CLINICAL STUDY PROTOCOL

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Protocol Number:	GCT1107-01 (PRO1107-001)
Protocol Title:	A Phase 1/2 Study of PRO1107 in Patients with Advanced Solid Tumors
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Protocol Approver:**	**Name:** PPD **Title:** PPD

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** This protocol was approved via electronic signature on the approval page appended to the document.

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The sponsor contact information page will be provided separately, listing the study responsible medical director, as well as the CRO(s), laboratory(ies) (names and addresses), and other technical/medical services used. Additional contact information may be found in the study specific manuals (eg, IMP Manual, Laboratory Manual).

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I agree to comply with the ICH Tripartite Guideline on GCP, the principles in the Declaration of Helsinki, and applicable national or regional regulations/guidelines.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study treatment, the conduct of the study, and the obligations of confidentiality.

Principal (Site) Investigator:	
Name (typed or printed):	
Institution and Address:	
Telephone Number:	

Signature: _____ Date: _____
(DD Mmm YYYY)

NOTE: The Coordinating Investigator section below is applicable only to the country-specific coordinating investigators within the European Union, where applicable.

Coordinating Investigator (where required):	
Name (typed or printed):	
Institution and Address:	

Signature: _____ Date: _____
(DD Mmm YYYY)

Note: If the address or telephone number of the Investigator changes during the course of the study, written notification will be provided by the Investigator to the sponsor, and a protocol amendment will not be required.

Completed and signed forms will be filed separately from the protocol.

PROTOCOL SYNOPSIS

Protocol Title

A Phase 1/2 Study of PRO1107 in Patients with Advanced Solid Tumors

Study Objectives and Corresponding Endpoints

Primary Objectives	Primary Endpoints
• Evaluate the safety and tolerability of GEN1107 • Identify the MTD, if reached, and recommended dose for expansion of GEN1107	• Type, incidence, severity, and seriousness of AEs per the NCI CTCAE, Version 5.0, and per Appendix K for ocular toxicities, and relatedness of AEs • Type, incidence, and severity of laboratory abnormalities • Incidence of DLTs
Secondary Objectives	**Secondary Endpoints**
• Assess the antitumor activity of GEN1107 • Assess the PK of GEN1107 • Assess the immunogenic potential of GEN1107 • Evaluate preliminary antitumor activity based on CA-125 tumor marker levels in subjects with ovarian cancer	• ORR per RECIST, Version 1.1 • DCR • PFS • DOR • PK parameters for GEN1107 related analytes • Incidence of ADA • CA-125 response per GCIG criteria for ovarian cancer
Exploratory Objectives	• **Exploratory Endpoints**
• Evaluate efficacy of GEN1107 • Assess exploratory biomarkers in relation to antitumor activity, safety, pharmacodynamics, and resistance to GEN1107	• OS • Exploratory biomarkers of GEN1107-mediated and disease-related effects

Abbreviations: ADA=antidrug antibodies; AE=adverse event; DCR=disease control rate; DLT=dose-limiting toxicity; DOR=duration of objective response; GCIG= Gynecological Cancer Intergroup; MTD=maximum tolerated dose; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetics; RECIST=response evaluation criteria in solid tumors.

Study Population

Key Inclusion Criteria

Per Protocol Amendment 2, the inclusion criteria 1 and 2 have been replaced by separate inclusion criteria for Parts A and B. Inclusion criteria 3-9 are the same for Parts A and B.

1. Updated per Protocol Amendment 2: for Part A, esophageal, GEJ, or gastric carcinoma; ESCC, and urothelial cancers (bladder, ureter, or renal pelvis) were removed (A.1). For Part B, additional detail was added (see B.1).

2. Updated per Protocol Amendment 2: for Part A, remains the same (A.2); for Part B, this information is incorporated into B.1.

   Part A:

   A.1. Patients must have pathologically confirmed diagnosis of one of the following tumor types:

   - Ovarian cancer (must have high grade epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer including serous, endometrioid, and clear cell carcinomas, and excluding mucinous, low grade, and those with a sarcomatous or neuroendocrine element)
   - Endometrial cancer (including endometrioid, serous, clear cell carcinomas, and carcinosarcoma, and excluding gastrointestinal mucinous type, low grade, mixed or undifferentiated carcinoma, and those with sarcomatous or mesonephric-like element)
   - TNBC, ie, ER-negative, PR-negative, and HER2-negative breast cancer as determined by a CLIA-certified (or local equivalent) laboratory following ASCO-CAP guidelines.
   - NSCLC

   A.2. Patients must have metastatic or unresectable locally advanced, recurrent disease not amenable to further local therapy and must have previously received therapies known to confer clinical benefit (unless ineligible to receive or refused to receive or therapy is unavailable in the region). Patients with NSCLC with ALK, EGFR, proto-oncogene tyrosine-protein kinase ROS (ROS1), v-RAF murine sarcoma viral oncogene homolog B (BRAF), or any other known actionable genomic alterations, must have received treatment with at least one therapy appropriate to the genomic alteration. If a standard-of-care therapy is available that has not been administered, the reason that the therapy is not appropriate must be documented. Patients who have not received all available therapies known to confer clinical benefit may still be eligible and must be informed of alternative treatment options that might be advantageous to the patient.

   Part B:

   B.1. Patients must have a histologically or cytologically confirmed metastatic or unresectable solid malignancy as specified below.

