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Clinical Trial Protocol

Clinical Trial Protocol Number	C-550-01
Title	A Phase 1/2, Open-Label, Multi-Arm Trial to Investigate the Safety, Tolerability, Pharmacokinetics, Biological, and Clinical Activity of AGEN1884 in Combination with AGEN2034 in Subjects with Metastatic or Locally Advanced Solid Tumors, and Expansion into Select Solid Tumors
Short Trial Name	Phase 1/2 Trial of AGEN1884 with AGEN2034 in Advanced Tumors
Trial Phase	Phase 1/2
Medical Monitor	[redacted]
Sponsor	Agenus Inc., 3 Forbes Road, Lexington, MA 02421, USA
Original Protocol:	27 September 2017
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– **Confidential** –

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List of Abbreviations

The following abbreviations and specialist terms are used more than once in this study protocol.

Term	Definition
ADA	anti-drug antibody
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APC	antigen-presenting cell
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
$AUC_{0-\infty}$	area under the drug concentration-time curve from time zero to infinity
AUC_{0-t}	area under the drug concentration-time curve from time of dosing to time of last observation
$AUC_{(t1-t2)-ss}$	area under the drug concentration-time curve within time span t1 to t2 at steady-state
BOR	best overall response
BUN	blood urea nitrogen
C	Celsius
CDL	combination dose level
CDL-1	combination de-escalation dose level “minus” 1
CFR	Code of Federal Regulations
CI	confidence interval
CL	systemic clearance
C_{max-ss}	maximum drug concentration observed at steady state
C_{min-ss}	minimum observed concentration at steady-state
CR	complete response
CRO	contract research organization
CRP	C-reactive protein
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte antigen-4
dL	deciliter
DCR	disease control rate
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
EC_{50}	half maximal effective concentration
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form

Term	Definition
FDA	United States Food and Drug Administration
FFPE	formalin fixed paraffin embedded
FSH	follicle-stimulating hormone
g	gram
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
h	hour
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HPV	human papilloma virus
ICF	informed consent form
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IERC	Independent Endpoint Review Committee
IgG1	immunoglobulin G1
IgG4	immunoglobulin G4
IgG4κ	immunoglobulin G4 antibodies with immunoglobulin kappa light chains
Igκ	immunoglobulin kappa
IL	interleukin
ILD	interstitial lung disease
IMP	investigational medicinal product
INR	international normalized ratio
irAE	immune-related adverse event
IRB	Institutional Review Board
IULN	institutional upper limit of normal
IV	intravenous
kg	kilogram
L	liter
lb	pound
LDH	lactate dehydrogenase
LFT	liver function test
LLN	lower limit of normal
λz	terminal disposition rate constant
m	month
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
µg	microgram
mg	milligram
min	minute
mL	milliliter

Term	Definition
mm	millimeter
mM	millimolar
MRI	magnetic resonance imaging
MSI^{HI}	micro-satellite instability-high
MTD	maximum tolerated dose
NCI	National Cancer Institute
NHMRC	National Health and Medical Research Council
NIMP	Non-investigational medical product
NK	natural killer
nM	nanomolar
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non–small-cell lung cancer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1/-L2	ligand 1 or 2 of programmed cell death protein 1
PFS	progression-free survival
PHI	protected health information
PI	Principal investigator
PK	pharmacokinetic(s)
PR	partial response
q	each, every
Q	calendar quarter
RANKL	receptor activator of nuclear factor kappa-B ligand
RBC	red blood cell
RCC	renal cell carcinoma
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RNA	ribonucleic acid
[redacted]	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SCCHN	squamous cell carcinoma of head and neck
SD	stable disease
SEA	*Staphylococcus* enterotoxin A
SHP-1/-2	Src homology region 2 domain–containing phosphatase 1 or 2
SJS	Stevens-Johnson Syndrome
SMC	Safety Monitoring Committee
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal elimination half-life
T3	triiodothyronine
T4	free thyroxine
TBNK	T-, B-, and natural killer cells

Term	Definition
TCR	T-cell receptor
TEAE	treatment-emergent adverse event
TEN	toxic epidermal necrolysis
t_{max}	time to maximum drug concentration
TNM	Tumor Node Metastasis
TPS	tumor proportion score
TRAE	treatment-related adverse events
Tregs	regulatory T cells
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
USP	US Pharmacopeia
Vd	volume of distribution
w	week
WBC	white blood cell

1 Synopsis

Trial Title	A Phase 1 / 2, Open-Label, Multi-Arm Trial to Investigate the Safety, Tolerability, Pharmacokinetics, Biological, and Clinical Activity of AGEN1884 in Combination with AGEN2034 in Subjects with Metastatic or Locally Advanced Solid Tumors, and Expansion into Select Solid Tumors
Trial Number	C-550-01
Sponsor	Agenus Inc., 3 Forbes Road, Lexington, MA 02421, USA
Phase	1 / 2
Trial Center/Country	Phase 1: approximately 5-10 enrolling centers globally. Phase 2: approximately 30-40 enrolling centers globally.
Planned Trial Period	First subject in: 12 Dec 2017 Last subject out: Q3, 2023 (estimated)
Trial Objectives	**Primary Objectives** **Phase 1:** • To assess the safety and tolerability of AGEN1884 in combination with AGEN2034 in subjects with locally advanced, recurrent, and/or metastatic solid tumors. **Phase 2:** • To assess the objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), as determined by the Independent Endpoint Review Committee (IERC). **Secondary Objectives** **Phase 1:** • To characterize the pharmacokinetic (PK) profiles of AGEN1884 and AGEN2034. • To correlate AGEN1884 and AGEN2034 exposure with target occupancy • To evaluate the immunogenicity of AGEN1884 in combination with AGEN2034 and assess potential impact on PK exposure and biological activity. **Phase 2:** • To assess the safety and tolerability of AGEN1884 in combination with AGEN2034 in subjects with locally advanced, recurrent, and/or metastatic solid tumors. • To characterize the PK profiles of AGEN1884 and AGEN2034. • To evaluate the immunogenicity of AGEN1884 in combination with AGEN2034 and assess potential impact on PK exposure and biological activity. • To assess ORR according to RECIST 1.1 as determined by investigator. • To assess duration of response (DOR), disease control rate (DCR), duration of stable disease (SD), time to response, and progression-free survival (PFS) time per RECIST 1.1 • To assess overall survival (OS) **Exploratory Objectives** [redacted]

	• To explore the association of programmed cell death protein 1 ligand (PD-L1) expression with clinical responses. [redacted] • To explore the association of PD-L1 expression with clinical outcomes.
Trial Design and Plan	This is a Phase 1/2, open-label study of AGEN1884 in combination with AGEN2034 in subjects with locally advanced, recurrent and/or metastatic solid tumors including cervical cancer. AGEN2034 is a novel, fully human monoclonal immunoglobulin G4 (IgG4) antibody, designed to block program cell death-1 (PD-1). AGEN1884 is a novel, fully human monoclonal immunoglobulin G1 (IgG1) antibody, designed to block cytotoxic T-lymphocyte antigen-4 (CTLA-4). The trial consists of 2 phases: • Phase 1: Dose escalation • Phase 2: Expansion in advanced cervical cancer **Phase 1: Dose Escalation:** The enrollment to the Phase 1 portion of the study is completed. The trial will consist of a 3+3 dose escalation that will evaluate different combination dose levels (CDL) of AGEN1884 and AGEN2034 in subjects with locally advanced, recurrent and/or metastatic solid tumors. Subjects may be enrolled to the following CDL cohorts: • **CDL1** - AGEN1884 1 mg/kg every 6 weeks + AGEN2034 1 mg/kg every 2 weeks (starting CDL) • **CDL2** - AGEN1884 1 mg/kg every 6 weeks + AGEN2034 3 mg/kg every 2 weeks (maximum planned CDL) • **CDL−1** - AGEN1884 0.3 mg/kg every 6 weeks + AGEN2034 1 mg/kg every 2 weeks (potential de-escalation CDL) Combination Dose Level 1 (CDL1) will be the first to be tested. Dose escalation will continue until the maximum planned CDL (CDL2) is shown to be safe or the maximum tolerated dose (MTD) is reached. The MTD is defined as the CDL below which ≥ 33% of subjects develop dose-limiting toxicities (DLT). The decision to escalate to the next cohort will be made by a Safety Monitoring Committee (SMC), based on safety assessments after all subjects of a cohort reached the end of the DLT observation period of 21 days. Should ≥2 DLTs be observed in CDL1, the SMC may open enrollment to CDL-1. The SMC will also select the CDL for Phase 2. Each subject will receive the combination treatment for a maximum of 24 months or until confirmed disease progression, unacceptable toxicity, or any criterion for withdrawal from the trial or the investigational medicinal products (IMPs) occur. Subjects who do not complete the DLT observation period of 21 days after the first dose, for reasons other than a DLT will be replaced. Additional subjects will be backfilled, concurrently with the 3+3 dose escalation schema at the lower cleared CDL, to ensure that each cohort enrolls at least 10 subjects. These additional subjects at each

	dose level will have the purpose of generating additional safety, PK, and [redacted] data, and will not undergo formal DLT observation. The SMC selected CDL2 (AGEN1884 1 mg/kg every 6 weeks + AGEN2034 3 mg/kg every 2 weeks) as the Recommended Phase 2 dose (RP2D). **Phase 2: Expansion in Select Tumors** To further characterize safety and efficacy, the following expansion cohort will be enrolled: Advanced cervical cancer In Phase 2, the RP2D of AGEN2034 and AGEN1884 will be administered for a maximum of 2 years or until confirmed progression, unacceptable toxicity, or any criterion for stopping the study drugs or withdrawal from the trial occurs. For the Phase 2 portion of the trial, an Independent Data Monitoring Committee (IDMC) will be established to evaluate safety and efficacy and an IERC will be established to adjudicate tumor response.
Planned Number of Subjects	**Phase 1** Approximately 20 subjects Final sample size may vary depending on the total number of dose levels to be tested, and subject replacement for DLT evaluation, if applicable. **Phase 2** Approximately 150 female subjects with advanced cervical cancer.
Trial Eligibility:	**Inclusion Criteria:** To be eligible for participation in this trial the subject must: 1. Voluntarily agree to participate by giving written informed consent. (Participation in pharmacogenomics testing is optional.) 2. Be ≥18 years of age. 3. Diagnosis: a. **Phase 1:** Male or female having a histologically or cytologically confirmed diagnosis of a locally advanced, recurrent, and/or metastatic solid tumor for which no standard therapy is available or standard therapy has failed. b. **Phase 2:** I. Female having (1) a histologically or cytologically confirmed diagnosis of squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix, and (2) locally advanced, recurrent, and/or metastatic disease at the time of enrollment. Histologic confirmation of the original primary tumor is required via pathology report. **Note**: The following cervical tumors are not eligible: minimal deviation/adenoma malignum, gastric type adenocarcinoma, clear cell carcinoma, and mesonephric carcinoma. II. Has cervical cancer and has relapsed after a platinum-based treatment (first line) regimen for locally advanced, recurrent, and/or metastatic disease; **Note**: Subjects who only received platinum-based chemotherapy concurrently with primary radiation (e.g., weekly cisplatin) or adjuvant chemotherapy following completion of radiation therapy (e.g., paclitaxel and carboplatin for ≤ 4 cycles) and progressed within

	6 months after treatment completion will be eligible as this systemic therapy will be considered first line. 4. Measurable Disease a. **Phase 1**: Have objective evidence of disease; the presence of measurable disease is not required. b. **Phase 2:** Have measurable disease on imaging based on RECIST version 1.1. **Note:** Subjects must have at least one "target lesion" to be used to assess response, as defined by RECIST version 1.1. Tumors within a previously irradiated field will be designated as "non-target" lesions unless progression is documented, or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy. **Note:** Measurable disease by RECIST 1.1 must be confirmed by independent central radiologic review prior to first dose. Subjects without centrally confirmed measurable disease at baseline will not be eligible for this trial. 5. Have a life expectancy of at least 3 months and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. 6. Have adequate organ function as indicated by the following laboratory values: a. Adequate hematological function defined by absolute neutrophil count (ANC) $\geq$ 1.5 x 10^9/L, platelet count $\geq$ 100 x 10^9/L, and hemoglobin $\geq$ 8 g/dL (without transfusions within 1 week of first dose). b. Adequate hepatic function based on a total bilirubin level $\leq$ 1.5 x the institutional upper limit of normal (IULN), aspartate aminotransferase (AST) level $\leq$ 2.5 x IULN, alanine aminotransferase (ALT) level $\leq$ 2.5 x IULN, and alkaline phosphatase $\leq$ 2.5 IULN. c. Adequate renal function defined as creatinine $\leq$ 1.5 x IULN OR calculated creatinine clearance $\geq$ 50 mL/min for subjects with creatinine levels > 1.5 x IULN (if no local guideline is available, creatinine clearance should be calculated using the Cockcroft-Gault Method). d. Adequate coagulation defined by international normalized ratio (INR) or prothrombin time $\leq$ 1.5 x IULN (unless the subject is receiving anticoagulant therapy); and activated partial thromboplastin time (aPTT) $\leq$ 1.5 x IULN (unless the subject is receiving anticoagulant therapy) 7. Other than the cancer for which the subject is enrolled, have no history of prior malignancy, with the exception of basal cell carcinoma of the skin, superficial bladder cancer, squamous-cell carcinoma of the skin, or has undergone potentially curative therapy with no evidence of that disease recurrence for 5 years since initiation of that therapy. **Note:** In Phase 2, the history and time requirement for no evidence of disease for 5 years does not apply to the cancer for which the subject is enrolled in the trial. 8. In Phase 2, subjects must provide a sufficient and adequate formalin fixed paraffin embedded (FFPE) tumor tissue sample preferably from the most recent biopsy of a tumor lesion, collected either at the time of or after the diagnosis of locally advanced, recurrent, and/or metastatic disease has been made AND from a site not previously irradiated. If no tumor tissue is available, a fresh biopsy will be required. **Note:** Tissue from needle or excisional biopsy or from resection is required.

	9. Female subjects must have a negative serum pregnancy test at screening (within 72 hours of first dose of study drug) if of childbearing potential or be of non-childbearing potential. Non-childbearing potential is defined as (by other than medical reasons): a. ≥45 years of age and has not had menses for greater than 1 year, b. Amenorrheic for ≥ 2 years without a hysterectomy and oophorectomy and a follicle-stimulating hormone (FSH) value in the postmenopausal range upon pretrial (screening) evaluation, c. Whose status is post hysterectomy, oophorectomy, or tubal ligation. 10. If of childbearing potential, female subjects must be willing to use 2 highly effective contraceptive measures (defined in the informed consent form [ICF]) throughout the study, starting with the screening visit through 120 days after the last dose of study drug. **Note:** Abstinence is acceptable if this is the established and preferred contraception for the subject. 11. Male subjects with a female partner(s) of childbearing potential must agree to use 2 highly effective contraceptive measures (defined in the ICF) throughout the trial starting with the screening visit through 120 days after the last dose of study drug is received. Males with pregnant partners must agree to use a condom; no additional method of contraception is required for the pregnant partner. **Note:** Abstinence is acceptable if this is the established and preferred contraception for the subject. 12. Is willing and able to comply with the requirements of the protocol. **Exclusion Criteria** The subject must be excluded from participating in the trial if the subject: 1. Is currently participating and receiving trial therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment. 2. Has an inadequate washout period prior to first dose of study drug defined as: a. Received systemic cytotoxic chemotherapy or biological therapy within 3 weeks before first dose, b. Received radiation therapy within 3 weeks before first dose, or c. Had major surgery within 4 weeks before first dose. 3. Has received prior therapy with: a. Any antibody/drug targeting T-cell co-regulatory proteins (immune checkpoints) such as anti–PD-1, anti–PD-L1, or anti–cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibodies b. For Phase 2: > 1 systemic treatment regimen for the locally advanced recurrent, and/or metastatic cervical cancer for which the subject is considered for the study. Subjects who received a systemic regimen immediately after progressing within 6 months of completing chemotherapy concurrent with primary radiation or adjuvant chemotherapy after radiation will only be considered as having 1 prior systemic regimen for the purpose of this criterion. **Note**: In Phase 1, prior treatment with a CTLA-4 antibody is permissible for subjects with metastatic melanoma. 4. Has persisting toxicity related to prior therapy of National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI-CTCAE)

	Grade >1 severity. **Note:** Sensory neuropathy or alopecia of Grade ≤2 is acceptable. 5. Is expected to require any other form of systemic or localized antineoplastic therapy while on trial (including maintenance therapy with another agent, radiation therapy, and/or surgical resection). 6. Has known severe hypersensitivity reactions to fully human monoclonal antibodies (NCI-CTCAE Version 4.03 Grade ≥3), any history of anaphylaxis, or uncontrolled asthma. 7. Is receiving systemic corticosteroid therapy ≤ 7 days prior to first dose of study treatment or receiving any other form of systemic immunosuppressive medication (corticosteroid use on study for management of immune-related adverse events (AE), and/or a premedication for intravenous (IV) contrast allergies/reactions is allowed). Subjects who are receiving daily corticosteroid replacement therapy are an exception to this rule. Examples of permitted therapy are daily prednisone at doses of 5 to 7.5 mg or equivalent hydrocortisone dose, and steroid therapy administered by topical, intraocular, intranasal, and/or inhalation routes. 8. Has a central nervous system (CNS) tumor, metastasis(es), and/or carcinomatous meningitis identified either on the baseline brain imaging obtained during the screening period OR identified prior to consent. **Note:** Subjects with history of brain metastases that have been treated may participate provided they show evidence of stable supra-tentorial lesions at screening (based on 2 sets of brain images performed ≥ 4 weeks apart, and obtained after the brain metastases treatment). In addition, any neurologic symptoms that developed either as a result of the brain metastases or their treatment must have resolved or be minimal and be expected as sequelae from treated lesions. For individuals who received steroids as part of brain metastases treatment, steroids must be discontinued ≥ 7 days prior to first dose of study drug. 9. Has active or history of autoimmune disease that has required systemic treatment within 2 years of the start of study treatment (i.e. with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (i.e., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of immunosuppressive systemic treatment. **Note:** Subjects with diabetes type 1, vitiligo, psoriasis, hypo-, or hyperthyroid disease not requiring immunosuppressive treatment are eligible. 10. Has had an allogeneic tissue/solid organ transplant. 11. Has or had interstitial lung disease (ILD) OR has had a history of pneumonitis that has required oral or IV corticosteroids. 12. Has an active infection requiring IV systemic therapy. 13. Has known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies). 14. Has known active Hepatitis B, Hepatitis C, or tuberculosis. Active Hepatitis B is defined as a known positive HBsAg result. Active Hepatitis C is defined by a known positive Hep C Ab result and known quantitative HCV RNA results greater than the lower limits of detection of the assay. 15. Has clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke or myocardial infarction within 6 months of enrollment, unstable angina, congestive heart failure (New York Heart Association class ≥II), or serious uncontrolled cardiac arrhythmia requiring medication. 16. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the

	subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator. 17. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial. 18. Is, at the time of signing informed consent, a regular user (including "recreational use") of any illicit drugs or had a recent history (within the last year) of substance abuse (including alcohol). 19. Is legally incapacitated or has limited legal capacity. 20. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of AGEN2034 and/or AGEN1884.
Dosage and Administration	**Phase 1:** • CDL1: AGEN1884 1 mg/kg every 6 weeks + AGEN2034 1 mg/kg every 2 weeks • CDL2: AGEN1884 1 mg/kg every 6 weeks + AGEN2034 3 mg/kg every 2 weeks • CDL-1: AGEN1884 0.3 mg/kg every 6 weeks + AGEN2034 1 mg/kg every 2 weeks (potential de-escalation CDL) **Phase 2:** AGEN1884 1 mg/kg every 6 weeks + AGEN2034 3 mg/kg every 2 weeks **Administration** AGEN2034 infusions should be administered IV first and over 30 min (-10 / +20 min) on Day 1, Day 15, and Day 29 of each treatment cycle. All infusions should be administered using an infusion pump. A central catheter is not required for infusion; however, if a subject has a central venous catheter in place, it is recommended that it be used for the infusion. Once the infusion is completed, all remaining drug solution in the line should be administered according to institutional guidelines for saline flushing. On Day 15 and Day 29 of each cycle, subjects should be observed for 30 minutes after AGEN2034 infusion has been completed. AGEN1884 should be administered over 30 minutes (-10 / + 20 min) and following the infusion of AGEN2034 on Day 1 of each treatment cycle; approximately 30 minutes after the administration of AGEN2034 is completed. Infusions will be followed immediately with a 15-minute saline flush of the IV line. Subjects should be observed for 30 minutes after the AGEN1884 infusion has been completed. Separate infusion bags and filters must be used for the infusion of each drug.
Planned Trial Duration	The maximum trial duration for a subject is estimated to be approximately 49 months. This includes a screening period; a planned treatment period of up to approximately 24 months; and a follow-up period of up to 12 months after the last treatment dose. The overall trial duration is expected to be approximately 73 months.
Schedule of Visits and Assessments	**Screening Period** Screening assessments will be conducted within 28 days prior to first treatment dose, with associated evaluations and procedures. **Treatment Period** The treatment period is divided into 6-week cycles, in which each cycle includes 3 administrations of AGEN2034 and 1 administration of AGEN1884, with associated evaluations and procedures that must be performed at specific timepoints. Each cycle begins with the combined administration of AGEN2034 and AGEN1884 on Day 1 (AGEN2034 will be administered before AGEN1884). Thereafter, AGEN2034 will be

	administrated every 2 weeks, completing the six-week cycle (timing of doses may be adjusted for management of adverse events [AE]). Subjects will be treated for up to 24 months or until confirmed disease progression or unacceptable toxicity. Tumor assessments will be conducted every 6 weeks (± 3 days) from first dose until disease progression is confirmed or a new line of therapy is initiated. **End-of-Treatment** ***Discontinuation Visit and Safety Follow-up Visit:*** All subjects who discontinue study treatment prematurely for any reason have a full safety evaluation at the time of discontinuation (Discontinuation Visit). A mandatory Safety Follow-up Visit should be scheduled 4 weeks after the last treatment administration. Subjects with an adverse drug reaction (ADR) ongoing at the Safety Follow-up Visit must be followed up until the ADR resolves, becomes stable, or is considered not clinically significant by the investigator. **Follow-up Phase** In Phase 1 and Phase 2, subjects who discontinue treatment will be followed for up to 12 months after the last dose of study drug or until death, withdrawal of consent, or becoming lost to follow-up. **Follow-up Visits** Clinic visits will include evaluations and procedures and will occur every 3 months until disease progression and/or start of a new line of therapy or up to 12 months following the last treatment administration. **Survival Follow-up** In Phase 2, subjects who present with progressive disease (PD) and/or start a new line of therapy before or after completing Follow-up Visit 1 (3 months from last study drug dose) will enter the Survival Follow-up period and will be contacted by phone every 2 months to assess for survival, and post-study treatments for up to 12 months from last treatment administration.
Endpoints	**Primary Endpoints:** **Phase 1** • Occurrence of DLTs in subjects in dose escalation during the first 21 days of treatment. • Frequency, severity, and duration of treatment-emergent AEs (TEAEs) and laboratory abnormalities using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03. **Phase 2:** • Confirmed ORR per RECIST 1.1, as determined by the IERC, in the analysis population. The ORR will be determined as the proportion of subjects with a confirmed best overall response of partial response (PR) or complete response (CR) and reported with 95% Wilson score confidence intervals (CIs). **Secondary Endpoints:** **Phase 1:** • AGEN2034 and AGEN1884 PK parameters which may include (but are not limited to) maximum observed concentration at steady-state (C_{max-ss}), minimum observed concentration at steady-state (C_{min-ss}), area under the drug concentration-time curve within time span t1 to t2 at steady-state ($AUC_{(t1-t2)-ss}$), area under the drug concentration-time curve from time zero to time t ($AUC_{(0-t)}$), area under the drug concentration-time curve from time zero to infinity ($AUC_{(0-\infty)}$), time to

	maximum drug concentration (t_{max}), terminal disposition rate constant (λz), terminal elimination half-life ($t_{1/2}$), systemic clearance (CL), and volume of distribution (Vd). • [redacted] • [redacted] • Anti-drug antibody (ADA) concentrations and potential impact on AGEN2034 and AGEN1884 PK exposure metrics **Phase 2:** • Frequency, severity, and duration of TEAEs and laboratory abnormalities, using NCI-CTCAE v4.03 • AGEN2034 and AGEN1884 PK parameters which may include (but are not limited to) C_{max-ss}, C_{min-ss}, $AUC_{(t1-t2)-ss}$, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, t_{max}, λz, $t_{1/2}$, CL, and Vd • ADA concentrations and potential impact on AGEN2034 and AGEN1884 PK exposure metrics • Confirmed ORR per RECIST 1.1, as determined by an investigator • DOR per RECIST 1.1, as determined by an IERC and investigator, in subjects with confirmed response, defined as time from first observation of response to first observation of documented disease progression (or death within 12 weeks after last tumor assessment). Subjects without an event at the analysis cutoff date will be censored on the date of last tumor assessment. • DCR, defined as proportion of subjects with CR, PR, or SD for at least 12 weeks • Duration of SD, measured from the start of treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including baseline measurements • Time to response, defined as the time from the first dose date to first observation of confirmed response, will be summarized among subjects with documented confirmed response. • PFS time, defined as time from first treatment administration to first observation of documented disease progression (or death within 12 weeks after last tumor assessment), per RECIST 1.1, as determined by an IERC and investigator. Subjects without an event at analysis cutoff date will be censored on date of last tumor assessment. PFS time will be summarized by median PFS and PFS rates. • OS time, defined as time from start of treatment to death. For subjects who are still alive at time of data cutoff for trial analysis or who are lost to follow-up, survival will be censored at the last recorded date that the subject is known to be alive as of the cutoff date for analysis. OS time will be summarized by median OS and OS rates. **Exploratory Endpoints:** [redacted] • [redacted] • [redacted] • [redacted]

	• Baseline expression of PD-L1 [redacted] • Baseline expression of PD-L1 association with clinical outcomes.
Statistical Considerations:	The total sample size is expected to be approximately 170 treated subjects. **Phase 1:** It is expected that approximately 20 subjects will be enrolled in the Phase 1 part of the trial. **Phase 2:** Phase 2 has 1 planned cohort of approximately 150 subjects: - advanced cervical cancer The primary endpoint of Phase 2, ORR, will be estimated as the binomial proportion of subjects with confirmed partial or complete best overall response per RECIST 1.1, as determined by an IERC, and will be reported using a two-sided 95% Wilson score CI. The sample size of 150 subjects provides 94% power to exclude an ORR of 10% by the lower limit of the 95% two-sided Wilson score CI, assuming a true ORR of 20%. Interim analyses will be performed to assess the safety and efficacy (using the ORR and selected secondary efficacy endpoints) when (1) data are available for approximately 30 subjects treated for at least 3 months and (2) approximately 3 months after approximately 100 subjects are dosed. No early stopping for efficacy will be performed, as a more complete safety assessment and evaluation of durability of responses are necessary for determination of risks and benefits. Consequently, the interim analyses will not affect the overall type I error. A non-binding futility analysis may be performed using methods described in the statistical analysis plan. Additional interim analyses for safety and efficacy assessment may be performed. Statistics for continuous variables may include means, medians, ranges, and appropriate measures of variability; statistics for binary endpoint will be summarized with counts and frequencies; and statistics for time-to-event will be summarized with median and 95% CI etc. as appropriate

2 Introduction and Rationale

In the past 2 decades, researchers have demonstrated the importance of the immune system in controlling cancer. Advances in our understanding of immuno-oncology have highlighted the dynamic interplay between host and tumor and have shown that a tumor's ability to evade the immune system can determine outcome. This has led to the development of therapies that are changing the landscape of modern oncology. Researchers have dissected numerous regulatory pathways that are exploited by cancer to evade immune response. The programmed cell death-1 (PD-1) and cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) proteins are the most extensively studied negative regulatory receptors, and whose pathways are the target of multiple therapies both approved by regulatory agencies and in development (Buchbinder & Desai 2016; Sharma & Allison 2015; Topalian et al. 2015). Initially used as monotherapies, PD-1 and CTLA-4 therapeutics are now being tested in combination with promising results, including their approval for patients with advanced stage melanoma. This protocol will trial the CTLA-4 antibody, AGEN1884, in combination with the PD-1 antibody, AGEN2034.

2.1 PD-1 and CTLA-4 Checkpoint Blockade

Inhibition of the PD-1 and CTLA-4 pathways by blockade of receptor-ligand interactions has been demonstrated in numerous clinical trials to result in objective clinical response and increased survival in several solid tumor indications. These studies have led to several regulatory approvals across the globe for single agents and combinations in various indications including melanoma, non–small cell lung cancer (NSCLC), renal cell carcinoma, head and neck cancers, Hodgkin lymphoma, and micro-satellite instability-high (MSI^{HI}) cancers.

2.1.1 CTLA-4 Pathway Blockade

CTLA-4 is a cell surface receptor that is expressed on activated T cells and functions as an important negative regulator of T cell function (Sharpe & Freeman 2002; Walker & Sansom 2015). CTLA-4 and CD28 exemplify a co-inhibitory-co-stimulatory system that acts to regulate T cell immune responses. These receptors share 2 ligands of the B7 family of immune-regulatory ligands, B7.1 (CD80) and B7.2 (CD86), expressed by activated antigen-presenting cells (APCs). CD80 and CD86 share approximately 25% amino acid sequence identity, and both engage CTLA-4 and CD28 receptors through a conserved motif (Zhang et al. 2003). CTLA-4 is also expressed by regulatory T cells (Tregs), which can impair tumor immunity by multiple suppressive mechanisms (Wing et al. 2008; Zou 2006). One such mechanism involves Treg-expressed CTLA-4 mediating the physical removal of CD80 and CD86 from the surface of activated APCs by a process termed trans-endocytosis, which can attenuate the immune-stimulatory potential of APCs (Qureshi et al. 2011). Emerging clinical and preclinical trial data support a secondary mechanism of action for anti-CTLA-4 antagonist antibodies involving the depletion of Tregs (Bulliard et al. 2013; Marabelle et al. 2013; Romano et al. 2015; Selby et al. 2013; Simpson et al. 2013). This mechanism involves the co-binding of anti-CTLA-4 antibodies to Tregs located within the tumor and fragment-crystallizable gamma receptor (FcγR)-expressing effector cells (e.g., natural killer (NK) or myeloid cells), resulting in antibody-dependent cellular cytotoxicity (ADCC) or phagocytosis (ADCP). The presence of tumor-associated Tregs is considered to be a major obstacle in achieving effective anti-tumor immunity during immunotherapy, because Tregs naturally contribute to tumor immune suppression by dampening the activation of tumor-specific effector T cells (Zou 2006).

Therefore, intra-tumoral Treg elimination is key to enhancing T cell responsiveness to weakly immunogenic antigens, such as tumor-associated antigens.

Blockade of the CTLA-4 pathway has been shown to be effective in the adjuvant treatment of resected melanoma and in the treatment of unresectable or metastatic melanoma. Additional indications for CTLA-4 pathway inhibitors are currently under investigation.

