd cycle (e.g., Cycle 5, Cycle 7, etc.); refer to Section 5.6.3
- Complete eye exam for AGS-16C3F subjects only will be done after the Cycle 5 Day 1 dose but before the Cycle 6 Day 1 dose, and as clinically indicated; refer to Section 5.6.5
- Complete ESQ at every scheduled and unscheduled visit; refer to Section 5.6.5.1
- PK and ADA blood samples will be collected for AGS-16C3F subjects only; refer to Table 1 and Table 2
- Disease assessment; refer to Section 5.5

5.2.7 Post-treatment Follow-Up Period (Safety Follow-Up visit)

All subjects will be required to have a Safety Follow-Up visit at least 28 days (+ 7 days) after the last dose. Every effort should be made to have this visit occur within the specified timeframe. If this visit cannot be performed within the specified timeframe (e.g., subject initiating new treatment, subject admitted to hospice), this visit should be scheduled as close as possible to the specified timeframe. To ensure subject's wellbeing and safety, a Safety Follow-Up visit performed outside of the window is strongly preferred over no Safety Follow-Up Visit.

Procedures below will be done during the Safety Follow-Up Visit, unless otherwise specified.

- Physical exam and body weight
- Vital signs; refer to Section 5.6.1
- ECG in triplicate (approximately 3-5 minutes in between ECGs). Ensure that the subject is in the same position for every reading; refer to Section 5.6.4
- ECOG Performance Status; refer to Appendix 12.5
- Hematology, chemistry, CRP, Thyroid Function Test, PT/aPTT, and uPCR; refer to Section 5.6.3
- Complete eye exam as clinically indicated; refer to Section 5.6.5
- Complete ESQ; refer to Section 5.6.5.1
- PK and ADA blood samples will be collected for AGS-16C3F subjects only, as specified in Table 1 and Table 2

5.3 Demographics and Baseline Characteristics

5.3.1 Demographics

Age at first dose, gender, sex, race, ethnicity, height, and body weight will be collected during the Screening visit for this study.

5.3.2 Medical History

Medical history will be recorded for all medical conditions within the past 5 years from the date of randomization. Please use the following list as a minimum guideline for what should be collected and entered into the eDC system.

- Record all cancer diagnoses.
- Record all diseases and/or diagnoses requiring cytotoxic treatment (e.g., including non-oncology treatments such as arthritis treated with methotrexate).
- Record all diseases and/or diagnoses of major organs (e.g., myocardial infarction, hepatitis).
- Record all non-renal cell cancer history.

5.3.3 Diagnosis of the Target Disease, Severity, and Duration of Disease

A complete medical history of the target disease will be recorded at Screening. This will include:

- RCC diagnosis (date and method of diagnosis, including dates of diagnostic procedures)
- TNM classification and disease stage at screening
- Metastasis diagnosis date
- Dates and type of previous therapy for RCC
- Other disease specific information as designated in the eCRF

5.4 Pharmacokinetics Assessment

The PK data for ADC and MMAF will be analyzed using noncompartmental method. Parameters to be assessed will include concentrations at the end of infusion or maximum observed concentration (C_{EOI} or C_{max}), concentrations at trough (C_{trough}), time to maximum observed concentration (T_{max}), partial area under the concentration time curve ($AUC\tau$) for Cycle 1 and 4, and either terminal or apparent terminal half-life ($t_{1/2}$) as appropriate. Additionally, clearance (CL) and volume of distribution at steady state (V_{ss}) will be included as appropriate. Descriptive statistics will be provided for the PK parameter estimates and subject concentration plots over time may be generated. Additional model-based analyses may be performed and reported separately.

5.5 Efficacy Assessment

Response and progression will be evaluated in this study using RECIST v.1.1, refer to Appendix 12.6. Investigator's radiographic disease assessment will be used for treatment decisions.

Disease assessments will be performed every 8 weeks (± 7 days) counting from C1D1. Bone imaging will be performed every 12 weeks (± 7 days) counting from C1D1 (only subjects with bone disease at screening).

Those subjects who discontinued the study for reasons other than objective disease progression by RECIST v.1.1 will continue to have disease assessments every 8 weeks (± 7

days) counting from C1D1. This will continue until subject has radiologically confirmed progression, initiates a new therapy, study closure or subject dies.

Scans will be read on site.

CT scan with contrast (chest, abdomen, and pelvis) is the preferred modality for tumor assessment. MRI is acceptable if local standard practice, or CT scans are contraindicated in a subject (e.g., subject is allergic to contrast media). All other RECIST-approved scanning methods such as x-ray are optional. PET-CT scans must use contrast. The modality chosen for the subject must be used throughout the study.

Additional instructions for imaging assessments can be found in the study guide. The assessment will include tumor measurements for target lesions, nontarget lesions, and any new lesions. An overall assessment will be characterized for a given time point evaluation. At the end of study for that subject, the best overall response to the study regimen will be characterized. To ensure comparability, the screening and subsequent assessment of response should be performed using identical techniques. The same individual should assess images for any 1 subject for the duration of the study if possible.

For subjects with known treated stable brain metastases at study entry, it is recommended that repeat imaging also include the brain and the same methods used to detect brain lesions at baseline are to be used to follow the lesions throughout the study.

Per RECIST v1.1, lesions that cannot be accurately measured such as bone lesions and previously radiated lesions should not be selected as measurable lesions.

Confirmation scans for CR or PR should be done at the next scheduled assessment. The site of disease progression as well as target or nontarget lesion should be documented in the eCRF. Additional imaging may be performed at any time to confirm suspected progression of disease.

5.5.1 Evaluation of Target Lesions

5.5.1.1 Complete Response (CR)

CR is defined as disappearance of all target and nontarget lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm from baseline measurement.

5.5.1.2 Partial Response (PR)

PR is defined as at least a 30% decrease in the sum of diameters (longest for nonnodal lesions, short axis for nodal lesions) of target lesions taking as reference to the baseline sum of diameters.

5.5.1.3 Stable Disease (SD)

SD is defined as neither sufficient decrease to qualify for PR nor sufficient increase to qualify for progressive disease taking as reference the smallest sum of diameters while on study drug.

5.5.1.4 Progressive Disease (PD)

PD is defined as at least a 20% increase in the sum of diameters (longest for nonnodal lesions, short axis for nodal lesions) of the 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. The appearance of 1 or more new lesions is also considered progression.

5.5.2 Evaluation of Nontarget Lesions

To achieve unequivocal progression on the basis of nontarget lesions, there must be an overall level of substantial worsening in nontarget disease such that, even in presence of SD or PR of target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of 1 or more nontarget lesions is usually not sufficient to qualify for unequivocal progression.

5.5.2.1 Complete Response (CR)

For CR of nontarget lesions, subjects must have disappearance of all nontarget lesions and all lymph nodes must be nonpathological in size (< 10 mm short axis).

5.5.2.2 NonCR/NonPD

NonCR/NonPD of nontarget lesions is defined as persistence of 1 or more nontarget lesions.

5.5.2.3 Progressive Disease (PD)

PD of nontarget lesions is defined as unequivocal progression of existing nontarget lesions or the appearance of 1 or more new lesions.

5.5.3 Evaluation of Time Point Response

The overall response status at each time point for subjects with measurable disease at baseline will be reported according to Table 1 in Appendix 12.6.

5.6 Safety Assessment

5.6.1 Vital Signs

Measurements consisting of blood pressure, heart rate, respiration rate, and temperature will be collected throughout this trial. Vital signs will be collected according to the schedule displayed in Table 1.

- For subjects randomized to AGS-16C3F, on the days of study drug administration, vital signs will be taken predose, and approximately 30 minutes after administration of study drug
- For subjects randomized to axitinib, vital signs will be taken once at each clinic visit

5.6.2 Adverse Events

See Section 5.7 for information regarding AE collection and data handling.

5.6.2.1 Adverse Events Requiring Treatment Modifications and/or Discontinuation of AGS-16C3F Administration

5.6.2.1.1 Thrombocytopenia

For thrombocytopenia without signs and symptoms of bleeding that the investigator considers clinically significant, the following AGS-16C3F dosing guidelines will be used.

Table 9 Recommended Guidelines for Thrombocytopenia

Grade	Description	Action
2	Present, without signs and symptoms of bleeding.	The dose may be administered or held at investigator discretion.
	Persistent (i.e., lasting for ≥ 5 weeks), without signs and symptoms of bleeding, and without documented bone marrow suppression.	The subject may be considered for a dose reduction to 1.2 mg/kg. Dose reduction must be discussed with and approved in writing by the Medical Monitor.
	Persistent (i.e., lasting for ≥ 5 weeks), without signs and symptoms of bleeding, and with documented bone marrow suppression.	The subject will be discussed with the Medical Monitor. The possible need for permanent discontinuation will be considered based on clinical benefit of treatment as well as review of overall patient profile (concomitant medication and medical history review, presence or absence of mucosal bleed, other AEs, etc.).
3	Present, without signs and symptoms of bleeding.	The dose will be held until platelet count improves to at least Grade 2 ($\geq 50 \times 10^9$/L).
	Present, without signs and symptoms of bleeding, and has not recovered to at least Grade 2 ($\geq 50 \times 10^9$/L) ≤ 5 weeks.	The subject will either be permanently discontinued or may be considered for a dose reduction to 1.2 mg/kg. Dose reduction must be discussed with and approved in writing by the Medical Monitor.
4	Present, without signs and symptoms of bleeding, and platelet count is confirmed with a repeat lab performed ≤ 72 hours.	Subject will be permanently discontinued.
	Present, without signs and symptoms of bleeding, and isolated (i.e., not confirmed with a repeat lab ≤ 72 hours after first assessment).	Dose will be held until platelet count improves to at least Grade 2 ($\geq 50 \times 10^9$/L)
	Present, without signs and symptoms of bleeding, and isolated (i.e., not confirmed with a repeat lab ≤ 72 hours after first assessment), and has not recovered to at least Grade 2 ($\geq 50 \times 10^9$/L) ≤ 5 weeks.	The subject will either be permanently discontinued or may be considered for a dose reduction to 1.2 mg/kg. Dose reduction must be discussed with and approved in writing by the Medical Monitor.

Beginning at Cycle 5 Day 1 and for all subsequent cycles, a bone marrow study or hematology consult, is strongly encouraged for all AGS-16C3F subjects whose predose platelet count is $< 75 \times 10^9$/L at any 2 timepoints. If a hematology consult and/or bone

marrow study is/are performed, the redacted report(s) will be timely submitted to the Sponsor.

5.6.2.1.2 Adverse Events of Possible Hepatic Origin

See Appendix 12.2 for detailed information on the monitoring and assessment of liver abnormalities, if the AE for a subject enrolled in a study and receiving study drug is accompanied by increases in liver function testing (LFT, e.g.: AST, ALT, bilirubin, etc.) or is suspected to be due to hepatic dysfunction.

Subjects with AEs of hepatic origin accompanied by Liver Function Test (LFT) abnormalities should be carefully monitored.