   Cohort 1: Ovarian cancer

- Patients must have histologically or cytologically confirmed high grade serous ovarian cancer, primary peritoneal cancer, or fallopian tube cancer.
- Patients must have received 1 to 4 prior lines of therapy.
- Patients must have received prior treatment with the following therapies:
  - Platinum chemotherapy
  - Prior bevacizumab treatment is required unless the patient has a documented contraindication or due to precautions/intolerance
  - Patients with known or suspected deleterious germline or somatic BRCA mutations and who achieved a complete or partial response to platinum-based chemotherapy must have been treated with PARP inhibitor as maintenance treatment unless the patient is not eligible for treatment with PARP inhibitor.
  - Mirvetuximab soravtansine, if appropriate and available in the enrollment region

- Note the following (all patients):
  - Adjuvant ± neoadjuvant therapy is considered 1 line of therapy. Maintenance therapy (eg, bevacizumab, PARP inhibitors) will be considered part of the preceding line of therapy (ie, not counted independently).
  - Therapy changed due to toxicity in the absence of progression will be considered part of the same line (ie, not counted independently).
  - Hormonal therapy alone (ie, without chemotherapy) will not be counted as a separate line of therapy.
- Patients must have platinum-resistant disease:
  - Patients who have only had 1 line of platinum-based therapy must have received at least 4 cycles of platinum and must have either had a response (CR or PR) or had non-measurable disease at the start of platinum-based therapy and then progressed between > 91 days and ≤ 183 days after the date of the last dose of platinum.
  - Patients who have received 2 to 4 lines of platinum-based therapy must have progressed on or within 183 days after the date of the last dose of platinum.

Cohort 2: TNBC

- Patients must have histologically or cytologically confirmed TNBC.
- Subjects for whom no designated SoC (eg, checkpoint inhibitors, PARP inhibitors, or antibody-drug conjugates) is available or appropriate and for whom single-agent chemotherapy is considered as the next line of treatment.
- Subjects should have received prior antibody-drug-conjugate treatment, if ADC as SoC is available and appropriate.
- Patients must be refractory to or have relapsed after at least 2 prior and a maximum of 4 prior lines of cytotoxic therapy (including ADCs) or chemotherapy for locally advanced and unresectable or metastatic breast cancer, of which a minimum of one line of treatment was in the metastatic setting (these will qualify regardless of triple-negative status at the time they were given).
- Note the following (all subjects):
  - Neoadjuvant/adjuvant therapy will qualify as 1 of the required prior regimens, if the development of locally advanced and unresectable or metastatic disease occurred within a 12-month period of time after completion of the neoadjuvant/adjuvant chemotherapy.
  - Prior antihormonal treatment for HR+ disease does not count against the total number of prior lines.

Cohort 3: Endometrial cancer

- Patients must have histologically or cytologically confirmed endometrial cancer (any subtype excluding neuroendocrine tumors or endometrial sarcoma).
- Patients must have received 1 to 3 prior lines of therapy in advanced, recurrent, or metastatic setting.
- Patients must have received prior platinum-based chemotherapy and a PD-(L)1 inhibitor.
- Note the following (all subjects):
  - Prior induction plus maintenance is considered 1 line of therapy, even if parts of the treatment regimen (induction or maintenance) are interrupted and/or resumed at a later date, in the absence of disease progression while on active treatment;
  - A switch/change in regimen due solely to toxicity or patient preference (and not disease progression) is not considered a separate line of therapy;
  - Neoadjuvant and/or adjuvant chemotherapy, or radical concurrent chemoradiation count as a first line of prior systemic therapy if there is documented disease progression within 6 months of chemotherapy completion.

Cohort 4: NSCLC

- Patients must have a histologically or cytologically confirmed diagnosis of advanced (unresectable, recurrent and/or metastatic) NSCLC without actionable genomic alterations.

- Patients must have radiographically progressed on or after at least 1 (but no more than 3) prior lines of systemic therapy for unresectable and/or metastatic NSCLC including prior platinum-based therapy or alternative chemotherapy if platinum ineligible (eg, a gemcitabine-containing regimen).
- Patients must have received and progressed on or after prior treatment with a PD-1/PD-L1 inhibitor alone or in combination with platinum-based chemotherapy. To be considered to have progressed on or after prior treatment with a PD-1/PD-L1 inhibitor, patients should have either received this therapy in the advanced setting or have experienced disease progression during "maintenance" treatment following radical concurrent chemoradiation or in the adjuvant setting.
- Neoadjuvant and/or adjuvant chemotherapy, and/or radical concurrent chemoradiation counts as a first line of prior systemic therapy if there is documented disease progression within 6 months of chemotherapy completion

3. Measurable disease at baseline as defined per RECIST, Version 1.1 (Eisenhauer et al., 2009).

Key Exclusion Criteria

1. Prior treatment with anti-PTK7-directed therapy.
2. Had progressive disease as best response while on treatment with an auristatin (eg, a vedotin or pelidotin)-based ADC as the most recent line of therapy.
3. Patients with primary platinum-refractory ovarian cancer, defined as a lack of response to or progression within 3 months after completing frontline platinum-containing therapy.
4. History of another malignancy within 3 years before the first dose of study drug, or any evidence of residual disease from a previously diagnosed malignancy. Exceptions are malignancies with a negligible risk of metastasis or death (eg, 5-year OS ≥90%), such as but not limited to, adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, breast ductal carcinoma in situ, or Stage I uterine cancer.
5. Known active central nervous system metastases, including carcinomatous meningitis. Patients with brain metastases may participate provided the metastases have been treated and are stable for at least 4 weeks prior to the first dose of study drug, they have no new or enlarging brain metastases and have discontinued corticosteroids prescribed for symptoms associated with brain metastases for at least 7 days prior to the first dose of study drug. Patients with a history of brain metastases, suspected new brain metastases, or a diagnosis of NSCLC or breast cancer should have a CT/ MRI scan of the brain at screening.
6. Patients with active or chronic corneal disorders, history of corneal transplantation, or any clinically significant corneal disease that prevents adequate monitoring of potential drug-induced keratopathy. Note: Patients with other active ocular conditions requiring ongoing therapy and/or monitoring must be discussed with the sponsor prior to enrollment.