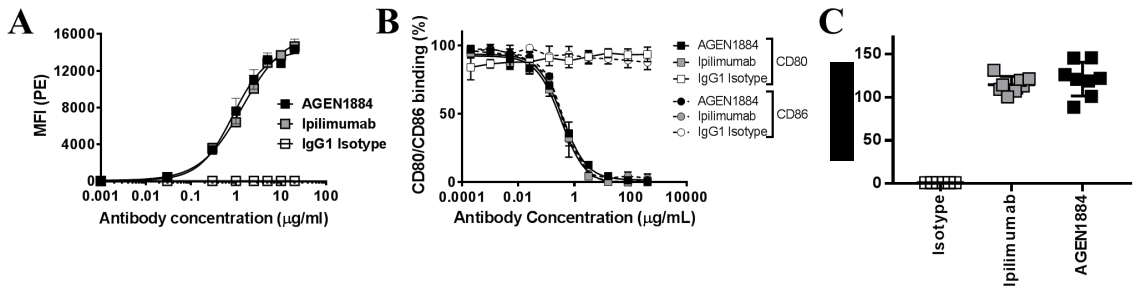
2.1.1.1 AGEN1884

AGEN1884 is a novel, fully human monoclonal immunoglobulin G1 (IgG1) antibody, designed to block CD80 and CD86 interactions to CTLA-4 in a manner comparable to ipilimumab. AGEN1884 is being evaluated in an ongoing Phase 1 trial as monotherapy in subjects with advanced and/or refractory malignancies (C-500-01, NCT02694822). A Phase 2a trial of AGEN1884 in combination with pembrolizumab has been initiated.

2.1.1.1.1 Summary of Preclinical Data

AGEN1884 is physicochemically comparable to ipilimumab (CTLA-4 specific IgG1 antibodies with immunoglobulin kappa (Igκ) light chains [IgG1κ]). Side-by-side *in vitro* pharmacological characterization of AGEN1884 and ipilimumab demonstrated that these 2 antibodies were functionally comparable. More specifically both antibodies: 1) bind human CTLA-4 with subnanomolar affinities (K_D 0.46 nM for AGEN1884 and 0.38 nM for ipilimumab) and have comparable relative cellular binding affinities to human CTLA-4 expressed recombinantly on cells (half maximal effective concentration (EC_{50}) 0.85 µg/mL for AGEN1884 and 1.39 µg/mL for ipilimumab) (Figure 1A); 2) potently block the binding of CD80 and CD86 to CTLA-4 (0.37/0.40µg/mL blocking of CD80/CD86 for AGEN1884 and 0.33 µg/mL blocking of both CD80/CD86 for ipilimumab) (Figure 1B); and 3) augment the activation of primary human T cells *in vitro* (Figure 1C).

Figure 1: *In vitro* Comparability of AGEN1884 and Ipilimumab



Head-to-head evaluation of AGEN1884 (black), commercial ipilimumab (gray), or IgG1 isotype antibody (white). (A) Antibody binding to human CTLA-4$^+$ recombinant Chinese hamster ovary (CHO) cells. (B) Antibody-mediated blockade for CTLA-4 binding to CD80 and CD86. (C) T cell–induced [redacted] release in SEA-stimulated peripheral blood mononuclear cells (PBMC) cultures. On the *x-axis*, antibody concentrations (µg/mL) or antibodies used are shown. Data shown are representative of at least 2 independent experiments.

The best indication of the safety profile of AGEN1884 both as monotherapy and in combination with anti-PD1 agents is expected to be the safety profile of ipilimumab, as specified in its label (Bristol-Myers Squibb USA 2017b) and reviewed in the literature (Camacho 2015; Boutros et al. 2016; Kumar et al. 2017).

2.1.1.1.2 Summary of Clinical Data

The Phase 1 dose escalation trial of AGEN1884, C-500-01, is evaluating the safety and tolerability of AGEN1884 at the following dose levels: 0.1, 0.3, 1, 3, 6, and 10 mg/kg every 3 weeks. The trial has completed dose escalation to 3 mg/kg every 3 weeks and will enroll subjects to the 6 mg/kg every 3 weeks cohort. As of 01 September 2017, a total of 25 subjects have been treated with AGEN1884. A total of 4 subjects did not complete the dose limiting toxicity (DLT) observation period of 28 days for reasons other than a DLT and were replaced. The maximum tolerated dose (MTD) has not been reached and enrollment continues. Overall the data reported here are based on a total of 77 administrations of AGEN1884, 22 administrations of 0.1 mg/kg, 11 administrations of 0.3 mg/kg, 22 administrations of 1 mg/kg, and 22 administrations of 3 mg/kg.

Based on the data from the 25 subjects treated at 0.1, 0.3, 1.0, and 3.0 mg/kg and on the cohorts that have cleared the DLT observation period and have been evaluated by the C-500-01 Safety Review Committee (SRC), comprised of all Principal Investigators and Sponsor medical monitor; as of the last SRC meeting on 01 June 2017, the dose levels up to and including 3.0 mg/kg every 3 weeks are considered to be well-tolerated and safe.

As of 01 September 2017, all 25 subjects at all dose levels experienced at least 1 treatment-emergent AE (TEAE). reported for the greatest proportion of subjects (observed in > 3 subjects) included fatigue (in 15 subjects; 60%); anemia (in 11 subjects; 44%); diarrhea (in 9 subjects; 36%); decreased appetite and abdominal pain (each in 7 subjects; 28%); nausea and vomiting (each in 6 subjects; 24%); and constipation, dyspnea, cough, and headache (each in 5 subjects; 20%); and dehydration, hypocalcemia, chest pain, urinary tract infection, and rash (each in 4 subjects; 16%). There were no relevant differences with regard to the frequency of the AEs across different dose levels. Of the Grade ≥ 3 TEAEs, anemia was reported in 4 subjects (16%); respiratory failure, fatigue, and abdominal pain were reported in 3 subjects (12%) and acute kidney injury, hyperbilirubinemia, hyponatremia, dehydration, diarrhea, dyspnea, and pneumonia were reported in 2 subjects (8%). No dose dependency for the occurrence of Grade ≥ 3 TEAEs was observed. In addition, 2 subjects experienced a Grade 5 event secondary to disease progression; in both cases, the investigator assessed the event as not related to study drug.

The most common TEAEs considered at least possibly related to AGEN1884 by the investigator were fatigue (in 11 subjects; 44%); rash and diarrhea (each in 6 subjects; 24%); and pruritus (in 5 subjects; 20%). Three Grade 3 TEAEs considered at least possibly related to AGEN1884 were reported: 2 events of Grade 3 fatigue were reported, one in a subject receiving 0.1 mg/kg and one in a subject receiving 1.0 mg/kg; and an event of Grade 3 pancytopenia in a subject receiving a dose of 0.3 mg/kg. Additionally, one event of Grade 4 colitis that required corticosteroid treatment and resulted in colon perforation requiring surgery occurred in a subject receiving 1 mg/kg.

As of 01 September 2017, 13 of the 25 subjects (52%) experienced treatment-emergent serious adverse event (SAEs). One SAE of Grade 4 autoimmune colitis was considered related to study treatment as assessed by the investigator: subject presented with Grade 4 colitis that was refractory to corticosteroid treatment and resulted in perforation of the colon requiring emergency surgery.

As of 01 September 2017, a single infusion-related reaction of chest pain was reported that did not present with clinically significant changes to the electrocardiogram (ECG) or changes to cardiac enzymes and resolved within 6 hours. No other infusion-related reactions/hypersensitivity have been reported.

Although efficacy is not the primary objective of the Phase 1 trial, as of 01 September 2017 1 subject has a confirmed complete response (CR), and 2 subjects had stable disease (SD) at 12 weeks following the first AGEN1884 administration.

Overall, AGEN1884 has been well tolerated. The majority of the observed AEs were consistent with the subjects' underlying cancer. Symptoms associated with immune-related AEs (irAEs) have been reported (diarrhea, colitis rash and pruritus), of which one immune-related colitis required treatment with corticosteroids and resulted in perforation of the colon requiring emergency surgery.

For detailed information on preclinical, manufacturing, administration, pharmacology, safety, and preliminary efficacy of AGEN1884, please refer to the AGEN1884 Investigator's Brochure.

2.1.2 PD-1 Pathway Blockade

The importance of immune surveillance in controlling outgrowth of neoplastic transformation is well described and consistent with a correlation between prevalence of tumor-infiltrating lymphocytes in cancer tissues and favorable prognosis in various malignancies (Disis 2010). Tumors can nevertheless evade recognition and destruction by the immune system by expressing soluble and cell-expressed molecules that naturally mediate immune suppression (Topalian et al. 2015). In this context, the PD-1 checkpoint inhibitor pathway has emerged as a significant mode by which tumors suppress immune control (Postow et al. 2015).

PD-1, or CD279, is a member of the immunoglobulin superfamily (IgSF) that negatively regulates T-cell responses to maintain peripheral tolerance and immune homeostasis (Zha et al. 2004). A range of T-cell subsets, including activated T effector cells, memory T cells, regulatory T cells, and T follicular helper cells, express PD-1. PD-1 is rapidly upregulated on T cells activated via their T-cell receptor (TCR). Under conditions of persistent antigenic exposure, such as in chronic pathogenic infections or within the tumor microenvironment, PD-1 expression can be sustained on antigen-specific T cells, leading to a state of dysfunction commonly referred to as T-cell exhaustion (Barber et al. 2006).

PD-1 signaling is mediated by 2 ligands: PD-1 ligand 1 (PD-L1 or CD274) and PD-1 ligand 2 (PD-L2 or CD273) (Latchman et al. 2001). PD-L1 is expressed on the cell surface of a range of immune and non-immune cell types, including APCs and tumor cells. Upon binding to PD-L1 or PD-L2, PD-1 signaling in T cells can potently attenuate TCR signaling, resulting in diminished cytokine and proliferative responses, reduced T effector cell cytolytic activity, and impaired central memory T-cell differentiation (Allie et al. 2011). Proximal to ligand binding, PD-1 recruits Src homology region 2 domain–containing phosphatase (SHP)-1 and SHP-2 proteins to an immunoreceptor tyrosine-based inhibitory motif and an immunoreceptor tyrosine-based switch motif within its intracellular domain (Chemnitz et al. 2004). This impairs phosphorylation of several key kinase proteins, including zeta chain–associated protein kinase 70, phosphatidylinositol 3-kinase, protein kinase B, casein kinase 2, and protein kinase C theta, thereby attenuating signaling through these gene regulatory pathways (Yokosuka et al. 2012).

Inhibition of the PD-1 pathway by blockade of receptor-ligand interactions has been demonstrated to improve clinical outcome in a range of malignancies. The therapeutic benefit of such a blockade in the treatment of subjects with cervical cancer is under investigation.

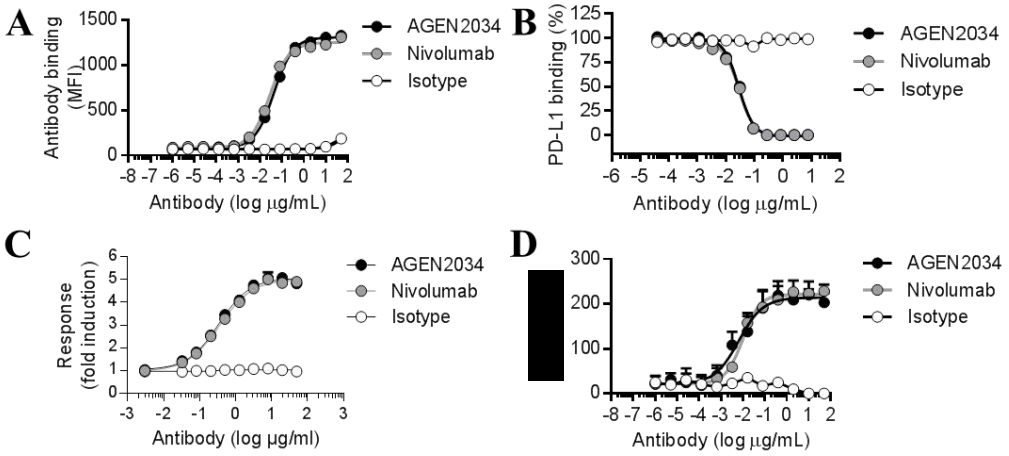
2.1.2.1 AGEN2034

AGEN2034 is a novel, fully human monoclonal immunoglobulin G4 (IgG4) antibody, designed to block PD-1 binding to PD-L1 and PD-L2, in a manner comparable to nivolumab. AGEN2034 is being evaluated in an ongoing Phase 1 trial as monotherapy in subjects with advanced and/or refractory malignancies with an expansion cohort of subjects with locally advanced, recurrent, and/or metastatic cervical cancer that has progressed after platinum doublet chemotherapy. (C-700-01, NCT03104699).

2.1.2.1.1 Summary of Preclinical Data

The utility of PD-1 as a therapeutic antibody target in human cancer has been well characterized. A human IgG4 antibody with immunoglobulin kappa light chains (IgG4κ) monoclonal antibody directed against PD-1 (nivolumab, Opdivo®) has been evaluated in thousands of patients covering a range of intravenous (IV) doses, from 0.1 mg/kg to 20 mg/kg (Topalian et al., 2012). AGEN2034 is physicochemically comparable to nivolumab (PD-1 specific IgG4 antibodies with Igκ light chains) and a side-by-side *in vitro* pharmacological characterization of AGEN2034 and nivolumab demonstrated that these 2 antibodies were functionally comparable. More specifically, both antibodies: 1) bind human PD-1 with subnanomolar affinities (K_D 0.14 nM for AGEN2034 and 0.12 nM for nivolumab) and have comparable relative cellular binding affinities to human T cells expressing PD-1 (EC_{50} 0.04 µg/mL for AGEN2034 and 0.03 µg/mL for nivolumab) (Figure 2A); 2) potently block the binding of PD-L1 to PD-1 (IC_{50} 0.03 µg/mL for both antibodies) (Figure 2B); and 3) augment the activation of recombinant PD-1 expressing and primary human T cells (Figure 2C-D).

Figure 2: *In vitro* Comparability of AGEN2034 and Nivolumab



Head-to-head evaluation of AGEN2034 (**black**), commercial nivolumab (**gray**), or IgG4 isotype antibody (**white**) for (**A**) antibody binding to PD-1+ CD4+ T cells in cultures of *Staphylococcus* enterotoxin A (SEA)-stimulated human - PBMCs; (**B**) antibody-mediated blockade for PD-1 binding to PD-L1; (**C**) inhibition of PD-1:PD-L1 signaling in a T-cell reporter assay; and (**D**) T cell–induced [redacted] release in SEA-stimulated PBMC cultures (D). On the x-axis, log converted antibody concentration (log µg/mL) are shown. Data shown are representative of 2 independent experiments.

The best indication of the safety profile of AGEN2034 both as monotherapy and in combination with anti-CTLA-4 agents is expected to be the safety profile of nivolumab, as specified in its label (Bristol-Myers Squibb USA 2017a) and reviewed in the literature (Weber et al., 2017).

2.1.2.1.2 Summary of Clinical Data

The Phase 1 dose escalation trial of AGEN2034, C-700-01, is evaluating the safety and tolerability of AGEN2034 at the following dose levels: 1, 3, and 10 mg/kg every 2 weeks.

The safety data for the C-700-01 study is as follows: as of July 26, 2018, a total of 50 subjects in the Phase 1 part of the trial have been recruited, enrolled, and treated in the Phase 1 dose escalation study: 1 mg/kg q2w: n=10; 3 mg/kg q2w: n=10; 10 mg/kg q2w: n=10; 6 mg/kg q3w: n=10; 10 mg/kg q3w: n=10. To date, no DLTs have been reported by any of the 50 subjects treated with AGEN2034 (Table 1 and Table 2).

Table 1: Phase 1 Demographics and Baseline Characteristics

		1 mg/kg q2w n=10	**3 mg/kg q2w** n=10	**10 mg/kg q2w** n=10	**6 mg/kg q3w** n=10	**10 mg/kg q3w** n=10	**All Subjects** N=50
Age (years)	Median	58.5	58.5	53.0	63.0	60.5	58.5
	Min, max	23, 77	31, 76	39, 73	40, 72	50, 79	23, 79
Gender, n (%)	Male	2 (20%)	2 (20%)	1 (10%)	1 (10%)	2 (20%)	8 (16%)
	Female	8 (80%)	8 (80%)	9 (90%)	9 (90%)	8 (80%)	42 (84%)
Race, n (%)	White	8 (80%)	6 (60%)	9 (90%)	9 (90%)	9 (90%)	41 (82%)
	African American	2 (20%)	1 (10%)	0	0	0	3 (6%)
	Asian	0	3 (30%)	1 (10%)	1 (10%)	1 (10%)	6 (12%)
Ethnicity, n (%)	Hispanic/ Latino	1 (10%)	0	1 (10%)	2 (20%)	1 (10%)	5 (10%)
	Not Hispanic/ Latino	9 (90%)	10 (100%)	9 (90%)	8 (80%)	9 (90%)	45 (90%)
ECOG performance status, n (%)	0	3 (30%)	3 (30%)	2 (20%)	3 (30%)	3 (30%)	14 (28%)
	1	7 (70%)	7 (70%)	8 (80%)	7 (70%)	7 (70%)	36 (72%)
Time since progression (months)	Median	1.54	0.89	1.91	2.56	1.64	1.66
	Min, max	0.7, 3.2	0.2, 11.2	0.6, 11.1	0.2, 10.3	0.2, 9.4	0.2, 11.2
Current cancer status, n (%)	Localized	3 (30%)	0	0	0	2 (20%)	5 (10%)
	Metastatic	7 (70%)	10 (100%)	10 (100%)	10 (100%)	8 (80%)	45 (90%)

Table 2: Phase 1 Subject Disposition

	1 mg/kg q2w n=10	3 mg/kg q2w n=10	10 mg/kg q2w n=10	6 mg/kg q3w n=10	10 mg/kg q3w n=10	All Subjects N=50
Discontinued from study, n (%)	4 (40%)	3 (30%)	1 (10%)	1 (10%)	2 (20%)	11 (22%)
Death	3 (30%)	2 (20%)	0	1 (10%)	0	6 (12%)
Withdrawal of consent	1 (10%)	0	1 (10%)	0	1 (10%)	3 (6%)
Continuing on study at time of data extract, n (%)	6 (60%)	7 (70%)	9 (90%)	9 (90%)	8 (80%)	39 (78%)
Follow-up time (days)						
Median	314.5	257.5	245.5	178.5	118.5	191.0
Min, max	49, 464	48, 368	45, 312	57, 200	50, 157	45, 464

Table 3: Summary of the TEAE Profile for AGEN2034

Subjects, n (%)	1 mg/kg q2w n=10	3 mg/kg q2w n=10	10 mg/kg q2w n=10	6 mg/kg q3w n=10	10 mg/kg q3w n=10	All Subjects N=50
TEAEs	10 (100%)	10 (100%)	10 (100%)	10 (100%)	9 (90%)	49 (98%)
Grade ≥3	7 (70%)	5 (50%)	6 (60%)	5 (50%)	3 (30%)	26 (52%)
Serious	5 (50%)	4 (40%)	2 (20%)	5 (50%)	1 (10%)	17 (34%)
TRAEs	8 (80%)	8 (80%)	10 (100%)	6 (60%)	4 (40%)	36 (72%)
Grade ≥3	1 (10%)	2 (20%)	2 (20%)	1 (10%)	1 (10%)	7 (14%)
Serious	2 (20%)	4 (40%)	0	2 (20%)	0	8 (16%)
TEAE leading to discontinuation	2 (20%)	2 (20%)	0	1 (10%)	0	5 (10%)
TEAE leading to death	1 (10%)	2 (20%)	0	0	0	3 (6%)
TRAE leading to death	0	1 (10%)	0	0	0	1 (2%)

TEAE: treatment-emergent adverse events; TRAE: treatment-related adverse events

A total of 49 of the 50 subjects treated to date have reported TEAEs (Table 3). The most common TEAEs (>20%) were fatigue (n=21 subjects), nausea (n=17), vomiting (n=13), decreased appetite (n=13), and diarrhea (n=11). Thirty-six subjects experienced a TEAE that was considered related to treatment (TRAE), with only 2 subjects experiencing a TRAE that resulted in treatment discontinuation. Both subjects were treated with 3 mg/kg q2w; 1 experienced hepatitis and the other experienced pneumonitis. Seven subjects reported a TEAE of grade ≥3 deemed related to treatment: pneumonitis: n=1 (3 mg/kg q2w); dyspnea: n=1 (3 mg/kg q2w); hepatitis, blood alkaline phosphatase increased, blood bilirubin increased, aspartate aminotransferase increased: n=1 (3 mg/kg q2w); skin rash: n=1 (10 mg/kg q2w); hyperglycemia: n=1 (6 mg/kg q3w).

A total of 17 subjects have reported serious TEAEs, while 8 subjects reported serious TRAEs: pneumonitis: n=2 (1 with 1 mg/kg q2w, 1 with 3 mg/kg q2w); diarrhea: n=1 (1 mg/kg q2w); hepatitis: n=1 (3 mg/kg q2w); nausea and vomiting n=1 (6 mg/kg q3w); adrenal insufficiency n=1 (3mg/kg q2w); confusion n=1 (3 mg/kg q2w), and uncoded n=1 (6 mg/kg q3w).

The efficacy data for the C-700-01 study is as follows: of the 38 evaluable subjects, 3 partial responses (PRs) (n=2 confirmed) were noted in subjects with cervical, ovarian, and breast cancers

in the 1-mg/kg and 3-mg/kg cohorts; DOR was 9, 7, and 2 months respectively and the first 2 responses are ongoing. At time of data cutoff, 23 subjects had SD, 13 of those for more than 12 weeks and 4 for more than 18 weeks, these were seen in 2 ovarian cancer subjects, 1 cervical cancer, and 1 endometrial cancer subject (Table 4).

Table 4: Phase 1 Summary of Best Overall Response by Treatment

Subjects, n	1 mg/kg q2w n=7	3 mg/kg q2w n=8	10 mg/kg q2w n=10	6 mg/kg q3w n=7	10 mg/kg q3w n=6	All Subjects N=38
Complete response	-	-	-	-	-	0
Partial response	1	2	-	-	-	3
Stable disease	3	4	6	6	4	23
Progressive disease	3	2	4	1	2	12

Overall response determined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Numbers in parentheses represent the duration of BOR for each subject.

2.1.2.2 Phase 2 Preliminary Results for AGEN2034

The RP2D for AGEN2034 established in Phase 1 was 3 mg/kg q2w. As of July 26, 2018, a total of 6 females with cervical cancer had been recruited, enrolled, and treated in the Phase 2 portion of the study (Table 5).

Table 5: Phase 2 Demographics and Baseline Characteristics

		3 mg/kg q2w n=6
Age (years)	Median	60.5
	Min, max	36, 67
Childbearing potential, n (%)	Yes	1 (16.7%)
	No	5 (83.3%)
Race, n (%)	White	6 (100%)
Ethnicity, n (%)	Hispanic/ Latino	1 (16.7%)
	Not Hispanic/ Latino	5 (83.3%)
ECOG performance status, n (%)	0	1 (16.7%)
	1	5 (83.3%)
Time since progression (months)	Median	1.69
	Min, max	0.8, 8.1
Current cancer status, n (%)	Localized	1 (16.7%)
	Metastatic	5 (83.3%)

The safety and tolerability summary are as follows: at time of data cutoff, no DLTs were reported for any of the subjects, and 5 of the 6 subjects reported a TEAE (Table 6).

Table 6: Phase 2 Summary of Treatment-Emergent Adverse Events for AGEN2034

Subjects, n (%)	3 mg/kg q2w n=6
TEAEs	5 (83.3%)
Grade ≥3	3 (50.0%)
Serious	3 (50.0%)
TRAEs	3 (50.0%)
Grade ≥3	1 (16.7%)
Serious	1 (16.7%)
TEAE leading to discontinuation	-
TEAE leading to death	-
TRAE leading to death	-

TEAE, treatment-emergent adverse event; TRAE: treatment-related adverse event.

TEAEs occurring in >1 subject included pyrexia (n=2) and abdominal pain (n=2), with 4 subjects having uncoded TEAEs. Three subjects experienced a TEAE of grade ≥3, including anemia, international normalized ratio (INR) increased, back pain, diarrhea, and abdominal pain. Serious TEAEs occurred in 3 subjects, including colitis, diarrhea, abdominal pain, back pain, diarrhea, and pyrexia (n=1 each). The events of diarrhea and colitis were considered related to treatment. One subject had a TRAE of grade ≥3, which was serious (diarrhea). No TEAEs led to treatment discontinuation or study withdrawal.

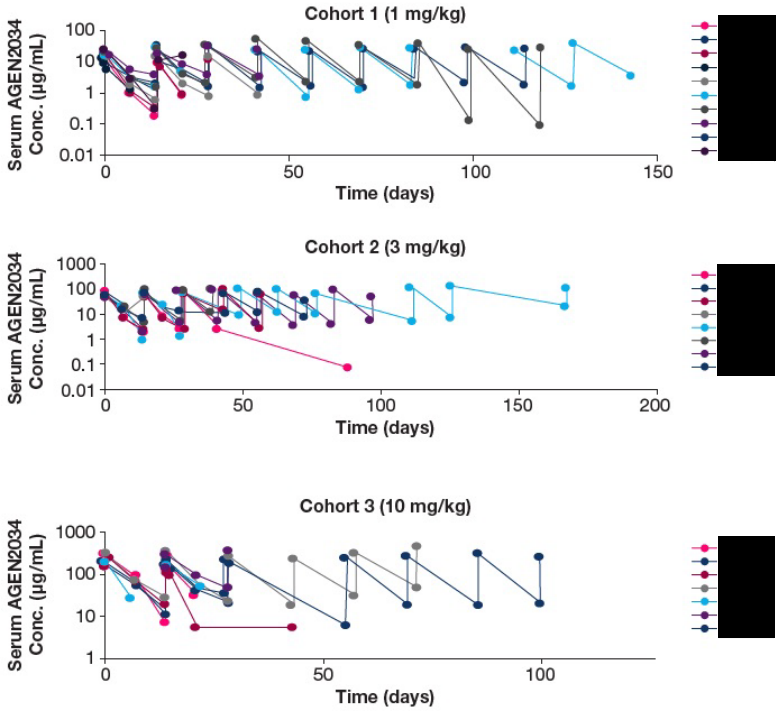
The clinical response is as follows: at time of data cutoff, a total of 9 subjects with cervical cancer had been treated with AGEN2034. The summary of best overall response (BOR) is listed in Table 7.

Table 7: Summary of Best Overall Response in Cervical Cancer Patients for AGEN2034

Subjects, n	PHASE 1 3 mg/kg q2w n=1	PHASE 1 10 mg/kg q2w n=2	PHASE 2 3 mg/kg q2w n=6	Total Cervical Cancer Population n=9
Complete response	-	-	-	-
Partial response	1	-	-	1
Stable disease	-	1	1	2
Progressive disease	-	1	3	4
Not evaluable			2	2

The PK profile of AGEN 2034 is depicted in Figure 3.

Figure 3: Phase 1 Pharmacokinetic Profile of AGEN2034



Anti-drug antibody (ADA) is negative in all subject samples tested to date. AGEN2034 was found to bind to target cell populations (CD4+ and CD8+ effector memory cells) hours after subjects were dosed, and 2 weeks following dosing, at all doses tested (Figure 4). AGEN2034 [redacted]) is functionally complete at all doses tested. Values of approximately 65% reflect loss of bound AGEN2034 during the freeze-thaw cycle to which the clinical samples were subjected.

Figure 4: [redacted]

AGEN2034 is a pharmacologically active, well-tolerated PD-1 antagonist antibody, demonstrating early signals of clinical activity in cervical and ovarian cancers, with no current DLTs. [redacted]. The Phase 2 expansion in subjects with relapsed/refractory cervical cancer is continuing to recruit (NCT03104699) Results for the expansion cohort and updated efficacy and safety data were presented at the European Society for Medical Oncology (ESMO) in 2018 (Drescher et al., 2018).

Additional supportive evaluation of doses on [redacted] are found in below.

2.1.3 [redacted]

Figure 5: Binding of AGEN2034 at Various Dose Levels and Serum AGEN2034 Concentrations

Overall, AGEN2034 has been well tolerated. The majority of the observed AEs were consistent with the subjects' underlying cancer. No infusion-related reactions/hypersensitivity considered possibly related to study treatment have been reported.

Note: in an additional cut off in December 2018 there were 2 infusion-related reactions, mild and moderate and they did not require drug discontinuation.

For detailed information on preclinical, manufacturing, administration, pharmacology, safety, and preliminary efficacy of AGEN2034, please refer to the AGEN2034 Investigator's Brochure and to the AGEN1884/AGEN2034 Bridging Investigator's Brochure.

2.1.4 Dual Blockade of the PD-1 and CTLA-4 Pathways

Antibody-mediated CTLA-4 blockade promotes the activation antigen-specific effector T cells and reduces the suppressive activity of Tregs, leading to enhanced anti-tumor immunity (Buchbinder & Desai 2016). By contrast, blockade of the PD-1 pathway can restore the responsiveness of tumor reactive T cells that have been inactivated following prolonged exposure to chronic stimulation, particularly within the tumor microenvironment (Wei et al. 2017). As such, there is a strong mechanistic rationale for the combination of PD-1 pathway and CTLA-4 pathway blockade. This is supported by the observation of distinct changes in the activation pattern of immune cell populations at the transcript and protein level in subjects receiving antibodies that inhibit the 2 pathways, particularly when administered concomitantly (Das et al. 2015).

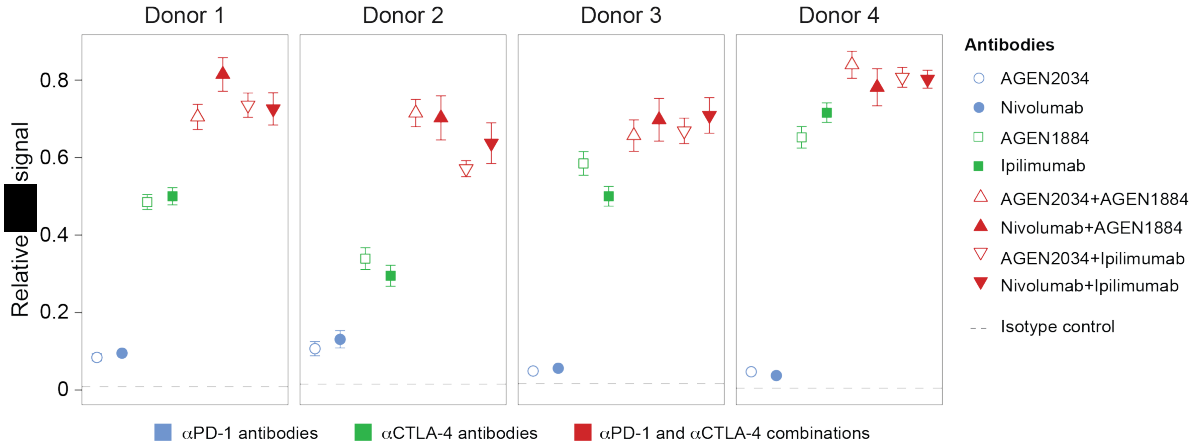
Antibodies blocking PD-1 and CTLA-4 have been combined in clinical studies covering a range of cancer indications. Although greater clinical efficacy has been observed compared to either agent alone, the initial combination studies also gave rise to increased irAEs. However, more

recently it has become apparent that the safety profile of combination regimens of PD-1 and CTLA-4 pathway blockade can be improved by modifying the dose and schedule of the respective antibodies, in particular the use of a lower and less frequent dose of the CTLA-4 antibody (Hellmann et al. 2017). The following sections summarize preclinical data and clinical experience with dual PD-1 and CTLA-4 pathway blockade and efforts to refine and optimize the combined therapy.