5.6.2.1.3 Other Adverse Events

Subjects who experience a Grade 4 toxicity other than those related to the eye, liver, and thrombocytopenia, as described in Sections 5.6.5, 5.6.2.1.2, 5.6.2.1.1 will be permanently discontinued from AGS-16C3F treatment. Laboratory AEs with a Grade 4 value, must be confirmed with a repeat analysis ≤ 72 hours before discontinuing subject from treatment.

See Sections 5.7.1 and 6.1 for additional guidance.

5.6.3 Laboratory Assessments

Below is a table of the safety laboratory tests that will be performed locally during the conduct of the study. See Table 1 for study visit collection dates.

Chemistry		**Coagulation**	**Urine**	**Hematology**
Sodium	BUN	PT/aPTT	uPCR	CBC including platelet number and differential
Potassium	Creatinine			
Chloride	Uric Acid			
Bicarbonate	Total bilirubin	**Thyroid Function**		
Total protein	Direct bilirubin	TSH		
Albumin	Alkaline phosphatase	Free T4		
Calcium	LDH			
Magnesium	AST (SGOT)			
Phosphorus	ALT (SGPT)			
Glucose	CRP			

5.6.3.1 Pharmacokinetic and ADA samples

Subjects randomized to AGS-16C3F, will have blood samples drawn for PK and ADA formation assessments. Refer to Table 1 and Table 2.

5.6.4 Electrocardiogram (ECG)

ECGs will be done in triplicate for all timepoints, approximately 3-5 minutes between each assessment. Ensure that the subject is in the same position for every reading.

ECGs will be collected at Screening, C1D1, and at the Safety Follow-Up visits.

For subjects randomized to AGS-16C3F, on C1D1, the ECGs will be taken predose (anytime predose on actual dosing day) and again 2 hours after the end of infusion, when the total prescribed dose has been administered (e.g., 2 h after the end of infusion).

For subjects randomized to axitinib, on C1D1, the ECGs will be taken predose (anytime predose on actual dosing day) only.

5.6.5 Ocular Assessments

A complete eye exam will be done during screening. Subjects randomized to AGS-16C3F, will have a complete eye exam done after the Cycle 2 Day 1 dose but before the Cycle 3 Day 1 dose, after the Cycle 5 Day 1 dose but before the Cycle 6 Day 1 dose, and as clinically indicated. Subjects randomized to axitinib, will have a complete eye exam done post baseline as clinically indicated. The frequency of ophthalmology follow-ups outside of protocol requirement is at the discretion of the Investigator and ophthalmologist.

The ophthalmologist will complete a study provided cover form, capturing all pertinent information, and submit it along with the ophthalmology report to the investigator. Please see the Study Guide for the form and for complete instructions.

At the screening (baseline) ophthalmology visit, the complete eye exam will consist of Visual Acuity with Snellen Chart, best corrected visual acuity (BCVA), intraocular pressure (IOP), extraocular movement (EOM), pupils, external exam, slit lamp exam, and dilated fundoscopic exam.

For post baseline ophthalmology visits, the complete eye exam will be the same as the baseline visit, but the dilated fundoscopic exam may be deferred if not clinically indicated (i.e., if there is no change in vision or if the vision change can be explained as a non-retinal event). If deferred, an undilated fundoscopic exam is still required as part of the full eye exam.

The Schirmer's test (with and without anesthetic) is optional if subject has dry eyes at screening (baseline).

5.6.5.1 Symptom Based Ocular AEs

Ocular symptoms reported by the subject during clinic visits will be graded per CTCAE v4.03 (i.e., symptom based assessment) and this will guide the treatment decision for that visit and the necessity for a follow up ophthalmology consult.

An Eye Symptom Questionnaire (ESQ) will be administered at every visit in the oncology clinic. Please see the Study Guide for the form and for complete instructions. During screening, the ESQ will be completed for both Cancer Treatment History and Screening sections.

The ocular symptom AEs must be collected in the eDC system.

If a subject reports ocular symptoms, the following guidelines may be used:

Table 10 Subject Reported Symptom Based Ocular AE (i.e., per CTCAE v4.03)

Grade	Study Treatment Action	Ophthalmology Referral
1	Continue per dose and schedule (i.e., AGS-16C3F 1.8 mg/kg q3w or axitinib 5 mg, twice daily)	May be done at Investigator discretion
2	May continue treatment per dose and schedule at Investigator discretion	Required; must occur prior to the subsequent cycle.
3	Hold treatment	Required; must occur prior to the subsequent cycle.

5.6.5.2 Clinical Ocular Adverse Events (AE)

Clinical Ocular AEs are objective findings (e.g., keratitis, macular edema, retinal degeneration) from the ophthalmology evaluation.

Clinical Ocular AE grading will be determined based on visual acuity (VA) change from screening (baseline).

This will be done as follows:

Step 1. Determine baseline VA for each eye. Subject should have the VA measured with or without glasses depending on the subject's requirement for daily use for distance vision. Use Table 12 and identify the row of the baseline vision for each eye.

Step 2. Subsequent eye exam VA (obtained under same conditions as screening [baseline]), determine if a change in vision is present. If so, use the row in Table 12 identified in Step 1, to locate the current VA and determine the number of line-of-vision-change from baseline for each eye; this is expressed as the number in parenthesis. Also note the grade of the VA for each eye.

Step 3. Between the two eyes, determine the eye with greater line-of-vision-change from baseline (delta). The Clinical Ocular AE grade for the subject is the grade of the worse (delta) eye. See examples 1 and 2 in Table 11. In the event both eyes have the same delta, then the Clinical Ocular AE grade comes from the eye with the worse new vision. See example 3 in Table 11.

Table 11 Examples of Clinical Ocular AE: Keratopathy

Example 1	Baseline (CC)	New VA (CC)	Lines VA Change	VA Grade	Clinical Ocular AE Grade
OD	20/20	20/50	(4)	3	Grade 3
OS	20/40	20/70	(3)	2	

Example 2	Baseline (SC)	New VA (SC)	Lines VA Change	VA Grade	Clinical Ocular AE Grade
OD	20/60	20/125	(4)	3	Grade 3
OS	20/100	20/200	(2)	4	

Example 3	Baseline (CC)	New VA (CC)	Lines VA Change	VA Grade	Clinical Ocular AE Grade
OD	20/30	20/80	(5)	3	Grade 4
OS	20/60	20/200	(5)	4	

5.6.5.2.1 Treatment Guidelines for Clinical Ocular Toxicities

Corneal Clinical Ocular AEs

- If Clinical Ocular AE is Grade 3, Medical Monitor will be consulted for treatment decision.
- If Clinical Ocular AE is Grade 4, subject will be permanently discontinued from study treatment.

Non-corneal Related Clinical Ocular AEs

- Clinical Ocular AEs other than ocular surface disease/keratopathy in nature, **irrespective of the grade, must be discussed with the Medical Monitor before the subsequent dose (per axitinib product label, patients treated with this product experienced both retinal artery and retinal vein occlusions. Please see product label for details)**.
- If the subject develops a need or is recommended to have cataract surgery while on treatment in the study, discuss each case with the Medical Monitor.

Table 12 Visual Acuity Grading Chart

Baseline vision (with or without correction, based on patient's daily functional distance vision)	**Grade 1*** (no change in vision from baseline)	**Grade 2** (delta vision change = Number of line change in vision from baseline)	**Grade 3** (delta vision change = Number of line change in vision from baseline)	**Grade 4** (delta vision change = Number of line change in vision from baseline)
20/20	20/20	20/25 (1) 20/30 (2) 20/40 (3)	20/50 (4) 20/60 (5) 20/70 (6) 20/80 (7) 20/100 (8) 20/125 (9)	20/200 (10) or worse
20/25	20/25	20/30 (1) 20/40 (2) 20/50 (3)	20/60 (4) 20/70 (5) 20/80 (6) 20/100 (7) 20/125 (8)	20/200 (9) or worse
20/30	20/30	20/40 (1) 20/50 (2) 20/60 (3)	20/70 (4) 20/80 (5) 20/100 (6) 20/125 (7)	20/200 (8) or worse
20/40	20/40	20/50 (1) 20/60 (2) 20/70 (3)	20/80 (4) 20/100 (5) 20/125 (6)	20/200 (7) or worse
20/50	20/50	20/60 (1) 20/70 (2) 20/80 (3)	20/100 (4) 20/125 (5)	20/200 (6) or worse
20/60	20/60	20/70 (1) 20/80 (2) 20/100 (3)	20/125 (4)	20/200 (5) or worse
20/70	20/70	20/80 (1) 20/100 (2) 20/125 (3)	N/A	20/200 (4) or worse
20/80	20/80	20/100 (1) 20/125 (2)	N/A	20/200 (3) or worse
20/100	20/100	20/125 (1)	N/A	20/200 (2) or worse
20/125	20/125	N/A	N/A	20/200 (1) or worse
20/200	20/200	N/A	N/A	Worse than 20/200

*Grade 1 is the same as screening (baseline) from a VA perspective. The Grade 1 Clinical Ocular AE will be an event when the AE is present (e.g., keratopathy) but there is no change in VA from baseline and the subject has little to no symptoms. If the AE is not treated aside from using artificial tears, then it would be considered Grade 1.

5.6.5.2.2 Ophthalmology Findings

The ophthalmology report along with the completed study provided cover form will be forwarded to the Investigator in a timely manner. The investigator will review the ophthalmology report to guide further treatment decisions. The ophthalmologist and/or Medical Monitor will be consulted as indicated in Section 5.6.5.2.1.

The redacted ophthalmology report will also be forwarded to the Sponsor in a timely manner.

5.7 Adverse Events and Other Safety Aspects

5.7.1 Definition of Adverse Events (AEs)

An AE is defined as any untoward medical occurrence in a subject administered a study drug or has undergone study procedures and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

This definition is broadened in this study to include any such occurrence (e.g., sign, symptom, or diagnosis) or worsening of pre-existing medical condition. Worsening indicates that the pre-existing medical condition has increased in severity, frequency, or duration of the condition or an association with significantly worse outcomes.

Interventions for pretreatment conditions (e.g., elective cosmetic surgery) or medical procedures that were planned before study enrollment are not considered AEs.

Some countries may have additional local requirements for events that are required to be reported as AEs or in an expedited manner similar to an SAE. In these cases, it is the investigator's responsibility to ensure these AEs or other reporting requirements are followed and the information is appropriately recorded in the eCRF accordingly.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical exam) should be defined as an AE only if the abnormality meets one of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention
- Requires interruption or discontinuation of study medication
- The abnormality or investigational value is clinically significant in the opinion of the investigator.

Disease progression should not be reported as an AE. Rather signs and symptoms associated with disease progression should be reported.

All AEs occurring after the first dose of investigational product observed by the investigator or reported by the subject (whether or not attributed to investigational product), will be reported in the eCRF. AEs will continue to be reported in the eCRF until 28 days post last dose, or at the subject's Safety Follow-Up visit, whichever occurs later. SAEs and medically significant AEs considered related to the investigational product by the investigator or the

Sponsor will be followed until resolved or considered stable. If a treatment-related adverse event is not resolved but is considered stable at the safety follow-up visit, this must be documented in the source documents.