Study Design

This is a global, open-label, multicenter Phase 1/2 study to evaluate the safety, tolerability, PK, and antitumor activity of GEN1107 in patients with advanced solid tumors. This study consists of 2 parts, Part A: dose escalation and dose level expansion, and Part B: tumor specific expansion.

Number of Planned Patients

Up to 280 patients may be enrolled in this study (up to 120 patients in Part A and up to 160 patients in Part B).

Part A: Dose Escalation and Dose Level Expansion

GEN1107 will initially be administered on Day 1 of a 21-day cycle via IV infusion at the planned doses outlined in the table below (Q3W, Dose Regimen 1).

Dose-escalation Schema for Q3W regimen (Dose Regimen 1)

GEN1107 Dose (mg/m^2)
8
15
30
45
60
75
90

Two alternative dosing regimens may also be investigated based on review of safety, antitumor activity, and PK data. In the first alternative dosing regimen (2Q4W, Dose Regimen 2), the dose would be administered on Day 1 and 8 of each 28-day cycle. CCI [redacted] The 2Q4W regimen will be evaluated as the first alternative dosing regimen. The CCI [redacted] will be based on review of safety, antitumor activity, and PK data from Q3W and 2Q4W regimens evaluated in clinic.

Dose-escalation Schema for 2Q4W regimen (Dose Regimen 2)

GEN1107 Dose (mg/m^2)
30
40
50

Dose-escalation Cohorts

Dose escalation and identification of the MTD will be guided by mTPI method (Ji et al., 2010). A minimum of 1 DLT-evaluable patient will initially be enrolled into each of the first 2 dose level cohorts (8 and 15 mg/m^2 dose levels) with Dose Regimen 1. A minimum of 3 patients will be enrolled into each cohort if a qualifying event (a DLT or any ≥ Grade 2 related AE) occurs in the first 2 dose levels or when Dose level 3 is reached with Dose Regimen 1 and at all dose levels with Dose Regimen 2 and 3. In dose escalation, additional enrollment is allowed to ensure at least 3 DLT-evaluable patients.

Dose-escalation Decisions

The DLT evaluation period for each patient is based on data obtained during their first 21 days of treatment for the Q3W regimen and 28 days for the 2Q4W and CCI regimen. When the required number of patients complete the respective regimen's DLT period, the DEC will evaluate all available safety data and make a recommendation on whether dose escalation should proceed. The DEC will take into account DLTs or qualifying events occurring in additionally enrolled patients at the actual dose level during their review. The Safety Committee will be involved if there is a lack of DEC alignment.

The mTPI method uses a Bayesian statistical framework, and a beta-binomial hierarchical model to compute the posterior probabilities of 3 intervals that reflect the relative distance between the toxicity rate at each dose level to the target DLT rate. The DEC can recommend escalating to the next dose level, staying at the current dose level, or de-escalating to a lower dose level. If the recommendation is to stay at the current dose level, the minimum number of patients required will be guided by the mTPI algorithm. Dosing decision rules are determined for a target DLT rate of 25% with a 5% margin.

The algorithm will stop if one of the following criteria is met:

- The maximum sample size has been achieved (approximately 54 patients total), or
- At least 6 patients have been treated at the presumed MTD (the decision can also be based on 5 subjects if no DLT has been observed on the respective dose level), or

- All doses explored appear to exceed the MTD

Decision Rules for Dose Escalation Based on the mTPI Method

	Number of enrollment at current dose level														
Number of DLT	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	D	S	S	S	E	E	E	E	E	E	E	E	E	E	E
2		DU	D	D	D	S	S	S	S	S	S	E	E	E	E
3			DU	DU	DU	D	S	S	S	S	S	S	S	S	S
4				DU	DU	DU	DU	D	S	S	S	S	S	S	S
5					DU	DU	DU	DU	DU	DU	D	S	S	S	S
6						DU	DU	DU	DU	DU	DU	DU	DU	S	S
7							DU	DU	DU	DU	DU	DU	DU	DU	DU
8								DU	DU	DU	DU	DU	DU	DU	DU
9									DU	DU	DU	DU	DU	DU	DU
10										DU	DU	DU	DU	DU	DU
11											DU	DU	DU	DU	DU
12												DU	DU	DU	DU
13													DU	DU	DU
14														DU	DU
15															DU

E = escalate to the next higher dose; D = de escalate to the next lower dose; DU = current dose is unacceptably toxic; S = stay at the current dose

Note: Target toxicity of 25% with equivalence interval of (20%, 30%). Prior distribution Beta (0.5, 0.5). To further enhance patient safety during dose escalation, the mTPI decision rule for 2 DLTs among 5 treated patients has been changed from "S" (stay) to "D" (de-escalate).