2.1.4.1 Summary of Preclinical Data for the Combination of AGEN1884 and AGEN2034

The enhanced combinatorial effect of AGEN1884 and AGEN2034 to activate human T cells was tested *in vitro* in multiple human donor peripheral blood mononuclear cell (PBMC) cultures. Furthermore, side-by-side comparisons with a combination of ipilimumab and nivolumab showed comparability to AGEN1884/AGEN2034 treatment in the various donors tested (Figure 6). The combinations of anti-PD-1 with anti-CTLA-4 antibodies further enhanced [redacted] secretion, as compared to single antibody incubation conditions. There were no significant differences in [redacted] secretion when comparing the 2 anti-PD1 antibodies (nivolumab and AGEN2034), the 2 anti-CTLA-4 antibodies (ipilimumab and AGEN1884), or the various combinations tested. These results support that an anti-CTLA-4 antagonist in combination with an anti-PD-1 antagonist may cooperate to enhance T cell responsiveness to weakly immunogenic antigens, such as tumor-associated antigens, and that AGEN1884 and AGEN2034 are comparable to the commercially available ipilimumab and nivolumab, respectively, alone and in combination.

Figure 6: Supernatant [redacted] Levels from Stimulated PBMCs Treated with Anti-CTLA-4 Antibodies (AGEN1884, Ipilimumab) or Anti-PD-1 Antibodies (AGEN2034, Nivolumab) Alone or in Combination



Cell supernatant [redacted] responses in PBMC cultures treated with SEA peptide and AGEN1884, ipilimumab, or isotype antibody (IgG1) plus AGEN2034, nivolumab or isotype antibody (IgG4). Donor 1 (KP49391), donor 2 (KP46842), donor 3 (KP49396), and donor 4 (KP48371). Antibodies were tested at a concentration of 10 µg/mL. On the y-axis, relative signals of [redacted] levels in the culture supernatant (pg/mL) are represented. Error bars indicate standard error of the mean (SEM) of 8 replicates.

A pilot trial in cynomolgus monkeys was performed in which AGEN1884 and AGEN2034 were dosed in combination at 10 mg/kg and 3 mg/kg respectively for a single intravenous bolus injection. The combination of AGEN1884/AGEN2034 was well tolerated at a single dose and

there were no related changes in clinical observations, food consumption, body weights, clinical chemistry or cytokines in plasma. Combination pharmacokinetics were not evaluated in the trial.

Refer to the AGEN1884/AGEN2034 Bridging Investigator's Brochure for detailed information on the combination.

The best indication of the safety profile of AGEN1884 in combination with AGEN2034 is expected to be the safety profile of the combination of ipilimumab and nivolumab, as specified in the nivolumab label (Bristol-Myers Squibb USA 2017b) and reviewed in the literature (Weber et al., 2017).

2.1.4.2 Clinical Experience with Dual PD-1 and CTLA-4 Blockade

2.1.4.2.1 Experience in Melanoma

Dual PD-1 and CTLA-4 blockade in the form of nivolumab and ipilimumab has been approved by the United States Food and Drug Administration (FDA) for the treatment of patients with metastatic melanoma on the basis of a 945 subject trial (Larkin et al. 2015). For the combination, nivolumab was given at a reduced dose (relative to the monotherapy dose) of 1 mg/kg every 3 weeks and ipilimumab was given at its full monotherapy dose of 3 mg/kg every 3 weeks for a total of 4 doses. After these 4 doses subjects received nivolumab alone at the standard monotherapy dose of 3 mg/kg every 2 weeks. The combination was more effective than either agent alone with improved overall response rate; 50% for the combination vs 40% for nivolumab alone), and improved progression-free survival (PFS) (median 11.5 months for the combination vs 6.9 months for nivolumab alone, hazard ratio 0.76). The benefits of the combination were most evident in the subset of subjects with lower PD-L1 expression measured by a tumor proportion score (TPS; percentage of viable tumor cells showing partial or complete membrane PD-L1 staining) of <5% (Wolchok et al. 2016).

This improved activity, however, was obtained at the cost of a substantial increase in toxicity. Treatment-related Grade 3 and 4 AEs were reported for 55% of subjects treated with the combination compared with 16% of subjects treated with nivolumab alone. Treatment-related AEs led to the discontinuation of 36% of combination subjects and 8% of nivolumab subjects (Larkin et al. 2015). These rates were also higher than those in subjects treated with ipilimumab alone.

More recently, pembrolizumab at the full monotherapy dose of 2 mg/kg every 3 weeks has been studied in combination with ipilimumab at a reduced dose of 1 mg/kg every 3 weeks for a total of 4 doses (one third of the dose used in the nivolumab trial given at the same schedule). After these 4 doses, subjects continued with pembrolizumab alone. Results from the melanoma expansion cohort of this trial with 107 evaluable subjects showed an independently reviewed objective response rate (ORR) of 51% (Long et al. 2016), which can be compared with the pembrolizumab monotherapy ORR of 33% obtained in an earlier trial (Robert et al. 2015). All but 2 of the 87 responding subjects maintained their responses at the time of data cutoff, with response duration ranging from greater than 6 weeks to greater than 43 weeks. Median PFS and overall survival (OS) have not been reached. Seventy percent of subjects were progression-free at 6 months. In a more recent summary of the trial the ORR has been reported to be 61% (Carlino et al. 2017). Treatment-related Grade 3 and 4 AEs were reported for 38% of subjects treated with the combination, and overall treatment-related AEs led to the discontinuation of one or both drugs in 22% of subjects. The most common treatment-related AEs included fatigue (any Grade, 46%), pruritus (any Grade,

39%), rash (any Grade, 39%; Grade 3-4, 3%) diarrhea (any Grade, 24%; Grade 3-4, < 1%), lipase increase (any Grade, 18%; Grade 3-4, 14%) and vitiligo (any Grade, 18%). Common immune-mediated AEs included hypothyroidism, hyperthyroidism, hypophysitis, pneumonitis, hepatitis, and colitis. These results indicate that the greater efficacy observed with the combination may be attainable with a reduced incidence of severe toxicity by the use of a lower dose of ipilimumab.

2.1.4.2.2 Experience in NSCLC

The most compelling data in support of a dual blockade of the PD-1 and CTLA-4 pathways has come from a cohort of treatment-naïve NSCLC subjects treated in the first-line setting with nivolumab at the full monotherapy dose of 3 mg/kg every 2 weeks combined with ipilimumab at a reduced dose of 1 mg/kg given either every 6 weeks (n=39) or every 12 weeks (n=38) (a reduction in dose and a less intense schedule). The confirmed ORR was 47% in subjects treated in the every-12-weeks cohort and 38% in subjects treated in the every-6-weeks cohort. With a median follow-up time of 12.8 and 11.8 months the median duration of response (DOR) was not reached in either cohort, with median follow-up times of 12.8 months (interquartile range [IQR] 9.3-15.5) in the ipilimumab every-12-weeks cohort and 11.8 months (6.7-15.9) in the ipilimumab every-6-weeks cohort. In subjects with PD-L1 of 1% or greater, confirmed objective responses were achieved in 12 (57%) of 21 subjects in the ipilimumab every-12-weeks cohort and 13 (57%) of 23 subjects in the ipilimumab every-6-weeks cohort. The ORR increased with increasing PD-L1 expression reaching 92% (12/13) in subjects with a TPS ≥50% (Goldman et al. 2017).

Grade 3-4 treatment-related AEs occurred in 37% of subjects in the ipilimumab every-12-weeks cohort and 33% of subjects in the every-6-weeks cohort; the most commonly reported Grade 3 or 4 treatment-related AEs were increased lipase (8% vs 0%), pneumonitis (5% vs 3%), adrenal insufficiency (3% vs 5%), and colitis (3% vs 5%) for every 12 weeks and every 6 weeks cohorts respectively. Even more importantly, treatment-related AEs (any Grade) led to treatment discontinuation in 11% of subjects in the every-12-weeks cohort and 13% subjects in the every 6 weeks cohort with no treatment-related deaths recorded (Hellmann et al. 2016; Hellmann et al. 2017). As in melanoma, these results indicate that a combination of PD-1 blockade and reduced intensity CTLA-4 blockade can be tolerable and result in substantially greater efficacy than either agent alone. In the same trial, a similar dose regimen as that proposed as the starting dose for this trial was evaluated in a previous cohort of 40 subjects with ipilimumab at the reduced dose of 1 mg/kg every 6 weeks in combination with nivolumab at the reduced dose of 1 mg/kg every 2 weeks. With this combination regimen, the ORR was 33%, Grade 3-4 treatment-related AEs occurred in 40% of subjects and only 8% discontinued treatment due to a treatment-related toxicity. This further reinforces that, the reduced intensity of CTLA-4 blockade in combination with PD-1 blockade is reasonable and tolerable.

2.1.4.2.3 Experience in Other Tumor Types

The combination of nivolumab and ipilimumab has also been studied in subjects with locally advanced or metastatic urothelial carcinoma who had progressed on ≥1 prior lines of chemotherapy. A comparison was made between a reduced dose of nivolumab (1 mg/kg) combined with the full monotherapy dose of ipilimumab (3 mg/kg) (n=26) and the full dose of nivolumab (3 mg/kg) combined with a reduced dose of ipilimumab (1 mg/kg) (n=104). The ORR was 38.5% and 26% for the 2 combinations respectively. The ORR to a monotherapy arm of nivolumab alone at 3 mg/kg was 24.4%. There was no indication in this tumor type of an increase in PFS or OS

with the combination therapy relative to monotherapy with nivolumab. The rates of Grade 3 or 4 AEs 30.8% and 31.7% respectively (Sharma et al. 2016).

Similar comparisons were made for nivolumab monotherapy at the full dose of 3 mg/kg every 2 weeks and combinations of nivolumab and ipilimumab (1 mg/kg and 3 mg/kg, and 3 mg/kg and 1 mg/kg) in subjects with small cell lung cancer (SCLC) who had disease progression after at least one previous platinum-containing regimen. Objective response was achieved in 10% (10/98) of subjects treated with nivolumab monotherapy, compared with 23% (14/61) of subjects receiving the 1 mg/kg and 3 mg/kg combination, and 19% (10/54) of subjects receiving the 3 mg/kg and 1 mg/kg combination. Grade 3-4 treatment-related AEs occurred in 13%, 30% and 19% of subjects respectively. Treatment-related AEs led to the discontinuation of 6%, 11% and 7% of subjects respectively (Antonia, López-Martin, et al. 2016).

Promising activity for the nivolumab/ipilimumab combination has also been demonstrated in subjects with metastatic renal cell carcinoma. The confirmed ORR for regimens of nivolumab 1 mg/kg and ipilimumab 3 mg/kg, and nivolumab 3 mg/kg and ipilimumab 1 mg/kg were the same at 40.4%. Despite the same degree of clinical efficacy, the nivolumab 3 mg/kg and ipilimumab 1 mg/kg regimen appeared to be better tolerated with 38% of subjects having Grades 3 or 4 treatment-related AEs compared to 62% of subjects treated with the nivolumab 1 mg/kg and ipilimumab 3 mg/kg combination (Hammers et al. 2017). As a result, the combination with the full dose of nivolumab and the reduced dose of ipilimumab was selected for further development.

Collectively, these clinical results highlight the potential for dual PD-1 and CTLA-4 pathway blockade to improve the proportion of subjects who might benefit from checkpoint immunotherapy. They also illustrate the importance of managing the severe toxicities that such therapies can induce and show an improved benefit / risk ratio for regimens in which the CTLA-4 antibody is given at a reduced dose and less intense schedule.

2.2 Rationale for Starting Dose Regimen

The first phase of this trial (Phase 1) will consist of a dose escalation in subjects with locally advanced, recurrent, and/or metastatic solid tumor for which no standard therapy exists or standard therapy has failed. The following combination dose levels (CDL) will be studied sequentially following a 3+3 design beginning with CDL1:

- **CDL1** (starting CDL):
  AGEN1884 1 mg/kg every 6 weeks + AGEN2034 1 mg/kg every 2 weeks
- **CDL2** (maximum planned CDL):
  AGEN1884 1 mg/kg every 6 weeks + AGEN2034 3 mg/kg every 2 weeks
- **CDL-1** (potential de-escalation CDL):
  AGEN1884 0.3 mg/kg every 6 weeks + AGEN2034 1 mg/kg every 2 weeks

The AGEN1884 dose corresponds to the reduced dose and reduced dose intensity regimen of ipilimumab that has been used successfully in multiple clinical studies (the standard ipilimumab regimen is 3 mg/kg every 3 weeks). The AGEN2034 starting dose is 1/3rd of the dose of nivolumab as originally approved (since adjusted to a flat dose of 240 mg every 2 weeks).

The starting CDL for the dose escalation portion of the trial is considered likely to be adequately tolerated for the following reasons:

- AGEN1884 has been shown to be functionally comparable to ipilimumab. Both are human IgG1 anti-CTLA-4 antibodies. Preclinical studies have shown that its binding affinity to CTLA-4, ability to block binding of CD80 and CD86 to CTLA-4, potential to activate human T cells *in vitro*, and NHP T cells *in vivo* are comparable to ipilimumab.
- AGEN2034 has been shown to be functionally comparable to nivolumab. Both are human IgG4 antibodies to PD-1. Preclinical studies have shown that its binding affinity to PD-1, binding to activated T cells, inhibition of PD-1:PD-L1 interactions, and potential to activate human T cells *in vitro* are comparable to nivolumab.
- The no observed adverse effect levels (NOAELs) for AGEN2034 and AGEN1884 in 4-week toxicology studies in cynomolgus monkey were 40 and 100 mg/kg respectively. Both antibodies were evaluated in an in vitro cytokine release assay in human whole blood with no significant findings. A single combined dose of AGEN2034 (3 mg/kg) and AGEN1884 (10 mg/kg) in cynomolgus monkey resulted in no clinical findings, blood chemistry or hematology findings, and no indication of cytokine release.
- AGEN2034 has been shown to be tolerated in cancer subjects, and below the MTD, at a dose of 3 mg/kg administered every 2 weeks. The proposed starting dose for combination is 1 mg/kg every 2 weeks.
- AGEN1884 has been shown to be tolerated in cancer subjects, and below the MTD, at a dose of 3 mg/kg administered every 3 weeks. A dose of 6 mg/kg every 3 weeks is currently being studied. AGEN1884 is also being studied in combination with pembrolizumab (200 mg every 3 weeks) at a 1 mg/kg dose given every 6 weeks.

A SMC will assess all safety data, including any DLTs, after all subjects of a dose level have reached the end of the DLT evaluation period.

Assessment of safety parameters will focus on potential acute side effects such as cytokine release syndrome caused by potential exaggerated pharmacological activity of AGEN2034 and AGEN1884 (i.e., overstimulation of cytokine-releasing hematological cells or damage of cytokine-containing cells by antibody-dependent cell-mediated cytotoxicity). Potential acute side effects include allergic reactions/hypersensitivities, including anaphylaxis (Chung 2008), which could develop as a consequence of an immunogenicity response and might be pronounced due to the immuno-stimulatory properties of either antibody, promoting an immune response against itself.

Evaluation of middle-term safety will cover incidence and severity of potential irAEs, which may not manifest until after several weeks of treatment (Boutros et al. 2016; Ott et al. 2017; Kumar et al. 2017; Weber et al. 2012). Such events may consist of persistent rash, diarrhea, colitis, autoimmune hepatitis, and conditions such as lupus, which may be detected by anti-nuclear antibodies (ANAs).

The Phase 1 portion of the study has completed enrollment with a recommended Phase 2 dose (RP2D) of AGEN1884 1 mg/kg q6w + AGEN2034 3 mg/kg q2w.

2.3 Rationale for Expansion Cohort

The following subject population will be enrolled in a separate expansion cohort:

- Subjects with locally advanced, recurrent, and/or metastatic cervical cancer.

In view of the potentiation of the anticancer activity of PD-1 blockade with the addition of CTLA-4 blockade, as demonstrated in a range of malignancies, there is a strong rationale for the combination of AGEN2034 and AGEN1884 in the treatment of subjects with cervical cancer. The greater activity of the AGEN2034 and AGEN1884 combination versus either antibody alone has been confirmed in T cell activation assays with human donor lymphocytes. The activity was shown to be comparable to that observed with nivolumab combined with ipilimumab in the same assay.

Preliminary clinical safety and response data are available from investigations of AGEN1884 (anti CTLA-4) as monotherapy [Study C-500-01], AGEN2034 (anti–PD 1) as monotherapy [Study C-700-01], and AGEN1884+AGEN2034 as combination therapy [Study C 550-01].

Study C-550-01 supports the use of AGEN1884 and AGEN2034 as combination therapy. Study C-550-01 Phase 1 (dose escalation, up to AGEN1884 1 mg/kg q6w + AGEN2034 3 mg/kg q2w) has been completed. Preliminary results show no discernable differences in observed safety and tolerability. An apparent pharmacodynamic dose response was seen, with the AGEN1884 + AGEN2034 combination therapy over individual monotherapy in other pharmacodynamic study. Since limited clinical efficacy information is available from the ongoing evaluations, the primary decisions for the RP2D were based on (1) the similar safety profiles between the 2 different dose regimens from Phase 1 and (2) the therapeutic goal to maximize clinical benefit for subjects.

2.3.1 Rationale for Treatment of Cervical Cancer

It is estimated that 12,800 new cases of cervical cancer will be diagnosed in the US in 2017, with 4,200 deaths attributable to this malignancy (Siegel et al. 2017). More widely, cervical cancer is the 4th most common cause of cancer death for women worldwide (Torre et al. 2015). Human papilloma virus (HPV) vaccination is expected to reduce the incidence of cervical cancer over time, however vaccination rates in female adolescents remain below 50% in many parts of the US (Reagan-Steiner et al. 2016) and unresectable or metastatic disease is likely to remain an important health concern as early detection programs do not have the adequate coverage in many geographies yet. The current standard of care for the first-line treatment of recurrent or metastatic cervical cancer is platinum-based chemotherapy with or without bevacizumab (National Comprehensive Cancer Network 2016; Tewari et al. 2014). Currently there are no regimens for the second line treatment of cervical cancer with proven benefit and clinical trials are often recommended for such subjects (Borcoman & Le Tourneau 2017).

The use of checkpoint protein blockade in the treatment of cervical cancer is supported by observations of high PD-L1 expression in cancers with viral etiology, including cervical cancer (Schumacher & Schreiber 2015; Mezache et al. 2015). The upregulation of PD-1 and PD-L1 was also shown to correlate with impaired immunity in high-risk HPV-related cervical cancer (Yang et al. 2013). Furthermore, initial trials of PD-1 therapeutic antibodies have demonstrated activity in this disease. In the KEYNOTE-028 trial 24 subjects with unresectable or metastatic PD-L1 positive cervical cancer, who had failed first-line therapy, received pembrolizumab at a dose of 10 mg/kg IV. every 2 weeks. Four subjects (17%) had a Response Evaluation Criteria in Solid Tumors (RECIST 1.1) PR with a median DOR of 26 weeks (Frenel et al. 2017). The safety profile

of pembrolizumab was consistent with that observed in trials in other tumor types. In the KEYNOTE-158 trial a similar group of cervical cancer subjects received pembrolizumab at a dose of 200 mg once every 3 weeks until disease progression or 2 years. In this second trial, 82 subjects have been treated regardless of PD-L1 biomarker status. The response rate in the 71 PD-L1 positive cancers was 14% including 3 subjects with CR. None of the 9 subjects with PD-L1 negative cancers responded. Again many of the responses were shown to be durable (Schellens et al. 2017). Finally, nivolumab has been studied in a trial of subjects with virus-associated cancers including 19 subjects with cervical cancer. Nivolumab was given at a dose of 240 mg every 2 weeks. Subjects were required to have had 2 or fewer prior treatment regimens for advanced disease and were unselected for PD-L1 expression. One subject had a CR and 4 subjects had PR for an overall response rate of 26%. In the trial population as a whole the response rate was higher in HPV positive cancers (28.6%) than in cancers with unknown HPV status (10.0%) (Hollebecque et al. 2017).

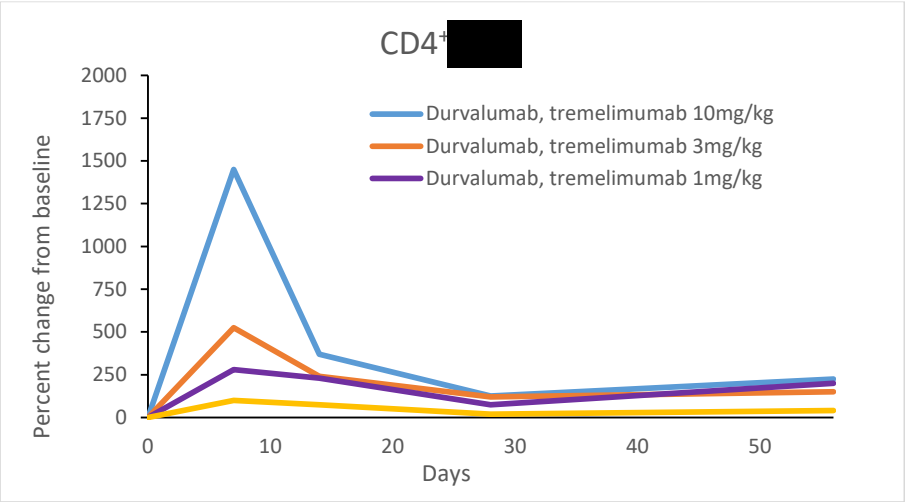
2.4 Rationale for Biomarker Assessment

Due to limited understanding of the biological activities induced by the combination of PD-1 and CTLA-4 blockade in cancer subjects, there can be no certainty that the doses examined will be associated with relevant anti-tumor immune activities. As a consequence, the trial will serve to: investigate biomarkers for the combination by monitoring immune cell subset activation status; and evaluate potential predictive/prognostic biomarker candidates related to the drug and/or cancer (e.g., level of PD-L1 tumor expression).

2.4.1 Assessment of [redacted] Expression

One biomarker that has been previously assessed in subjects treated with anti-CTLA-4 and anti-PD-1 antibodies is [redacted], a nuclear protein associated with cellular proliferation. Expression of [redacted] is used as a measure of cellular proliferation. A clinical trial with tremelimumab an anti-CTLA-4 antibody in combination with durvalumab, an anti-PD-L1 antibody showed an antibody dose dependent increase in peripheral T-cell proliferation as measured by the expression of [redacted] (Figure 7), suggesting that [redacted] is a biomarker that correlates with the effect of the antibody combination on circulating T cells (Antonia, Goldberg, et al. 2016). Other reports have demonstrated T cell [redacted] upregulation after treatment with ipilimumab and nivolumab in combination (Das et al. 2015; Callahan et al. 2010). Measuring [redacted] expression on circulating T cells could aid in the selection of pharmacologically active doses to carry into early clinical studies of the combination of AGEN1884 and AGEN2034.

Figure 7: Effect of different regimens of the combination of different doses of tremelimumab (anti-CTLA-4 antibody) and durvalumab (anti-PD-L1 antibody) on CD4+ T-cell proliferation measured by [redacted]



(adapted from Antonia, López-Martin, et al. 2016)

2.4.2 Assessment of PD-L1 Expression in Tumors

PD-L1 expression has been associated with response to PD-1 blockade. In treatment of naive NSCLC, a PD-L1 expression level of ≥50% TPS was used as a companion diagnostic parameter for treatment with pembrolizumab.

There is limited data available on PD-L1 expression in cervical cancer, particularly in subjects with metastatic disease who have relapsed after initial therapy. In a recent publication by Reddy et al. (Reddy et al. 2017), 34% of subjects with cervical cancer were PD-L1 positive. On June 12, 2018, the US FDA approved pembrolizumab for patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test (Food and Drug Administration, 2018). In KEYNOTE-158, 98 subjects have been treated regardless of PD-L1 biomarker status. The response rate in the 81 PD-L1 positive cancers was 16% including 3 subjects with CR (Chung et al., 2018).

In this study, the hypothesis is that subjects with PD-L1 expression will have improved anti-tumor response, [redacted]

2.5 Trial Design

This Phase 1/2 trial will include approximately 170 subjects overall and will aim to provide preliminary data on the efficacy and safety of the combination of AGEN1884 and AGEN2034 in the treatment of subjects with locally advanced, recurrent, and/or metastatic cervical cancer who have relapsed after platinum-based chemotherapy.

The trial consists of 2 phases:

- Phase 1: Dose Escalation
- Phase 2: Expansion Cohort

  –advanced cervical cancer

The trial is designed with the safety of subjects in mind with an initial "3+3" dose escalation design in the Phase 1 portion of the trial. Based on the comparability of AGEN1884 and AGEN2034 to, respectively, nivolumab and ipilimumab in nonclinical pharmacology and toxicology studies, it is anticipated that one of the 2 planned Phase 1 doses will be selected for the Phase 2 portion of the trial.

The Phase 2 portion of the trial will enroll approximately 150 subjects with cervical cancer. This sample size of 150 subjects will provide at least 94% power to exclude an ORR of 10% by the lower limit of the 95% two-sided Wilson confidence interval (CI), assuming an ORR of 20% as the target treatment effect for the combination of AGEN1884 and AGEN2034. This design will provide a basis for a pivotal trial of the AGEN1884 and AGEN2034 combination in this subject population if the clinical efficacy and safety data indicate that this is merited.

Along with the trial design, a risk mitigation strategy will be implemented to proactively manage immune-related AEs as well as to monitor immunogenicity. The trial design and protocol builds on the aggregate knowledge of immunotherapy combinations to mitigate risk while at the same time attempt to maximize the potential benefit to subjects in a disease that even with the recent approvals, remains, for most subjects, a high unmet medical need.

2.6 Objectives

2.6.1 Primary Objective

Phase 1:

- To assess the safety and tolerability of AGEN1884 in combination with AGEN2034 in subjects with locally advanced, recurrent, and/or metastatic solid tumors.

Phase 2:

- To assess the ORR according to RECIST 1.1, as determined by the Independent Endpoint Review Committee (IERC).

2.6.2 Secondary Objectives

Phase 1:

- To characterize the pharmacokinetic (PK) profiles of AGEN1884 and AGEN2034
- To correlate AGEN1884 and AGEN2034 exposure with target occupancy
- To evaluate the immunogenicity of AGEN1884 in combination with AGEN2034 and assess potential impact on PK exposure and biological activity

Phase 2:

- To assess the safety and tolerability of AGEN1884 in combination with AGEN2034 in subjects with locally advanced, recurrent, and/or metastatic solid tumors

- To characterize the PK profile of AGEN1884 and AGEN2034
- To evaluate the immunogenicity of AGEN1884 in combination with AGEN2034 and assess potential impact on PK exposure and biological activity
- To assess ORR according to RECIST 1.1 as determined by investigator
- To assess DOR, disease control rate (DCR), duration of SD, time to response, and PFS time per RECIST 1.1
- To assess OS

2.6.3 Exploratory Objectives

[redacted]

- To explore the association of programmed cell death protein 1 ligand (PD-L1) expression with clinical responses.

[redacted]

- To explore the association of PD-L1 expression with clinical outcomes.

2.7 Overall Risk/Benefit Assessment

The risk-benefit relationship has been carefully considered in the planning of this trial.

The risks of exposure to the AGEN1884 and AGEN2034 combination:

- Infusion-related reactions.
- Increase in irAEs, which constitute a unique spectrum of AEs that occur via activation of the subject's immune system and that can sometimes lead to serious and even fatal events (Boutros et al. 2016; Kumar et al. 2017; Weber et al. 2012).
- Potential for increased treatment discontinuation
- Potential for increased immunogenicity

Infusion-related reactions are a risk inherent to administration of any recombinant protein to humans. The incidence of immunogenicity and the character or severity of immunogenicity-induced side effects cannot be predicted by animal models because humanized or fully human proteins usually provoke a much stronger immune response in rodents or non-human primates than in humans. However, for both AGEN1884 and AGEN2034, clinical signs of hypersensitivity were not observed in pilot 4-week IV repeat-dose toxicity studies conducted in cynomolgus monkeys and have not been observed in the subjects treated to date in the Phase 1 studies. Neither antibody showed findings in an in vitro cytokine release assay in human whole blood.

Immune-related AEs are events that are drug-related and can be explained by an immune phenomenon after other etiologies have been ruled out. Relevant clinical safety experience has been generated with several PD-1 pathway–blocking monoclonal antibodies and with the combination with CTLA-4 agents (Ott et al. 2017; Boutros et al. 2016; Kumar et al. 2017).

The safety data available for AGEN1884 is summarized in Section 2.1.1.1. Overall, AGEN1884 at doses up to 3 mg/kg administered every 3 weeks has been well tolerated, with no significant drug-related Grade 3 or higher events to report. A dose of 6 mg/kg every 3 weeks is under investigation. AGEN2034 has been shown to be tolerated at a dose of 3 mg/kg administered every 2 weeks, with no significant drug-related Grade 3 or higher events to report.

For the reasons noted previously, it is anticipated that the safety profile of ipilimumab in combination with nivolumab will provide a good estimate for the safety and tolerability of the AGEN1884 and AGEN2034 combination. Ipilimumab was initially combined with nivolumab at doses of 3 mg/kg and 1 mg/kg respectively with both antibodies being given every 3 weeks to subjects with previously untreated melanoma (Larkin et al. 2015). Treatment-related Grade 3 or 4 AEs were reported in 55% of subjects, most commonly diarrhea (9.3%), colitis (7.7%), rash (4.8%), and fatigue (4.2%). Grade 3 or 4 elevations in liver transaminases were also common. Thirty-six percent of subjects receiving the combination discontinued treatment due to a treatment-related adverse event. The combination appeared to be more effective than either agent alone, most notably in subjects with PD-1 negative tumors, however it was recognized that the toxicity was too high to make this treatment widely acceptable.

An improved safety profile was demonstrated in the KEYNOTE-029 trial of 153 subjects with advanced melanoma and no prior immune checkpoint inhibitor therapy (Carlino et al. 2017; Long et al. 2016). Subjects received the PD-1 antibody pembrolizumab at a dose of 2 mg/kg every 3 weeks and ipilimumab at a reduced dose of 1 mg/kg every 3 weeks. Grade 3 or 4 treatment-related AEs occurred in 45% of subjects. Treatment-related adverse events (AEs) led to discontinuation of pembrolizumab and ipilimumab in 14% of subjects. A high proportion of subjects (61%) achieved an objective response indicating that the benefit/risk relationship for this combination regimen was improved relative to the 3 mg/kg ipilimumab with 1 mg/kg nivolumab combination.

A further reduction in the dose and dose intensity of ipilimumab was tested in the CHECKMATE-012 trial. In this trial 78 subjects with chemotherapy-naïve advanced NSCLC were randomized to receive nivolumab at a dose of 3 mg/kg every 2 weeks in combination with ipilimumab at a dose of 1 mg/kg every 6 weeks or every 12 weeks. Grade 3 or 4 treatment-related AEs occurred in 37% of subjects in the ipilimumab every-12-weeks cohort and 33% of subjects in the every-6-weeks cohort. The most commonly reported Grade 3 or 4 treatment-related AEs were increased lipase (8% vs 0%), pneumonitis (5% vs 3%), adrenal insufficiency (3% vs 5%), and colitis (3% vs 5%). Treatment-related AEs (any Grade) prompted treatment discontinuation in 11% and 13% of subjects in the every-12-weeks and every-6-weeks cohorts respectively (Goldman et al. 2017). These results indicate a substantial improvement in safety and tolerability relative to the earlier nivolumab/ipilimumab combination regimens. Furthermore, this improvement in safety did not appear to be at the expense of efficacy. The overall response rate was 43% for the pooled population, higher than the response rate for nivolumab alone in this subject population (Carbone et al. 2017). More promising still, the response rates in subgroups of subjects with ≥1% and ≥50% PD-L1 expression were 57% and 92% respectively (Goldman et al. 2017). Although these findings

should be regarded as preliminary in view of the subgroup size, they illustrate the potential of combined PD-1 and CTLA-4 checkpoint blockade to effectively treat an aggressive cancer that until a few years ago was primarily treated with chemotherapy.