The following attributes must be assigned by the investigator: description; dates of onset and resolution; severity; assessment of relatedness to investigational product, action taken, serious status and criteria.

It will be left to the investigator's clinical judgment whether or not an AE is of sufficient severity to require the subject's removal from treatment. However, the Medical Monitor will be consulted prior to the subject being discontinued from study for safety reasons.

5.7.2 Definition of Serious Adverse Events (SAEs)

An AE is considered "serious" if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- Results in death
- Is life threatening (an AE is considered "life-threatening" if, in the view of either the investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death)
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly, or birth defect
- Requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious)
- Other medically important events

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Safety events of interest on the medicinal products administered to the subject as part of the study (e.g., study drug, comparator, background therapy) that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of the medicinal product(s)
- Suspected abuse/misuse of the medicinal product(s)
- Inadvertent or accidental exposure to the medicinal product(s)

Medication error involving the medicinal product(s) (with or without subject exposure to the Sponsor medicinal product, e.g., name confusion)

5.7.3 Criteria for Causal Relationship to the Study Drug

AEs that fall under either "Possible" or "Probable" should be defined as "AEs whose relationship to the study drugs could not be ruled out".

Causal relationship to the study drug	Criteria for causal relationship
Not Related	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and/or in which other drugs, chemicals or underlying disease provide plausible explanations.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on re- administration (rechallenge) or withdrawal (dechallenge).

5.7.4 Criteria for Defining the Severity of an Adverse Event

All AEs, including abnormal clinical laboratory values, will be graded using the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Event (CTCAE) guidelines (Version 4.03).

5.7.4.1 Study Specific Ocular Toxicity Grading Criteria

Refer to Section 5.6.5.

5.7.5 Reporting Procedures for All Serious Adverse Events (SAEs)

All SAEs occurring after the first dose of investigational product observed by the investigator or reported by the subject (whether or not attributed to investigational product), will be reported to the sponsor. SAEs considered related to the investigational product by the investigator or the Sponsor will be followed until resolved or considered stable.

All SAEs that occur up to the last formal follow-up observational period, must be reported ≤ 1 working day of discovery or notification of the event.

In the case of a SAE, the investigator must contact the sponsor by fax or email immediately (within 24 hours of awareness).

The investigator must complete and submit a SAE worksheet containing all information that is required by local and/or regional regulations to the sponsor by email or fax immediately (within 24 hours of awareness).

For contact details, see [Section II Contact Details of Key Sponsor's Personnel]. Fax or email the SAE Worksheet to:

Astellas Pharma Global Development, Inc.
Pharmacovigilance
Fax number 1-888-396-3750
Alternate North America Fax number 1-847-317-1241
Email: safety-us@astellas.com

The investigator should notify the IRB/IEC/REB of SAEs occurring at the site and other AE reports received from Sponsor, in accordance with local requirements and procedures.

If there are any questions, or if clarification is needed regarding the SAE, please contact the Sponsor's Medical Monitor/Expert or his/her designee (see Section II Contact Details of Key Sponsor's Personnel).

The SAE form should be completed with all available information but at the very bare minimum the following information is required for a case to be valid:

- Identifiable subject (Subject number)
- Identifiable reporter (e.g., investigator)
- A description of the SAE, and
- Suspect drug

In addition to the above 4 critical information to establish a valid case, the following information is needed to assess the regulatory reporting requirement and Sponsor's causal attribution:

- Causality
- Event description
- Event onset date
- Study drug treatment dates

Post initial SAE report submission, the investigator will promptly submit any relevant information that becomes available (e.g., information that impacts causality, changes event outcome, changes event severity).

The Sponsor or Sponsor's designee will submit, as necessary, expedited safety reports (i.e., SUSAR [Suspected Unexpected Serious Adverse Reaction report]) to the pertinent regulatory agencies in the appropriate format according to International Conference on Harmonization (ICH) guidelines and applicable country-specific legal requirements, and will inform the investigators of such regulatory reports. Investigators must submit safety reports as required by their Institutional Review Board (IRB)/Independent Ethics Committee (IEC). Documentation of the submission to and receipt by the IRB/IEC must be retained by the site.

The Sponsor will notify all investigators of all expedited safety reports from all ongoing clinical studies with AGS-16C3F.

You may contact the Sponsor's Medical Monitor or IRB/IEC, depending on the nature of issue, for any questions related to subject safety, welfare, and/or rights.

5.7.6 Follow-up of Adverse Events

SAEs and medically significant AEs considered related to the investigational product by the investigator or the Sponsor will be followed until resolved or considered stable.

If a treatment-related adverse event is not resolved but is considered stable at the safety follow-up visit, this must be documented in the source documents.

Please refer to Appendix 12.2 for detailed instructions on Drug Induced Liver Injury (DILI).

5.7.7 Monitoring of Common Serious Adverse Events

Common serious adverse events are SAEs commonly anticipated to occur in the study population independent of drug exposure. SAEs classified as "common" are provided in Appendix 12.3 for your reference. The list does NOT change your reporting obligations or prevent the need to report an AE meeting the definition of an SAE as detailed above. The purpose of this list is to alert you that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of "common SAEs" as specified in Appendix 12.3. The Sponsor will monitor these events throughout the course of the study for any change in frequency. Any changes to this list will be communicated to the participating investigational sites. Investigators must report individual occurrences of these events as stated in Section 5.7.5.

5.7.8 Procedure in Case of Pregnancy

If a female subject or partner of a male subject becomes pregnant during the study dosing period or ≤ 6 months from the discontinuation of dosing, the investigator should report the information to the Sponsor as if it is an SAE. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data etc., should be included in this information.

The investigator will follow the medical status of the mother, as well as the fetus, as if the pregnancy is an SAE and will report the outcome to the Sponsor.

When the outcome of the pregnancy falls under the criteria for SAEs (spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly [including anomaly in a miscarried fetus]), the investigator should respond in accordance with the report procedure for SAEs. Additional information regarding the outcome of a pregnancy (which is categorized as an SAE) is mentioned below.

- ″Spontaneous abortion″ includes miscarriage, abortion and missed abortion
- Death of an infant within 1 month after birth should be reported as an SAE regardless of its relationship with the study drug
- If an infant dies more than 1 month after the birth, it should be reported if a relationship between the death and intrauterine exposure to the study drug is judged as ″possible″ by the investigator
- In the case of a delivery of a living newborn, the ″normality″ of the infant is evaluated at the birth

- Unless a congenital anomaly are identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination

5.7.9 Emergency Procedures and Management of Overdose

The effects of overdose of this product are not known.

In the event of suspected AGS-16C3F overdose, the subject should be observed closely for signs of toxicity and as necessary and appropriate, receive supportive care. The Medical Monitor must be immediately notified of an overdose or a suspected overdose.

In the event of suspected overdose for axitinib, refer to the approved Package Insert, SPC, or local product information supplied by the manufacturer for the agent.

5.7.10 Supply of New Information Affecting the Conduct of the Study

When new information becomes available necessary for conducting the clinical study, the Sponsor will inform all investigators involved in the clinical study as well as the regulatory authorities. Investigators should inform the IRB/IEC of such information when needed.

5.8 Test Drug Concentration

Blood samples for the determination of serum AGS-16C3F concentrations will be collected according to Table 2.

- Cycle 1, Day 1: predose (before the AGS-16C3F infusion), end of infusion (EOI), 4 hours, and Days 2 (24 hours), 4 (72 hours), and 15 (336 hours) post infusion
- Cycle 2, Day 22: predose (before the AGS-16C3F infusion)
- Cycle 3, Day 43: predose (before the AGS-16C3F infusion)
- Cycle 4, Day 64: predose (before the AGS-16C3F infusion), end of infusion (EOI), 4 hours, and Days 65 (24 hours), 67 (72 hours), and 78 (336 hours) post infusion
- Cycle 6, Day 106: predose (before the AGS-16C3F infusion)

Blood sampling, processing, storage and shipment instructions will be provided in the Lab Manual. Samples will be shipped to and analyzed by a Sponsor designated analytical laboratory. Please refer to the Lab Manual for more detailed information.

5.9 Total Amount of Blood

The approximate amount of blood to be collected from each subject at each time point is for all laboratory assessments is included in Appendix 12.4.

6 DISCONTINUATION

6.1 Discontinuation of Individual Subject(s)

A discontinuation is a subject who enrolled in the study and for whom study treatment is permanently discontinued prematurely for any reason.

The subject is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The

investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

If a subject is discontinued from the study with an ongoing AE or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until the condition stabilizes or no longer is clinically significant.

The subject will be discontinued from treatment if any of the following occurs:

- Subject develops objective disease progression per RECIST v.1.1 criteria based on investigator assessment.
- Subject develops clinical progression (if objective disease progression is not evaluated).
- Subject develops a Grade 4 or unacceptable AE as assessed by the Investigator (Refer also to Section 5.6.2.1.3 and Section 5.6.5.2.1)
- Investigator decides that it is in the subject's best interest to discontinue.
- Subject declines further study participation (i.e., study withdrawal).
- A significant protocol deviation or non-compliance occurs with a subject that compromises study objectives or subject safety.
- Subject is lost to follow-up despite reasonable efforts by the Investigator to locate the subject.
- The study is terminated by the Sponsor.

The Medical Monitor must be contacted before a subject is discontinued from study treatment for reasons other than objective disease progression per RECIST v.1.1.

6.2 Discontinuation of the Site

If an investigator intends to discontinue participation in the study, the investigator must immediately inform the Sponsor.

6.3 Discontinuation of the Study

The Sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns. If the Sponsor terminates the study for safety reasons, the Sponsor will immediately notify the investigator and subsequently provide written instructions for study termination.

7 STATISTICAL METHODOLOGY

The statistical analysis will be coordinated by the responsible biostatistician of Astellas. A Statistical Analysis Plan (SAP) will be written to provide details of the analysis, along with specifications for tables, listings and figures to be produced. The SAP will be finalized before the database soft lock at the latest. Any changes from the analyses planned in SAP will be justified in the Clinical Study Report (CSR).

Prior to Database Lock, a Final Review of Data and TLFs Meeting will be held to allow a review of the clinical trial data and to verify the data that will be used for analysis set classification. If required, consequences for the statistical analysis will be discussed and documented. A meeting to determine analysis set classifications may also be held prior to database lock.

In general, all data will be summarized with descriptive statistics (number of subjects, mean, standard deviation, minimum, median and maximum) for continuous endpoints, and frequency and percentage for categorical endpoints.

7.1 Sample Size

For subjects with metastatic RCC that has progressed after at least 2 prior lines of therapy, a median PFS of 4 months is anticipated for the control agent. It is hypothesized that AGS-16C3F will improve median PFS in such subjects by 2 months (i.e., 4 vs 6 months). Under the assumption of exponential distribution of PFS, such an improvement corresponds to a hypothesized hazard ratio of 0.667. If this hypothesized hazard ratio is true, 110 PFS events provide 80% power to achieve a one-sided p-value of 0.1 or smaller. Such a result will be achieved when the observed hazard ratio is 0.783 or smaller; and the observed difference in median PFS is 1.1 months or larger if the observed median for the control arm is 4 months. Assuming accrual of approximately 7 subjects per month for 18 months, 110 PFS events are projected 24 months after the date the first subject is randomized. Approximately 134 subjects may be enrolled to accommodate for up to 10% of subjects who may become lost to-follow-up.