Patients who are not considered DLT evaluable may be replaced. De-escalation to a lower dose level may be performed at any time by the Sponsor in consultation with the DEC. The DEC may also recommend evaluation of intermediate dose levels not exceeding the MTD.

Additional patients may be enrolled at dose levels previously determined to be safe (after clearing the DLT criteria), up to a total of approximately 9 patients per dose cohort to obtain additional safety and tolerability information.

During dose escalation, if a patient tolerates at least 2 cycles of GEN1107 without achieving CR, additional treatment cycles at a higher dose level demonstrated to be safe may be administered at the discretion of the Investigator and upon approval by the Medical Monitor.

Patients enrolled at these dose levels may be selected based on their tumor types to inform Part B tumor-specific decisions.

Dose-limiting Toxicity

DLTs will be graded according to NCI CTCAE, Version 5.0, except for ocular toxicities which will be graded per Appendix K. The DLT evaluation period is 21 days of treatment for the Q3W regimen and 28 days for the 2Q4W and CCI regimens. A DLT is defined as any of the following during the DLT evaluation period if considered not clearly and incontrovertibly due to the underlying disease or extraneous causes by either the Investigator or the Sponsor:

- Any death not clearly due to the underlying disease or extraneous causes
- ≥ Grade 3 non-hematologic toxicity, with the following exceptions:
  - Grade 3 fatigue lasting ≤7 days
  - Grade 3 nausea, vomiting, or diarrhea that resolves to Grade 2 or less within 72 hours with adequate supportive care
  - ≥ Grade 3 electrolyte or serum chemistry abnormality resolving within 72 hours, unless the patient has clinical symptoms, in which case these abnormalities are considered DLTs

regardless of duration

- ≥ Grade 3 amylase/lipase elevation not associated with signs/symptoms of pancreatitis

- The abnormality meets the definition of DILI
- Grade 4 anemia or Grade 3 anemia lasting >7 days (transfusions permitted)
- Grade 4 neutropenia lasting >7 days
- Grade 4 thrombocytopenia lasting >7 days, or ≥ Grade 3 thrombocytopenia with clinically significant bleeding
- Febrile neutropenia (ANC <1000/µL with a single oral temperature measurement of ≥38.3ºC [101ºF] or a temperature of ≥ 38ºC [100.4ºF] sustained over a 1-hour period)

Patients experiencing a DLT within the DLT evaluation period should discontinue GEN1107 immediately. If requested by the Investigator, a patient with a DLT may continue in the trial only after discussion with the sponsor. For this decision, a thorough benefit-risk assessment of the individual patient by the Investigator is required. If a patient experiences a toxicity that would have qualified as a DLT, but that occurs after the DLT evaluation period, the patient's benefit-risk must be thoroughly assessed and consultation with the Safety Committee may be considered.

Part A: Dose Level Expansion

If recommended by the DEC, up to 4 dose cohorts across dose regimens may be expanded up to a total of approximately 18 patients per dose level to obtain additional safety, PK, PD, and antitumor activity data to estimate the optimal biological dose and inform selection of the doses for the expansion cohorts, to further support dose optimization in Part B. Patients enrolled at these dose levels may be selected based on their tumor types to inform Part B tumor-specific decisions.

Maximum Tolerated Dose/ Recommended Expansion Doses

The identification of the MTD will be guided by the mTPI method.

The recommended doses for cohort expansion will be selected based on an integrated analysis of safety, tolerability, PK, PD, and antitumor activity data from Part A.

Part B: Tumor-Specific Expansion

Part B will be initiated at 2 or more potential recommended expansion doses based on a comprehensive analysis of safety, tolerability, PK, PD, and antitumor activity data from Part A in up to 4 different tumor-specific cohorts of up to 40 patients per cohort, each cohort evaluating up to 2 potential recommended expansion doses. The recommended doses for expansion may be the MTD or a lower dose level from Part A and different dose levels may be selected for each expansion cohort. Patients in each cohort will be randomized with a 1:1 ratio to receive 1 of the recommended expansion doses of GEN1107 (approximately 20 patients in each dose level). If the Safety Committee determines that only one dose level is appropriate for further testing for a particular tumor type, an initial 20 patients may be evaluated at that dose level. Additional dose levels may be tested based on the totality of available data. If supported by the risk benefit profile, it is feasible to enroll approximately20 additional patients after enrolling the initial 20 patients at a selected dose level.

Dose reductions or delays for individual patients may be implemented at the discretion of the Investigator based on the individual patient toxicity profile after consultation with and agreement from the study Medical Monitor.

Safety and antitumor activity will be continuously monitored throughout the study by the Sponsor. An ongoing, quarterly review of patient safety and SAEs will be conducted by the Safety Committee during Part B. After the initial 20 patients (approximately 10 patients in a dose level) are enrolled and randomized in each cohort, the Safety Committee will review the data and confirm whether enrollment should continue (to accrue a total of 20 patients in a dose level), based on cumulative safety and activity data.

Test Product, Dose, and Mode of Administration

GEN1107 will be administered IV as a 30-minute infusion on Day 1 of each 21-day treatment cycle (Regimen 1), on Day 1 and 8 of each 28-day cycle (Regimen 2), or on CCI [redacted].