The combination of 2 immune checkpoint agents can lead to an increased immunogenicity as observed in the nivolumab/ipilimumab trials where ADA against nivolumab was reported in 37.8% of subjects compared to 12.3% with nivolumab monotherapy while ADAs against ipilimumab remained the same at 6-8%. To monitor this risk, immunogenicity for both AGEN1884 and AGEN2034 will be proactively monitored.

The current trial is designed to mitigate the risk of toxicity from the AGEN1884 and AGEN2034 combination. The Phase 1 portion of the trial follows a 3+3 dose escalation design, and the doses of both antibodies are lower than the standard doses of ipilimumab and nivolumab as currently approved. Importantly, a reduced-intensity regimen of doses every 6 weeks rather than every 3 weeks has been selected for AGEN1884 on the basis of the improved safety and tolerability profile reported for this schedule for ipilimumab. The Phase 2 portion of the trial will explore the activity of the selected combination regimen in the treatment of subjects with locally advanced, recurrent, and/or metastatic cervical cancer who have relapsed after platinum-containing doublet chemotherapy. There is no regimen with proven clinical benefit currently available to these subjects and the combination of PD-1 and CTLA-4 blockade offers an opportunity to improve on the 14-26% response rates observed with PD-1 blockade alone.

Based on the available data both from approval and literature with ipilimumab and nivolumab and from clinical data to date with AGEN1884 and AGEN2034, the risk-benefit ratio of the proposed treatment combination with AGEN1884 and AGEN2034 is considered favorable. To further manage the potential for added risk in this trial there will be pro-active monitoring for immunogenicity and pro-active management of immune-related AEs.

3 Investigational Plan

This is a Phase 1, open-label, dose-escalation trial in subjects with locally advanced, recurrent, and/or metastatic solid tumors, with a consecutive Phase 2 expansion to evaluate efficacy in subjects with locally advanced, recurrent, and/or metastatic cervical cancer that has progressed after a platinum-based therapy.

3.1 Phase 1: Dose Escalation

Phase 1 has completed enrollment.

The trial will consist of a 3+3 dose escalation that will evaluate different CDL of AGEN1884 and AGEN2034 in subjects with locally advanced, recurrent, and/or metastatic solid tumors.

Subjects may be enrolled to the following CDL:

Starting CDL

CDL1: AGEN1884 1 mg/kg every 6 weeks + AGEN2034 1 mg/kg every 2 weeks

Maximum planned CDL

CDL2: AGEN1884 1 mg/kg every 6 weeks + AGEN2034 3 mg/kg every 2 weeks

Potential de-escalation CDL

CDL−1: AGEN1884 0.3 mg/kg every 6 weeks + AGEN2034 1 mg/kg every 2 weeks

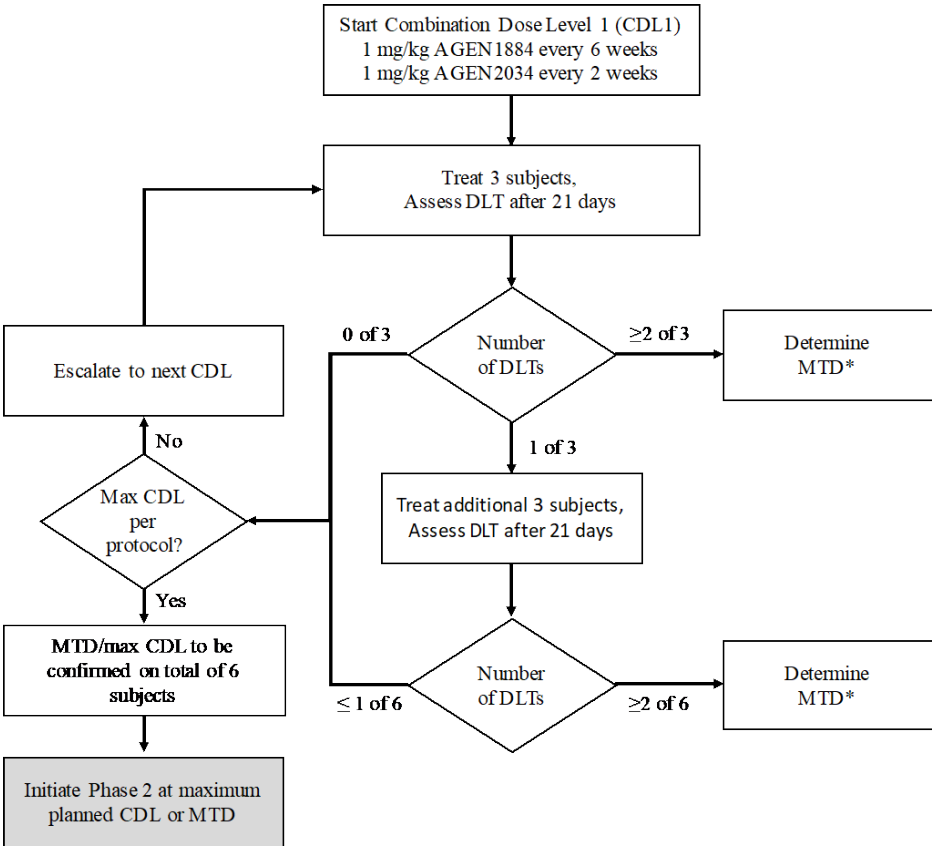
Subjects will receive AGEN2034 every 2 weeks and AGEN1884, every 6 weeks, on the same day as an AGEN2034 administration. Subjects will receive AGEN1884 in combination with AGEN2034 for a maximum of 24 months or until confirmed progression, unacceptable toxicity, or any criterion for stopping the study drug or withdrawal from the trial occurs. Each subject will remain on the CDL assigned at trial entry.

Combination Dose Level 1 (CDL1) will be the first to be tested. Dose escalation will continue until the maximum planned CDL is shown to be safe or the MTD is reached. The MTD is defined as the CDL below which ≥33% DLT are observed. The maximum planned CDL or the MTD defined in the Phase 1 will be used for Phase 2. A schematic of dose escalation is presented in Figure 8.

The DLT observation period for the dose escalation portion of Phase 1 is the first 21 days following administration of AGEN1884 and AGEN2034. Within each cohort in the dose escalation phase, consecutively enrolled subjects may initiate treatment ≥48 hours after the prior enrolled subject initiated treatment. Subjects who do not complete the DLT evaluation period for reasons other than a DLT will be replaced. The decision to escalate to the next cohort will be made by the SMC, based on safety assessments after all subjects of a cohort reached the end of the DLT evaluation period.

The Phase 1 portion of the study has completed enrollment. The RP2D is AGEN1884 1 mg/kg q6w + AGEN2034 3 mg/kg q2w.

Figure 8: Dose Escalation Schematic



CDL: combination dose level; DLT: dose-limiting toxicity; MTD: maximum tolerated dose;
* Should ≥2 subjects in CDL1 develop DLTs, the combination dose will be de-escalated to CDL-1 and 3 subjects will be enrolled.

3.1.1 Dose Escalation Criteria

For each dose level, DLTs are assessed during the first 21 days following administration of AGEN1884 and AGEN2034.

Dose escalation, de-escalation, and/or re-escalation from starting CDL1

- If 0 of 3 subjects at CDL1 experiences a DLT, escalation to CDL2 will occur.
- If 1 of 3 subjects at CDL1 experiences a DLT, this cohort will be expanded to 6 subjects.
  - If 1 of 6 subjects experiences a DLT, escalation to CDL2 will occur.
  - If ≥2 of 6 subjects experiences a DLT, the combination dose will be de-escalated to from CDL1 to CDL-1 and 3 subjects will be enrolled.
    - If no more than one DLT is observed in the first 3 subjects in CDL-1, 3 additional subjects will be enrolled at CDL-1.
    - Should ≤1 of 6 subjects in CDL-1 develop a DLT, the SMC may decide to re-escalate from CDL-1 to CDL1 and enroll 3 additional subjects in CDL1.

- If 0 of the 3 new subjects in CDL1 develop a DLT, an additional 3 subjects will be enrolled to CDL1.
- If > 1 of the 3 new subjects in CDL1 develop a DLT, enrollment to CDL1 will be closed and CDL-1 will be considered the MTD.
- If ≥ 4 of the 12 subjects enrolled in CDL1 develop a DLT, CDL-1 will be considered the MTD.
- If ≤ 3 of the 12 subjects enrolled in CDL1 develop a DLT, CDL1 will be considered the MTD.

- If ≥2 of 3 subjects develop a DLT in CDL1, the combination dose will be de-escalated to CDL-1 and 3 subjects will be enrolled.
  - If no more than one DLT is observed in the first 3 subjects in CDL-1, 3 additional subjects will be enrolled at CDL-1.
  - Should ≤1 of 6 subjects in CDL-1 develop a DLT, the SMC may decide to re-escalate from CDL-1 to CDL1 and enroll 3 additional subjects in CDL1.
    - If 0 of the 3 new subjects in CDL1 develop a DLT, an additional 3 subjects will be enrolled to CDL1.
    - If > 1 of the 3 new subjects in CDL1 develop a DLT, enrollment to CDL1 will be closed and CDL-1 will be considered the MDT
    - If ≥ 4 of the 12 subjects enrolled in CDL1 develop a DLT, CDL-1 will be considered the MDT.
    - If ≤ 3 of the 12 subjects enrolled in CDL1 develop a DLT, CDL1 will be considered the MDT.

Dose Escalation at CDL2 (maximum planned CDL)

CDL2 is the highest combination dose level planned to be tested. Enrollment in CDL2 will begin if 0 of 3 or ≤ 1 of 6 subjects in CDL1 experiences a DLT.

- If ≤1 of 3 subjects at CDL2 experiences a DLT, then an additional 3 subjects will be enrolled.
  - If ≤1 of 6 subjects experiences a DLT, CDL2 will be considered the RP2D.
  - If ≥2 of 6 subjects experiences a DLT, dose escalation will be paused and the SMC may define CDL1 as the MTD.
- If ≥2 of 3 subjects at CDL2 experiences a DLT, dose escalation will be paused and the SMC may define CDL1 as the MTD.

It is conceptually acceptable to de-escalate to an intermediate, not pre-defined and not previously-studied CDL, if evaluation of toxicity at such a dose is desired. If this approach is taken, 3 new subjects should be enrolled at the new intermediate dose, and the following rules should be used to determine further enrollment at this dose level:

- If ≤1 of 3 subjects at the intermediate CDL experiences a DLT, then an additional 3 subjects will be enrolled.
  - If ≤1 of 6 subjects experiences a DLT, the intermediate CDL will be considered the RP2D and an additional 4 subjects may be enrolled.

  - If ≥2 of 6 subjects experiences a DLT, dose escalation will be paused and the SMC may define CDL immediately below the intermediate in which ≤ 1 of 6 subjects experienced a DLT as the MTD.
- If ≥2 of 3 subjects at the intermediate CDL experiences a DLT, dose escalation will be paused and the SMC may define CDL immediately below the intermediate in which ≤ 1 of 6 subjects experienced a DLT as the MTD.

The decision to expand a cohort to 6 subjects, to de-escalate, re-escalate, and/or to open enrollment to the Efficacy Phase will be made by the SMC based on safety assessments after all subjects in dose escalation at a CDL have reached the end of the DLT evaluation period. See Section 9.1 for a description of the SMC.

3.1.2 Dose-Limiting Toxicity

For Phase 1, dose-escalation, drug-related AEs will be adjudicated as follows:

- All Grade 5 AEs will be considered DLTs
- Any Grade 4 hematologic AEs will be considered DLTs with the exception of:
  - Grade 4 lymphopenia
  - Grade 4 neutropenia lasting ≤ 48 hours that is not associated with fever or other clinically significant symptoms
  - Thrombocytopenia < 25,000/mm^3 that is not associated with bleeding.
  - Other Grade 4 hematologic AEs that last less than 7 days
- Any Grade 4 non-hematologic, non-laboratory AEs will be considered DLTs
- Grade 4 non-hematologic laboratory AEs with the exception of:
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- The following Grade 3 non-hematologic AEs will be considered as DLTs:
  - Any Grade 3 irAE that does not resolve to ≤ Grade 1 or to baseline with immunosuppressive therapy within 3 weeks of its onset
  - Any Grade 3 central nervous system (CNS)-related irAE regardless of duration, or reversibility
  - Any other non-immune-related Grade 3 AE with the exception of isolated Grade 3 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- The following Grade 3 non-hematologic AEs will not be considered as DLTs:
  - Any Grade 3 endocrinopathy that is adequately controlled by hormonal replacement
  - Grade 3 AE of tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor)
  - A Grade 3 infusion reaction which resolves within 6 hours to ≤ Grade 1

- Transient (≤24 hours) Grade 3 fatigue, local reactions, headache, nausea, or emesis that resolves to Grade ≤1
- Transient (≤6 hours) Grade 3 flu-like symptoms or fever, which are controlled with medical management.

- Any ≥ Grade 2 eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks of the initiation of topical therapy OR requires systemic treatment will be adjudicated as a DLT

Any DLT will immediately lead to permanent withdrawal of AGEN1884 and AGEN2034.

3.1.3 Stopping Rules for Toxicity

The SMC will meet to review any cohort under evaluation as well as the safety of all cohorts. Should >33% subjects on any dose level experience toxicities that meet DLT criteria but occur after the DLT observation period or in subjects not included in the DLT analysis set, enrollment will be held, and the occurrences will be thoroughly evaluated by the committee. The SMC will then make recommendations to re-open enrollment or to initiate other changes in trial conduct (such as protocol amendments).

If there is a subject death within 30 days of AGEN1884 and/or AGEN2034 administration for reasons not related to the subject's disease progression, the trial will be put on hold to accrual and treatment held for subjects on study. The SMC will evaluate the cause of the event and recommend the appropriate change in study conduct. If the event is determined to be related to AGEN1884 and/or AGEN2034, then a study amendment and/or other corrective action plan will be established. If the event is determined not to be related to the AGEN1884 and/or AGEN2034, then the study will re-open to accrual and subjects on study will resume treatment.

3.1.4 Backfill Expansion Enrollment for Each Dose Level Cohort in the Phase 1

Concurrent with the 3+3 dose escalation schema, additional subjects will be backfilled to ensure that each combined dose level cohort enrolls at least 10 subjects:

- Once the safety of the CDL1 cohort is established, enrollment for CDL2 will begin. When accrual of first 3 subjects in the CDL2 cohort is paused for the 21-day safety assessment and DLT observation, enrollment of ≤ 7 subjects to backfill the CDL1 cohort may begin.
- When the safety of CDL2 has been established in 3 subjects, an additional ≤ 7 subject will be enrolled to CDL2.

Backfill expansion enrollment of subjects for each cohort does not to have to be sequential (i.e., a wait of 48 hours between 2 subjects is not required). Subjects enrolled to backfill each dose level cohort will have the purpose of generating additional safety, PK, and [redacted] data, and will not undergo formal DLT observation.

3.2 Phase 2: Expansion in Select Solid Tumors

The SMC reconvened at the end of April 2018 to analyze Cohort Dose Level 2, and as no DLT were observed and having analyzed all AE data for the period, the SMC recommended that the Phase II dose (RP2D) would be the CDL**2** (maximum planned CDL): AGEN1884 1 mg/kg every 6 weeks + AGEN2034 3 mg/kg every 2 weeks.

Given that there is no standard of care established for second line treatment of locally advanced, recurrent, and/or metastatic cervical cancer, these subjects would be eligible for the Phase 2 portion of the trial, in the expansion cohort of the specified population as follows:

advanced cervical cancer.

In Phase 2, enrollment of subjects does not to have to be sequential (i.e., a wait of 48 hours between 2 subjects is not required). Subjects will receive AGEN1884 in combination with AGEN2034 for a maximum treatment duration of 24 months or until confirmed PD, unacceptable toxicity, or any criterion for stopping the study drug or withdrawal from the trial occurs.

For the Phase 2 portion of the trial, an Independent Data Monitoring Committee (IDMC) will be established to evaluate safety and efficacy and an IERC will be established to adjudicate tumor response.

3.3 Planned Number of Subjects

The planned number of subjects for this trial is:

Phase 1

Approximately 20 subjects.

The final sample size may vary depending on the total number of dose levels tested, and subject replacement for DLT evaluations.

Phase 2

Approximately 150 subjects with advanced cervical cancer.

3.3.1 Subject Replacement Strategy

In Phase 1, subjects who do not complete the DLT observation period defined in Section 3.1 for reasons other than a DLT may be replaced. A subject who discontinues in Phase 2 will not be replaced.

3.4 Planned Trial Duration

The maximum trial duration for a subject is estimated to be approximately 49 months. This includes a screening period, a planned treatment period of up to approximately 24 months, and a follow-up period of up to 12 months after the last treatment dose.

The overall trial duration is expected to be approximately 70 months.

First subject in: 12 Dec 2017

Last subject out (after follow-up): Q3 2023.

3.5 Definition of End of Trial

If the trial is not terminated for a reason provided in Section 4.4.3, the end of the trial is defined as 12 months after the last subject has received the last planned treatment dose.

3.6 Medical Care of Subjects After End of Trial

At the end of the protocol-specified periods of active study therapy, the Sponsor will not continue to supply study drug to subjects/investigators unless the Sponsor chooses to extend the trial. The

investigator should ensure that the subject receives appropriate standard of care to treat the condition after the trial.

Upon withdrawal from study treatment, subjects may receive the care upon which they and their physicians agree. Subjects will be followed for survival and AEs as specified in Section 7.

4 Selection of Trial Population

4.1 Target Population

Phase 1:

Male and female subjects over the age of 18 years with locally advanced, recurrent, and/or metastatic solid tumors for which no standard therapy is available or standard therapy has failed.

Phase 2:

Female subjects over the age of 18 years with locally advanced, recurrent, and/or metastatic cervical cancer who have relapsed after a platinum-based treatment regimen.

After the interim analyses, subsequent enrollment of subjects may be based on biomarker enrichment (including but not limited to PD-L1 expression). In such cases, tumor tissue must be positive for the selected entry biomarker prior to subject enrollment.

4.2 Inclusion Criteria

For inclusion in the trial, **all** the following inclusion criteria must be fulfilled as no waivers will be permitted:

1. Voluntarily agree to participate by giving written informed consent. (Participation in pharmacogenomics testing is optional.)
2. Be ≥18 years of age.
3. Diagnosis:
    a. **Phase 1:** Male or female having a histologically or cytologically confirmed diagnosis of a locally advanced, recurrent, and/or metastatic solid tumor for which no standard therapy is available or standard therapy has failed.
    b. **Phase 2:**
        I. Female having (1) a histologically or cytologically confirmed diagnosis of squamous-cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix, and (2) locally advanced, recurrent, and/or metastatic at the time of enrollment. Histologic confirmation of the original primary tumor is required via pathology report.

            Note: The following cervical tumors are not eligible: minimal deviation/adenoma malignum, gastric type adenocarcinoma, clear cell carcinoma, and mesonephric carcinoma.

        II. Has cervical cancer and has relapsed after a platinum-based treatment (first line) regimen for locally advanced, recurrent, and/or metastatic disease;

Note: Subjects who only received platinum-based chemotherapy concurrently with primary radiation (e.g., weekly cisplatin) or adjuvant chemotherapy following completion of radiation therapy (e.g., paclitaxel and carboplatin for ≤ 4 cycles) and progressed within 6 months after treatment completion will be eligible as this systemic therapy will be considered first line.

4. Measurable disease
    a. **Phase 1**: Have objective evidence of disease; the presence of measurable disease is not required.
    b. **Phase 2:** Have measurable disease on imaging based on RECIST version 1.1.

       Note: Subjects must have at least one "target lesion" to be used to assess response, as defined by RECIST version 1.1. Tumors within a previously irradiated field will be designated as "non-target" lesions unless progression is documented, or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

       Note: Measurable disease by RECIST 1.1 must be confirmed by independent central radiologic review prior to first dose. Subjects without centrally confirmed measurable disease at baseline will not be eligible for this trial.
5. Have a life expectancy of at least 3 months and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
6. Have adequate organ function as indicated by the following laboratory values:
    a. Adequate hematological function defined by absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L, platelet count ≥ 100 x 10^9/L, and hemoglobin ≥ 8 g/dL (without transfusions within 1 week of first dose).
    b. Adequate hepatic function based on a total bilirubin level ≤ 1.5 x the institutional upper limit of normal (IULN), aspartate aminotransferase (AST) level ≤ 2.5 x IULN, alanine aminotransferase (ALT) level ≤ 2.5 x IULN, and alkaline phosphatase ≤ 2.5 IULN.
    c. Adequate renal function defined as creatinine ≤ 1.5 x IULN **OR** calculated creatinine clearance ≥ 50 mL/min for subjects with creatinine levels > 1.5 x IULN (if no local guideline is available, creatinine clearance should be calculated using the Cockcroft-Gault Method).
    d. Adequate coagulation defined by international normalized ratio (INR) or prothrombin time ≤ 1.5 x IULN (unless the subject is receiving anticoagulant therapy); and activated partial thromboplastin time (aPTT) ≤ 1.5 x IULN (unless the subject is receiving anticoagulant therapy)
7. Other than the cancer for which the subject is enrolled, have no history of prior malignancy, with the exception of basal cell carcinoma of the skin, superficial bladder cancer, squamous-cell carcinoma of the skin, or has undergone potentially curative therapy with no evidence of that disease recurrence for 5 years since initiation of that therapy.

Note: In Phase 2, the history and time requirement for no evidence of disease for 5 years does not apply to the cancer for which the subject is enrolled in the trial.

8. In Phase 2, subjects must provide a sufficient and adequate formalin fixed paraffin embedded (FFPE) tumor tissue sample preferably from the most recent biopsy of a tumor lesion, collected either at the time of or after the diagnosis of locally advanced, recurrent, and/or metastatic disease has been made AND from a site not previously irradiated. If no tumor tissue is available, a fresh biopsy will be required. (See Section 6.2.2.1 for details.)

   Note: Tissue from needle or excisional biopsy or from resection is required.

9. Female subjects must have a negative serum pregnancy test at screening (within 72 hours of first dose of study drug) if of non-childbearing potential or be of non-childbearing potential. Non-childbearing potential is defined as (by other than medical reasons):
   a. ≥45 years of age and has not had menses for greater than 1 year,
   b. Amenorrheic for ≥ 2 years without a hysterectomy and oophorectomy and a follicle-stimulating hormone (FSH) value in the postmenopausal range upon pretrial (screening) evaluation,
   c. Whose status is post hysterectomy, oophorectomy, or tubal ligation.
10. If of childbearing potential, female subjects must be willing to use 2 highly effective contraceptive methods (defined in the informed consent form [ICF]) throughout the study, starting with the screening visit through 120 days after the last dose of study drug.

    Note: Abstinence is acceptable if this is the established and preferred contraception for the subject.

11. Male subjects with a female partner(s) of childbearing potential must agree to use 2 highly effective contraceptive measures (defined in the ICF) throughout the trial starting with the screening visit through 120 days after the last dose of study drug is received. Males with pregnant partners must agree to use a condom; no additional method of contraception is required for the pregnant partner.

    Note: Abstinence is acceptable if this is the established and preferred contraception for the subject.

12. Is willing and able to comply with the requirements of the protocol.

4.3 Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigation device within 4 weeks of the first dose of treatment.
2. Has an inadequate washout period prior to first dose of study drug defined as:
   a. Received systemic cytotoxic chemotherapy or biological therapy within 3 weeks before first dose,
   b. Received radiation therapy within 3 weeks before first dose, or

c. Had major surgery within 4 weeks before first dose.

3. Has received prior therapy with:

   a. Any antibody/drug targeting T-cell co-regulatory proteins (immune checkpoints) such as anti–PD-1, anti–PD-L1, or anti–cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibodies

   b. For Phase 2: > 1 systemic treatment regimen for locally advanced, recurrent, and/or metastatic cervical cancer for which the subject is considered for the study. Subjects who received a systemic regimen immediately after progressing within 6 months of completing chemotherapy concurrent with primary radiation or adjuvant chemotherapy after radiation will only be considered as having 1 prior systemic regimen for the purpose of this criterion.

      Note: In Phase 1, prior treatment with a CTLA-4 antibody is permissible for subjects with metastatic melanoma.

4. Has persisting toxicity related to prior therapy of National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI-CTCAE) Grade >1 severity.

   Note: Sensory neuropathy or alopecia of Grade ≤2 is acceptable.

5. Is expected to require any other form of systemic or localized antineoplastic therapy while on trial (including maintenance therapy with another agent, radiation therapy, and/or surgical resection).

6. Has known severe hypersensitivity reactions to fully human monoclonal antibodies (NCI-CTCAE Version 4.03 Grade ≥3), any history of anaphylaxis, or uncontrolled asthma.

7. Is receiving systemic corticosteroid therapy ≤ 7 days prior to the first dose of study treatment or receiving any other form of systemic immunosuppressive medication (corticosteroid use on study for management of immune-related AEs, and/or a premedication for IV contrast allergies/reactions is allowed). Subjects who are receiving daily corticosteroid replacement therapy are an exception to this rule. Examples of permitted therapy are daily prednisone at doses of 5 to 7.5 mg or equivalent hydrocortisone dose, and steroid therapy administered by topical, intraocular, intranasal, and/or inhalation routes.

8. Has a CNS tumor, metastasis(es), and/or carcinomatous meningitis identified either on the baseline brain imaging obtained during the screening period OR identified prior to consent.

   Note: Subjects with history of brain metastases that have been treated may participate provided they show evidence of stable supra-tentorial lesions at screening (based on 2 sets of brain images, performed ≥ 4 weeks apart, and obtained after the brain metastases treatment). In addition, any neurologic symptoms that developed either as a result of the brain metastases or their treatment must have resolved or be minimal and be expected as sequelae from treated lesions. For individuals who received steroids as part of brain metastases treatment, steroids must be discontinued ≥ 7 days prior to first dose of study drug.

9. Has active or history of autoimmune disease that has required systemic treatment within 2 years of the start of study treatment (i.e. with use of disease modifying agents,

corticosteroids, or immunosuppressive drugs). Replacement therapy (i.e., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of immunosuppressive systemic treatment.

Note: Subjects with diabetes type 1, vitiligo, psoriasis, hypo-, or hyperthyroid disease not requiring immunosuppressive treatment are eligible.

10. Has had an allogenic tissue/solid organ transplant.
11. Has or had interstitial lung disease (ILD) OR has had a history of pneumonitis that has required oral or IV corticosteroids.
12. Has an active infection requiring IV systemic therapy.
13. Has known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
14. Has known active Hepatitis B, Hepatitis C, or tuberculosis. Active Hepatitis B is defined as a known positive HBsAg result. Active Hepatitis C is defined by a known positive Hep C Ab result and known quantitative HCV RNA results greater than the lower limits of detection of the assay.
15. Has clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke or myocardial infarction within 6 months of enrollment, unstable angina, congestive heart failure (New York Heart Association class ≥II), or serious uncontrolled cardiac arrhythmia requiring medication
16. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
17. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
18. Is, at the time of signing informed consent, a regular user (including "recreational use") of any illicit drugs or had a recent history (within the last year) of substance abuse (including alcohol).
19. Is legally incapacitated or has limited legal capacity.
20. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of AGEN2034 and/or AGEN1884.

4.4 Criteria for Subject Withdrawal

4.4.1 Withdrawal from Treatment

The subject must be withdrawn in the event of any of the following:

- Occurrence of an event that would have been considered an exclusion criterion prior to enrollment, that is clinically relevant and affects the subject's safety, and if discontinuation is considered necessary by the investigator and/or Sponsor.

- Radiological Disease Progression, defined by RECIST 1.1 as defined in Section 6.2.4.3, unless the subject is considered to derive clinical benefit from the treatment by the investigator, is clinically stable and there is agreement with the Sponsor (Section 5.4.7).

  Clinical stability is defined by:

  - Absence of new symptoms and signs indicating clinically significant disease progression.
  - No decline in ECOG performance status.
  - Absence of rapid progression of disease or progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

    Note: For Phase 2, tumor assessments should be performed every 6 weeks (± 3 days) from first treatment dose until RECIST 1.1-defined disease progression has been established by the blinded independent central radiology review. Furthermore, if study drug is discontinued as a result of unacceptable toxicity, tumor assessments should continue every 6 weeks (± 3 days) until RECIST1.1-defined disease progression has been established by the blinded independent central radiology review. Imaging is required every 6 weeks (± 3 days) for those subjects with confirmed PD who remain on study treatment per protocol (Section 5.4.7) until treatment is discontinued.

- Clinical Disease Progression, in absence of radiologic progression on the basis of RECIST 1.1 including 1 or more of the following:
  - Signs and/or symptoms consistent with clinically significant progression of disease, including worsening of laboratory values, appearance of new lesion/worsening of the lesion best seen clinically.
  - Decline in ECOG performance status.
  - Tumor progression at critical anatomical sites that requires urgent medical intervention (e.g., CNS metastasis with potential for cord progression).
  - Initiation of chronic opiates, or initiation of chemotherapy or new antineoplastic therapy, palliative radiation therapy, or surgery.
- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks OR requires systemic treatment;
- Any Grade ≥ 3 skin drug-related AE or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN).
- Any Grade ≥ 2 drug-related pneumonitis or interstitial lung disease that does not resolve after dose delay and systemic corticosteroids (also see Table 11);
- Any Grade 2 or 3 drug-related toxicity that does not resolve in ≤ 6 weeks;
- Any Grade 3 drug-related bronchospasm, hypersensitivity reaction, or infusion-related reaction, regardless of duration; with the exception of Grade 3 infusion-related reactions resolving within 6 hours and controlled with medical management;

- Any Grade 3 non-skin, drug-related AE lasting > 7 days (which are also considered to be DLTs during dose escalation). Exceptions include the following for uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reactions, infusion reactions, endocrinopathies, and laboratory abnormalities:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation;
  - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation;
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation;
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation (also see Table 12):
      - AST or ALT > 8 x ULN;
      - Total bilirubin > 5 x ULN;
      - Concurrent AST or ALT > 3 x ULN AND total bilirubin > 2 x ULN;
- Any Grade 4 drug-related AE or laboratory abnormality, except for the following events, which do not require discontinuation:
  - Grade 4 neutropenia < 7 days;
  - Grade 4 lymphopenia or leukopenia;
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset;
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued treatment;
- Tumor flare phenomenon, defined as local pain, irritation, or rash localized at sites of known or suspected tumor does not require treatment discontinuation.
- Any requirement for ≥ 10 mg per day of prednisone or equivalent for more than 6 weeks;
- Any recurrence of a Grade 3 or 4 drug-related toxicity;
- Dose delay of AGEN1884 which results in no AGEN1884 dosing for more than 12 weeks;
- Dose delay of AGEN2034 which results in no AGEN2034 dosing for more than 6 weeks;

- If AGEN2034 administration is discontinued, permanently discontinue AGEN1884. If AGEN1884 administration is discontinued, a discussion with the Sponsor should be held regarding discontinuing or continuing AGEN2034 alone.
- Occurrence of AEs, resulting in discontinuation of study drug that is desired or considered necessary by the investigator and/or the subject (if applicable).
- Occurrence of pregnancy (if applicable).
- Use of a non-permitted concomitant drug, as defined in Section 5.5.2, in which the pre-defined consequence is withdrawal from study drug (Sponsor may be contacted to discuss whether study treatment must be discontinued).
- Noncompliance for non-medical reasons (Section 6.2.1.11)
- Other reasons may be cited by the investigator and will be described in the electronic case report form (eCRF)

4.4.2 Withdrawal from the Trial (Per Subject)

Subjects are free to discontinue the trial at any time without giving their reasons. A subject must be withdrawn in the event of any of the following:

- Withdrawal of the subject's consent.
- Lost to follow-up
- Participation in any other therapeutic trial during the treatment duration of this trial.