7.2 Analysis Set

Detailed criteria for analysis sets will be defined in Classification Specifications and the allocation of subjects to analysis sets will be determined prior to database hard-lock.

7.2.1 Full Analysis Set (FAS)

The full analysis set (FAS) will consist of all subjects who are randomized in accordance with the intention-to-treat (ITT) principle. This will be the primary analysis set for efficacy analyses. The subjects will be grouped for purposes of the analysis according to the treatment assigned by the randomization, regardless of whether the subject receives the correct drug assignment.

7.2.2 Per Protocol Set (PPS)

The per protocol set (PPS) will consist of the subset of the FAS who do not meet criteria for PPS exclusion. These criteria are to capture relevant non-adherence to the protocol and will be defined in the SAP. The sensitivity analysis for the primary and key secondary efficacy endpoints will be performed on PPS. Selected demographic and baseline characteristics may also be summarized for the PPS.

7.2.3 Safety Analysis Set (SAF)

The safety analysis set (SAF) will consist of all subjects who receive at least one dose of study drug (AGS-16C3F or axitinib), with treatment assignments designated according to actually study treatment received. The SAF will be used for summaries of all safety variables.

7.2.4 Pharmacokinetic Analysis Set (PKAS): AGS-16C3F Only

The pharmacokinetic analysis set (PKAS) consists of the study population for which sufficient serum concentration data is available to facilitate derivation of at least one PK parameter and for whom the time of dosing on the day of sampling is known. Additional subjects may be excluded from the PKAS at the discretion of the pharmacokineticist. Any formal definitions for exclusion of subjects or time-points from the PKAS will be documented in the Classification Specifications and determined in the Classification Meeting.

7.2.5 Pharmacodynamic Analysis Set (PDAS)

A pharmacodynamic marker has not yet been established for this target.

7.3 Demographics and Other Baseline Characteristics

7.3.1 Demographics

Detailed information on subject demographics and other baseline characteristics will be reported. All baseline summary tables will be generated by treatment group for the FAS, PPS and SAF. If the analysis sets are identical the tables will only be presented only once in the CSR.

7.3.2 Medical History

A detailed medical history for each subject will be obtained during screening period and will be summarized by treatment group for the FAS, PPS and SAF.

7.3.3 Disease History

Data collected on RCC diagnosis, metastasis, histology, and additional relevant biological information will be summarized by treatment group for the FAS, PPS and SAF. Each subject's complete cancer history will be listed.

7.3.4 Previous and Concomitant Medications

The frequency of prior and concomitant medications categorized by preferred term (PT) will be summarized by treatment group for FAS, PPS and SAF. Medications will be coded using the WHO drug dictionary. Medications will be counted by the number of subjects who took each medication. The number and percentage of subjects who received prior therapies and the type of therapy will also be summarized by treatment group.

7.4 Analysis of Efficacy

Efficacy analyses will be conducted on the FAS and PPS. The FAS will be considered as primary and the PPS will be used as secondary to assess the robustness of the results from the statistical analyses based on the FAS.

The PFS, DRC, ORR, DOR, and OS will be summarized using descriptive statistics. The survival curve and median for time-to-event variables will be estimated using the Kaplan-Meier method and will be reported along with the corresponding 95% confidence interval (CI) calculated using Greenwood's formula.

For the inference comparison of the primary and secondary efficacy endpoints between the treatment groups, 2 stratification factors will be included: ECOG Performance Status (0 or 1) and the number of prior systemic RCC regimens (2 or > 2 for clear cell; 1 or > 1 for non-clear cell). Clear cell subjects with 2 prior lines of systemic treatment and non-clear cell subject with 1 prior line of systemic treatment will be grouped to the same stratum under the assumption that they have similar prognosis. Similarly, clear cell subjects with 3 or more prior lines of treatment and non-clear cell subjects with 2 or more prior lines of treatment will be allocated to the same stratum. Histology will not be used as a stratification variable in inferential comparison because a limited number of non-clear cell subjects is expected to be enrolled in the study (no more than 26 non-clear cell histology).

7.4.1 Analysis of Primary Endpoint

7.4.1.1 Primary Analysis

The primary efficacy endpoint is progression-free survival (PFS), defined as the time from the date of randomization to the earliest of documented disease progression as defined by RECIST v 1.1 per investigator radiology review, or death from any cause. Disease assessment will continue until disease progression, even after the originally assigned treatment is discontinued.

The primary analysis of investigator assessed PFS will be performed in accordance with the ITT principle in the FAS. All subjects who undergo randomization will be included in the primary analysis and grouped according to the treatment groups assigned by randomization.

For the primary analysis of PFS, the difference in treatment effect between treatment groups will be tested using the stratified log rank test (on ECOG Performance Status and the number of prior systemic RCC regimens) at a one-sided 0.1 significance level.

Estimation of the hazard ratio for treatment and its corresponding one-sided 90% CI will be determined using a stratified Cox proportional hazards model (on ECOG Performance Status and the number of prior systemic RCC regimens), without any other covariate. A two-sided 95% CI will also be reported in the clinical study report. Homogeneity in the hazard ratios between strata will be examined by Wald's test. The corresponding results without stratification will be reported as supplemental analyses. The adequacy of the model will be evaluated, including an assessment of the proportional hazards assumption (Therneau, 2000).

For the primary analysis, PFS will be right-censored for subjects who meet one or more of the following conditions:

- Subjects with no post-baseline disease assessments unless death occurred prior to the first planned assessment (in which case death will be considered a PFS event)

- Subjects who initiate subsequent anti-cancer therapy or intervention in the absence of documented progression
- Subjects who die or have disease progression after missing 2 or more consecutively scheduled disease assessment visits
- Subjects who are last known to be alive and progression-free on or before the data cut-off date

For such subjects, PFS will be right-censored according to the conventions described in Table 13. These conventions are based on the May 2007 FDA Guidance for Industry "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics".

Table 13 Date of Progression or Censoring for PFS

Situation	Date of Progression or Censoring	Outcome
Death or disease progression between planned disease assessments	Date of death or first disease assessment showing disease progression, whichever occurs first	Progressed
Death before first planned disease assessment	Date of death	Progressed
No post-baseline disease assessments	Date of randomization	Censored
Non-protocol anti-cancer treatment started before death or without documentation of disease progression beforehand	Date of last disease assessment prior to start of non-protocol anti-cancer treatment	Censored
Death or disease progression after missing 2 or more consecutively scheduled disease assessments	Date of last disease assessment visit without documentation of disease progression that is before the missed visit	Censored
Alive and without documentation of disease progression	Date of last disease assessment	Censored

7.4.1.2 Secondary Analysis

Sensitivity analyses will be performed to evaluate the robustness of the PFS results derived under the primary analysis (Bhattacharya 2009, Carroll 2007, Stone 2011). Such sensitivity analyses will assess potential sources of bias due to 1) differences between the planned and actual schedule of disease assessments, 2) censoring for subsequent anti-cancer therapy, 3) symptomatic or non-radiological disease progression, and 4) missed disease assessments due to reasons such as protocol deviations, consent withdrawal, and subjects lost to follow-up. The corresponding PFS results without stratification will be reported as supplemental analyses.

The same analyses of the primary PFS will be conducted using the PPS.

7.4.1.3 Subgroup Analysis

Exploratory subgroup analyses may be conducted to assess potential heterogeneity of treatment effects across levels of baseline characteristics such as age, gender, ECOG

Performance Status, the number of prior systemic RCC regimens and histology. Analyses will be performed for the FAS and PPS.

7.4.2 Analysis of Secondary Endpoints

Progression-free survival by blinded central radiology review and overall survival, defined as the time from the date of randomization until the date of death from any cause, will be evaluated as secondary endpoints. They will be analyzed using the same methodology as described for the primary endpoint in Section 7.4.1 as appropriate.

Best overall response will be tabulated for each treatment group using the crude portion of subjects whose best response during the course of protocol treatment is Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD) and non-evaluable (NE). Tumor response will be determined using RECIST v 1.1. The primary analysis of the secondary tumor response endpoints will be based on investigator's assessments; the secondary sensitivity analyses of these endpoints will be performed based on the assessments by blinded central review. A best response CR or PR must be confirmed no less than 28 days after the criteria for response after first met. Disease control rate (DCR) will be estimated for each treatment group based on the crude proportion of subjects who have a best overall response of CR, PR or SD. For DCR, SD with a minimum duration of 6 months from the date of randomization is required. Objective response rate (ORR) will be estimated for each treatment group based on the crude proportion of subjects who have a best overall response of CR or PR. The method of Clopper and Pearson will be used to calculate two-sided 95% CIs for DCR and ORR, by treatment group, both overall and within stratification strata.

The inferential comparison between treatment groups for both DCR and ORR will be made using the stratified Cochran-Mantel-Haenszel chi-square test at a two-sided significance level of 0.05. An estimate of the relative risk (RR) of not experiencing OR with axitinib arm as the reference level will be provided as a measure of relative treatment effect. The RR and two-sided 95% CI will be estimated using stratified Mantel-Haenszel method. Homogeneity in ECOG Performance Status by number of prior treatments strata will be examined at a significance level of 0.05 by two-sided Breslow-Day test. Similarly, the RR of not experiencing DC will be estimated with its two-sided 95% CI.

Duration of objective response (DOR) is defined as the time from the date of the first response of CR or PR (whichever is first recorded), and subsequently confirmed, to the first date of documented progressive disease or death due to any cause. The DOR will be summarized descriptively using the 25^{th}, 50^{th} and 75^{th} percentile (and 95% CI) of the Kaplan-Meier curve for subjects who have best overall response of confirmed CR or PR, by treatment group, both overall and within randomization strata. The DOR will be censored using the same censoring rules, whenever applicable, as PFS.

Each of the secondary endpoints described above will be performed for the FAS and PPS. For the purpose of hypothesis generation, subgroup may be performed for selected baseline characteristics.

7.4.3 Analysis of Exploratory Endpoints

Not Applicable.

7.5 Analysis of Safety

7.5.1 Adverse Events

Safety will be evaluated based on the incidence of AEs (including Grade 3 and 4 AEs, treatment-related adverse events, serious adverse events, and AEs requiring discontinuation of study drug), laboratory changes and vital signs. AEs will be coded to system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) dictionary and will be graded according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE), version 4.03. Ocular toxicities based on ophthalmology exams reported on the Eye Exam eCRFs will be graded using the study specific ocular criteria and these will be separately tabulated. The number and percentage of AEs, SAEs, AEs leading to discontinuation, and AEs related to study drug will be summarized by SOC, PT and treatment group. The number and percentage of AEs by severity will also be summarized. All summaries of AEs will include only treatment-emergent events unless otherwise stated. Listings of AEs, SAEs, deaths, and events leading to discontinuation of study treatment will be presented.