Duration of Treatment

Patients will continue to receive study treatment until the first instance of disease progression, unacceptable toxicity, Investigator decision, consent withdrawal, study termination by the Sponsor, pregnancy, or death. Patients may continue treatment with GEN1107 beyond RECIST 1.1 progression if they have Investigator-assessed clinical benefit, no rapid disease progression, tolerance to trial treatment, do not have threat to vital organs or critical anatomical sites (eg, central nervous system metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention, stable ECOG PS, and continuing treatment would not delay any intervention to prevent serious complications of disease progression. The decision should be discussed with the sponsor. If progression is confirmed on the next tumor assessment, GEN1107 should be discontinued.

Determination of Sample Size

Up to 280 patients are expected to be enrolled in this study. This number assumes that up to approximately 120 patients may be enrolled in Part A and up to an additional approximately 160 patients will be enrolled in Part B (up to approximately 40 patients in 4 tumor-specific expansion cohorts).

In Part B, after the initial 20 patients (approximately 10 patients in a dose level) are enrolled and randomized in each cohort, the Safety Committee will review the data and confirm whether enrollment should continue (to accrue a total of 20 patients in a dose level), based on cumulative safety and activity data.

No formal hypothesis testing is planned for the expansion cohorts. The sample size for expansion cohorts was determined based on the precision of the estimate. With a sample size of 20 patients per cohort, assuming a 30% ORR, the 95% exact CI is (12%, 54%) and the 80% exact CI is (17%, 47%). Assuming a 20% ORR, the 95% exact CI is (6%, 44%) and the 80% exact CI is (9%, 36%).

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
acMMAE	antibody-conjugated monomethyl auristatin E
ADA	antidrug antibody
ADC	antibody-drug conjugate
AE	adverse event
ALC	absolute lymphocyte count
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
AMP	auxiliary medicinal product
ANC	absolute neutrophil count
ASCO-CAP	American Society of Clinical Oncology-College of American Pathologists
AST	aspartate aminotransferase
ATS	all-treated patients
AUC	area under the curve
β-hCG	beta human chorionic gonadotropin
BCVA	best corrected visual acuity
BRAF	v-RAF murine sarcoma viral oncogene homolog B
BRCA	breast cancer susceptibility gene
BSA	body surface area
C_{eoi}	concentration at the end of infusion
C_{max}	maximum concentration
C_{trough}	trough concentration
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CLIA	Clinical Laboratory Improvement Amendments
CMP	comprehensive metabolic panel
cCR	confirmed complete response
CR	complete response
cPR	confirmed partial response
CRF	case report form
CRO	contract research organization
CT	computed tomography
CXDX	Cycle X, Day X
CYP3A	cytochrome P450 3A
DE	DLT-evaluable
DEC	Dose Escalation Committee
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
dMMR	deficient in mismatch repair
DNA	deoxyribonucleic acid
DOR	duration of objective response
EDC	electronic data capture
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form

Abbreviation	Definition
EE	efficacy evaluable
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EOT	end of treatment
ER	estrogen receptor
ESCC	esophageal squamous cell carcinoma
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FGFR	fibroblast growth factor receptor
FIH	first-in-human
FRα	folate receptor alpha
GCIG	Gynecological Cancer Intergroup
G-CSF	granulocyte colony-stimulating factor
GEJ	gastroesophageal junction
GLP	Good Laboratory Practice
GM-CSF	granulocyte, macrophage colony-stimulating factor
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
Hgb	hemoglobin
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
HRD	homologous recombination deficiency
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IHC	immunohistochemistry
IIV	interindividual variability
ILD	interstitial lung disease
IMP	investigational agent medicinal product
IND	investigational new drug
IRB	institutional review board
IRR	infusion-related reaction
IV	intravenous
LC-MS/MS	liquid chromatography with tandem mass spectrometry
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	monomethyl auristatin E
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NEI	National Eye Institute
NGS	next generation sequencing
NSAIDs	non-steroid anti-inflammatory drugs
NSCLC	non-small cell lung cancer

Abbreviation	Definition
NTD	non-tolerated dose
OCT	optical coherence tomography
ORR	objective response rate
OS	overall survival
PARP	poly-ADP ribose polymerase
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PK	pharmacokinetic(s)
PKE	PK-evaluable
pMMR	proficient in mismatch repair
PO	per oral (by mouth)
PPoS	predictive probability of success
PR	partial response
PR	progesterone receptor
PROC	platinum-resistant ovarian cancer
PTK7	protein tyrosine K 7
PT/PTT/INR	prothrombin time/partial thromboplastin time/international normalized ratio
Q3W	every 3 weeks
Q4W	every 4 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
ROS1	proto-oncogene tyrosine-protein kinase ROS
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SOE	schedule of events
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TAb	total antibody
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
TNBC	triple-negative breast cancer
ULN	upper limit of normal
uMMAE	unconjugated monomethyl auristatin E
UPC	urine protein/creatinine ratio
USP	United States Pharmacopeia
WFI	water for injection

1. INTRODUCTION

1.1. PTK7

PTK7 is a highly conserved member of the pseudokinase family of receptor tyrosine kinases. PTK7 is overexpressed on the surface of many solid tumors, including breast, lung, esophageal, gastric, bladder, endometrial, ovarian cancer, and head and neck cancer, as well as hematological malignancies. Although lacking detectable catalytic tyrosine kinase activity, PTK7 overexpression is intimately involved in Wnt signaling and promotes cancer cell stemness, survival and tumor progression (Ataseven et al., 2013; Chen et al., 2014; Cui et al., 2021; Damelin et al., 2017; Gärtner et al., 2014; Jiang et al., 2012; Lin et al., 2012; Liu et al., 2017; Özçelik et al., 2020; Prebet et al., 2010; Shin et al., 2013; Wang et al., 2014; Xiang et al., 2022).