If a subject has failed to attend scheduled trial assessments, the investigator must determine the reasons and the circumstances as completely and accurately as possible.

In case of premature withdrawal from the trial, the investigations scheduled for the Discontinuation Visit should be performed (Section 6.1.3.1) if possible, with focus on the most relevant assessments. In any case, the appropriate eCRF section must be completed.

4.4.3 Premature Discontinuation of the Entire Trial (All Subjects)

The entire trial may be discontinued prematurely in the event of any of the following:

- New information leading to unfavorable risk-benefit judgment of AGEN1884 and/or AGEN2034, e.g., due to:
  - Occurrence of significant previously unknown adverse reactions, or unexpectedly high intensity or incidence of known adverse reactions.
  - Other unfavorable safety findings.

    Note: Evidence of inefficacy may arise from this trial or from other trials, and unfavorable safety findings may arise from clinical or nonclinical examinations (e.g., toxicology).
- Sponsor's decision that continuation of the trial is unjustifiable for medical or ethical reasons.
- Poor enrollment of subjects, making completion of the trial within an acceptable timeframe unlikely.

- Discontinuation of development of AGEN1884 and/or AGEN2034.

Health authorities and Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be informed about trial discontinuation in accordance with applicable regulations.

The entire trial may be terminated or suspended upon request of health authorities.

5 Study drugs and Treatment

5.1 Investigational Medicinal Product (IMP)

It is the responsibility of the investigator to ensure that IMP is only dispensed to trial subjects. The IMP must be dispensed only from official trial sites by authorized personnel according to local regulations.

The IMP's for this trial are AGEN1884 and AGEN2034. Refer to the respective Investigator's Brochures and/or Pharmacy Manual for additional details.

5.1.1 AGEN1884

AGEN1884 is a novel, fully human monoclonal IgG1 antibody designed to block CTLA-4.

AGEN1884 drug product is supplied as a sterile, single-use solution for IV injection in a 2-mL or 10-mL glass vial glass vial. AGEN1884 should be stored in a refrigerator at 2°C to 8°C.

Each drug product 10-mL vial contains a withdrawable volume of 5 mL, with 50 mg AGEN1884 at a nominal concentration of 10 mg/mL formulated in [redacted]

Each drug product 2-mL vial contains a withdrawable volume of 1 mL, with 50 mg AGEN1884 at a nominal concentration of 50 mg/mL formulated in [redacted]

5.1.2 AGEN2034

AGEN2034 is a novel, fully human monoclonal IgG4 antibody designed to block PD-1.

AGEN2034 drug product is supplied as a sterile, single-use solution for IV injection in a 2-mL or 10-mL glass vial. AGEN2034 should be stored in a refrigerator at 2°C to 8°C.

Each drug product 10-mL vial contains a withdrawable volume of 5 mL, with 50 mg AGEN2034 at a concentration of 10 mg/mL formulated in 20 mM histidine, 250 mM sorbitol, 0.01% polysorbate 80, pH 6.0.

Each drug product 2-mL vial contains a withdrawable volume of 1 mL with 50 mg AGEN2034 at a nominal concentration of 50 mg/mL formulated in 20 mM histidine, 250 mM sorbitol, 0.02% polysorbate 80, pH 6.0.

5.2 Packaging and Labeling

Study drug packaging and labeling will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Practice guidelines.

All study drug must be kept in a secure place under appropriate storage conditions. The Sponsor or its representatives must be granted access on reasonable request to check drug storage, dispensing procedures, and accountability records. Refer to the Pharmacy Manual for additional details.

5.3 Storage and Dispensing

The product storage manager should ensure that study drugs are stored in accordance with the environmental conditions (temperature, light, and humidity) as determined in the Pharmacy Manual. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed, and Agenus should be contacted immediately.

Study drug documentation must be maintained including all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (e.g., required diluents, administration sets).

Please refer to the current version of the Investigator's Brochures and/or Pharmacy Manuals for complete storage, handling, dispensing, and infusion information for AGEN1884 and AGEN2034.

5.3.1 AGEN1884

For application in this trial, AGEN1884 drug product must be diluted with 0.9% saline solution (sodium chloride injection). Detailed information on infusion bags and medical devices to be used for preparation of dilutions and subsequent administration is provided in the Pharmacy Manual.

AGEN1884 will be shipped in transport cool containers (2°C to 8°C) that are monitored with temperature control devices.

AGEN1884 drug product must be stored at 2°C to 8°C until use, with a temperature log maintained daily. All medication boxes supplied to each trial center must be stored carefully, safely, and separately from other drugs.

Once the vial is punctured, the AGEN1884 drug product must be diluted into appropriate volume of 0.9% saline solution in an infusion bag immediately. Infusion from the bag should begin within 4 hours of vial puncture when the bag is stored at room temperature or within 24 hours when the bag is stored at 5°C ± 3°C (refrigerated conditions).

Any unused portion of solution should be discarded in biohazard waste disposal, with final disposal by accepted local and national standards of incineration.

5.3.2 AGEN2034

For application in this trial, AGEN2034 drug product must be diluted with 0.9% saline solution (sodium chloride injection). Detailed information on infusion bags and medical devices to be used for preparation of dilutions and subsequent administration is provided in the Pharmacy Manual.

AGEN2034 will be shipped in transport cool containers (2°C to 8°C) that are monitored with temperature control devices.

AGEN2034 drug product must be stored at 2°C to 8°C until use, with a temperature log maintained daily. All medication boxes supplied to each trial center must be stored carefully, safely, and separately from other drugs.

Once the vial is punctured, the AGEN2034 drug product must be diluted into appropriate volume of 0.9% saline solution in an infusion bag immediately. Infusion from the bag should begin within 4 hours of vial puncture when the bag is stored at room temperature or within 24 hours when the bag is stored at 5°C ± 3°C (refrigerated conditions).

Any unused portion of solution should be discarded in biohazard waste disposal, with final disposal by accepted local and national standards of incineration.

5.4 Dosage and Administration

Relevant clinical laboratory results essential for subject management decisions (hematology, biochemistry, LFTs) must be available and reviewed before administration of AGEN1884 and/or AGEN2034. The duration of each treatment cycle is 6 weeks (42 days).

5.4.1 AGEN2034

AGEN2034 infusions should be administered IV first and over 30 min (-10 / +20 min) on Day 1, Day 15, and Day 29 of each treatment cycle. All infusions should be administered using an infusion pump. A central catheter is not required for infusion; however, if a subject has a central venous catheter in place, it is recommended that it be used for the infusion. Once the infusion is completed, all remaining drug solution in the line should be administered according to institutional guidelines for saline flushing.

Separate infusion bags and filters must be used for the infusion of each drug.

On Day 15 and Day 29 of each cycle, subjects should be observed for 30 minutes after AGEN2034 infusion has been completed.

5.4.2 AGEN1884

AGEN1884 should be administered over 30 minutes (-10 / + 20 min) and following the infusion of AGEN2034 on Day 1 of each treatment cycle; approximately 30 minutes after the administration of AGEN2034 is completed. Infusions will be followed immediately with a 15-minute saline flush of the IV line. Modifications of the infusion rate due to infusion-related reactions are described in Section 5.4.5.

Subjects should be observed for 30 minutes after the AGEN1884 infusion has been completed.

Separate infusion bags and filters must be used for the infusion of each drug.

5.4.3 Treatment Regimen

The following CDLs **could have been studied** in Phase 1:

AGEN2034/AGEN1884 Combination Dose Level 1 (CDL1):

Agent	Dose	Schedule	Duration of treatment
AGEN2034	1 mg/kg	every 2 weeks	Up to 24 months
AGEN1884	1 mg/kg	every 6 weeks	

AGEN2034/AGEN1884 Combination Dose Level 2 (CDL2):

Agent	Dose	Schedule	Duration of treatment
AGEN2034	3 mg/kg	every 2 weeks	Up to 24 months
AGEN1884	1 mg/kg	every 6 weeks	

AGEN2034/AGEN1884 Combination Dose Level-1 (CDL-1):

Agent	Dose	Schedule	Duration of treatment
AGEN2034	1 mg/kg	every 2 weeks	Up to 24 months
AGEN1884	0.3 mg/kg	every 6 weeks	

Subjects will be treated for up to 24 months, regardless of dose delays, as long as the subject meets criteria to remain on therapy.

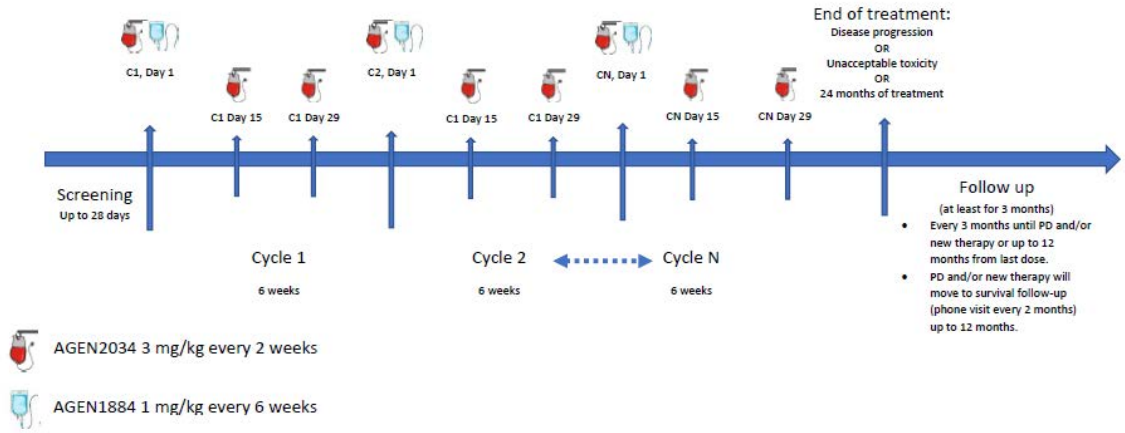
The following CDL has been chosen for Phase 2:

AGEN2034/AGEN1884 Combination Dose Level 2 (CDL2):

Agent	Dose	Schedule	Duration of treatment
AGEN2034	3 mg/kg	every 2 weeks	Up to 24 months
AGEN1884	1 mg/kg	every 6 weeks	

Phase 2 treatment is depicted in Figure 9. The duration of each treatment cycle is 6 weeks (42 days).

Figure 9: Phase 2 Treatment



5.4.4 Premedications

Premedications should not be administered routinely prior to dosing of study drugs. See Section 5.4.5 for subsequent premedication recommendations following AGEN1884- or AGEN2034-related infusion reactions.

5.4.5 Treatment of Infusion-Related Reactions

Acute infusion reactions (which can include cytokine release syndrome, angioedema, or anaphylaxis) are different from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: allergic reaction/hypersensitivity (including drug fever); arthralgia (joint pain); bronchospasm; cough; dizziness; dyspnea (shortness of breath); fatigue (asthenia, lethargy, malaise); headache; hypertension; hypotension; myalgia (muscle pain); nausea; pruritus/itching; rash/desquamation; rigors/chills; sweating (diaphoresis); tachycardia; tumor pain (onset or exacerbation of tumor pain due to treatment); urticaria (hives, welts, wheals); vomiting.

For individual subjects, once the AGEN1884 and/or AGEN2034 infusion rate has been decreased by 50% or interrupted due to an infusion-related reaction, it must remain decreased for all subsequent infusions to that subject. If the subject has a second infusion-related reaction that is Grade ≥2 on the slower infusion rate, infusion should be stopped, and the subject should discontinue treatment. If a subject experiences a Grade 3 or Grade 4 infusion-related reaction at any time, the subject must discontinue treatment. If an infusion reaction occurs, all details about drug preparation and infusion must be recorded.

Should infusion reaction be considered a significant safety issue by the SMC, the SMC might decide to recommend premedication with an antihistamine and acetaminophen approximately 30 to 60 minutes before each dose of AGEN1884 and/or AGEN2034 (e.g., 25–50 mg diphenhydramine, 500–650 mg paracetamol IV, or oral equivalent acetaminophen). This regimen may be modified based on local treatment standards and guidelines, as appropriate.

Table 8 shows treatment guidelines for subjects who experience an infusion reaction associated with administration of AGEN1884 and/or AGEN2034.

Subjects receiving AGEN1884 and/or AGEN2034 should be monitored for infusion reactions. This includes the measurement of vital signs for at least 30 minutes after infusion. Subjects will remain in the clinic under close supervision for the duration of this monitoring period. Subjects with mild or moderate infusion reactions may receive AGEN1884 and/or AGEN2034 with close monitoring. Premedication with an antipyretic or antihistamine for subsequent treatment administration may be considered. For severe infusion reactions, AGEN1884 and or/AGEN2034 infusion must be discontinued, and appropriate medical therapy should be administered. Should severe infusion reaction occur to any of the drugs, the other will also be discontinued.

Subjects who do not experience any infusion-related toxicity Grade 1 or higher during or after the infusion may be released from monitoring after one hour if they are otherwise stable. Subjects with any infusion-related toxicity must be managed as per the guidelines in Table 8, and monitoring will continue until any infusion-related toxicity has abated to less than Grade 1 and at least one hour has passed from the completion of the entire infusion and flush. All subjects will be given information on and instructions regarding both infusion-related toxicity, which is expected to be most likely in the hour after completion of the infusion, and immune-related AEs, before leaving the trial site. This will include instructions on when and how to return for immune-mediated toxicities associated with CTLA-4 and/or PD-1 blockade.

Once the AGEN2034 infusion rate has been decreased by 50% or interrupted due to an infusion-related reaction, it must remain decreased for all subsequent infusions. If the subject has a second infusion-related reaction that is Grade ≥ 2 on the slower infusion rate, infusion should be stopped, and the subject should discontinue treatment. If a subject experiences a Grade 3 or Grade 4 infusion-related reaction at any time, the subject must discontinue treatment. If an infusion reaction occurs, all details about drug preparation and infusion must be recorded.

Table 8: AGEN1884 and AGEN2034 Infusion-Related Reaction Management Guidelines

CTCAE Grade	Treatment	Premedication at Subsequent Dose Administration
Grade 1:	Increase monitoring of vital signs as medically indicated until the subject is	None.

CTCAE Grade	Treatment	Premedication at Subsequent Dose Administration
Mild reaction; infusion interruption not indicated; intervention not indicated.	deemed medically stable in the opinion of the investigator.	
Grade 2: Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, nonsteroidal anti-inflammatories (NSAIDS), narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	Stop infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to the following: • IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate. Otherwise, dose administration will be held until symptoms resolve, and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug administration.	Subject may be pre-medicated 1.5 h (± 30 minutes) prior to infusion with the following: • Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). • Acetaminophen 500-1000 mg PO (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates). Grade 4: Life-threatening; pressor or ventilatory support indicated.	Stop infusion. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization is indicated. Subject is permanently discontinued from further study drug administration.	No subsequent dosing.

5.4.6 Dose Modifications and Treatment Delay

5.4.6.1 Dose Reductions

No dose reductions are allowed. Each subject will stay on the CDL assigned in the trial unless treatment needs to be stopped. Dose reductions or dose escalations of AGEN1884 or AGEN2034 are not permitted.

5.4.6.2 Treatment Delay

5.4.6.2.1 Criteria for Treatment Delay

AGEN1884 and/or AGEN2034 administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related AE with the following exceptions:
  - Do not delay treatment for Grade ≥ 2 fatigue and laboratory abnormalities except for:
    - Delay dosing for Grade ≥ 2 serum creatinine (more than 1.5x baseline) toxicity;
    - If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity;
- Any Grade ≥ 3 skin drug-related AE or suspected SJS or TEN
- Any Grade ≥ 3 drug-related laboratory abnormality with the following exceptions for lymphopenia, AST, ALT, or total bilirubin:
  - Grade 3 lymphopenia does not require a dose delay.
  - If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity
  - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity.
- Any AE, laboratory abnormality or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of trial medication.

Subjects receiving AGEN1884 in combination with AGEN2034 who have drug-related toxicities that meet the criteria for dose delay, should have both drugs (AGEN1884 and AGEN2034) delayed until retreatment criteria are met.

After at least 6 months of study participation, treatment may be delayed one time for up to 14 days for reasons not related to an AE (e.g. subject holiday, etc.).

5.4.6.2.2 Criteria to Resume Treatment

Subjects may resume treatment with AGEN1884 and/or AGEN2034 when drug-related AE(s) resolve(s) to Grade 1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.

- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-Grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT or total bilirubin.
    - Subjects with combined Grade 2 AST/ALT **AND** total bilirubin values meeting discontinuation parameters (Section 4.4.1) should have treatment permanently discontinued.
- Drug-related Grade 2 pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment. (Exception: Study treatment does not need to be delayed/interrupted for subjects who experience immune-related hypothyroidism [Grades 1-2]).
- Subjects who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ≤ 10 mg/day.

AGEN1884 should be dosed with AGEN2034 at the specified interval regardless of any delays in intervening AGEN2034 doses if the criteria to resume treatment are met. However, in order to maintain periodic synchronized dosing of AGEN1884 and AGEN2034, the dosing days of AGEN1884 and AGEN2034 may be adjusted within a permitted ± 5-day window, as long as consecutive AGEN2034 doses are given at least 10 days apart. AGEN1884 may be delayed beyond the 5-day window, if needed, to synchronize with the next AGEN2034 dose. This will permit periodic AGEN1884 dosing to be synchronized with AGEN2034 dosing.

5.4.7 Treatment Beyond Disease Progression

Consistent with RECIST 1.1, subjects who experience equivocal PD on imaging during the trial may continue treatment until re-evaluation using the same imaging modality at the next scheduled assessment (i.e., 6 weeks later) to confirm PD. This is especially important for subjects who are doing well clinically.

Subjects will be permitted, with the Sponsor's approval, to continue with treatment beyond initial RECIST 1.1 defined PD as long as they meet the following criteria:

- Investigator-assessed clinical benefit from the treatment;
- Is clinically stable (see definition in Section 4.4.1);
- Subject is tolerating study drug; and
- There is agreement with the Sponsor.

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment. The following criteria need to be taken into consideration:

- Absence of clinical symptoms and signs (including worsening of laboratory values) indicating disease progression.

- No decline in ECOG performance status.
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

Subjects should discontinue study therapy upon evidence of further progression, defined as an additional 10% or greater increase in tumor burden from time of initial progression (including all target lesions and new measurable lesions).

Imaging is required every 6 weeks (± 3 days) for those subjects with confirmed PD who remain on treatment until treatment is discontinued.

At the time of initial progression. new lesions are considered measurable if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of ≥ 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden measurement if the longest diameter increases to ≥ 10 mm (except for pathological lymph nodes, which must have an increase in short axis to ≥ 15 mm).

5.5 Concomitant Treatments

5.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the eCRF including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date will also be included on the eCRF.

Palliative and supportive care is permitted during the course of the trial for underlying medical conditions and management of symptoms.

Surgery for tumor control or symptom management is not permitted during the trial. Palliative radiotherapy is permitted to a single lesion if considered medically necessary by the treating physician as long as the lesion is NOT a RECIST 1.1 defined target lesion and treatment is NOT administered for tumor control. Trial therapy should be held during the course of palliative radiotherapy and should be resumed no earlier than the next scheduled administration of trial therapy. The specifics of the radiation treatment, including the location, will be recorded.

All concomitant medications received within 30 days before the first dose of study treatment through the Safety Follow-up Visit and Follow-up Visit 1 (3 months from last study drug dose) should be recorded.

5.5.1.1 Rescue Medications and Supportive Care

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined below.

For guidelines for continuing treatment with AGEN2034, see Section 5.4.6.2.2.

- Diarrhea: Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic subjects, infectious

etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered. All subjects who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

- Anemia: Consider a potential immunologic etiology. Transfusions and/or erythropoietin may be utilized as clinically indicated for the treatment of anemia, erythropoietin could be used following American society of Clinical Oncology (ASCO) guidelines but should be clearly noted as concurrent medications. Study treatment may resume as early as the day following transfusion. The timing to resume treatment is based on investigator judgment.
- Neutropenia: Prophylactic use of colony-stimulating factors including Granulocyte Colony-Stimulating Factor (G-CSF), PEGylated G-CSF, or Granulocyte Macrophage Colony-Stimulating Factor GM CSF is not allowed in this trial. Therapeutic use of G-CSF is allowed in subjects with Grade 3-4 febrile neutropenia. Consider a potential immunologic etiology.
- Thrombocytopenia: Transfusion of platelets may be used if clinically indicated. Immune thrombocytopenia purpura (ITP) should be ruled out before initiation of platelet transfusion. Study treatment may resume as early as the day following transfusion. The timing to resume treatment is based on investigator judgment.
- Anti-infectives: Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.
- Adverse events with a potential immunologic etiology (immune-related AEs; irAEs): identification, evaluation, and management of adverse experiences of a potential immunologic etiology. Depending on the type and severity of an irAE, oral or IV treatment with a corticosteroid should be considered, in addition to appropriate symptomatic treatment of a given condition (see Section 5.6 for management algorithms). These are also considered AEs of special interest (AESI) and should be reported to the Sponsor per Section 7.2.2.2.

5.5.2 Prohibited and/or Restricted Treatments

As stated in the exclusion criteria (Section 4.3), subjects must not have had chemotherapy, radiotherapy (other than palliative bone-directed radiotherapy), as described in Section 5.5.1, major surgery, or received another investigational agent within 28 days before the start of study treatment.

Subjects are prohibited from receiving the following therapies and treatments during the Screening and Treatment during this trial:

- Immunotherapy not specified in this protocol.
- Chemotherapy.
- Investigational agents other than AGEN1884 or AGEN2034.
- Surgery for symptom management or tumor control.
- Growth factors (granulocyte colony-stimulating factor or granulocyte macrophage colony-stimulating factor). Exception: Erythropoietin and darbepoietin alpha may be prescribed

following ASCO guidelines. Therapeutic use of G-CSF is allowed in subjects with Grade 3-4 febrile neutropenia.

- Radiation therapy for tumor control.
- Glucocorticoids for any purpose other than to modulate symptoms from an irAE, or for use as a pre-medication in subjects with a known history of an IV contrast allergy administered as part of computed tomography (CT) radiography.

  Note: Replacement doses of corticosteroids (for example, prednisone 5-7.5 mg daily) are permitted while on trial.

  Note: Use of inhaled or topical corticosteroid is permitted.
- Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial.
- Subjects may receive other medications that the investigator deems to be medically necessary.
- Medications listed in the Exclusion Criteria are prohibited in this trial.
- There are no prohibited therapies during the Post-Treatment Follow-up Phase

5.5.3 Other Restrictions and Precautions

The following non-drug therapies must not be administered or performed during the trial (and within 28 days before the start of study treatment):

- Major surgery (excluding prior diagnostic biopsy).
- Herbal remedies with immunostimulating properties (e.g., mistletoe extract) or that are known to potentially interfere with major organ function (e.g., hypericin).
- Subjects should not abuse alcohol or other drugs during the study.

5.6 Recommendations for Management of Immune-Related Adverse Events (irAEs)

Immuno-oncology agents such as AGEN1884 and AGEN2034 are associated with irAEs. Early recognition and management of irAEs may mitigate severe toxicity. Investigators should also monitor subjects closely for potential irAEs, which may manifest at the earliest after weeks of treatment. Such events may consist of persistent rash, diarrhea, colitis, autoimmune hepatitis, pneumonitis, encephalitis, arthritis, glomerulonephritis, cardiomyopathy, or uveitis and other inflammatory eye conditions.

Management Algorithms have been developed to assist investigators in assessing and managing the following groups of irAEs: Gastrointestinal, Pulmonary, Dermatological, Renal, Hepatic, Neurological, and Endocrine among others.

Adverse events (both non-serious and serious) associated with drug exposure and consistent with an immune phenomenon may represent an immunologic etiology. These immune-related AEs may be predicted based on the nature of the study drugs, their mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. An irAE can occur shortly after the first dose or several months after the last dose of treatment. Particular attention should be paid to AEs that may be suggestive of potential irAEs as outlined below.

Immune-related AEs are considered are considered AESIs and should be reported to the Sponsor per Section 7.2.2.2 from the time of consent to participate in the study up to at least 90 days (Follow-up Visit 1) from last study drug administration.

5.6.1 Dermatological irAEs

Rule out non-inflammatory causes, if non-inflammatory cause is identified, treat accordingly, and continue therapy per protocol (Table 9).

Table 9: Dermatological irAE Management Algorithm

Dermatological irAEs		
Grade of Rash (NCI-CTCAE v4.03)	**Management**	**Follow-Up**
Grade 1–2 Covering ≤30% body surface area.	• Symptomatic therapy (e.g., antihistamines, topical corticosteroids). • Continue AGEN1884 / AGEN2034 therapy per protocol.	• If persists >1 to 2 weeks or recurs: Consider skin biopsy. • Delay AGEN2034/AGEN1884 therapy. • Consider 0.5–1 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper corticosteroids over at least 1 month; consider prophylactic antibiotics for opportunistic infections; and resume AGEN1884 / AGEN2034 therapy per protocol. • **If worsens:** treat as Grade 3–4.
Grade 3–4 Covering >30% body surface area; life-threatening consequences.	• Delay or discontinue AGEN1884 / AGEN2034 therapy per protocol • Consider skin biopsy • Dermatology consult • 1–2 mg/kg/day methylprednisolone IV or IV equivalent	• If improves to Grade 1: taper corticosteroids over at least 1 month; add prophylactic antibiotics for opportunistic infections • Resume AGEN2034/AGEN1884 therapy per protocol

5.6.2 Gastrointestinal irAEs

Rule out non-inflammatory causes, if non-inflammatory cause is identified, treat accordingly, and continue therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis (Table 10).

Table 10: Gastrointestinal irAEs Management Algorithm

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE v4.03)	**Management**	**Follow-Up**
Grade 1 Diarrhea: <4 stools/day over baseline. Colitis: asymptomatic.	• Continue AGEN1884 / AGEN2034 therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms • Educate subject to report worsening immediately • Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g. American Dietetic Association colitis diet), and loperamide • **If worsens:** treat as Grade 2 or 3–4.
Grade 2 Diarrhea: 4–6 stools per day over baseline; IV fluids indicated <24 h; not interfering with activities of daily living (ADL). Colitis: abdominal pain; blood in stool	• Delay AGEN1884 / AGEN2034 therapy per protocol. • Symptomatic treatment.	• **If improves to Grade 1:** resume AGEN1884 / AGEN2034 therapy per protocol. • **If persists >5 to 7 days or recurs:** 0.5–1 mg/kg/day methylprednisolone or equivalent. • When symptoms improve to Grade 1, taper corticosteroids over at least 1 month; consider prophylactic antibiotics for opportunistic infections; resume AGEN1884 / AGEN2034 therapy per protocol. • If worsens or persists >3 to 5 days with oral corticosteroids: treat as Grade 3–4.
Grade 3 to 4 Diarrhea (Grade 3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 h; interfering with ADL. Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs. Grade 4: life-threatening, perforation	• Discontinue AGEN1884 / AGEN2034 therapy per protocol. • 1–2 mg/kg/day methylprednisolone IV or equivalent. • Add prophylactic antibiotics for opportunistic infections. • Consider lower endoscopy.	• **If improves:** continue corticosteroids until Grade 1, then taper over at least 1 month. • If persists >3 to 5 days or recurs after improvement: add infliximab 5 mg/kg (if no contraindication). **Note**: infliximab should not be used in cases of perforation or sepsis.

5.6.3 Pulmonary irAEs

Rule out non-inflammatory causes, if non-inflammatory cause is identified, treat accordingly, and continue therapy per protocol. Evaluate with imaging and pulmonary consultation (Table 11).

Table 11: Pulmonary irAE Management Algorithm

Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4.03)	**Management**	**Follow-Up**
Grade 1 Radiographic changes only.	• Consider delay of AGEN1884 / AGEN2034 therapy per protocol. • Monitor for symptoms every 2–3 days. • Consider pulmonary and infectious disease consults.	• Re-image every ≥3 weeks. • **If worsens:** treat as Grade 2 or Grade 3–4.
Grade 2 Mild to moderate new symptoms	• Delay AGEN1884 / AGEN2034 therapy per protocol. • Pulmonary and infectious disease consults. • Monitor symptoms daily; consider hospitalization. • 1 mg/kg/day methylprednisolone IV or oral equivalent. • Consider bronchoscopy, lung biopsy.	• Re-image every 1–3 days. • **If improves:** when symptoms return to near baseline, taper corticosteroids over at least 1 month, then resume AGEN1884 / AGEN2034 therapy per protocol, and consider prophylactic antibiotics. • If not improving after 2 weeks or worsening: treat as Grade 3–4.
Grade 3–4 Severe new symptoms; new/ worsening hypoxia; life-threatening	• Discontinue AGEN1884 / AGEN2034 therapy per protocol. • Hospitalize. • Pulmonary and infectious disease consults. • 2–4 mg/kg/day methylprednisolone IV or IV equivalent. • Add prophylactic antibiotics for opportunistic infections. • Consider bronchoscopy, lung biopsy.	• **If improves to baseline:** taper corticosteroids over at least 6 weeks. • **If not improving after 48 hours or worsening:** add additional immunosuppression (e.g., infliximab, cyclophosphamide, IV immunoglobulin, mycophenolate mofetil).

5.6.4 Hepatic irAEs

Rule out non-inflammatory causes, if non-inflammatory cause is identified, treat accordingly, and continue therapy per protocol. Consider imaging for obstruction (Table 12).

Table 12: Hepatic irAE Management Algorithm

Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v4.03)	**Management**	**Follow-Up**
Grade 1 AST or ALT >ULN to 3 x ULN and/or total bilirubin >ULN to 1.5 x ULN.	• Continue AGEN1884 / AGEN2034 therapy per protocol.	• Continue LFT monitoring per protocol. • **If worsens:** treat as Grade 2 or Grade 3–4.
Grade 2 AST or ALT >3 to ≤5 x ULN and/or total bilirubin >1.5 to ≤3 x ULN.	• Delay AGEN1884 / AGEN2034 therapy per protocol. • Increase frequency of monitoring to every 3 days. • If subject has concurrent AST or ALT > 3 x ULN AND total bilirubin > 2 x ULN, Discontinue AGEN1884 / AGEN2034 therapy per protocol.	• **If returns to baseline:** resume routine monitoring; resume AGEN1884 / AGEN2034 therapy per protocol. • **If elevations persist >5 to 7 days or worsen:** 0.5–1 mg/kg/day methylprednisolone IV or oral equivalent. When LFT returns to Grade 1 or baseline, taper corticosteroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume AGEN1884 / AGEN2034 therapy per protocol.
Grade 3–4 AST or ALT >5 x ULN and/or total bilirubin >3 x ULN.	• Discontinue AGEN1884 / AGEN2034 therapy per protocol. • Increase frequency of monitoring to every 1–2 days. • 1–2 mg/kg/day methylprednisolone IV or oral equivalent*. • Add prophylactic antibiotics for opportunistic infections. • Consult gastroenterology. • Consider obtaining magnetic resonance imaging (MRI)/CT scan of liver and liver biopsy if clinically warranted.	• **If returns to Grade 2:** taper corticosteroids over at least 1 month of full cycle treatment. • **If does not improve in >3 to 5 days, worsens or rebounds:** add mycophenolate mofetil 1 g twice daily. If no response within an additional 3–5 days, consider other immunosuppressants per local guidelines.