7.5.2 Laboratory Assessments

Laboratory data will be summarized by shift tables (baseline toxicity grade versus worst postbaseline severity grade of toxicity) and Grade 3 and 4 values, by treatment group. Laboratory results will also be displayed in listings.

7.5.3 Vital Signs

Descriptive statistics will be used to summarize vital sign results for each scheduled time point and changes from baseline by treatment group. Vital signs data will be displayed in listings.

7.5.4 Physical Examination

Physical examination will be listed by treatment group.

7.5.5 Electrocardiograms

The 12-lead ECG results will be summarized by treatment group and scheduled time point.

7.6 Analysis of Pharmacokinetics

The PK data for ADC and MMAF will be analyzed using the noncompartmental method. Parameters to be assessed will include concentrations at the end of infusion or maximum observed concentration (C_{EOI} or C_{max}), concentrations at trough (C_{trough}), time to maximum observed concentration (T_{max}), partial area under the concentration time curve (AUC_{τ}) for Cycle 1 and 4, and either terminal or apparent terminal half-life ($t_{1/2}$) as appropriate. Additionally, clearance (CL) and volume of distribution at steady state (V_{ss}) will be included as appropriate. Descriptive statistics will be provided for the PK parameter estimates and

subject concentration plots over time may be generated. Additional model-based analyses may be performed and reported separately.

Descriptive statistics for the incidence of human native antibody (AGS-16C3) and antibody drug conjugate (AGS-16C3F) antibody formation will be provided by treatment group.

7.6.1 Concentration-Response Relationship Analysis

Pharmacokinetic dose proportionality and concentration-response relationship will be assessed.

7.7 Protocol Deviations and Other Analyses

Protocol deviations, as defined in Section 8.1.6, will be summarized for all randomized subjects by treatment group and total as well as by site. A data listing will be provided by site and subject.

The protocol deviation criteria will be uniquely identified in the summary table and listing. The unique identifiers will be as follows:

PD1 - Entered into the study even though they did not satisfy entry criteria,

PD2 - Developed withdrawal criteria during the study and was not withdrawn,

PD3 - Received wrong treatment or incorrect dose,

PD4 - Received excluded concomitant treatment.

7.8 Independent Data-Monitoring Committee Oversight

The study will have an Independent Data-Monitoring Committee (IDMC) overseeing the study. The committee is comprised of an oncologist (PPD , MD), a biostatistician (PPD , Ph.D), and an ophthalmologist (PPD , MD). The IDMC will conduct safety reviews at prespecified times during the study to make a recommendation for continuation of recruitment, protocol modification or study discontinuation for safety reasons.

The full procedures for IDMC safety review will be described in a separate IDMC charter.

7.9 Handling of Missing Data, Outliers, Visit Windows, and Other Information

Imputation methods for missing data, if applicable, and the definitions for windows to be used for analyses by visit will be outlined in the SAP.

8 OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

8.1 Procedure for Clinical Study Quality Control

8.1.1 Data Collection

The investigator will enter data collected using an Electronic Data Capture (eDC) system. Medidata RAVE will be utilized for this study. In the interest of collecting data in the most

efficient manner, the investigator should record data (including laboratory values) in the eCRF within 14 days after the data become available.

The investigator is responsible to ensure that all data in the eCRFs and queries are accurate and complete and that all entries are verifiable with source documents. These documents must be appropriately maintained by the site.

The monitor must verify the data in the eCRFs with source documents and confirm that there are no inconsistencies between them.

Specific guidance on which forms should be completed by the investigator can be found in the data entry guidelines.

8.1.2 Specification of Source Documents

Source data must be available at the site to document the existence of the study subjects and to substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the subject.

The following information should be included in the source medical records:

- Demographic data (age, sex, race, ethnicity, height and body weight); refer to Section 5.3.1
- Inclusion and exclusion criteria details
- Participation in study and original signed and dated informed consent forms
- Visit dates
- Medical history; refer to Section 5.3.2
- Physical examination details
- Key efficacy and safety data, (as specified in the protocol)
- AEs and concomitant medication
- Eye symptom questionnaire
- Results of relevant examinations (e.g., ECG charts, X-ray films etc.)
- Laboratory printouts
- Dispensing and return of study drug details
- Reason for premature discontinuation (if applicable)
- Randomization number (if applicable)
- Any data not specifically listed above, that is generated during the subject's participation in this study.

8.1.3 Clinical Study Monitoring

The Sponsor or delegated CRO is responsible for monitoring the clinical study to ensure that subject's human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and GCP, and study data reported by the investigator/sub-investigator are accurate and complete and that they are verifiable with study-related records such as source documents. The Sponsor is responsible for assigning

study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

8.1.4 Direct Access to Source Data/Documents

The investigator and the study site must accept monitoring and auditing by the Sponsor or delegated CRO as well as inspections from the IRB/IEC and relevant regulatory authorities. In these instances, they must provide all study-related records, such as source documents (refer to Section 8.1.2) when they are requested by the Sponsor monitors and auditors, the IRB/IEC, or regulatory authorities. The confidentiality of the subject's identities shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

8.1.5 Data Management

Data Management will be coordinated by the Sponsor in accordance with the standard operating procedures (SOPs) for data management. All study specific processes and definitions will be documented by Data Management. eCRF completion will be described in the eCRF instructions. Coding of medical terms and medications will be performed using MedDRA and World Health Organization (WHO) Drug Dictionary respectively.

8.1.6 Protocol Deviations

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety, and welfare of subjects. The investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to trial subjects.

A protocol waiver is a documented prospective approval of a request from an investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

For the purposes of this protocol, deviations requiring notification to Sponsor are defined as any subject who:

- Did not sign the appropriate informed consent form
- Entered into the study even though they did not satisfy entry criteria.
- Developed withdrawal criteria during the study and not withdrawn
- Received wrong treatment or incorrect dose.
- Received excluded concomitant treatment.
- Experienced SAE(s) not reported as defined in the protocol

If a deviation impacts the safety of a subject, the investigator must contact the Sponsor immediately.

The Sponsor will follow up with the investigator, as applicable, to assess the deviation and the possible impact to the safety and/or efficacy of the subject to determine subject continuation in the study.

The investigator will also assure that deviations meeting IRB/IEC and applicable regulatory authorities' criteria are documented and communicated appropriately. All documentation and communications to the IRB/IEC and applicable regulatory authorities will be provided to the Sponsor.

NOTE: Other deviations outside of the categories defined above that are required to be reported by the IRB/IEC in accordance with local requirements will be reported, as applicable.

8.1.7 End of Trial in All Participating Countries

The end of trial in all participating countries is defined as the Last Subject's Last Visit.

8.2 Ethics and Protection of Subject Confidentiality

8.2.1 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/ Competent Authorities (CA)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent form and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent form and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any substantial amendments to the protocol will require IEC/IRB approval prior to implementation of the changes made to the study design at the site. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Any SAEs that meet reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to Sponsor.

If required by local regulations, the investigator shall make accurate and adequate written progress reports to the IEC/IRB at required or appropriate intervals. The investigator shall make an accurate and adequate final report to the IEC/IRB within 90 days after the close-out visit or termination of the study.

8.2.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

8.2.3 Informed Consent of Subjects

8.2.3.1 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject or his/her guardian or legal representative, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject or his/her guardian or legal representative, the person who administered the informed consent and any other signatories according to local requirements. A copy of the signed informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

The signed consent forms will be retained by the investigator and made available (for review only) to the study monitor, auditor, regulatory authorities, and other applicable individuals upon request.

8.2.3.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information

- The investigator or his/her representative will immediately inform the subject verbally whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue to participate in the study. The communication must be documented in the subject's medical records and must document whether the subject is willing to remain in the study or not.
- The investigator must update their ICF and submit it for approval to the IRB/IEC. The investigator or his/her representative must obtain written informed consent from the subject on all updated ICFs throughout their participation in the study. The investigator must re-consent subjects with the updated ICF even if relevant information was provided orally. The investigator or his/her representative who obtained the written informed consent and the subject should sign and date the informed consent form. A copy of the signed informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must be made in the subject's records documenting the re-consent process.

8.2.4 Subject Confidentiality

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Such medical information may be given only after approval of the subject to the subject's physician or to other appropriate medical personnel responsible for the subject's well-being.

The Sponsor shall not disclose any confidential information on subjects obtained during the performance of their duties in the clinical study without justifiable reasons.

The Sponsor affirms the subject's right to protection against invasion of privacy. Only a subject identification number and/or initials will identify subject data retrieved by the Sponsor. However, the Sponsor requires the investigator to permit the Sponsor, Sponsor's representative(s), the IRB/IEC and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study.

The Sponsor will ensure that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal and/or regional legislation related to the privacy and protection of personal information (i.e. Health Insurance Portability and Accountability Act [HIPAA]).

8.3 Administrative Matters

8.3.1 Arrangement for Use of Information and Publication of the Clinical Study

Information concerning the study drug, patent applications, processes, unpublished scientific data, the Investigator's Brochure and other pertinent information is confidential and remains the property of the Sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The investigator may use this information for the purpose of the study only. It is understood by the investigator that the Sponsor will use the information obtained during the clinical study in connection with the development of the drug and therefore may disclose it as required to other clinical investigators or to regulatory agencies. In order to allow for the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide the Sponsor with all data obtained during the study.

Publication of the study results is discussed in the Clinical Study Agreement.

8.3.2 Documents and Records Related to the Clinical Study

In order to start the study, the investigator and/or study site is required to provide the following documentation to the Sponsor:

- Financial disclosure in compliance with federal regulation 21CFR Part 54
- Signed and dated FDA form 1572
- Signed Investigator's Statement in this protocol
- Current Curricula Vitae of all investigators
- Local regulatory authority notification or approval to conduct study (if applicable)
- Written IRB approval of the protocol, protocol amendments (if applicable), informed consent forms, and materials provided to subjects including a membership list or FWA information (COPY)
- Fully executed study contract
- Laboratory certification
- Dated laboratory normal reference ranges
- Current subject/investigator indemnity insurance (if applicable)

The investigator will archive all study data (e.g., Subject Identification Code List, source data, eCRFs, and Investigator's File) and relevant correspondence. These documents are to

be kept on file for the appropriate term determined by local regulation (for US sites, 2 years after approval of the NDA/BLA or discontinuation of the IND). The Sponsor will notify all sites when these events occur.

The investigator agrees to obtain the Sponsor's agreement prior to disposal, moving, or transferring of any study-related records. The Sponsor will archive and retain all documents pertaining to the study according to local regulations.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes.

8.3.3 Protocol Amendment and/or Revision

Any substantial changes to the study that arise after approval of the protocol must be documented as protocol amendment. Non-substantial changes (administrative changes) to the protocol will be documented in a protocol administrative letter and these changes will be incorporated into the protocol at the next protocol amendment opportunity.

All protocol amendments must be submitted and approved by the IRB/IEC and Competent Authority approval or notification may be required. The changes will become effective only after the approval of the Sponsor, the investigator, the IRB/IEC and regulatory authorities (if applicable). Amendments to this protocol must be signed by the Sponsor and the investigator.