Low levels of PTK7 protein expression have been reported in normal tissues such as the digestive tract, urinary bladder, kidney, mammary gland, lung, ovary, uterus, and dendritic cells (Damelin et al., 2017); however, expression in normal tissue is lower than on tumors. PTK7 is thus a promising target for novel anti-cancer therapy.

1.2. GEN1107

GEN1107 is a novel ADC that is directed to PTK7. GEN1107 is comprised of:

- A humanized IgG1 antibody CCI that specifically and selectively binds PTK7
- A hydrophilic, protease-cleavable linker
- MMAE, an anti-microtubule agent, as the payload

Upon binding to PTK7 on the surface of malignant cells, GEN1107 is internalized and MMAE released through enzymatic cleavage of the linker. Binding of MMAE to tubulin disrupts the microtubule network within the cell and induces mitotic cell cycle arrest, leading to cell death.

GEN1107 has demonstrated broad anticancer activity in a range of nonclinical models and tumor types. GEN1107 was highly potent on human PTK7-expressing tumor cells in cytotoxicity studies in vitro. In multiple tumor cell line-derived xenograft mouse models, robust and sustained tumor growth inhibition was observed after treatment with a single dose of GEN1107, with complete tumor regression achieved in CCI models tested.

The in vivo PK in rats showed that GEN1107 is stable in circulation and displays PK characteristics indistinguishable from the parent antibody. In the GLP toxicity study in cynomolgus monkeys, GEN1107-related toxicities were primarily bone marrow suppression and lymphoid depletion in thymus, with clinical manifestation of decreased blood cell counts including neutropenia, leukopenia, and anemia; the toxicity profile was consistent with MMAE toxicities and reversible. The HNSTD of GEN1107 was determined to be CCI, the highest dose tested.

Ophthalmology exam was conducted in the study. No GEN1107-related ophthalmic findings were observed.

A complete summary of nonclinical data is provided in the GEN1107 IB.

1.3. PTK7-Expressing Tumors

This FIH study is being conducted to evaluate the safety, tolerability, PK, and antitumor activity of GEN1107 in patients with 1 of the following types of metastatic or unresectable, locally advanced, solid tumors:

- Epithelial ovarian cancer
- Endometrial cancer
- TNBC, ie, hormone receptor negative and HER2-negative
- NSCLC
- Esophageal, gastric, or GEJ adenocarcinoma
- ESCC
- Urothelial cancer

Each of these tumor types has been previously shown to have high expression levels of PTK7 as summarized in Table 1.

Table 1: PTK7 Expression in Selected Tumor Types

Tumor type[d]	**TCGA[a]**		**Tempus[b]**		**CPTAC[c]**	
	Number of samples (n)	High PTK7[e]	Number of samples (n)	High PTK7[f]	Number of samples (n)	High PTK7[g]
Endometrial carcinoma	181	91%	155	79%	113	91%
TNBC	115	90%	231	71%	-	-
NSCLC - squamous	498	81%	316	49%	207	86%
NSCLC - adeno	515	75%			207	87%
Bladder urothelial carcinoma	407	65%	22	18%	-	-
Ovarian carcinoma	427	53%	64	75%	102	97%
Esophageal carcinoma	181	50%	-	-	-	-
Stomach adenocarcinoma	413	16%	16	25%	-	-

Abbreviations: CPTAC = Clinical Proteomic Tumor Analysis Consortium; NSCLC = non-small cell lung carcinoma; TCGA = The Cancer Genome Atlas; TNBC = triple negative breast cancer.

[a] Based upon data generated by the TCGA Research Network: https://www.cancer.gov/tcga.

[b] Based upon the Tempus database.
[c] Based on the CPTAC database: https://proteomics.cancer.gov/programs/cptac.
[d] Tumor indications listed in descending order of percentage of tumor samples having expression of target above the TCGA dataset's median.
[e] Percentage of tumor samples in an indication with PTK7 mRNA expression above the TCGA dataset's median.
[f] Percentage of tumor samples in an indication with PTK7 mRNA expression above the Tempus dataset's median.
[g] Percentage of tumor samples in an indication with PTK7 protein expression above the CPTAC dataset's median.

Eligible patients must have metastatic or unresectable locally advanced disease following prior systemic therapies known to confer clinical benefit. As summarized below, these patients have a high unmet medical need and may be candidates for investigational therapies such as GEN1107.

1.4. Therapeutic Options

1.4.1. Ovarian Cancer

Advanced ovarian cancer has a varied clinical course but is generally considered incurable with current therapies. Typical chemotherapy consists of a platinum-based doublet, with some patients receiving bevacizumab concurrently with chemotherapy. Patients who experience a complete or partial response after chemotherapy may be candidates to receive maintenance treatment. Bevacizumab is indicated for patients who have HRD-negative tumors (Burger et al., 2011; Oza et al., 2015; Perren et al., 2011; Tewari et al., 2019) and PARP inhibitors plus bevacizumab are indicated for patients with HRD-positive tumors (Gonzalez Martin, 2022; Monk et al., 2022; NCCN, 2023; Ray-Coquard, 2022).