*The recommended starting dose for Grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

5.6.5 Endocrine irAEs

Rule out non-inflammatory causes, if non-inflammatory cause is identified, treat accordingly, and continue therapy per protocol. Consider visual field testing, endocrinology consultation, and imaging (Table 13).

Table 13: Endocrine irAE Management Algorithm

Endocrine irAEs		
Endocrine Disorder	**Management**	**Follow-Up**
Asymptomatic TSH abnormality	• Continue AGEN1884 / AGEN2034 therapy per protocol. • If TSH <0.5 x lower limit of normal (LLN) or TSH >2 x ULN, or consistently out of range in 2 subsequent measurements: include free thyroxine (fT4) at subsequent cycles as clinically indicated; consider endocrinology consult and/or treatment per institutional guidelines.	
Symptomatic endocrinopathy	• Evaluate endocrine function. • Consider pituitary scan. • **Symptomatic with abnormal lab/pituitary scan:** delay AGEN1884 / AGEN2034 therapy per protocol; 1–2 mg/kg/day methylprednisolone IV or oral equivalent; initiate appropriate hormone therapy. • No abnormal lab/ pituitary MRI scan but symptoms persist: repeat labs in 1–3 weeks/MRI in 1 month.	• **If improves (with or without hormone replacement):** taper corticosteroids over at least month and consider prophylactic antibiotics for opportunistic infections. • Resume AGEN1884 / AGEN2034 therapy per protocol • Subjects with adrenal insufficiency may need to continue corticosteroids with mineralocorticoid component • Consider consulting endocrinologist
Suspicion of adrenal crisis (e.g., severe dehydration, hypotension, shock out of proportion to current illness)	• Delay or discontinue AGEN1884 / AGEN2034 therapy per protocol. • Rule out sepsis. • Stress dose of IV corticosteroids with mineralocorticoid activity. • IV fluids. • Consult endocrinologist. • If adrenal crisis ruled out, treat as above for symptomatic endocrinopathy.	

5.6.6 Renal irAEs

Rule out non-inflammatory causes, if non-inflammatory cause is identified, treat accordingly, and continue therapy per protocol (Table 14).

Table 14: Renal irAE Management Algorithm

Renal irAEs		
Grade of Creatinine Elevation (NCI-CTCAE v4.03)	**Management**	**Follow-Up**
Grade 1 Creatinine > upper limit of normal (ULN) and > than baseline but ≤ 1.5x baseline.	• Continue AGEN1884 / AGEN2034 therapy per protocol • Monitor creatinine weekly	• **If returns to baseline:** resume routine creatinine monitoring per protocol. • **If worsens:** treat as Grade 2 or Grade 3–4.
Grade 2-3 Creatinine > 1.5x baseline to ≤ 6x ULN	• Delay AGEN1884 / AGEN2034 therapy per protocol • Monitor creatinine every 2-3 days • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy	• **If returns to Grade 1:** taper corticosteroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume AGEN1884 / AGEN2034 therapy and routine creatinine monitoring per protocol. • If elevations persist > 7 days or worsen: treat as Grade 4.
Grade 4 Creatinine > 6x ULN.	• Discontinue AGEN1884 / AGEN2034 therapy per protocol • Monitor creatinine daily • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrologist • Consider renal biopsy	• **If returns to Grade 1:** taper corticosteroids over at least 1 month and add prophylactic antibiotics for opportunistic infections.

5.6.7 Neurological irAEs

Rule out non-inflammatory causes, if non-inflammatory cause is identified, treat accordingly, and continue therapy per protocol (Table 15).

Table 15: Neurological irAE Management Algorithm

Neurological irAEs		
Grade of Neurological Toxicity (NCI-CTCAE v4.03)	**Management**	**Follow-Up**
Grade 1 Asymptomatic or mild symptoms; intervention not indicated.	• Continue AGEN1884 / AGEN2034 therapy per protocol.	• Continue to monitor subject. • **If worsens:** treat as Grade 2 or Grade 3–4.
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay AGEN1884 / AGEN2034 therapy per protocol. • Treat symptoms per local guidelines. • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent.	• **If returns to baseline:** resume AGEN1884 / AGEN2034 therapy per protocol. • **If worsens**: treat as Grade 3-4.
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue AGEN1884 / AGEN2034 therapy per protocol. • Obtain neurology consult. • Treat symptoms per local guidelines. • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent. • Add prophylactic antibiotics for opportunistic infections.	• **If improves to Grade 2:** taper corticosteroids over at least 1month. • **If worsens or atypical presentation:** consider IV immunoglobulin or other immunosuppressive therapies per local guidelines.

6 Trial Assessments and Procedures

Schedules of assessments and procedures are presented in Table 16 (Phase 1), Table 17 (Phase 2), and Table 18 (Schedule of ECG, ADA, and PK Assessments for Phase 2).

Table 16: Schedule of Assessments and Procedures for Phase 1

	Screening	Treatment Phase																End of Treatment		Follow-up[1]		
Treatment Cycle / Scheduled Visit		Cycle 1								Cycle 2					Subsequent Cycles			Discontinuation Visit	Safety Follow-up	Visit 1	Visit 2	Visits 3 and 4
Visits Schedule (days)		1	2	4	8	15	16	22	29	1	4	8	15	29	1	15	29	At Discontinuation	4w from last dose	3m from last dose	6m from last dose	3m from previous visit
Schedule Window (days) window [1]						±3		±3	±3	±3			±3	±3	+3	±3	±3	± 3	± 3	± 7	± 7	± 7
Administrative Procedures	<-28 days																					
Informed consent	X																					
Review of inclusion / exclusion criteria	X	X																				
Issue Emergency Medical Support and Subject Card	X																					
Review of medical history, demographics, and baseline symptoms	X																					
Review of prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cancer disease details and prior treatment	X																					
Subsequent antineoplastic therapy status																		X	X	X	X	X
Clinical Procedures / Assessments	<-7 days																					
Review of AEs[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full Physical Examination	X																	X				
Focused Physical Examination		X						X	X	X			X	X	X	X	X		X	X	X	X
Vital Signs	X	X				X			X	X			X	X	X	X	X	X	X	X	X	X
Weight (prior to dosing)	X	X				X			X	X			X	X	X	X	X					
12-lead ECG[4]	X	X				X	X		X	X			X	X	X			X	X			
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Imaging Assessments[5]	<-14 days																					
Tumor Imaging	X	Every 6 weeks (±3 days) from first dose until treatment discontinuation.																				
Brain Imaging	X																					
Central Laboratory Procedures / Assessments[6]	<-7 days																					
Blood for Serum PK and/or ADA Assays		X[7,8]			X	X[8,9]			X[8,9]						X[10,11]			X	X	X		

	Screening	Treatment Phase																End of Treatment		Follow-up[1]		
Treatment Cycle / Scheduled Visit		Cycle 1								Cycle 2					Subsequent Cycles			Discontinuation Visit	Safety Follow-up	Visit 1	Visit 2	Visits 3 and 4
Visits Schedule (days)		1	2	4	8	15	16	22	29	1	4	8	15	29	1	15	29	At Discontinuation	4w from last dose	3m from last dose	6m from last dose	3m from previous visit
Schedule Window (days) window [1]						±3		±3	±3	±3			±3	±3	+3	±3	±3	± 3	± 3	± 7	± 7	± 7
Blood for Biomarkers, [redacted] assay (whole blood, PBMC, serum, and/or plasma)		X			X	X			X						X[10]			X	X	X	X	
Local Laboratory Procedures / Assessments[14]	< -7 days																					
Core serum chemistry[15]							X	X	X	X			X	X	X	X	X					
Full serum chemistry[16]	X																	X	X	X		
Hematology tests[17]	X				X	X	X	X	X	X			X	X	X	X	X	X	X	X		
Coagulation tests[18]	X						X	X		X			X		X			X	X	X		
Endocrine function tests[19]	X						X	X		X			X		X			X	X	X		
Urinalysis[20]	X						X	X		X					X			X	X	X		
Serum pregnancy test	X[21]																					
Urine pregnancy test		X[21]								X					X			X	X	X		
Study drug administration[22]																						
AGEN2034		X				X			X	X			X	X	X	X	X					
AGEN1884		X								X					X							

Abbreviations: ADA: anti-drug antibody; AEs: Adverse Events; d: day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; HPV: human papilloma virus; m: month; PBMC: peripheral blood mononuclear cell; PK: pharmacokinetics; w: week.

Note: Where applicable, assessments performed prior to treatment unless otherwise indicated.

[1] Visit window +/- 3 days, unless noted. All subjects who discontinue treatment will have at least one Follow-up Visit at 3 months (± 7 days) from last treatment dose. Subjects who discontinue due to disease progression and/or start of a new line of therapy will then end participation in the trial. Subjects who received the maximum administrations of the combination of AGEN2034 and AGEN1884; who have achieved a complete response (CR) according to RECIST 1.1; or who have discontinued treatment due to reasons other than disease progression and/or start of a new line of therapy will be in Follow-up for up to 12 months from last treatment dose or until disease progression and/or start of a new line of therapy. Every effort should be made to collect subject information on the start of new antineoplastic therapy, disease progression, and survival status.

[2] Treatment administration and associated procedures for that visit may be delayed for treatment-related AEs beyond the window and subsequent schedule adjusted accordingly.

[3] Adverse events will be documented from time of consent until the End-of-Treatment Safety Follow-up Visit, after which only TEAEs will be documented through the Follow-up Period of up to 12 months after the last study drug administration or until disease progression and/or initiation of a new line of therapy. DLTs will be assessed during the first 3 weeks of study treatment for the first 3 subjects at each dose level.

[4] 12-lead ECG on Cycle 1 Day 1 before AGEN2034 administration and 30 min (-10 / + 20 minutes) after AGEN1884 infusion; on Cycle 1 Days 15, 22, and 29, 30 min (-10 / + 20 minutes) after AGEN2034 infusion; Cycle 2 Day 1, 30 min (-10 / + 20 minutes) after AGEN1884 infusion; on subsequent indicated visits, 30 min (-10 / + 20 minutes) after last treatment infusion, if no infusion given, then anytime during visit; Discontinuation Visit and Safety Follow-up Visit.

[5] The initial tumor imaging will be performed within 14 days prior to first dose. Scans performed as part of routine clinical management are acceptable for use as screening scan if they are of diagnostic quality and < -28 days prior to first dose; and brain MRI if <-21 days prior to first dose. For subjects with no previous history of brain metastases, screening brain imaging will need to be obtained; except for subjects with cervical cancer, cutaneous squamous-cell carcinoma, gastric/gastroesophageal junction cancer, head and neck squamous-cell carcinoma, ovarian cancer, prostate cancer, mesothelioma, or urothelial carcinoma, for whom this scan is necessary only if clinically indicated. MRI is the preferred brain imaging modality; however, CT is acceptable if an MRI is clinically contraindicated. On-study imaging will be performed every 6 weeks (+/- 3 days), or more frequently if clinically indicated. The timing of imaging assessments should follow calendar days and should not be adjusted for delays in treatment administration or for visits. The same imaging technique should be used in a subject throughout the trial. Additional imaging at Discontinuation Visit and Safety Follow-up Visit is not required provided imaging assessments have been performed per schedule.

[6] Unless otherwise specified, samples should be collected before treatment. For correlation studies, no more than 240 mL of whole blood/week should be taken. This is in addition to other routine blood tests scheduled for the trial and needed for medical care.

[7] PK will be collected at 4 timepoints; before administration of AGEN2034 (one sample), at 30 (± 15) minutes, 2 hours (± 15 minutes), and 4 hours (± 15 minutes) post-administration of AGEN1884.

[8] ADA for both AGEN1884 and AGEN2034 will be assessed predose.

[9] Before administration of AGEN2034, 30 (± 15) minutes, 2 hours (± 15 minutes), and 4 hours (± 15 minutes) post-administration of AGEN2034.

[10] Assessed at cycles 3, 6, 7, and 8 only

[11] One PK sample before administration of AGEN2034 and one PK sample at 30 (± 15) minutes post-administration of AGEN1884. ADA sample for AGEN2034 will be collected prior to AGEN2034 administration. ADA sample for AGEN1884 will be collected after AGEN2034 infusion and prior to AGEN1884 administration.

[12] Before administration of AGEN2034 and between end of AGEN2034 infusion and start of AGEN1884 infusion.

[13] Before administration of AGEN2034.

[14] For screening, laboratory tests should be performed within 7 days prior to the first dose of study treatment. Unless otherwise specified, for treatment phase visits, laboratory tests may be collected up to 48 hours before visits and results must be available before treatment.

[15] Core serum chemistry: alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN)/total urea, calcium, chloride, creatinine, glucose, magnesium, phosphorus/phosphates, potassium, sodium, total bilirubin; Results must be available prior to dosing.

[16] Full serum chemistry: core serum chemistry and albumin, amylase, cholesterol, creatine kinase, C-reactive protein (CRP), gamma glutamyl transferase (GGT), lactate dehydrogenase (LDH), lipase, total protein, triglycerides, uric acid; Results must be available prior to dosing.

[17] Hematology Tests: absolute eosinophil count, absolute lymphocyte count, absolute neutrophil count (ANC), hematocrit, hemoglobin, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelet count, red blood cell (RBC), white blood cell (WBC) and differential count; Results must be available prior to dosing.

[18] Coagulation Tests: activated partial thromboplastin time (aPTT), Prothrombin time - international normalized ratio (INR); Results must be available prior to dosing.

[19] Endocrine function tests: free thyroxine (T4), thyroid-stimulating hormone (TSH); basal cortisol in the absence of corticosteroid treatment. Results must be available prior to dosing at the subsequent visit.

[20] Urinalysis including blood, glucose, protein, specific gravity, and microscopic exam if abnormal; Results must be available prior to dosing.

[21] Serum β-human chorionic gonadotropin (β-HCG) pregnancy test for women of childbearing potential at screening within 72 hours of first treatment dose (if performed earlier in screening period then a urine pregnancy test may be performed prior to first dose); urine pregnancy test at all other indicated visits (centers where urine pregnancy testing is not routine may substitute with serum β-HCG pregnancy test); Results must be available prior to dosing.

[22] AGEN2034 should be administered first, and within 30 min (-10/+20 min). Subjects must be observed for 30 min post-infusion for infusion-related reactions. If administration of one infusion is delayed due to an AE, the other is delayed as well and in this case, treatment visits may be delayed beyond the window of 3 days and schedules for subsequent visits should be adjusted accordingly.

Table 17: Schedule of Assessments and Procedures for Phase 2

	Screening	Treatment Phase									End of Treatment		Follow-up[1]			Survival Follow Up[2]
Treatment Cycle / Scheduled Visit		Cycle 1						Subsequent Cycles			Discontinuation Visit	Safety Follow-up	Visit 1	Visit 2	Visits 3 and 4	Telephone
Visits Schedule (days)		1	2	8	15	16	29	1	15	29	At Discontinuation	4 w from last dose	3 m from last dose	6 m from last dose	3 m from previous visit	Every 2 months
Schedule Window (days)[3]					±3		±3	±3	±3	±3	± 3	± 3	± 7	± 7	± 7	±14
Administrative Procedures	< -28 days															
Informed consent[3]	X															
Review of inclusion / exclusion criteria	X	X														
Issue Emergency Medical Support and Subject Card	X															
Review of medical history, demographics, and baseline symptoms	X															
Review of prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CC disease details and prior treatment	X															
Subsequent antineoplastic therapy status											X	X	X	X	X	X
Survival status																X
Tumor Biopsies / Archival Tissue Collection[4]	< -28 days															
Tumor tissue	X							X[4]								
Clinical Procedures / Assessments	< -7 days															
Review AEs[5, 21]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Full Physical Examination	X										X					
Focused Physical Examination		X			X		X	X	X	X		X	X	X	X	
Vital Signs	X	X			X		X	X	X	X	X	X	X	X	X	
Weight (prior to dosing)		X			X		X	X	X	X						
12-lead ECG	See Table 18 for ECG assessments in Phase 2															
ECOG Performance Status	X	X			X		X	X	X	X	X	X	X	X	X	
Imaging Assessments[6]	< -21 days															
Tumor Imaging	X	Every 6 weeks (±3 days) from first dose until treatment discontinuation.														
Brain Imaging[7] (if clinically indicated)	X															

	Screening	Treatment Phase									End of Treatment		Follow-up[1]			Survival Follow Up[2]
Treatment Cycle / Scheduled Visit		Cycle 1						Subsequent Cycles			Discontinuation Visit	Safety Follow-up	Visit 1	Visit 2	Visits 3 and 4	Telephone
Visits Schedule (days)		1	2	8	15	16	29	1	15	29	At Discontinuation	4 w from last dose	3 m from last dose	6 m from last dose	3 m from previous visit	Every 2 months
Schedule Window (days) [3]					±3		±3	±3	±3	±3	± 3	± 3	± 7	± 7	± 7	±14
Central Laboratory Procedures / Assessments	< -7 days															
Blood for PK and ADA	See Table 18 for PK and ADA assessments for Phase 2															
Blood for ctDNA[8]		X					X	X[9]			X					
PGx (whole blood)[10]	X															
Blood for PBMC[11]		X		X			X	X[9]			X					
Local Laboratory Procedures / Assessments[12]	< -7 days															
Core serum chemistry[13]					X		X	X	X	X						
Full serum chemistry[14]	X										X	X	X			
Hematology tests[15]	X				X		X	X	X	X	X	X	X			
Coagulation tests[16]	X				X			X			X	X	X			
Endocrine function tests[17]	X							X			X	X	X			
Urinalysis[18]	X				X			X			X	X	X			
Serum pregnancy test	X[19]															
Urine pregnancy test		X[18]						X			X	X	X			
Study drug administration[20]																
AGEN2034		X			X		X	X	X	X						
AGEN1884		X						X								

Abbreviations: ADA: anti-drug antibody; AEs: Adverse Events; CC: cervical cancer; d: day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; IERC: Independent Endpoint Review Committee; m: month; PBMC: peripheral blood mononuclear cell; PK: pharmacokinetic(s); w: week.

Note: Where applicable, assessments performed prior to treatment unless otherwise indicated.

[1] All subjects who discontinue treatment will have at least one Follow-up Visit at 3 months (± 7 days) from last treatment dose (Follow-up Visit 1). Subjects who discontinue due to disease progression and/or start of a new line of therapy will then move into Survival Follow-up for up to 12 months from last study drug dose. Every effort should be made to collect subject information on the start of any new antineoplastic therapies and survival status. Subjects who received the maximum administrations of the combination of AGEN2034 and AGEN1884; who have achieved a complete response (CR) according to RECIST 1.1; or who have discontinued treatment due to reasons other than disease progression and/or start of a new line of therapy will be in Follow-up for up to 12 months from last study drug dose or until disease progression and/or start of a new line of therapy. Upon disease progression and/or start of a new line of therapy, subjects will then move into Survival Follow-up for up to 12 months from last study drug dose. Every effort should be made to collect subject information on the start of any new antineoplastic therapies and survival status.

[2] Following the Follow-up Visit 1 (3 months from last dose), subjects that present(ed) with PD and/or start new line of therapy before or after discontinuation from study treatment

will move into Survival Follow-up and should be contacted by telephone every 2 months for up to 12 months from last treatment dose to assess for survival status. Every effort should be made to collect subject information on the start of any new antineoplastic therapies and survival status.

[3] Treatment administration and associated procedures for that visit may be delayed for treatment-related AEs beyond the window and subsequent schedule adjusted accordingly. Informed consent may fall outside of the 28-day screening window as long as all of the assessments used for screening are within their respective screening windows.

[4] Tumor tissue for biomarker analysis from a biopsy of a tumor lesion not previously irradiated must be available for PD-L1 expression and HPV evaluation. Should tissue only be sufficient for PD-L1 expression assessment, the subject may still be enrolled and HPV status will not be assessed. Only biopsies obtained at the time of or after the diagnosis of locally advanced, recurrent, and/or metastatic disease will be evaluated for PD-L1 expression. If a tumor biopsy was obtained from a target lesion during eligibility assessment, it is preferred to obtain a new baseline scan. Biopsy of lesions on study should be limited to non-target lesions or new lesions if their pathologic etiology is ambiguous. FOR SUBSEQUENT EVEN CYCLES: An **optional biopsy** is desired at Cycle 2 Day 1 (+/-3) ONLY and, if provided, should be collected ***before*** study drug administration on Cycle 2 Day 1.

[5] Adverse events will be documented from the time of consent through at least Follow-up Visit 1 (3 months from last study drug dose). All AEs will be followed for at least 30 days and all AESIs will be followed for at least 90 days after last study drug administration regardless of relationship to study drug.

[6] The initial tumor imaging will be performed within 21 days prior to first dose. Scans performed as part of routine clinical management are acceptable for use as screening scan if they are of diagnostic quality and <-21 days prior to first dose. For subjects with no previous history of brain metastases, screening brain imaging will need to be obtained only if clinically indicated. MRI is the preferred brain imaging modality; however, CT is acceptable if an MRI is clinically contraindicated. On-study imaging will be performed every 6 weeks (+/- 3 days), or more frequently if clinically indicated. The timing of imaging assessments should follow calendar days and should not be adjusted for delays in treatment administration or for visits. The same imaging technique should be used in a subject throughout the trial. Additional imaging at Discontinuation Visit and Safety Follow-up Visit is not required provided imaging assessments have been performed per schedule.

[7] Screening brain imaging is only necessary if clinically indicated. MRI is the preferred brain imaging modality; however, CT is acceptable if an MRI is clinically contraindicated.

[8] Blood samples for circulating DNA assessments to be collected pre-dose on Days 1 and 29 of Cycle 1, on Day 1 of Cycles 2 and 3, and at the discontinuation visit.

[9] Assessed at Cycles 2 and 3.

[10] Blood sample for PGx is collected only if an optional PGx consent is signed.

[11] Whole blood for PBMC to be collected pre-dose on Days 1, 8, 29 of Cycle 1, on Day 1 of Cycles 2, and 3 and at the discontinuation visit.

[12] For screening, laboratory tests should be performed within 7 days prior to the first dose of study treatment. Unless otherwise specified, for treatment phase visits, laboratory tests may be collected up to 48 hours before visits and results must be available before treatment.

[13] Core serum chemistry: alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN)/total urea, calcium, chloride, creatinine, glucose, magnesium, phosphorus/phosphates, potassium, sodium, total bilirubin; Results must be available prior to dosing.

[14] Full serum chemistry: core serum chemistry and albumin, amylase, cholesterol, creatine kinase, C-reactive protein (CRP), gamma glutamyl transferase (GGT), lactate dehydrogenase (LDH), lipase, total protein, triglycerides, uric acid; Results must be available prior to dosing.

[15] Hematology Tests: absolute eosinophil count, absolute lymphocyte count, absolute neutrophil count (ANC), hematocrit, hemoglobin, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelet count, red blood cell (RBC), white blood cell (WBC) and differential count; Results must be available prior to dosing.

[16] Coagulation Tests: activated partial thromboplastin time (aPTT), Prothrombin time - international normalized ratio (INR); Results must be available prior to dosing.

[17] Endocrine function tests: free thyroxine (T4), thyroid-stimulating hormone (TSH); basal cortisol in the absence of corticosteroid treatment. Results must be available prior to dosing at the subsequent visit.

[18] Urinalysis including blood, glucose, protein, specific gravity, and microscopic exam if abnormal; Results must be available prior to dosing.

[19] Serum β-human chorionic gonadotropin (β-HCG) pregnancy test for women of childbearing potential at screening within 72 hours of first treatment dose (if performed earlier in screening period then a urine pregnancy test may be performed prior to first dose); urine pregnancy test at all other indicated visits (centers where urine pregnancy testing is not routine may substitute with serum β-HCG pregnancy test); Results must be available prior to dosing.

[20] AGEN2034 should be administered first, and within 30 min (-10/+20 min). Subjects must be observed for 30 min post-infusion for infusion-related reactions. If administration of one infusion is delayed due to an AE, the other is delayed as well and in this case, treatment visits may be delayed beyond the window of 3 days and schedules for subsequent visits should be adjusted accordingly.

[21] Visits on Days 2, 4, and 16 (for non-selected sites) that contain only review of AEs, concomitant medications, and ECOG status should be planned as on-site visits, particularly in Cycle 1, but if on the day of the planned visit the subject is not experiencing any AEs that would necessitate a physical evaluation or other follow-up, then the telephone/telemedicine call may serve as the visit if the subject prefers not to travel to the site that day. AEs, concomitant medications, and ECOG status must all be documented in the source notes from the call.

Table 18: Schedule of ECG, ADA, and PK Assessments for Phase 2

Notes:

- 'Predose' means just prior to any study drug administration (maximum 6 hr prior); 'Postdose' time is calculated from the start time of the first study drug on Day 1 of the cycle.
- 'Cycle' refers to a 6-week cycle relative to AGEN1884 administration frequency.
- The order of study assessments should be ECG, then PK sample, then ADA sample, and then any other blood sample(s) if they are coincident.

Study Visit	Timepoint	12-Lead ECG	Sample Type		
			PK		ADA
		(in triplicate and within 0.25 hr prior to paired PK if coincident)	All Subjects	Subset of Subjects (up to 25 subjects)	All Subjects
Screening		X	X	X	
Cycle 1, Day 1	Predose	X	X	X	X
	2 ± 0.5 hr postdose	X	X	X	
Cycle 1, Day 4	72 ± 6 hr postdose			X	
Cycle 1, Day 6*	120 ± 6 hr postdose			X	
Cycle 1, Day 8	168 ± 6 hr postdose			X	
Cycle 1, Day 15	336 ± 6 hr postdose but prior to AGEN2034 dose	X	X	X	X
Cycle 1, Day 29	672 ± 6 hr postdose but prior to AGEN2034 dose		X	X	
Cycle 2, Day 1	Predose		X	X	
Cycle 3, Day 1	Predose		X	X	
Cycle 4, Day 1	Predose	X	X	X	X
	2 ± 0.5 hr postdose	X	X	X	
Cycle 4, Day 4*	72 ± 6 hr postdose			X	
Cycle 4, Day 6*	120 ± 6 hr postdose			X	
Cycle 4, Day 8*	168 ± 6 hr postdose			X	
Cycle 4, Day 15	336 ± 6 hr postdose but prior to AGEN2034 dose		X	X	
Cycle 4, Day 29	672 ± 6 hr postdose but prior to AGEN2034 dose		X	X	
Cycle 5, Day 1	Predose	X	X	X	X
Cycle 9, Day 1	Predose	X	X	X	X
Cycle 13, Day 1	Predose	X	X	X	X
Cycle 17, Day 1	Predose	X	X	X	X
Discontinuation Visit		X	X	X	X
Safety/Follow-up Visit	Safety Follow-up Visit 1 (4 weeks from last dose) Follow-up Visit 1 (3 months from last dose)	X	X	X	X

*Visits on Cycle 1, Day 6 and Cycle 4, Days 4, 6, and 8 are only required for subjects at sites selected to perform the additional PK sampling as noted in this table. These blood draw only visits may be performed by a qualified vendor closer to the subject's home for convenience, provided the samples are processed, shipped, and/or stored per the laboratory manual. The 2 hr postdose PK sample should never be taken during infusion, but shortly following end of infusion (for those infusions that go longer than the protocol recommended durations).

6.1 Visit Requirements

6.1.1 Screening

Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose of study treatment as described below:

- Within 28 days prior to first dose:
  - Administrative screening.
  - For subjects in Phase 2, tumor biopsy and/or archival tissue collection for PD-L1 expression analysis.
- Within 14 days (Phase 1) or 21 days (Phase 2) prior to the first dose of study treatment:
  - Tumor imaging, unless diagnostic quality tumor imaging is available for exams prior to the first dose of study treatment. Measurable disease by RECIST 1.1 must be confirmed by independent central radiologic review prior to first dose. Subjects without centrally confirmed measurable disease at baseline will not be eligible for this trial.
  - Brain MRI (or CT if MRI clinically contraindicated), unless adequate imaging is available for exams within 28 days prior to the first dose of study treatment (Phase 1). In Phase 2, brain imaging is only performed if clinically indicated.
- Within 7 days prior to the first dose of study treatment:
  - Laboratory tests.
  - Clinical procedures and assessments.
  - If result of one or more screening assessments do not meet criteria for the study but are expected to improve (with or without intervention), assessments may be repeated once as long as the final results used for eligibility are completed within the protocol-defined window prior to study treatment.
- Within 72 hours prior to the first dose of study treatment:
  - For women of reproductive potential, a serum pregnancy test will be performed within 72 hours prior to first dose of study treatment. If a serum pregnancy test was performed during screening but earlier than 72 hours prior to first dose, a urine pregnancy test may be performed prior to first dose. A negative pregnancy test collected within 72 hours prior to first dose must be available prior to the administration of the first dose.

During the screening period, attention must be given to washout periods for prior treatments and prohibited medications.

Results from assessments performed during the initial screening period are acceptable in lieu of repeating a screening test if performed within the specified time frame and the results meet the inclusion/exclusion criteria.

Screen failures must be documented and the reason for the failure must be recorded.

6.1.2 Treatment Period

Visit requirements are outlined in Section 6 – Trial Assessments and Procedures. Specific procedure-related details are provided in Section 6.2 - Trial Procedures.

Subject should continue to receive all assessments as defined in the Treatment phase of the Schedule of Assessments while they are actively receiving treatment.

6.1.3 End-of-Treatment Visits

Visit requirements are outlined in Section 6 – Trial Assessments and Procedures. Specific procedure-related details are provided above in Section 6.2 - Trial Procedures.

6.1.3.1 Discontinuation Visit

The Discontinuation Visit should occur at the time study drug is discontinued for any reason. If the Discontinuation Visit occurs 4 weeks from the last dose of study treatment, at the time of the mandatory Safety Follow-up Visit, procedures do not need to be repeated. Procedures at the time of discontinuation are detailed in Section 6.1.3.2 Safety Follow-up Visit.

6.1.3.2 Safety Follow-up Visit (4 weeks from last dose)

The mandatory Safety Follow-Up Visit should be conducted for all subjects approximately 4 weeks after the last dose of study drug or before the initiation of a new antineoplastic treatment, whichever comes first. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first. Subjects with an adverse drug reaction (ADR) ongoing at the Safety Follow-up Visit must be followed up until the ADR resolves, becomes stable, or is considered not clinically significant by the investigator.

6.1.4 Follow-up Phase (Up to 12 months from Safety Follow-up Visit)

In Phase 1 and Phase 2, subjects who discontinue treatment for any reason, will have at least one Follow-up visit at 3 months (± 7 days) from last study drug dose.

Subjects who received the maximum administrations of the combination of AGEN2034 and AGEN1884; who have achieved a CR according to RECIST 1.1; or who have discontinued treatment due to reasons other than disease progression and/or start of a new line of therapy, will be followed for up to 12 months after the last dose of study drug or until death, withdrawal of consent, or becoming lost to follow-up.

In Phase 1, subjects who discontinue due to disease progression and/or start of a new line of therapy will then end participation in the trial.

In Phase 2, subjects who discontinue due to disease progression and/or start of a new line of therapy will then move into Survival Follow-up for up to 12 months from last study drug dose.