Written verification of IRB/IEC approval will be obtained before any amendment is implemented. Modifications to the protocol that are administrative in nature do not require IRB/IEC approval, but will be submitted to the IRB/IEC for their information, if required by local regulations.

If there are changes to the Informed Consent Form, written verification of IRB/IEC approval must be forwarded to the Sponsor. An approved copy of the new Informed Consent Form must also be submitted to the Sponsor.

8.3.4 Insurance of Subjects and Others

The Sponsor has covered this study by means of an insurance of the study according to national requirements. The name and address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured are provided in the Investigator's File.

8.3.5 Signatory Investigator for Clinical Study Report

ICH E3 guidelines recommend and EU Directive 2001/83/EC requires that a final study report which forms part of a marketing authorization application be signed by the representative for the Coordinating Investigator(s) or the Principal Investigator(s). The representative for the Coordinating Investigator (s) or the Principal Investigator(s) will have the responsibility to review the final study results to confirm to the best of his/her knowledge it accurately describes the conduct and results of the study. The representative for Coordinating Investigator(s) or the Principal Investigator(s) will be selected from the participating investigators by the Sponsor prior to database lock.

9 QUALITY ASSURANCE

The Sponsor is implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented, recorded, and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s).

The Sponsor or Sponsor's designee may arrange to audit the clinical study at any or all investigational sites and facilities. The audit may include on-site review of regulatory documents, eCRFs, and source documents. Direct access to these documents will be required by the auditors.

10 STUDY ORGANIZATION

10.1 Independent Data-Monitoring Committee

The study will have an Independent Data-Monitoring Committee (IDMC) overseeing the study. The IDMC will conduct safety reviews at prespecified times during the study to make a recommendation for continuation of recruitment, protocol modification or study discontinuation for safety reasons.

The IDMC will operate under the Study’s IDMC Charter.

10.2 Other Study Organization

Not applicable.

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Company Reports:

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AGS-16C3F Investigator's Brochure, on file at Astellas.

12 APPENDICES

12.1 List of Excluded Concomitant Medications

The investigator may prescribe any medication necessary to ensure the safety and wellbeing of the subject during the study. Please refer to Section 5.1.3.2 for additional information.

The following medications are likely to influence evaluation of the safety, pharmacokinetics or efficacy of AGS-16C3F or axitinib, and will be strictly prohibited. If the investigator determines that any of the following medications are necessary to provide adequate medical support, the subject must be withdrawn from further study drug administration. If the use of prohibited medications is necessary to treat an AE and the use is temporary (e.g., dexamethasone used for nausea), this is permitted.

AGS-16C3F	**Axitinib**

• Chemotherapy, radiotherapy, immunotherapy or other medications intended for antitumor activity
  ○ Palliative radiation is permitted provided it does not interfere with subject safety and efficacy of the study drug being administered. Palliative radiation cannot be administered to any target lesion. Medications used to treat bone metastases (e.g., zoledronic acid, denosumab, etc.) are allowed provided they are not initiated at the same time as Cycle 1 Day 1.
• Investigational products or therapy other than AGS-16C3F
	• Chemotherapy, radiotherapy, immunotherapy or other medications intended for antitumor activity
	  ○ Palliative radiation is permitted provided it does not interfere with subject safety and efficacy of the study drug being administered. Palliative radiation cannot be administered to any target lesion. Medications used to treat bone metastases (e.g., zoledronic acid, denosumab, etc.) are allowed provided they are not initiated at the same time as Cycle 1 Day 1.
	• Investigational products or therapy
	• Strong CYP3A4/5 inducers[1]

[1] The drugs defined as CYP Substrates with Narrow Therapeutic Range by FDA's guidance - Guidance for Industry Drug Interaction Studies - Study Design, Data analysis, and Implications for Dosing and Labeling): http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf)

Examples for excluded inhibitors, inducers and substrates for enzymes and transporters are provided below. Subjects must have discontinued treatment with any of the following for at least 2 weeks prior to the first dose of study drug. This is not intended to be a comprehensive list. There could also be additional new drugs and marketed drugs that could be identified as inhibitors/inducers with continued research. Investigators will consult individual drug labels to determine liability of the drugs.

Strong CYP3A Inhibitors
boceprevir
clarithromycin
conivaptan
grapefruit juice
indinavir
itraconazole
ketoconazole
lopinavir/ritonavir
mibefradil
nefazodone
nelfinavir
posaconazole
ritonavir
saquinavir
telaprevir
telithromycin
voriconazole

CYP3A4/5 Inducers	
rifampin	dexamethasone
phenytoin	carbamazepine
rifabutin	rifapentin
phenobarbital	St. John's wort

Additional information for inhibitors/inducers/substrates of enzymes/transporters can be found in FDA's guidance (Guidance for Industry Drug Interaction Studies - Study Design, Data analysis, and Implications for Dosing and Labeling)[1] and from the Division of Clinical Pharmacology of Indiana University[2].

1. http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf
2. http://medicine.iupui.edu/clinpharm/ddis/main-table/

12.2 Liver Safety Monitoring and Assessment

Any subject enrolled in a clinical study with active drug therapy and reveals an increase of serum aminotransferases (AT) to > 3 × ULN (to > 5 × ULN in subjects with liver metastases), or bilirubin > 2 × ULN, should undergo detailed testing for liver enzymes (including at least ALT, AST, ALP, and TBL). Testing should be repeated within 48-72 hours of notification of the test results. For studies for which a central laboratory is used, alerts will be generated by the central lab regarding moderate and severe liver abnormality to inform the investigator, study monitor and study team. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

Confirmed abnormalities will be characterized as moderate and severe where ULN:

	ALT or AST		**Total Bilirubin**
Moderate	> 3 x ULN (in subjects without liver metastases), > 5 x ULN (in subjects with liver metastases)	or	> 2 x ULN
Severe*	> 3 x ULN	and	> 2 x ULN

In addition, the subject should be considered to have severe hepatic abnormalities for any of the following:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks (in the absence of liver metasteses)
- ALT or AST > 3 × ULN and INR > 1.5 (If INR testing is applicable/evaluated).
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

The investigator may determine that abnormal liver function results, other than as described above, may qualify as moderate or severe abnormalities and require additional monitoring and follow-up.

Follow-up Procedures

Confirmed moderate and severe abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and laboratory tests. The site should complete the Liver Abnormality eCRF (LA-CRF) or appropriate document. Subjects with confirmed abnormal liver function testing should be followed as described below.

Confirmed moderately abnormal LFTs should be repeated 2-3 times weekly then weekly or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic.

Severe hepatic liver function abnormalities as defined above , in the absence of another etiology may be considered an important medical event and may be reported as a Serious

Adverse Event (SAE). The Sponsor should be contacted and informed of all subjects for whom severe hepatic liver function abnormalities possibly attributable to study drug are observed.

To further assess abnormal hepatic laboratory findings, the investigator is expected to:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new onset-diseases should be recorded as 'adverse events' on the AE page of eCRF. Illnesses and conditions such as hypotensive events, and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Non-alcoholic steatohepatitis (NASH) is seen in obese hyperlipoproteinemic, and/or diabetic subjects and may be associated with fluctuating aminotransferase levels. The investigator should ensure that the medical history form captures any illness that pre-dates study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including non-prescription medication, complementary and alternative medications), alcohol use, recreational drug use, and special diets. Medications, including dose, should be entered on the concomitant medication page of the eCRF. Information on alcohol, other substance use, and diet should be entered on the LA-CRF or an appropriate document.
- Obtain a history of exposure to environmental chemical agents.
- Based on the subject's history, other testing may be appropriate including:
    - acute viral hepatitis (A,B, C, D, E or other infectious agents).
    - ultrasound or other imaging to assess biliary tract disease
    - other laboratory tests including INR, direct bilirubin
- Consider gastroenterology or hepatology consultations.
- Submit results for any additional testing and possible etiology on the LA-CRF or an appropriate document.

Study Discontinuation

In the absence of an explanation for increased LFT's, such as viral hepatitis, pre-existing or acute liver disease, presence of liver metastases, or exposure to other agents associated with liver injury, the subject may be discontinued from the study. The investigator may determine that it is not in the subject's best interest to continue study enrollment. Discontinuation of treatment should be considered if:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks (in subjects without liver metasteses
- ALT or AST > 3 × ULN and TBL > 2 × ULN or INR > 1.5 (If INR testing is applicable/evaluated)
- ALT or AST > 5 × ULN and (TBL > 2 × ULN in subjects with liver metasteses)
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

In addition, if close monitoring for a subject with moderate or severe hepatic laboratory tests is not possible, drug should be discontinued.

*Hy's Law Definition-Drug-induced jaundice caused by hepatocellular injury, without a significant obstructive component, has a high rate of bad outcomes, from 10–50% mortality (or transplant)." The 2 "requirements" for Hy's Law are: (1) Evidence that a drug can cause hepatocellular-type injury, generally shown by an increase in transaminase elevations higher 3 times the upper limit of normal ("2 x ULN elevations are too common in treated and untreated subjects to be discriminating"). (2) Cases of increased bilirubin (at least 2 x ULN) with concurrent transaminase elevations at least 3 x ULN and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated alkaline phosphatase) or Gilbert's syndrome.

Reference

Temple R. Hy's law: Predicting Serious Hepatotoxicity. Pharmacoepidemiol Drug Saf. 2006 April;15(Suppl 4):241-3.

Guidance for Industry titled "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" issued by FDA on July 2009.

12.3 Common Serious Adverse Events

The following is a list of SAEs that the Sponsor considers to be associated with the disease state being studied. The list does NOT change your reporting obligations, or prevent the need to report an AE meeting the definition of an SAE as detailed in Section 5.7.2. The purpose of this list is to alert you that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of "common serious adverse events". You are required to follow the requirements detailed in Section 5.7.5.

Signs/symptoms commonly reported in metastatic RCC subjects often associated to disease progression are:

- Pain
- Weight loss (weight loss not considered cachexia by investigators is excluded)
- Anemia
- Hypercalcemia
- Proteinuria

For expedited reporting of suspected unexpected serious adverse reactions (SUSARs), single occurrences of the above events may be excluded from expedited reporting to regulatory authorities. If aggregate analysis of these events indicates they occur more frequently with study drug, an expedited safety report may be submitted to the regulatory authority.