Patients with PROC are typically treated with single-agent chemotherapy, with or without bevacizumab. Common agents, including paclitaxel, topotecan, or pegylated liposomal doxorubicin, yield ORRs of approximately 13% and a median PFS of 3 to 4 months in large, randomized trials (AVASTIN USPI, 2022; Gaillard et al., 2021; Hamanishi et al., 2021; Moore et al., 2021; Pujade-Lauraine et al., 2021). Bevacizumab may be added to chemotherapy for patients who have received 1-2 prior lines of treatment and no prior exposure to bevacizumab, resulting in ORRs of 28% and a median PFS of 6.8 months (AVASTIN USPI, 2022). The addition of bevacizumab to chemotherapy is associated with an increased incidence of adverse events including hypertension, gastrointestinal perforation, and fistulas.

Mirvetuximab soravtansine-gynx received FDA accelerated approval in November 2022 for treatment of adult patients with FRα-positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received 1-3 prior systemic treatment regimens. The VENTANA FOLR1 (FOLR1-2.1) RxDx assay used in the registration study identifies tumors with ≥75% tumoral membranous expression with 2-3+ intensity, which is estimated to include approximately 36% of PROC patients (Matulonis et al., 2023). Mirvetuximab soravtansine-gynx is approved with a black box warning for ocular toxicities, including visual impairment, keratopathy, dry eye, photophobia, eye pain, and uveitis.

1.4.2. Endometrial Cancer

First-line systemic treatment for patients with advanced endometrial cancer pMMR typically includes carboplatin and paclitaxel doublet chemotherapy (Miller et al., 2020). For patients with tumors dMMR, carboplatin and paclitaxel doublet chemotherapy plus dostarlimab followed by single-agent dostarlimab recently demonstrated improved results compared to chemotherapy, and received FDA approval in July 2023 (JEMPERLI USPI, 2023).

Options for patients with recurrent disease after first-line chemotherapy include pembrolizumab or dostarlimab for patients with dMMR tumors (ORRs of 48% and 42.3%, respectively) or pembrolizumab plus lenvatinib for patients with pMMR tumors (ORR of 30%, a median PFS of 6.6 months, and a median OS of 17.4 months) (JEMPERLI USPI, 2023; KEYTRUDA USPI, 2023).

There is no standard treatment for patients who have failed carboplatin, paclitaxel, and immune checkpoint inhibitors: single-agent chemotherapy may produce an ORR of approximately 15% and a median PFS of less than 4 months (JEMPERLI USPI, 2023; KEYTRUDA USPI, 2023).

1.4.3. Triple-negative Breast Cancer

First-line therapy for patients with advanced TNBC includes chemotherapy with or without pembrolizumab, based on PD-L1 expression status (Cortes et al., 2022).

Targeted therapies have recently become available for treatment of recurrent TNBC, including trastuzumab deruxtecan for second-line treatment of patients with HER2-low disease (ORR of 52.6%, median PFS of 9.9 months, and median OS of 23.4 months) (Modi et al., 2022), and sacituzumab govitecan for third or later lines of treatment (ORR of 35%, median PFS of 5.6 months, and median OS of 12.1 months) (Bardia et al., 2021).

For patients who have recurrent disease following these agents, there is no standard treatment. Single-agent chemotherapy is an option, producing objective responses in approximately 5% of patients with relapsed or refractory disease (Bardia et al., 2021).

1.4.4. Non-small Cell Lung Cancer

Patients with advanced NSCLC without actionable genomic alterations are generally treated with platinum-based chemotherapy in combination with anti-PD-(L)1 agents. For patients with PD-L1-high tumors (Tumor Proportion Score ≥50%), anti-PD-(L)1 checkpoint inhibitor monotherapy or doublet is a treatment option. For patients whose tumors harbor actionable genomic alterations, targeted therapies may be available such as those targeting EGFR, ALK, ROS1, RET, MET, BRAF MEK, and NTRK.

For NSCLC without actionable genomic alterations that has progressed following platinum-based chemotherapy and immune checkpoint inhibitors, single-agent chemotherapy may be an option and produces response rate of less than 10% and a median PFS of less than 4 months (KEYTRUDA USPI, 2023; OPDIVO USPI, 2023). For NSCLC with actionable genomic alterations that has progressed following targeted therapies and platinum-based

chemotherapy, single-agent chemotherapy may also be an option, with outcomes similar to NSCLC without actionable genomic alterations.

1.4.5. Esophageal, Gastric, or Gastroesophageal Junction Adenocarcinoma

Patients with HER2-negative esophageal, gastric, or GEJ adenocarcinoma typically receive platinum- and fluoropyrimidine-based chemotherapy in combination with anti-PD-(L)1 agents (Janjigian et al., 2021; Rha, 2023). For patients with HER2-positive tumors, standard treatment is chemotherapy plus trastuzumab (HERCEPTIN USPI, 2020). Accelerated approval of chemotherapy and trastuzumab plus pembrolizumab was recently granted by the US FDA (KEYTRUDA USPI, 2023).

Most patients are refractory or have recurrent disease after frontline therapy. Ramucirumab plus paclitaxel produces an ORR of 28%, a median PFS of 4.4 months, and a median OS of 9.6 months in the second-line setting (CYRAMZA USPI, 2020). Trastuzumab deruxtecan is an option for patients with HER2-positive gastroesophageal adenocarcinoma who have received a prior trastuzumab-based regimen and is associated with an ORR of 40.5%, a median PFS of 5.6 months, and a median OS of 12.5 months (ENHERTU USPI, 2022).