Specific procedure-related details are provided above in Section 6.2 - Trial Procedures.

6.1.5 Survival Follow-up (Phase 2 only)

There is no Survival Follow-up for Phase 1.

For subjects in Phase 2, after Follow-up Visit 1 (3 months after last dose of study drug), subjects with PD and/or who start new line of therapy before or after completing Follow-up Visit 1 will

move into Survival Follow-up. Subjects should be contacted by telephone to assess for survival status every 2 months for up to 12 months after their last dose of study drug.

6.2 Trial Procedures

The schedules of events in Section 6 summarize the trial procedures to be performed at each visit in Phase 1 (Table 16) and Phase 2 (Table 17 and Table 18). Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled timepoints if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In these cases, such evaluations/testing will be performed in accordance with clinical judgment.

6.2.1 Administrative Procedures

6.2.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject prior to participating in the clinical trial and for optional pharmacogenomics research.

6.2.1.2 General Informed Consent

Consent must be documented by the subject's dated signature along with the dated signature of the person conducting the consent discussion. A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The investigator is responsible for ensuring that a careful and thorough informed consent procedure is implemented before a subject enters the trial and at any time during the trial, should ICF changes be introduced. This includes, but is not limited to: (1) allowing ample time for this review by the subject; (2) ensuring that qualified medical personnel are available to directly answer questions that a subject may have; (3) ensuring that each potential trial subject understands that his or her medical treatment will not be otherwise affected based on the decision whether or not to participate in the trial, that his or her participation is completely voluntary, and that he or she can opt to stop participation in the trial at any time for any reason; and (4) ensuring a full copy of the signed ICF is given to the subject to take home for his or her medical records. The process for obtaining informed consent should also be noted in the subject's source documentation.

The initial ICF, any subsequent revised written ICF, and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

The informed consent will adhere to IRB/ERC requirements, applicable laws, and regulations and Sponsor requirements.

6.2.1.3 Consent for Pharmacogenomics Assessment

Participation in the pharmacogenomics portion of the trial is optional and requires separate informed consent. Participation in the pharmacogenomics portion of the trial will not affect

participation in the trial. Subjects may withdraw consent from pharmacogenomics portion of the trial without withdrawing from the trial.

Specimens that may be used for pharmacogenomics testing include: blood and tumor specimens collected during this trial.

The investigator or qualified designee will explain the optional pharmacogenomics assessment portion of the consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to pharmacogenomics assessment. A copy of the informed consent will be given to the subject.

6.2.1.4 Review of Inclusion and Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

6.2.1.5 Emergency Medical Support and Subject Card

All subjects will be given an Emergency Medical Support and Subject Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with an Emergency Medical Support and Subject Card immediately after the subject provides written informed consent.

6.2.1.6 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions; history of hepatitis B virus (HBV), hepatitis C virus (HCV), HIV and/or HPV; and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the investigator. Medical history will also include an assessment of smoking history.

History of the cancer under study will be recorded ***separately*** (see Section 6.2.1.9); all other cancer history should be captured in the medical history.

For subjects in Phase 2, in addition, record any prior cancer other than cervical cancer even if diagnosed greater than 10 years prior to Visit 1.

6.2.1.7 Review of Baseline Symptoms

Baseline symptoms will be assessed for each subject at screening. Baseline symptoms will be Graded and recorded according to NCI-CTCAE Version 4.03. Baseline symptoms will be characterized in terms including seriousness, causality to previous treatment, toxicity grading, and action(s) taken if any.

6.2.1.8 Review of Prior and Concomitant Medications

6.2.1.8.1 Prior Medications

All medication — other than chemotherapy — taken by the subject within 30 days before starting the trial will be recorded. In addition, all treatments for a prior cancer other than current cancer will be recorded, even if taken greater than 30 days prior to Visit 1.

Prior treatments for the current cancer will be recorded ***separately*** (see Section 6.2.1.9) and not listed as a prior medication.

6.2.1.8.2 Concomitant Medications

Record medication, if any, taken by the subject during the trial from the date of consent through the 30-day Safety Follow-up Visit. After the Safety Follow-up Visit, record all medications related to reportable SAEs and AESIs as defined in Section 7.2.2.2.

6.2.1.9 Cancer Disease Details and Prior Treatment

Obtain current cancer disease details and prior treatment for all subjects including:

- Detailed history of the tumor, including histopathological diagnosis, grading, and staging in accordance with the eighth edition of the American Joint Committee on Cancer staging manual (AJCC-8) Tumor Node Metastasis (TNM) classification at diagnosis.
- All therapy used for prior treatment of the disease under study (including but not limited to surgery, radiotherapy [including total radiation dose received and general treatment field], and any systemic treatment) – and for each therapy, complete dosing schedule, and their corresponding best response.
- Any other conditions treated with chemotherapy, radiation therapy, or immunotherapy.
- Current cancer signs and symptoms, and side effects from current and/or previous antineoplastic treatments.
- Current cancer disease status.
- Relevant somatic or germline mutations detected.
- Chronic viral infection status, if available.
- Human epidermal growth factor receptor 2 (HER2) status, if available.
- Smoking history.
- Tumor markers, including but not limited to, molecular/genetic or immunohistochemistry markers (e.g., PSA, CA125, AFP, *BRACA*, PD-L1 status, etc) if applicable and if available
- HPV status, if available.

6.2.1.9.1 Subsequent Antineoplastic Therapy

The investigator or qualified designee will review all new antineoplastic therapy initiated after the last dose of study drug. If a subject initiates a new antineoplastic therapy within 4 weeks after the last dose of study drug, the Safety Follow-up Visit must occur before the first dose of the new therapy. Once new antineoplastic therapy has been initiated, subjects in Phase 2 will move into Survival Follow-up.

6.2.1.10 Assignment of Subject Trial Number

After a subject signs an ICF, the subject will be assigned a unique, sequential subject number. Once a number is assigned, it cannot be reassigned if the original subject is found to be ineligible or withdraws consent.

6.2.1.11 Trial Compliance

Any delay from the protocol-specified AGEN2034 or AGEN1884 dosing frequency which is due to toxicity and which results in > 6 weeks between AGEN2034 or AGEN1884 doses requires consultation between the investigator and the Sponsor, and written documentation of the collaborative decision on subject management.

Administration of trial medication will be witnessed by the investigator and/or trial staff. The total volume of study treatment infused will be compared to the total volume prepared to determine compliance with each dose administered.

Any reason for noncompliance should be documented. Noncompliance is defined as a subject missing >1 cycle of study treatment for non-medical reasons. If 1 cycle was missed and the interval between the subsequent treatment cycle and the last administered treatment cycle is longer than 4 weeks for non-medical reasons, criteria for insufficient compliance are met.

6.2.2 [redacted]

[redacted]

6.2.3 Clinical Assessments and Procedures

6.2.3.1 Review of Adverse Events

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Schedule of Assessments and Procedures and more frequently if clinically indicated. Adverse experiences will be Graded and recorded throughout the trial and during the follow-up period according to NCI-CTCAE Version 4.03 (see Section 7). Toxicities will be characterized in terms including seriousness, causality, toxicity grading, and action taken with regard to study treatment.

Comprehensive assessment of any AE experienced by the subject will be performed throughout the course of the trial, from time of the subject's consent. Trial site personnel will report any AE, whether observed by the investigator or reported by the subject (Section 7.2). Given the intended mechanism of action, particular attention should be given to AEs that may result from enhanced T-cell activation, such as dermatitis, colitis, hepatitis, uveitis, or other immune-related reactions. When clinically indicated, ophthalmologic examinations should be considered for signs or symptoms of uveitis.

An immune-related AE (irAE) may be defined as an AE of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an AE immune-related. Immunological, serological and histological (biopsy) data should be used to support the diagnosis of an immune-related toxicity. Following the guidance described in Section 7.2.2.2, certain irAEs should also be reported to the Sponsor as AESIs.

The reporting period for AEs is described in Section 7.2.1.

6.2.3.2 Physical Examination

6.2.3.2.1 Full Physical Examination

The investigator or qualified designee will perform a complete physical exam during the screening period, as per Section 6 – Trial of Assessments and Procedures. Clinically significant abnormal findings should be recorded as medical history. After consent, new clinically significant abnormal findings should be recorded as AEs.

6.2.3.2.2 Focused Physical Examination

For cycles that do not required a full physical exam in Phase 1 (Table 16) or Phase 2 (Table 17), the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to study treatment administration. New clinically significant abnormal findings should be recorded as AEs. Focused physical exam does not need to be repeated on Cycle 1 Day 1 if full screening physical examination was completed within 2 days prior.

6.2.3.3 Vital Signs, Height, and Weight

Vital signs, height, and weight will be measured and recorded as specified in Phase 1 (Table 16) and Phase 2 (Table 17). The investigator or qualified designee will take vital signs at the specified times including prior to the administration of each dose of study treatment. Vital signs include temperature, pulse, respiratory rate, and blood pressure. Weight should be measured prior to dosing. Height will be measured at Visit 1 only.

6.2.3.4 12-lead Electrocardiogram (ECG)

A standard 12-lead ECG will be performed using local standard procedures at screening and as specified in Phase 1 (Table 16). Clinically significant abnormal findings at Screening should be recorded as medical history.

6.2.3.4.1 Expanded Electrocardiogram Evaluation

In Phase 2, expanded ECG evaluation will occur with 12-lead ECG tracings recorded in *triplicate* at the schedule shown in Table 18.

Every attempt should be made to use the same ECG machine for all measurements within a subject, and ECG values should be computer-generated. Clinically significant abnormal findings at Screening should be recorded as medical history.

6.2.3.5 Eastern Cooperative Oncology Group (ECOG) Performance

ECOG status will be assessed (see Appendix II) at screening, prior to the administration of each dose of study treatment and during the Follow-up Period as specified in Phase 1 (Table 16) and Phase 2 (Table 17).

6.2.4 Imaging Assessments

6.2.4.1 Tumor Imaging

In Phase 1, the initial tumor imaging will be performed within 14 days prior to first dose; however, scans performed as part of routine clinical management are acceptable for use as screening scan if they are of diagnostic quality and performed < 28 days prior to first dose. On-study imaging will be performed every 6 weeks (± 3 days) from first treatment dose (or more frequently if clinically indicated).

In Phase 2, the initial tumor imaging will be performed within 21 days prior to first dose; however, scans performed as part of routine clinical management are acceptable for use as screening scan if they are of diagnostic quality and performed < 21 days prior to first dose. All subjects must have an independent central radiologic review confirm measurable disease by RECIST 1.1 prior to the first dose. Subjects without centrally confirmed measurable disease at baseline will not be eligible for this trial. On-study imaging will be performed every 6 weeks (± 3 days) from first treatment dose (or more frequently if clinically indicated). Imaging studies will be submitted for central review by the IERC.

The timing of on-study treatment imaging should follow calendar days in reference to Cycle 1 Day 1 and should not be adjusted for delays in treatment administration or for visits. Additional imaging at the Discontinuation Visit and Safety Follow-up Visit is not required provided imaging assessments have been performed per schedule.

Throughout the trial, the same imaging technique should be used in a subject. In general, lesions detected at baseline should be followed using the same imaging methodology and preferably the same imaging equipment at subsequent tumor evaluation visits. The investigator may perform scans in addition to a scheduled trial scan for medical reasons or if PD is suspected.

6.2.4.2 Brain Imaging

MRI is the preferred brain imaging modality; however, CT is acceptable if an MRI is clinically contraindicated.

In Phase 1, subjects with no previous history of brain metastases are required to have brain imaging at screening (within 14 days prior to first treatment dose) unless adequate imaging is available for exams within 28 days prior to the first dose of study treatment; except for subjects with cervical cancer, cutaneous squamous-cell carcinoma, gastric/gastroesophageal junction cancer, head and neck squamous-cell carcinoma, ovarian cancer, prostate cancer, mesothelioma, or urothelial carcinoma, for whom brain imaging is necessary only if clinically indicated.

In Phase 2, brain imaging should only be conducted if clinically indicated.

During the trial, brain CT/MRI scans (with contrast if not contraindicated) should be conducted if clinically indicated by development of new specific symptoms.

6.2.4.3 Response Assessment

Response assessment will be performed according to RECIST 1.1 (Eisenhauer et al. 2009) in Phase 1 and Phase 2. In Phase 1, response will be assessed by an investigator; in Phase 2 response will be assessed by an investigator and by an IERC.

For all subjects, tumor response assessment will be performed by CT or MRI of the chest/abdomen/pelvis (plus other regions as required for specific tumor types) and other established assessments of tumor burden if CT/MRI imaging is insufficient for the individual subject. All scans performed at baseline and other imaging performed as clinically required (other supportive imaging) will be repeated at subsequent visits. In general, lesions detected at baseline should be followed using the same imaging methodology and preferably the same imaging equipment at subsequent tumor evaluation visits.

For each subject, the investigator will designate 1 or more of the following measures of tumor status to follow for determining response: CT or MRI images of primary and/or metastatic tumor masses, physical examination findings, and results of other assessments. All available images collected during the trial period will be considered. The most appropriate measures to evaluate a subject's tumor status should be used. Measure(s) chosen for sequential evaluation during the trial must correspond to measures used to document progressive tumor status that qualifies the subject for enrollment.

In Phase 2, radiographic images used for local determination of disease progression will be read centrally and reviewed by a blinded IERC. The IERC will make a determination as to whether criteria for tumor response or progression according to RECIST 1.1 have been met.

Before stopping treatment for any subject, equivocal disease progression should be confirmed by imaging, preferably 6 weeks (but not later) after the equivocal progression has been observed. If progression is based on occurrence of a new lesion in an area not scanned at baseline, further on-trial scan 6 weeks later should be considered before performing the end-of-treatment visit.

Symptomatic deterioration **suspected to be secondary to PD** should be confirmed by imaging to document objective progression, preferably before stopping treatment but no later than 2 weeks after clinical progression has been diagnosed.

Tumor responses to treatment will be assigned based on evaluation of response of target, non-target, and new lesions according to RECIST 1.1 (all measurements should be recorded in metric notation); see (Eisenhauer et al. 2009). Assessment of tumor response by the IERC will be defined in the IERC Charter.

- To assess objective response, tumor burden at baseline will be estimated and used for comparison with subsequent measurements. At baseline, tumor lesions will be categorized in target and non-target lesions as described in (Eisenhauer et al. 2009).

Results for these evaluations will be recorded with as much specificity as possible so that pre- and post-treatment results will provide the best opportunity for evaluating tumor response.

Any CR or PR should be confirmed as described in (Eisenhauer et al. 2009).

Subjects who experience PD per RECIST 1.1 but are clinically stable may continue treatment until confirmatory imaging at the next scheduled timepoint (i.e., 6 weeks later) using the same imaging modality.

In the case of a PR or CR, a confirmatory CT or MRI scan must be conducted ≥28 days later.

The investigator may perform scans in addition to a scheduled trial scan for medical reasons or if PD is suspected.

6.2.5 Pharmacokinetic, Pharmacodynamic, Genetic, and Other Assessments

Sample collection, labeling, storage, and shipment instructions will be provided in the operations/laboratory manual.

A full chain of custody will be maintained for all samples throughout their lifecycle. The Sponsor will keep oversight of the entire life cycle through internal procedures, monitoring of trial sites, and auditing of external laboratory providers.

6.2.5.1 Pharmacokinetic Assessments

Blood samples for assessment of the pharmacokinetics of AGEN2034 will be collected during Phase 1 for all subjects at the timepoints described in Table 16. For Phase 2, the PK blood sample schedule is detailed in Table 18, including additional PK blood samples in up to 25 subjects at selected sites.

6.2.5.2 Immunogenicity Assessments

Blood samples for assessment of the immunogenicity of AGEN2034 will be collected for all subjects at the time points described in Phase 1 (Table 16).

The immunogenicity assessment will be conducted to detect and measure ADA (antibody against AGEN2034 and AGEN1884) for Phase 2 at the timepoints described in Table 18.

6.2.5.3 Blood Biomarker Assessments

To complete all assessments on blood samples (whole blood, plasma, and serum), the Sponsor or designated contract research organization (CRO) will provide instructions and necessary supplies to the site, including shipping materials and prepaid mailers. Refer to the Laboratory Manual for detailed information.

[redacted] Collection and storage of samples will be detailed in the Laboratory Manual. The panel of biomarkers might be adjusted based on results from ongoing research related to anti–PD1/PD-L1 and anti-CTLA-4 therapies and/or safety.

[redacted]

[redacted]

6.2.5.3.2 Phase 2

[redacted]

6.2.5.4 Pharmacogenomics Assessments (Optional)

The Sponsor may conduct research on DNA (blood) or tumor tissue specimens collected during this trial. This research may include genetic analysis (DNA) and gene expression profiling (RNA).

Germline (inherited) variants will be investigated in DNA extracted from the whole blood. For this purpose, an additional 4 mL of whole blood (PGx sample) will be collected at screening. Additionally, tumor biopsy samples may be used for the extraction of DNA to study tumor genetics (somatic variations). Participation is optional for subjects being recruited at sites whose IEC/IRB has approved pharmacogenomics assessments and a pharmacogenomics ICF (optional) is signed.

All samples collected during the trial will be kept confidential. For this purpose, the samples will be given a label connected with a code assigned at the start of the Main Study (coded trial subject number). Outside the study center, no one will be able to link the subject's identity to the subject number. The link between the subject's identity and the subject number will only be known by a limited number of authorized personnel. Information about race, ethnicity, sex, medical history, etc, may be available to scientists studying the PGx blood samples. Such information might be important for research or public health purposes. Genomic analysis results will not be reported back to the sites.

Participation in pharmacogenomics portion of the trial is optional and requires separate informed consent. Participation in the pharmacogenomics portion of the trial will not affect participation in the trial. Subjects may withdraw consent from pharmacogenomics portion of the trial without withdrawing from the trial. Consent and withdrawal of consent (if applicable) for pharmacogenomics assessments will be documented in the eCRF.

6.2.6 Local Laboratory Tests

It is essential that the Sponsor be provided with a list of laboratory normal ranges before shipment of study drug. Any change in laboratory normal ranges during the trial will additionally be forwarded to the CRO and the Sponsor.

Blood samples will be collected from non-fasted subjects. All routine laboratory analyses will be performed at a laboratory facility local to the investigational site.

The overall amount of blood to be drawn for safety laboratory testing, pregnancy testing, and exploratory biomarker investigation from a single subject with a body weight ≤70 kg (154 lb) must not exceed 120 mL/week.

Laboratory tests for screening should be performed within 7 days prior to the first dose of study treatment. Subsequent predose laboratory procedures can be conducted up to 48 hours prior to dosing.

Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of study treatment.

The report of the results must be retained as a part of the subject's medical record or source documents. Blood samples for trial-related tests will be collected at timepoints specified in Table 16 and Table 17.

Laboratory tests are shown in Table 19.

Table 19: Required Local Laboratory Panel Tests

Full Chemistry
Albumin
Alkaline phosphatase[1]
ALT (SGPT)[1]
Amylase
AST (SGOT)[1]
BUN/total urea[1]
Calcium[1]
Chloride[1]
Cholesterol
Creatine kinase
Creatinine[1]
CRP
GGT
Glucose[1]
LDH
Lipase
Magnesium[1]
Phosphorus/phosphates[1]
Potassium[1]
Sodium[1]
Total bilirubin[1]
Total protein
Triglycerides
Uric acid

Hematology
Absolute lymphocyte count
ANC
Hematocrit
Hemoglobin
MCH
MCHC
MCV
Platelet count
RBC
WBC and differential count

Coagulation Studies
aPTT
Prothrombin time (INR)

Endocrine Function Tests
T4
TSH
Basal cortisol

Pregnancy Tests
Serum pregnancy test
Urine pregnancy test

ALT: alanine aminotransferase; ANC: absolute neutrophil count; aPTT: activated partial thromboplastin time; AST: aspartate aminotransferase; BUN: blood urea nitrogen; CRP: C-reactive protein; FSH: follicle-stimulating hormone; GGT: gamma glutamyl transferase; INR: international normalized ratio; LDH: lactate dehydrogenase; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; RBC: red blood cell; SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase; T4: free thyroxine; TSH: thyroid-stimulating hormone; WBC: white blood cell.

[1]Core serum chemistries.

7 Adverse Events

The adverse event reporting period begins from the time that the subject signs the ICF through and including at least 90 calendar days (Follow-up Visit 1) after the last study drug dose for AESIs and at least 30 days (Safety Follow-up Visit) for all other AEs. All treatment-related AEs/SAEs should be followed until resolution or stabilization. Any SAE occurring after the reporting period must be promptly reported if a causal relationship to the investigational drug is suspected. If the subject begins a new antineoplastic therapy, only the safety reporting of AESIs and death must be reported for the duration of 90 days from the last study drug dose irrespective of a new intervening treatment.

7.1 Adverse Event Definitions

7.1.1 Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with use of a medicinal product, whether or not considered related to the medicinal product. In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

The investigator is required to Grade the severity/intensity of each AE. Investigators will reference NCI-CTCAE v4.03, which is a descriptive terminology that can be used for AE reporting. A general grading (severity/intensity) scale is provided at the beginning of the referenced document, and specific event Grades are also provided. If a particular AE severity/intensity is not specifically Graded by the guidance document, the investigator is to revert to the general definitions of Grade 1 through Grade 5 and use his/her best medical judgment.

The 5 general Grades of AE severity are:

Grade 1: Mild
Grade 2: Moderate
Grade 3: Severe
Grade 4: Life-threatening or disabling
Grade 5: Death related to AE

According to the Sponsor's convention, if a severity/intensity of Grade 4 or 5 is applied to an AE, the investigator must also report the event as an SAE as per Section 7.2.2. However, a laboratory abnormality with a severity/intensity of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria described below.

In the case of death, the primary cause of death or the event leading to death should be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this respective event; death will not be recorded as separate event. Only if no cause of death can be reported (e.g., sudden death, unexplained death), might the death *per se* be reported as an SAE.

Investigators must also systematically assess the causal relationship of AEs to the IMP or to AGEN2034 using the following definitions. Decisive factors for assessment of causal relationship of an AE to AGEN1884 or to AGEN2034 include, but may not be limited to, temporal relationship between the AE and AGEN1884 and/or AGEN2034, known side effects of AGEN2034 and or AGEN1884, medical history, concomitant medication, course of the underlying disease, and trial procedures.

Not related: Not suspected to be reasonably related to AGEN2034 or to AGEN1884. AE could not medically (pharmacologically/clinically) be attributed to the AGEN2034 under trial in this clinical trial protocol. A reasonable alternative explanation must be available.

Related: Suspected to be reasonably related to AGEN1884 or to AGEN2034. AE could medically (pharmacologically/clinically) be attributed to the AGEN1884 or to AGEN2034 under trial in this clinical trial protocol.

7.1.2 Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (e.g., on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation, or are considered otherwise medically important by the investigator. If an abnormality fulfills these criteria, the identified medical condition (e.g., anemia, increased ALT) must be reported as the AE rather than the abnormal value itself.

7.1.3 Adverse Drug Reaction

Adverse drug reactions (ADR) are defined in this trial as any AEs suspected to be related to AGEN1884 and/or AGEN2034 by the investigator and/or Sponsor.

7.1.4 Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.

  Note: The term "life-threatening" in this definition refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- An overdose of Sponsor's product, as defined in Section 7.5.
- Is otherwise considered as medically important.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based on appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in subject hospitalization, or development of drug dependency or drug abuse.

For purposes of reporting, any suspected transmission of an infectious agent via an IMP is also considered a serious adverse reaction, and all such cases should be reported in an expedited manner as described in Section 7.2.2.

7.1.5 Events That Do Not Meet the Definition of an SAE

Elective hospitalizations to administer or to simplify study treatment or trial procedures (e.g., overnight stay to facilitate chemotherapy and related hydration therapy application) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (e.g., undesirable effects of any administered treatment) must be documented and reported as SAEs.

7.1.6 Events not to be Considered as AEs/SAEs

Medical conditions present at the initial trial visit that do not worsen in severity or frequency during the trial are defined as baseline medical conditions and are **not** to be considered AEs.

7.1.7 AE/SAEs Observed in Association with Disease Progression

Disease progression recorded in the course of efficacy assessments only, but without any adverse signs or symptoms, should not be reported as an AE. However, if adverse signs or symptoms occur in association with disease progression, these should be recorded as AEs and as SAEs if they meet any seriousness criteria.

7.1.8 Predefined Potential AEs of Special Interest for Safety Monitoring

Selected non-serious and SAEs defined below are considered AESI and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

- Infusion-related reactions per NCI-CTCAE v.4.03
- An elevated AST or ALT lab value that is greater than or equal to 3× the ULN and an elevated total bilirubin value that is greater than or equal to 2× the ULN and, at the same time, an alkaline phosphatase lab value that is less than 2× the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.

  Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.
- Any AE that is reasonably suspected to be immune-mediated (i.e., an irAE).

AESIs (both non-serious and serious AEs) identified in this guidance document will be followed from the date of first dose through 90 days (Follow-up Visit 1) following discontinuation of treatment, or 30 days after the initiation of a new antineoplastic therapy, whichever is earlier, regardless of attribution to study drug.

Subjects should be assessed for possible AESIs prior to each dose. Lab results should be evaluated, and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an AE thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible irAE, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

Any infusion reaction, regardless of Grade, must be reported in an expeditious manner and will be considered an AESI. The reporting of AESI is described in Section 7.2.2.2.

7.2 Methods of Recording and Assessing Adverse Events

At each trial visit, the subject will be queried on changes in his/her condition. During the reporting period of the trial, any unfavorable changes in the subject's condition will be recorded as AEs, whether reported by the subject or observed by the investigator.

Complete, accurate, and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the eCRF. Among these AEs, all SAEs and all non-serious AESIs must be additionally documented and reported using the appropriate report form as described in Section 7.2.2.

It is important that each AE report include a description of the event, its duration (onset and resolution dates and times to be completed when it is important to assess time of AE onset relative to recorded treatment administration time), its severity, causal relationship with study treatment, any other potential causal factors, any treatment administered, or other action taken (including dose modification or discontinuation of the IMP), and outcome. In addition, serious cases should be identified, and the appropriate seriousness criteria documented.

Specific guidance can be found in the eCRF Completion and Monitoring Conventions.

7.2.1 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance begins when the subject is consented and continues through at least Follow-up Visit 1 (3 months from last dose of study drug). All AEs (including SAEs) will be followed for at least 30 days (Safety Follow-up Visit) and all AESIs will be followed for at least 90 days after the last study drug administration (Follow-up Visit 1).

7.2.2 Procedure for Reporting SAEs / AESIs

All adverse reactions will be reported to the FDA according to 21 Code of Federal Regulations (CFR) 312.32 and according to applicable regulatory authorities and institutional ethics committees.

7.2.2.1 Serious Adverse Events

In the event of any new SAE (of any Grade) occurring during the reporting period, the investigator must immediately (i.e., ≤24 hours after becoming aware of the event) inform the Sponsor or designee by telephone, fax, or e-mail.

By electronic media [redacted]

or

Paper (Fax: [redacted]).

For the following SAEs the reporting period to the Sponsor is ≤ 8 hours after becoming aware of the event:

- drug-related death after less than 30 days of dosing
- drug-related life-threatening event.

When an event (or follow-up information) is reported by telephone, a written report must be sent immediately thereafter by fax or e-mail.

Reporting procedures and timelines are the same for any new information on a previously reported SAE (= follow-up).

For names, addresses, telephone, and fax numbers for SAE reporting, see information included on the SAE report form.

All written reports should be transmitted using the SAE report form, which must be completed by the investigator following specific completion instructions. The AE section of the eCRF must be completed. Relevant pages from the eCRF may be provided in parallel (e.g., medical history, concomitant drugs).

In all cases, information provided in the SAE report form must be consistent with data on the event that is recorded in the corresponding eCRF sections.

The investigator/reporter must respond to any request for follow-up information (e.g., additional information, outcome, and final evaluation, specific records where needed) or to any question the Sponsor or designee may have regarding the AE within the same timelines as described for initial reports. This is necessary to permit a prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the company to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made by the responsible monitor, although in exceptional circumstances the Sponsor's global drug safety department may contact the investigator directly to obtain clarification or to discuss a particularly critical event.

7.2.2.2 Adverse Events of Special Interest

In the event of a non-serious AESI, the investigator must complete the AESI report form and send it to the Sponsor/designee immediately, within 24 hours. Names, addresses, and telephone and fax numbers for AESI reporting will be included on the report form. Serious AESIs must be reported in an expedited manner as SAEs, as outlined above.

7.2.2.3 Safety Reporting to Health Authorities, Independent Ethics Committees / Institutional Review Boards, and Investigators

The Sponsor will send appropriate safety notifications to health authorities in accordance with applicable laws and regulations.

The investigator must comply with any applicable site-specific requirements related to reporting of SAEs (and in particular deaths) involving his/her subjects to the IEC/IRB that approved the trial.

In accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, the Sponsor or designee will inform the investigator of "findings that could adversely affect the safety of subjects, impact the conduct of the trial, or alter the IEC's/IRB's approval/favorable opinion to continue the trial." In accordance with respective regulations, the Sponsor or designee will inform the investigator of AEs that are both serious and unexpected and are considered to be related to the administered product (suspected unexpected serious adverse reactions [SUSARs]). The investigator should place copies of safety reports in the investigator site file. National regulations with regard to safety report notifications to investigators will be taken into account.

When specifically required by regulations and guidelines, the Sponsor or designee will provide appropriate safety reports directly to the concerned Health Authority and lead IEC/IRB, and will maintain records of these notifications. When direct reporting by the Sponsor or designee is not clearly defined by national or site-specific regulations, the investigator will be responsible for

promptly notifying the concerned IEC/IRB of any safety reports provided by the Sponsor or designee, and for filing copies of all related correspondence in the investigator site file.

7.3 Monitoring of Subjects with Adverse Events

Adverse events are recorded and assessed continuously throughout the trial starting at the time the subject consents (Section 7.2.1) up to at least 30 days from last dose for all AEs and up to 90 days from last dose for AESI.

After the Safety Follow-up Visit (4 weeks from last dose of study drug), all AEs will be documented for at least 30 days and AESIs will be documented for at least 90 days.

All SAEs ongoing at the post-treatment Safety Follow-up Visit must be monitored and followed by the investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up."

Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

7.4 Pregnancy and *In Utero* Drug Exposure

Only pregnancies considered by the investigator as related to study treatment (e.g., resulting from a drug interaction with a contraceptive medication) are considered as AEs.

However, all pregnancies with an estimated conception date during the period defined in Section 7.2.1 must be recorded by convention in the AE page/section of the eCRF.

The same rule applies to pregnancies in female subjects and in female partners of male subjects. The investigator must notify the Sponsor or designee in an expedited manner of any pregnancy using the pregnancy report form, which must be transmitted according to the same process as described for SAE reporting in Section 7.2.2.

Investigators must actively follow up, document, and report the outcome of these pregnancies, even if subjects are withdrawn from the trial. A separate consent will be obtained for follow-up of these subjects.

The investigator must notify the Sponsor or designee of these outcomes using the pregnancy report form and, in case of abnormal outcome, the SAE report form if the subject sustains an event and the parent-child/fetus AE report form when the child/fetus sustains an event).

Any abnormal outcome must be reported in an expedited manner, as described in Section 7.2.2, whereas normal outcomes must be reported within 45 days from delivery.

In the event of a pregnancy in a subject occurring during the course of the trial, the subject must be discontinued from trial medication immediately. The Sponsor or designee must be notified without delay and the subject must be followed as described above.