12.4 Blood Sample Requirements

Assessment		Whole Blood (ml)
Screening	Chemistry Panel	5
	Hematology (CBC with differential)	5
	Thyroid Function Test	2
	PT/aPTT	2
Screening Total		14
Cycle 1, Week 1, Day 1	Chemistry Panel	5
	Hematology (CBC with differential)	5
	PT/aPTT	2
	AGS-16C3F PK	15
	ADA formation	3
Cycle 1, Week 1, Day 2	AGS-16C3F PK	3
Cycle 1, Week 1, Day 4	AGS-16C3F PK	3
Cycle 1, Week 3, Day 15	AGS-16C3F PK	3
Cycle 1 Total		39
Cycle 2, Week 1, Day 1	Chemistry Panel	5
	Hematology (CBC with differential)	5
	PT/aPTT	2
	AGS-16C3F PK	3
Cycle 2 Total		15
Cycle 3, Week 1, Day 1	Chemistry Panel	5
	Hematology (CBC with differential)	5
	PT/aPTT	2
	AGS-16C3F PK	3
Cycle 3 Total		15
Cycle 4, Week 1, Day 1	Chemistry Panel	5
	Hematology (CBC with differential)	5
	PT/aPTT	2
	AGS-16C3F PK	15
	ADA formation	3
Cycle 4, Week 1, Day 2	AGS-16C3F PK	3
Cycle 4, Week 1, Day 4	AGS-16C3F PK	3
Cycle 4, Week 3, Day 15	AGS-16C3F PK	3
Cycle 4 Total		39
Cycle 5, Week 1, Day 1	Chemistry Panel	5
	Hematology (CBC with differential)	5
	PT/aPTT	2
Cycle 5 Total		12
Cycle 6, Week 1, Day 1	Chemistry Panel	5
	Hematology (CBC with differential)	5
	PT/aPTT	2
	AGS-16C3F PK	3
	ADA formation	3
Cycle 6 Total		18
Starting at Cycle 6	Chemistry Panel	5
Every 3 Weeks	Hematology (CBC with differential)	5
	PT/aPTT	2
(Every 12 Weeks)	(AGS-16C3F PK)	(3)
	(ADA formation)	(3)
Every 3 and (12) Weeks Total		12 (18)
Safety Follow-Up	Chemistry Panel	5
	Hematology (CBC with differential)	5

Assessment		Whole Blood (ml)
	Thyroid Function Test	2
	PT/aPTT	2
	AGS-16C3F PK	3
	ADA formation	3
Safety Follow-Up Total		20

12.5 ECOG Performance Status

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

Reproduced from: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFaddden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J CLin Oncol. 1982;5:649-55.

12.6 Response Evaluation Criteria In Solid Tumors (RECIST) v.1.1

Table 1 – Time point response: patients with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 2 – Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Table 3 – Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.
a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Reproduced from: Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-247.

13 ATTACHMENT 1: SUBSTANTIAL AMENDMENT 5

I. The purpose of this amendment is:

Substantial Changes
1. Remove the Disease Assessment and Survival Assessment after the Safety Follow-up Visit
DESCRIPTION OF CHANGE:
"Disease Assessment" and "Survival" are removed from the study design and Flow Chart (Figure 1). These assessments will no longer be conducted after the Safety Follow-up visit.
RATIONALE:
Disease Assessment and Survival data will no longer be collected and analyzed.
2. Update the Schedule of Assessments (Table 1) and AGS-16C3F Pharmacokinetic Sampling Time Points (Table 2)
DESCRIPTION OF CHANGE:
The Schedule of Assessments is updated as follows: • Pharmacokinetics (AGS16C3F) is removed at the Safety Follow-up. • Anti-AGS16C3F samples are removed at the Safety Follow-up. The AGS-16C3F Pharmacokinetic Sampling Time Points is updated as follows: • Q12W (every 12 weeks) and footnote § are removed. • Safety Follow-up is removed. These assessments and time points are also removed from the study design and Sections 5.2.6.2, 5.2.7 and 5.8.
RATIONALE:
These samples are longer collected and analyzed.
3. Delete the Post Safety Follow-Up Visit
DESCRIPTION OF CHANGE:
The Post-Safety Follow-Up visit (Section 5.2.8) is removed.
RATIONALE:
The data will no longer be analyzed.
4. Update Reading of Scans
DESCRIPTION OF CHANGE:

The requirement that scans be submitted in digital format for blinded independent central review is deleted. Scans will be read on site only.
RATIONALE:
The data will no longer be analyzed by a blinded independent central reviewer.

Nonsubstantial Changes
1. Update Key Sponsor Personnel
DESCRIPTION OF CHANGE:
Contact details for the 24-hour contact for serious adverse events (SAEs), clinical research contacts and medical monitor/medical expert are revised. Section 5.7.5, Reporting Procedures for All Serious Adverse Events is updated with revised 24-hour contact information for SAEs.
RATIONALE:
Contact details of sponsor personnel are updated based on changes to study personnel.
2. Update Planned Study Period
DESCRIPTION OF CHANGE:
The end date of the planned study period is changed to 3Q2020.
RATIONALE:
This change is made to allow more time in which to complete the study.
3. Update References
DESCRIPTION OF CHANGE:
Deleted Ellenberg et al, 1985 and Wieand et al 1987 references from the Reference list.
RATIONALE:
The references are deleted, because they are not cited in the protocol.
4. Minor Administrative-type Changes
DESCRIPTION OF CHANGE:
Include minor administrative-type changes (e.g., typos, format, numbering and consistency throughout the protocol), update the format of the Protocol History and Investigator's Signature section for consistency with the GPF 9.0 template, and updated the style of references to conform with the Astellas Style Guide.

RATIONALE:
To provide clarifications to the protocol and to ensure complete understanding of study procedures.

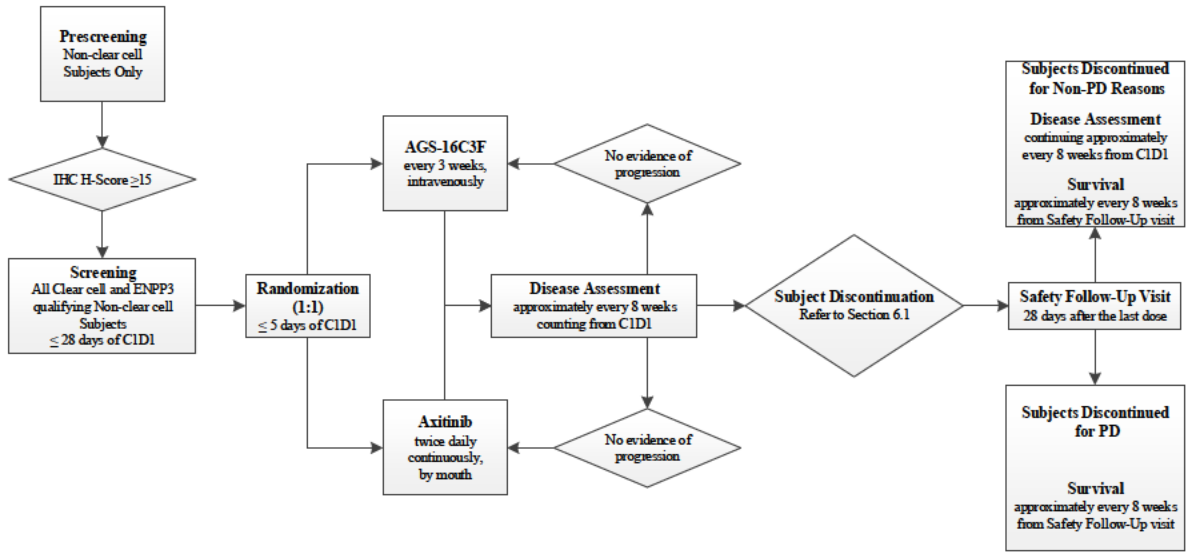
II. Amendment Summary of Changes:

IIA. Substantial Changes

V. Flow Chart and Schedule of Assessments
Figure 1 Flow Chart

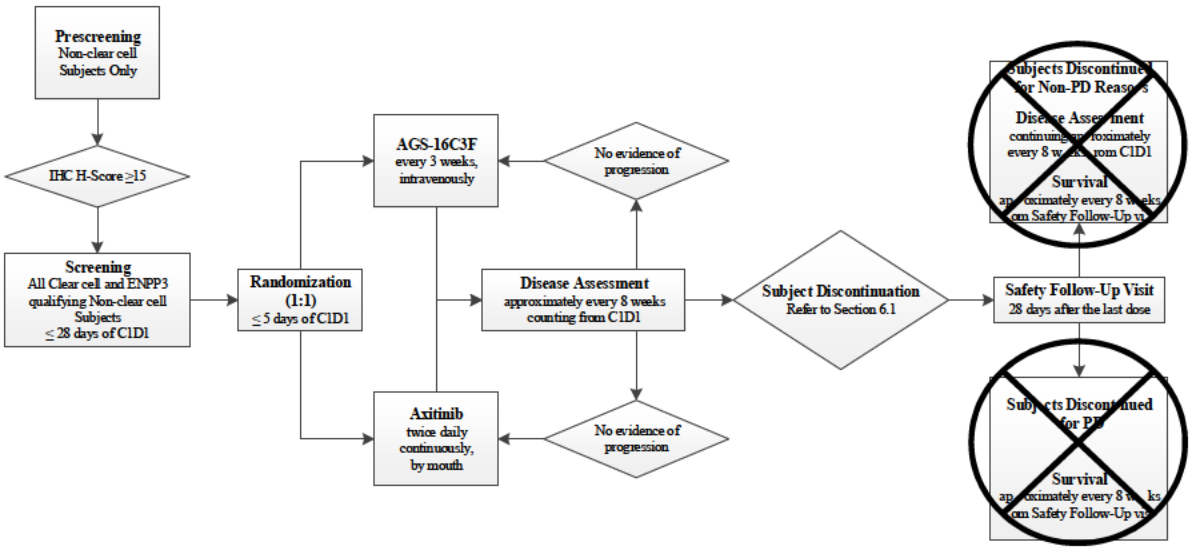
WAS:

Figure 1 Flow Chart



IS AMENDED TO:

Figure 1 Flow Chart



V. Flow Chart and Schedule of Assessments

Table 1 Schedule of Assessments

WAS:

			Cycle 1[t]				Cycles 2-4[t]							C5[t]	C6[t]	Treatment Period beginning Cycle 7[t]	Safety F/U [s]
Procedures	Screen[a]	Cycle	1				2	3		4				5	6		
		Week	1	1	1	3	4	7	8-9	10	10	10	12	13	16		
		Day	1	2	4	15	22	43	50-57	64	65	67	78	85	106		
Eye Symptom Questionnaire [u]	X		X	X[u]	X[u]	X[u]	X	X	X	X	X[u]	X[u]	X[u]	X	X	Q3W	X
PK [m] (AGS-16C3F Subjects Only)			X	X	X	X	X	X		X	X	X	X		X	Q12W from C6	X
anti-AGS-16C3F antibody formation [n] (AGS-16C3F Subjects Only)			X							X					X	Q12W from C6[n]	X
Disease Assessment [o]	X		<---------- Q8W from C1D1 ---------->														
Bone Imaging [p]	X		<---------- Q12W from C1D1[p] ---------->														
Brain Imaging [p]	X																
AGS-16C3F Administration [q] (AGS-16C3F Subjects Only)			X				X	X		X				X	X	Q3W	
Tumor Tissue [r]	X		<---------- **PRN** ---------->														

o Disease assessments (CT and/or MRI; refer to Section 5.5) will be done every 8 weeks (± 7 days) counting from C1D1.