7.5 AGEN1884 and/or AGEN2034 Overdose

An overdose is defined as any dose 5% greater than the highest daily dose included in the clinical trial protocol. Any overdose must be recorded in the trial medication section of the eCRF.

For monitoring purposes, any case of overdose, whether or not associated with an AE (serious or non-serious), must be reported to the Sponsor's or designated CRO's global drug safety department in an expedited manner using the SAE report form.

There is no data on AGEN1884 or AGEN2034 overdose to date. Data available with agents from the same class indicate that the correlation between dose and toxicity is relatively flat.

The investigator should use his or her clinical judgment when treating an overdose of AGEN1884 and/or AGEN2034.

8 Statistical Considerations

This section outlines the core elements of the planned statistical summaries and analyses for the data collected in this trial. Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a Statistical Analysis Plan (SAP), which will be maintained by the Sponsor. The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment. If, after the data are locked, changes are made to the SAP, then these deviations to the plan will be documented, in the Clinical Trial Report (CSR).

8.1 Sample Size

The trial includes 2 phases: Phase 1: Dose Escalation Phase, and Phase 2: Efficacy Phase. The total sample size for both phases is expected to be approximately 170 treated subjects.

8.1.1 Phase 1

It is expected that approximately 20 subjects will be enrolled in the Phase 1 part of the trial. The sample size in the Phase 1 is not driven by statistical hypothesis testing, but by clinical considerations. Final sample size in this phase may vary depending on the total number of dose levels to be tested, and subject replacement for DLT evaluation, if applicable.

8.1.2 Phase 2

The Phase 2 part is a single-arm study of the AGEN1884 and AGEN2034 combination in advanced cervical cancer. The aim in this phase is to detect preliminary evidence of clinical activity. The primary endpoint is the confirmed ORR per IERC based on RECIST v1.1. ORR will be estimated as a binomial proportion of confirmed responses and reported with 95% Wilson score CI; the CI will be interpreted as a plausible range for a true (unobserved) ORR.

Phase 2 is expected to enroll approximately 150 subjects. With 150 subjects in the final analysis, the power to exclude the ORR of 10% by the lower limit of the 95% Wilson score interval is 94% assuming a true ORR for the combination of AGEN1884 and AGEN2034 of 20%. The sample size will provide ≥ 77% probability to observe an AE with and underlying rate of ≥ 1%. With 100 subjects in an interim analysis, the power to exclude an ORR of 10% by the lower limit of the two-sided 95% Wilson score interval will be 87.1% assuming a true ORR of 20%.

Interim analyses will be performed to assess the safety and efficacy (using the ORR and selected secondary efficacy endpoints) when (1) data are available for approximately 30 subjects treated for at least 3 months and (2) approximately 3 months after approximately 100 subjects are dosed. No early stopping for efficacy will be performed, as a more complete safety assessment and evaluation of durability of responses are necessary for determination of risks and benefits.

Consequently, interim analyses will not affect the overall type I error. A non-binding futility analysis may be performed using methods described in the statistical analysis plan. Additional interim analyses for safety and efficacy assessment may performed.

8.2 Endpoints

8.2.1 Primary Endpoints

Phase 1

- Occurrence of DLTs in subjects in dose escalation during the first 21 days of treatment.
- Frequency, severity, and duration of treatment-emergent AEs (TEAEs) and laboratory abnormalities using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03.

Phase 2:

- Confirmed ORR per RECIST 1.1, as determined by the IERC, in the analysis population. The ORR will be determined as the proportion of subjects with a confirmed BOR of PR or CR and reported with 95% Wilson score CIs.

8.2.2 Secondary Endpoints

Phase 1:

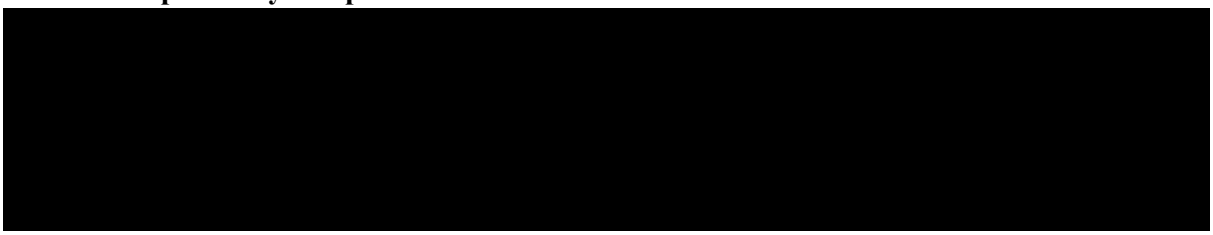
- AGEN1884 and AGEN2034 PK parameters which may include (but are not limited to) maximum observed concentration at steady-state ($C_{max\text{-}ss}$), minimum observed concentration at steady-state ($C_{min\text{-}ss}$), area under the drug concentration-time curve within time span t1 to t2 at steady-state ($AUC_{(t1\text{-}t2)\text{-}ss}$), area under the drug concentration-time curve from time zero to time t ($AUC_{(0\text{-}t)}$), area under the drug concentration-time curve from time zero to infinity ($AUC_{(0\text{-}\infty)}$), time to maximum observed concentration (t_{max}), terminal disposition rate constant (λz), terminal elimination half-life ($t_{1/2}$), systemic clearance (CL), and volume of distribution (Vd)
- [redacted]
- [redacted]
- ADA concentrations and potential impact on AGEN1884 and AGEN2034 PK exposure metrics

Phase 2:

- Frequency, severity, and duration of TEAEs and laboratory abnormalities, using NCI-CTCAE v4.03.
- AGEN1884 and AGEN2034 PK parameters which may include (but are not limited to) $C_{max\text{-}ss}$, $C_{min\text{-}ss}$, $AUC_{(t1\text{-}t2)\text{-}ss}$, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}\infty)}$, t_{max}, λz, $t_{1/2}$, CL, and Vd.
- ADA concentrations and potential impact on AGEN1884 and AGEN2034 PK exposure metrics.
- Confirmed ORR per RECIST 1.1, as determined by an investigator.

- DOR per RECIST 1.1, as determined by an IERC and investigator, in subjects with confirmed response, defined as time from first observation of response to first observation of documented disease progression (or death within 12 weeks after last tumor assessment). Subjects without an event at the analysis cutoff date will be censored on the date of last tumor assessment.
- DCR, defined as proportion of subjects with CR, PR, or SD for at least 12 weeks.
- Duration of SD, measured from the start of treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including baseline measurements.
- Time to response, defined as the time from the first dose date to first observation of confirmed response, will be summarized among subjects with documented confirmed response.
- PFS time, defined as time from first treatment administration to first observation of documented disease progression (or death within 12 weeks after last tumor assessment), per RECIST 1.1, as determined by an IERC and investigator. Subjects without an event at analysis cutoff date will be censored on date of last tumor assessment. PFS time will be summarized by median PFS and PFS rates.
- OS time, defined as time from start of treatment to death. For subjects who are still alive at time of data cutoff for trial analysis or who are lost to follow-up, survival will be censored at the last recorded date that the subject is known to be alive as of the cutoff date for analysis. OS time will be summarized by median OS and OS rates.

8.2.3 Exploratory Endpoints:



- Baseline expression of PD-L1

- Baseline expression of PD-L1 association with clinical outcomes.

8.3 Analysis Sets

The following analysis sets will be defined and used separately for Phase 1 and 2, as applicable:

- **Phase 1 DLT analysis set**: All subjects with data used for implementing the confirmation of the safety of the combination. These subjects should have received all study treatment administrations in the DLT evaluation period or should have stopped treatment because of DLTs in the DLT evaluation period.
- **Safety analysis set**: All subjects who have received ≥1 dose of study treatment.

- **Pharmacokinetics analysis set**: All subjects who have completed ≥1 infusion of study drug, and who have provided sufficient concentration measurements.
- **Evaluable efficacy analysis set**: All subjects in Phase 2 who have received ≥1 dose of study treatment and have measurable disease at baseline, according to the IERC assessment.

8.4 Description of Statistical Analyses

8.4.1 General Considerations

All data recorded during the trial will be presented in individual data listings performed on the safety analysis set. All data will be evaluated as observed, and no imputation method for missing values will be used unless otherwise specified. All data will be presented in a descriptive manner. Statistical inference of the primary efficacy endpoint will be performed for the efficacy expansion cohort (Phase 2), based on the pre-planned corresponding significance level.

Descriptive statistics will be used in general to summarize trial results, i.e., statistics for continuous variables may include means, standard deviations, medians, and ranges (min, max). Categorical variables will be summarized by counts and percentages. Statistics for time-to-event data will be summarized with median and 95% CIs, as appropriate. Unless otherwise specified, calculation of proportions will be based on the number of subjects in the analysis set of interest. Counts of missing observations will be included in the denominator and presented as a separate category if not otherwise specified in the SAP.

The DLT analysis set is the underlying dataset for determination of the safety. Safety analyses will be performed on the safety analysis set. Analyses of PK variables will be performed on the PK analysis set. The primary analysis of the ORR and other efficacy variables will be based on the evaluable efficacy analysis set, defined as all subjects dosed with study drug who had measurable disease at baseline by IERC assessment. Details of the analysis will be described in the SAP.

Unless otherwise specified, endpoint analyses described in the following will be performed separately for Phase 1 and Phase 2 portions of the trial.

8.4.2 Analysis of Primary Endpoints

8.4.2.1 Confirmation of the Safety of the Combination (Phase 1)

For determination of safety of the combination, individual subject data from the Phase 1 part of the trial will be reported. In addition, for final statistical analysis, the following will be summarized:

- At dose level 1 and dose level -1, number and proportion of subjects in the DLT analysis set who experience a DLT during the DLT evaluation period.
- At each dose level, number, and proportion of TEAEs experienced by subjects in the DLT analysis set during the DLT evaluation period.

8.4.2.2 Confirmed ORR per RECIST 1.1 by IERC (Phase 2)

The primary endpoint for Phase 2 is the ORR according to RECIST 1.1, as determined by IERC. ORR will be estimated as the binomial proportion of subjects with BOR of PR or CR, taking into account the following requirement for confirmation: for PR or CR, confirmation of the response

according to RECIST 1.1 will be required at no sooner than 4 weeks after initial documentation of CR or PR. ORR will be reported with two-sided, 95% Wilson score CI.

8.4.3 Analysis of Secondary Endpoints

8.4.3.1 Efficacy Parameters

Efficacy parameters including confirmed ORR according to RECIST 1.1, as determined by investigator, and DCR will be summarized as a binomial proportion and reported with Wilson score 95% CIs.

For each subject with a confirmed response, TTR and DOR according to RECIST 1.1, as determined by IERC (Phase 2 only) and/or investigator (Phase 1 and 2) will be summarized using descriptive statistics.

Duration of response, PFS, and OS time will be analyzed using the Kaplan-Meier method and displayed graphically where appropriate. The median event time and 95% CI for the median will be provided, if available at the time of analysis.

8.4.3.2 Pharmacokinetic Profile

Both noncompartmental (NCA) and compartmental modeling (e.g., population PK [PopPK]) will be used to analyze AGEN2034 and AGEN1884 PK.

The PK parameters to be estimated and reported may include, but may not be limited to: $C_{max\text{-}ss}$, $C_{min\text{-}ss}$, $AUC_{(t1\text{-}t2)\text{-}ss}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, t_{max}, λ_z, $t_{½}$ or HL, CL, and Vd.

8.4.3.3 Immunogenicity

Anti-drug antibody concentrations in correlation with AGEN2034 and AGEN1884 PK exposure matrix will be summarized.

8.4.3.4 Exploratory Biomarkers

[redacted]

8.4.4 Safety Analyses

The extent of exposure to AGEN1884 and AGEN2034 will be characterized by duration (weeks), number of administrations, cumulative dose (mg/kg), dose intensity (mg/kg/week), relative dose intensity (actual dose given/planned dose), number of dose reductions, and number of dose delays.

Safety analyses will be performed on the safety analysis set. Safety endpoints will be tabulated by dose level and cohort, using descriptive statistics.

Safety assessments will be based on incidence of AEs, including AESIs, ADRs, immunogenicity, and changes in vital signs (including body weight), ECG, and laboratory values (hematology and serum chemistry).

The on-treatment period is defined as time from first dose of study treatment to last dose of study treatment plus 30 days, or the earliest date of new antineoplastic therapy minus 1 day, whichever occurs first.

8.4.4.1 Adverse Events

AEs will be coded according to Medical Dictionary for Regulatory Activities (MedDRA). Severity of AEs will be Graded using NCI-CTCAE toxicity grading scale (Version 4.03) whenever possible.

Treatment-emergent AEs are AEs with onset dates during the on-treatment period, or the worsening of an event during the on-treatment period. Incidence of TEAEs, regardless of attribution, and AEs defined as related to AGEN1884 and/or AGEN2034 will be summarized by system organ class and preferred term and described in terms of severity and relationship to AGEN1884 and/or AGEN2034.

Emphasis in the analysis will be placed on AEs classified as treatment emergent. Adverse events leading to death or discontinuation of study treatment, events classified as NCI-CTCAE Grade 3 or higher, study drug-related events, and SAE will be summarized.

Descriptive statistics will be examined for indications of dose-related ADRs.

8.4.4.2 Laboratory Variables

Laboratory results will be classified by Grade according to NCI-CTCAE. The worst on-trial Grades after first study treatment will be summarized. Shifts in toxicity grading from first treatment to highest Grade will be displayed. Results for variables that are not part of NCI-CTCAE will be presented as below, within, or above normal limits. Only subjects with post-baseline laboratory values will be included in these analyses.

8.4.4.3 Physical Examination (Including Vital Signs and 12-lead ECG)

Physical examination data, including vital signs (body temperature, respiratory rate, heart rate, and blood pressure) and 12-lead ECG data will be presented.

8.5 Interim Analysis and Final Analysis

Phase 2 is designed to have at least 2 interim analyses of the primary endpoint and selected secondary efficacy and safety endpoints. No early stopping for efficacy will be performed, as a more complete assessment of safety and durability of responses will be required for evaluation of risks and benefits. Consequently, the overall type I error will not be affected by interim analyses. A non-binding futility analysis may be performed using methods described in the SAP.

The first interim analysis will be performed when data are available for approximately 30 subjects treated for at least 3 months. The primary analysis of efficacy and safety data will include all subjects dosed prior to a borderline date (specified as at least 3 months prior to the data cutoff). Another interim analysis, to determine the possibility of regulatory filing for accelerated approval, will be performed 3 months after approximately 100 subjects have been dosed and will include, as the primary analysis of safety and efficacy, all subjects in the evaluable efficacy analysis set among the first approximately 100 subjects dosed. Sensitivity safety analyses will be performed on all subjects in the safety analysis set dosed as of the data cutoff. Details of the interim analyses will be provided in a separate SAP.

Additional interim analyses for safety and efficacy assessment may be performed.

The final analysis will be performed after study completion.

The primary analysis set for efficacy assessment will be the evaluable efficacy analysis set. The primary analysis set for safety assessment will be the safety analysis set.

The interim analyses may include PD-L1 expression data. Details will be provided in a separate SAP.

9 Trial Governance and Oversight

9.1 Safety Monitoring Committee

An SMC will regularly review safety data to ensure subjects' safety throughout the trial.

The SMC will include permanent members from the Sponsor and/or CRO:

- Sponsor: medical monitor, pharmacovigilance physician, and trial statistician.
- CRO: trial physician
- Investigational Site: principal investigator (PI)

During the Phase 1 portion of the trial, the SMC will evaluate safety data and decide on DLTs relevant for the treatment and will advise on pursuing the next CDL of AGEN1884 and AGEN2034. The SMC recognizes that with the limited prior human experience with combination AGEN1884 and AGEN2034, a conservative approach will be adopted in ascribing the relationship of the treatment-related toxicity to the drug.

At each SMC review, all safety information of the participating subjects will be reviewed, and the SMC will decide by consensus on continuation, modification, or suspension of the trial.

The SMC may modify the frequency of meetings as deemed appropriate during the course of the trial. The specific working procedures will be described in a separate SMC charter.

9.2 Independent Endpoint Review Committee (IERC)

For the Phase 2 portion of the trial, a central facility will read and interpret all radiographic scans for subjects enrolled in the trial. Data for all images will be transferred from trial sites to the central reading center for evaluation. Scans will be evaluated at the central facility in accordance with RECIST 1.1. Imaging data will be transferred to the designee at regular intervals. A manual from the vendor will be provided to each trial site.

For all subjects in Phase 2, the IERC will perform a blinded determination as to whether RECIST 1.1 criteria for tumor response or progression have been met. The IERC will be composed of a minimum of 3 properly qualified members.

The role of the IERC will be to review radiographic image findings and physical findings for determination of the timepoint for overall response and date of disease progression (per RECIST 1.1) for each subject. The full membership, mandate, and processes of the IERC will be detailed in a separate IERC Charter.

9.3 Independent Data Monitoring Committee (IDMC)

For the Phase 2 portion of the trial, an IDMC will be established supplement the routine trial monitoring outlined in this protocol. The voting members of the committee are external to and independent of the Sponsor. The members of the IDMC must not be involved with the trial in any other way (e.g., they cannot be trial investigators) and must have no competing interests that could affect their roles with respect to the trial. The IDMC will include 4 oncologists (a minimum of 2 of which are experienced in Cervical Cancer) and 1 external statistician. The IDMC will make recommendations to the Sponsor at specified intervals (when every 10 additional subjects have been enrolled and completed the first cycle of treatment; and, once all participants have been enrolled, at least once every 3 months) regarding steps to ensure both subject safety and the continued ethical integrity of the trial. Also, the IDMC will review interim trial results, consider the overall risk and benefit to trial participants (see Section 8.5– Interim Analysis and Final Analysis) and recommend to the Sponsor if the trial should continue in accordance with the protocol, or if a stop or modification of the protocol is required.

Specific details regarding responsibilities and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the trial governance structure; and requirements for and proper documentation of IDMC reports, minutes, and recommendations will be described in a separate charter that is reviewed and approved by the IDMC. The IDMC will monitor the trial at an appropriate frequency, as described in the detailed IDMC charter. The IDMC will also make recommendations to the Sponsor protocol team regarding steps to ensure both subject safety and the continued ethical integrity of the trial.

10 Ethical and Regulatory Aspects

10.1 Ethics Review

The trial protocol, subject information and consent form, Investigator's Brochures and Addenda, any written instructions to be given to the subject, available safety information, subject recruitment procedures (e.g., trial website), information about payments and compensation available to the subjects and documentation evidencing the investigator's qualifications will be approved by the IRB/EC per local regulations prior to trial start. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the trial or planned analysis will be documented in a protocol amendment. The investigator must submit and, where necessary, obtain IRB/EC and/or Sponsor approval for all subsequent protocol amendments and changes to the ICF or changes of the investigational site, facilities, or personnel. The investigator should notify the IRB/EC of protocol deviations or SAEs occurring at the site and other AE reports received from the Sponsor in accordance with local procedures.

Safety updates for AGEN1884 and AGEN2034 will be prepared by the Sponsor or its representative as required, for submission to the relevant IRB.

10.2 Responsibilities of the Investigator

The investigator is responsible for conduct of the trial at his/her site. He/she will ensure that the trial is performed in accordance with the clinical trial protocol and the approved protocol amendments; the current version of the Declaration of Helsinki (Ethical Principles for Medical

Research Involving Human Subjects), ICH Good Clinical Practice (ICH E6 (R2) GCP); and applicable Health Authority requirements and national and state laws. In particular, the investigator must ensure that only subjects who have given their written informed consent are included into the trial.

According to the US Code of Federal Regulations Part 54.2 (e), for trials conducted in any country that could result in a product submission to the FDA for marketing approval and could contribute significantly to the demonstration of clinical activity and safety of an IMP (which are considered "covered clinical trials" by the FDA), the investigator and all sub-investigators are obliged to disclose any financial interest which they, their spouses or their dependent children may have in the Sponsor or the Sponsor's product under trial. This information is required during the course of the trial and for 12 months following completion of the trial.

10.3 Subject Information and Informed Consent

An unconditional prerequisite for a subject's participation in the trial is his/her written informed consent. The subject's written informed consent to participate in the trial must be given before any trial-related activities are carried out.

Adequate information must therefore be given to the subject by the investigator before informed consent is obtained. In addition to providing this written information to a potential subject, the investigator will inform the subject verbally of all pertinent aspects of the trial. The language used in doing so must be chosen so that the information can be fully and readily understood by lay persons.

Informed consent will be obtained for participation in the trial and for optional participation in pharmacogenomics assessments. The investigator or authorized designee will explain to each subject the objectives of the pharmacogenomics assessments. Subjects will be told that they are free to refuse to participate at any time and for any reason. A separate, specific signature will be required to document a subject's agreement to participate in pharmacogenomics assessments. Subjects who decline to participate will not provide a separate signature. Additionally, should a female subject become pregnant in during the trial, a separate informed consent for follow-up of the pregnancy will be obtained.

The ICF must be signed and personally dated by the subject (or the subject's legally authorized representative) and investigator. The signed and dated declaration of informed consent will remain at the investigator's site and must be safely archived by the investigator so that the forms can be retrieved at any time for monitoring, auditing, and inspection purposes. A copy of the signed and dated information and ICF should be provided to the subject, or their legally authorized representative, before participation in the trial.

Whenever important new information becomes available that may be relevant to the subject's consent, the written subject information sheet and any other written information provided to subjects will be revised by the Sponsor or designee and be submitted again to the IEC/IRB for review and favorable opinion. The agreed upon, revised information will be provided to each subject in the trial for signing and dating. The investigator will explain the changes to the previous version to the subject. Case history or clinical records for each subject should document the informed consent process and that written informed consent was obtained using the revised ICF for continued participation in the trial.

10.4 Subject Identification and Privacy

In compliance with ICH GCP guidelines, it is a requirement that the investigator and institution permit authorized representatives of the Sponsor, regulatory authorities, and IRB direct access to review the subject's original medical records at the site for verification of trial-related procedures and data.

Measures to protect confidentiality include: only the trial number, subject number, subject initials, and date of birth will identify the subject on the eCRF or other documents submitted to the Sponsor. This information will be used in the database for subject identification. Subject names or addresses will not be entered on the eCRF or in the database. No material bearing a subject's name will be kept on file by the Sponsor. Subjects will be informed of their rights within the ICF.

In studies conducted in the United States, confidentiality of subject's personal data will be protected in accordance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996 and national data protection laws, as applicable. HIPAA regulations require that in order to participate in the trial, a subject must sign an authorization from the trial that he or she has been informed of following:

- What Protected Health Information (PHI) will be collected from subjects in this trial;
- Who will have access to that information and why;
- Who will use or disclose that information;
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws;
- The information collected about the research trial will be kept separate from the subject's medical records, but the subject will be able to obtain the research records after the conclusion of the trial;
- Whether the authorization contains an expiration date; and
- The rights of a research subject to revoke his or her authorization.

In the event that a subject revokes authorization to collect or use his or her PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled trial period.

10.5 Emergency Medical Support and Subject Card

Subjects enrolled in this clinical trial will be provided with emergency medical support cards during their trial participation, which will be furnished by the Sponsor or designee. The emergency medical support card is based on the need to provide clinical trial subjects with a way of identifying themselves as participating in a clinical trial, and subsequently give health care providers access to information about this participation that may be needed to determine the course of the subject's medical treatment.

This service is designed to provide information to health care providers who are not part of the clinical trial. Clinical trial investigators, who are already aware of the clinical trial protocol and treatment, have other means of accessing the necessary medical information for management of emergencies occurring in their subjects.

The first point of contact for all emergencies will be the clinical trial investigator caring for the affected subject. The investigator agrees to provide his or her emergency contact information on the card for this purpose. If the investigator is available when an event occurs, he/she will answer any questions. Any subsequent action will follow the standard processes established for the investigators.

In cases in which the investigator is not available, the site will provide the appropriate means to contact a physician. This includes provision of a 24-hour contact number at the facility, whereby the health care providers will be given access to an appropriate physician to assist with the medical emergency.

10.6 Clinical Trial Insurance and Compensation to Subjects

Insurance coverage shall be provided for each country participating to the trial. Insurance conditions shall meet good local standards, as applicable.

10.7 Health Authorities

The clinical trial protocol and any applicable documentation (e.g., IMP dossier, subject information, and ICF) will be submitted or notified to health authorities by the Sponsor or designated CRO in accordance with regulations of the countries involved in the trial.

11 Trial Management

11.1 Sponsor and Trial Administrative Structure

The Sponsor of this trial is Agenus Inc.

In countries where a local Sponsor is required a qualified local legal Sponsor will be designated by Agenus and will act as the legal Sponsor for the trial and will fulfill the obligations that this role entails. In these cases, the local legal Sponsor shall, to the extent required by the applicable laws and regulations, interact with regulatory and health authorities on behalf of the Sponsor in connection with this trial.

Details of logistical and administrative structures and associated procedures will be defined in a separate manual of operations, which will be prepared by the Sponsor or designated CRO.

11.2 Investigational Sites

The trial will be global, with approximately 5-10 enrolling centers participating in Phase 1 and approximately 30-40 centers in Phase 2.

11.3 Trial Coordination/Monitoring

The Sponsor will coordinate the trial and may delegate certain trial activities to CROs, including certain laboratory assessments, safety reporting, biostatistics, etc. The Sponsor’s clinical operations department will oversee activities performed by CROs.

11.4 Data Collection

The eCRF is the primary data collection instrument for the trial. The clinical site will keep eCRFs current to enable the monitor to review the subjects' status throughout the course of the trial. To maintain confidentiality, only the trial number, subject number, subject initials, and date of birth will identify the subject on the eCRF. All data requested on the eCRF must be supported by and be consistent with the subject's source documentation.

Source documents are the original documents, data, records, and certified copies of original records of clinical findings, observations, and activities from which the subject's eCRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, ECG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, X-rays, and correspondence.

All missing data must be explained. When a required laboratory test, assessment, or evaluation has not been done or an "Unknown" box is not an option on the eCRF, a note should be created verifying that the field was "Not Done" or "Unknown". For any entry errors made, the error(s) must be corrected, and a note explaining the reason for change should be provided.

The investigator will sign and date the subject eCRF casebook indicating that the data on the eCRF have been assessed. Each completed eCRF will be electronically signed and dated by the PI, once all data for that subject is final.

11.5 Investigator Site File and Archiving

The investigator will be provided with an investigator site file upon initiation of the trial. This file will contain all documents necessary for the conduct of the trial and will be updated by the site throughout the trial. It must be available for review by the monitor; be ready for Sponsor audit as well as for inspection by health authorities during and after the trial; and safely archived for ≥15 years (or per local requirements or as otherwise notified by the Sponsor) after the end of the trial. Documents to be thus archived include the subject identification list and signed subject ICFs. If archiving of the investigator site file is no longer possible at the site, the investigator must notify the Sponsor.

All original subject files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. In any case, the investigator should ensure that no destruction of medical records is performed without the Sponsor's written approval.

11.6 Monitoring, Quality Assurance, and Inspection by Health Authorities

This trial will be monitored in accordance with the ICH Guidance on GCP (ICH E6 (R2)) The site monitor will visit the trial site at regular intervals.

Representatives of the Sponsor's quality assurance unit or a designated organization, as well as health authorities, must be permitted to inspect all trial-related documents and other materials at the site, including investigator site file, completed eCRFs, ICFs, and the subjects' original medical records/files.

The clinical trial protocol, data capture procedures, and data handling, including final clinical trial report, will be subject to independent quality assurance activities. Audits may be conducted at any time during or after the trial to ensure the validity and integrity of trial data.

11.7 Publication Policy

11.7.1 Clinical Trial Report

After completion of the trial, a clinical trial report according to ICH E3 will be written by the Sponsor or designated CRO.

11.7.2 Publications

All information provided regarding the trial, as well as all information collected/documented during the course of the trial, will be regarded as confidential. The Sponsor reserves the right to release literature publications based on the results of the trial. Results from the trial will be published/presented as per the Sponsor's publication strategy.

Inclusion of the investigator in the authorship of any multi-center publication will be based upon substantial contribution to the design, analysis, interpretation of data, drafting, and/or critically revising any manuscript(s) derived from the trial. The investigator acknowledges that the trial is part of a multi-center trial and agrees that any publication by the investigator of the results of the trial conducted at his/her research site shall not be made before the first multi-center publication. In the event, there is no multi-center publication within fifteen (15) months after the trial has been completed or terminated at all trial sites, and all data has been received, the investigator shall have the right to publish its results from the trial, subject to the notice requirements described herein and subject to acknowledgement of the Sponsor as appropriate. The investigator shall provide the Sponsor thirty (30) days to review a manuscript or any poster presentation, abstract or other written or oral material that describes the results of the trial for the purpose only of determining if any confidential or patentable information is disclosed thereby. If the Sponsor requests in writing, the investigator shall withhold any publication or presentation an additional sixty (60) days solely to permit the Sponsor to seek patent protection.

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Appendix I - Eastern Cooperative Group (ECOG) Performance Scale

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

[1] (Oken et al. 1982)

Appendix II - Signature Pages and Responsible Persons for the Trial

Agenus, Inc.	C-550-01	Phase 1/2 Trial of AGEN1884 with AGEN2034 in Advanced Tumors Amendment 5, 26 September 2019

Signature Page – Protocol Lead

Title	A Phase 1/2, Open-Label, Multi-Arm Trial to Investigate the Safety, Tolerability, Pharmacokinetics, Biological, and Clinical Activity of AGEN1884 in Combination with AGEN2034 in Subjects with Metastatic or Locally Advanced Solid Tumors, and Expansion into Select Solid Tumors
Clinical Trial Amendment, Date	Amendment 5, 26 September 2019
Previous Amendment, Date	Amendment 4, 15 April 2019

I approve the design of this clinical trial.

[redacted] [redacted]

Signature Date of Signature

Name, academic degree	[redacted]
Function	
Institution	Agenus Inc.
Address	3 Forbes Road, Lexington, MA 02421, USA
Telephone number	[redacted]
E-mail address	

Signature Page – Principal Investigator

Trial Title	A Phase 1/2, Open-Label, Multi-Arm Trial to Investigate the Safety, Tolerability, Pharmacokinetics, Biological, and Clinical Activity of AGEN1884 in Combination with AGEN2034 in Subjects with Metastatic or Locally Advanced Solid Tumors, and Expansion into Select Solid Tumors
Clinical Trial Amendment, Date	**Amendment 5, 26 Septepmber 2019**
Previous Amendment, Date	**Amendment 4, 15 April 2019**
Center Number	_____
Principal Investigator	_____

I, the undersigned, am responsible for the conduct of the trial at this site and affirm that:

- I understand and will conduct the trial according to the clinical trial protocol, and the approved protocol amendments; the current version of the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects), ICH Good Clinical Practice (ICH Topic E6 GCP) as adopted by the applicable Health Authority requirements and national and state laws.
- I will not deviate from the clinical trial protocol without prior written permission from the Sponsor, and prior review and written approval from the Institutional Review Board or Independent Ethics Committee, except where necessary to prevent immediate danger to the subject.

I understand that some regulatory health authorities require the Sponsors of clinical trials to obtain and supply, when required, details about the investigators' ownership interests in the Sponsor or investigational medicinal product and information regarding any financial ties with the Sponsor. The Sponsor will use any such information that is collected solely for the purpose of complying with the regulatory requirements. I therefore agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children), and to provide updates as necessary.

_____ _____

Signature Date of Signature

Name, academic qualifications _____

Position (job title) _____

Institution _____

Address _____

Telephone number _____

E-mail address _____