[p] Required only if clinically indicated. Post screening bone imaging will be done only for subjects with bone disease at screening. The imaging method will be any imaging modality per local or institutional standard of care (SOC) (e.g., NaF PET, MRI Bone, Tc-99 Bone Scan, etc.)

r Paraffin-embedded tumor tissue from primary or metastasis (excluding bone), for immunohistochemical studies to be conducted at a Sponsor specified CLIA certified laboratory. This is required for all non-clear cell histology subjects before Screening. Clear cell histology subjects must also provide tissue but at any point during the study. If no archive tissue is available; a biopsy may be performed to obtain tissue. Post screening, this is optional for all subjects who may have new biopsies performed.

IS AMENDED TO:

Procedures	Screen[a]	Cycle	Cycle 1[tr]				Cycles 2-4[tr]							C5[tr]	C6[tr]	Treatment Period beginning Cycle 7[tr]	Safety F/U [sq]
		Cycle	1				2	3		4				5	6		
		Week	1	1	1	3	4	7	8-9	10	10	10	12	13	16		
		Day	1	2	4	15	22	43	50-57	64	65	67	78	85	106		
Eye Symptom Questionnaire [uu]	X		X	X[uu]	X[uu]	X[uu]	X	X	X	X	X[uu]	X[uu]	X[uu]	X	X	Q3W	X
PK [m] (AGS-16C3F Subjects Only)			X	X	X	X	X	X		X	X	X	X		X	~~Q12W from C6~~	~~X~~
anti-AGS-16C3F antibody formation [n] (AGS-16C3F Subjects Only)			X							X					X	~~Q12W from C6[n]~~	~~X~~
Disease Assessment ~~[o]~~	X		~~Q8W from C1D1~~														
Bone Imaging ~~[p]~~	X		~~Q12W from C1D1[p]~~														
Brain Imaging ~~[p]~~	X																
AGS-16C3F Administration [oq] (AGS-16C3F Subjects Only)			X				X	X		X				X	X	Q3W	
Tumor Tissue ~~[pr]~~	X		~~PRN~~														

o Disease assessments (CT and/or MRI; refer to Section 5.5) will be done every 8 weeks (± 7 days) counting from C1D1.

[p] Required only if clinically indicated. Post screening bone imaging will be done only for subjects with bone disease at screening. The imaging method will be any imaging modality pe local or institutional standard of care (SOC) (e.g., NaF PET, MRI Bone, Tc-99 Bone Scan, etc.)

~~pr~~ Paraffin-embedded tumor tissue from primary or metastasis (excluding bone), for immunohistochemical studies to be conducted at a Sponsor specified CLIA certified laboratory. Th required for all non-clear cell histology subjects before Screening. Clear cell histology subjects must also provide tissue but at any point during the study. If no archive tissue is availab a biopsy may be performed to obtain tissue. ~~Post screening, this is optional for all subjects who may have new biopsies performed.~~

VI. PK Sampling Collection Schema

WAS:

Table 2 AGS-16C3F PK Sampling Time Points

Cycle	Study Day	Time	Window
1	1	Predose	Anytime Predose *
		EOI	Within 2 min after EOI
		4 h†	± 15 min
	2	24 h from Day 1†	± 4 h
	4	72 h from Day 1†	± 1 day
	15	336 h from Day 1†	± 4 h
2	22	Predose	Anytime Predose §
3	43	Predose	Anytime Predose §
4	64	Predose	Anytime Predose §
		EOI	Within 2 min after EOI
		4 h†	± 15 min
	65	24 h from day 64†	± 4 h
	67	72 h from day 64†	± 1 day
	78	336 h from day 64†	± 4 h
6	106	Predose	Anytime Predose §
Q12W (starting at C6)		Predose	Anytime Predose §
Safety FU			At SFU Visit

IS AMENDED TO:

Table 2 AGS-16C3F PK Sampling Time Points

Cycle	Study Day	Time	Window
1	1	Predose	Anytime Predose *
		EOI	Within 2 min after EOI
		4 h†	± 15 min
	2	24 h from Day 1†	± 4 h
	4	72 h from Day 1†	± 1 day
	15	336 h from Day 1†	± 4 h
2	22	Predose	Anytime Predose §
3	43	Predose	Anytime Predose §
4	64	Predose	Anytime Predose §
		EOI	Within 2 min after EOI
		4 h†	± 15 min
	65	24 h from day 64†	± 4 h
	67	72 h from day 64†	± 1 day
	78	336 h from day 64†	± 4 h
6	106	Predose	Anytime Predose §
Q12W (starting at C6)		Predose	Anytime Predose §
~~Safety FU~~			~~At SFU Visit~~

IV. Synopsis, Study Design Overview and 2 Study Objective(s), Design and Endpoints
2.2.1 Study Design

DELETED:

~~All subjects will be followed for survival approximately every 8 weeks from the Safety Follow-Up visit. This will be done by telephone, until death or study closure, whichever occurs first. A standard of care clinic visit can be used in lieu of a telephone call, if the subject is already coming to clinic.~~

5 Treatments and Evaluation
5.2.6.2 Cycles 5 and Beyond

WAS:

a. Vital Signs
b. Predose PK predose PK sample collection for AGS-16C3F subjects on Cycles 6 and every 12 weeks thereafter. Predose PK sample for Cycles 6 and every 12 weeks thereafter must be collected anytime before AGS-16C3F drug administration on the day of infusion.

IS AMENDED TO:

a. Vital Signs
b. ~~Predose PK predose PK sample collection for AGS-16C3F subjects on Cycles 6 and every 12 weeks thereafter. Predose PK sample for Cycles 6 and every 12 weeks thereafter must be collected anytime before AGS-16C3F drug administration on the day of infusion.~~

5 Treatments and Evaluation
5.2.8 Post Safety Follow-Up Visit

DELETED:

~~5.2.8 Post Safety Follow-Up Visit~~

~~All subjects will be followed for survival approximately every 8 weeks from the Safety Follow-Up visit. This will be done by telephone, until death or study closure, whichever occurs first. A standard of care clinic visit can be used in lieu of a telephone call, if the subject is already coming to clinic.~~

~~Those subjects who discontinued the study for reasons other than objective disease progression by RECIST v.1.1 will continue to have disease assessments every 8 weeks (± 7 days) counting from C1D1. This will continue until subject has radiologically confirmed progression, initiates a new therapy, study closure or subject dies.~~

~~Any subjects who had a positive immunogenicity result will continue to have immunogenicity samples collected for testing every 12 weeks until it returns to negative or baseline value.~~

5 Treatments and Evaluation *5.5 Efficacy Assessment*
WAS:
Scans will be read on site and also submitted in digital format for blinded independent central review. Details of scan submission to independent central radiology vendor will be provided in a separate manual.
IS AMENDED TO:
Scans will be read on site. ~~and also submitted in digital format for blinded independent central review. Details of scan submission to independent central radiology vendor will be provided in a separate manual.~~

5 Treatments and Evaluation *5.8 Test Drug Concentration*
DELETED:
• ~~Q12W (starting at Cycle 6): predose (before the AGS-16C3F infusion)~~ • ~~Safety Follow-Up visit~~

IIB. Nonsubstantial Changes

Title Page
WAS:
Version 1.0: 16 Sep 2015 Version 2.0: 22 Jan 2016 (Amendment 1) Version 3.0: 27 May 2016 (Amendment 2) Version 4.0: 18 Jul 2017 (Amendment 3)
IS AMENDED TO:
Version 1.0: 16 Sep 2015 Version 2.0: 22 Jan 2016 (**Substantial** Amendment 1) Version 3.0: 27 May 2016 (**Substantial** Amendment 2) Version 4.0: 18 Jul 2017 (**Substantial** Amendment 3) **Version 5.0: 09 Feb 2018 (Substantial Amendment 4)**

I. Investigator's Signature
WAS:
Protocol AGS-16C3F-15-3, A Multi-center, Open Label, Randomized Phase 2 Study of

AGS-16C3F vs. Axitinib in Metastatic Renal Cell Carcinoma, Version 5.0 (Amendment 4)
IS AMENDED TO:
~~Protocol AGS-16C3F-15-3,~~ A Multi-center, Open Label, Randomized Phase 2 Study of AGS-16C3F vs. Axitinib in Metastatic Renal Cell Carcinoma~~,~~ **ISN/Protocol AGS-16C3F-15-3** Version ~~5~~6.0 **Incorporating Substantial** ~~(~~Amendment ~~45)~~ **29 July 2020**

II. Contact Details of Key Sponsor's Personnel

WAS:

24h-Contact for Serious Adverse Events (SAEs) See Section 5.7.5	24h Quintiles Medical Emergency Contact Center: 1-973-659-6677 1-570-819-8565 Please fax or email the SAE Worksheet to: Astellas Pharma Global Development, Inc. Pharmacovigilance Fax number: 1-888-396-3750 Alternate North America Fax number 1-847-317-1241 Email: safety-us@astellas.com
Medical Monitor/Medical Expert:	PPD
Clinical Research Contacts:	PPD , Medical and Development PPD

IS AMENDED TO:

24h-Contact for Serious Adverse Events (SAEs) See Section 5.7.5	24h Quintiles Medical Emergency Contact Center: 1-973-659-6677 1-570-819-8565 Please fax ~~or email~~ the SAE Worksheet to: Astellas Pharma Global Development, Inc. **Medical Safety** Pharmacovigilance Fax number: 1-888-396-3750 ~~Alternate North America Fax number 1-847-317-1241~~ Email: ~~S~~safety-**US**~~us~~@astellas.com
Clinical Research Contacts	PPD

	PPD
Medical Monitor/Medical Expert:	PPD
~~Clinical Research Contacts:~~	PPD

IV. Synopsis, Phase of Development
WAS:
Phase 2
IS AMENDED TO:
~~Phase~~ 2

IV. Synopsis, Planned Study Period
WAS:
From 2Q2016 to 3Q2018
IS AMENDED TO:
From 2Q2016 to **3Q2020** ~~3Q2018~~

5 Treatments and Evaluation *5.7.5 Reporting Procedures for All Serious Adverse Events (SAEs)*
WAS:
For contact details, see [Section II Contact Details of Key Sponsor's Personnel]. Fax or email the SAE Worksheet to: Astellas Pharma Global Development, Inc. Pharmacovigilance

Fax number 1-888-396-3750 Alternate North America Fax number 1-847-317-1241 Email: safety-us@astellas.com
IS AMENDED TO:
For contact details, see [Section II Contact Details of Key Sponsor's Personnel]. Fax or email the SAE Worksheet to: Astellas Pharma Global Development, Inc. **Medical Safety** Pharmacovigilance Fax number 1-888-396-3750 ~~Alternate North America Fax number 1-847-317-1241~~ Email: **S**~~s~~afety-**US**~~us~~@astellas.com

11 References *5.8 Test Drug Concentration*
DELETED:
~~Ellenberg SS, Eisenberger MA. An efficient design for phase III studies of combination chemotherapies. Cancer Treatment Reports. 1985;69:1147–1154.~~ ~~Wieand S, Therneau T. A two-stage design for randomized trials with binary outcomes. Controlled Clinical Trials. 1987;8:20–28.~~

14 SPONSOR'S SIGNATURES

Astellas Signatories

(Electronic signatures are attached at the end of the document.)

PPD	Medical Science,
PPD	Development
PPD	Data Science,
PPD	Development