For patients with recurrent disease following these therapies, single-agent chemotherapy, such as docetaxel, paclitaxel, and irinotecan may be an option, with response rates of 7 to 16% and a median PFS of 2.9 to 3.5 months (CYRAMZA USPI, 2020; ENHERTU USPI, 2022). For patients who have failed at least 2 prior lines of therapy, trifluridine and tipiracil improved survival compared to placebo (median OS of 5.7 versus 3.6 months) (LONGSURF USPI, 2023).

Patients with this tumor type were allowed under Protocol versions 1.0 and 2.0 but are no longer being enrolled in this study from Protocol version 3.0 onward.

1.4.6. Esophageal Squamous Cell Carcinoma

Standard frontline therapy for ESCC is platinum and fluoropyrimidine-based chemotherapy plus anti-PD-(L)1 agents. Other frontline treatment options include the combination of nivolumab and ipilimumab.

For patients with progressive disease after frontline therapy, single-agent chemotherapy such as irinotecan and paclitaxel are options and are associated with a median PFS of approximately 4 months and a median OS of approximately 8 months (Lee et al., 2019; Yamamoto et al., 2021).

Patients with this tumor type were allowed under Protocol versions 1.0 and 2.0 but are no longer being enrolled in this study from Protocol version 3.0 onward.

1.4.7. Urothelial Cancer

Standard first-line treatment for platinum-eligible patients with urothelial cancer includes platinum-based chemotherapy followed by avelumab maintenance therapy for tumors that did not progress with first-line platinum-containing chemotherapy. For patients who are

ineligible for any platinum-based combination chemotherapy, options include pembrolizumab as a single agent or in combination with enfortumab vedotin (targeting Nectin-4), which received FDA accelerated approval in April 2023 (PADCEV USPI, 2023).

PD-(L)1 inhibitors are an option for second-line treatment, with ORRs of approximately 20% and a median OS of 10 months (Bellmunt et al., 2017; Fradet et al., 2019; Patel et al., 2018; Sharma et al., 2017).

For patients who had previously received platinum-containing chemotherapy and a PD-(L)1 inhibitor, enfortumab vedotin monotherapy is an option and was reported to induce an ORR of 41%, a median PFS of 6 months, and a median OS of 13 months (Powles et al., 2021).

Options for subsequent therapies that have received accelerated regulatory approval in the US include sacituzumab govitecan (targeting Trop-2), which was reported to induce an ORR of 27.7% with median duration of 7.2 months, in patients who had progressed on platinum-based combination chemotherapy and checkpoint inhibitors (TRODELVY USPI, 2023). Erdafitinib (targeting fibroblast growth factor receptor [FGFR]2 and FGFR3) was associated with an ORR of 32.2% and a median response duration of 5.4 months in FGFR2- or FGFR3-positive patients with progressive disease after receiving at least one prior systemic chemotherapy (BALVERSA USPI).

For patients with recurrent disease following platinum-based chemotherapy, single-agent chemotherapy (including paclitaxel, docetaxel, or vinflunine) is a treatment option, with an ORR of approximately 11.4%, a median PFS of 3.3 months, and a median OS of 7.4 months (Bellmunt et al., 2017).

Patients with this tumor type were allowed under Protocol versions 1.0 and 2.0 but are no longer being enrolled in this study from Protocol version 3.0 onward.

1.5. GEN1107 Clinical Development

As summarized above, patients with advanced cancers who have recurrent disease following standard therapies have a high unmet medical need and may be candidates for investigational therapies such as GEN1107. This study is the first-in-human study of GEN1107, and there is no other active clinical trial of GEN1107. A complete summary of clinical and nonclinical data relevant to the investigational product and its study in human patients is provided in the IB.

GCT1107-01 is an open-label, multicenter Phase 1/2 study to evaluate the safety, tolerability, PK, and antitumor activity of GEN1107 in patients with advanced solid tumors. At the time of protocol version 3.0, the study is in the dose-escalation and dose level expansion portion (Part A). No DLTs have occurred and the MTD has not been reached. The pre-planned dose levels of 8, 15, 30, 45, and 60 mg/m^2 Q3W were explored initially, and 2 intermediate dose levels of 37.5 and 52.5 mg/m^2 Q3W were explored subsequently after observation of multiple Grade 3 or 4 neutropenia at dose level 60 mg/m^2 Q3W.

Based on the clinical findings, ocular toxicities are identified risks for GEN1107. An overview of the cases reported to date is provided in the Investigator's Brochure. Premedication with vasoconstrictor and other preventive therapies such as eye lubricant and

cooling eye pads are required to reduce the risk of ocular toxicities. Refer to Section 5.3.2 for pre-medication and preventive ocular therapy for mitigation of ocular toxicity.

1.5.1. Anticipated Risks in Patients

The main findings from the GLP toxicology study in cynomolgus monkeys were decreased blood cell counts including neutropenia, leukopenia, and anemia. In addition, ADCs containing MMAEs have been associated with neutropenia, leukopenia, anemia and thrombocytopenia. These cytopenias may lead to risks of infections including reactivation of chronic viral infections, febrile neutropenia, and bleeding. Blood cell counts must be carefully monitored and appropriate supportive care employed (transfusions, prophylactic or therapeutic antibiotics, and/or growth factors) according to standard clinical practice and published/established guidelines (eg, ASCO and NCCN). Refer to Section 5.6 for recommended dose modifications due to hematologic toxicities.

ADCs containing MMAE are associated with peripheral neuropathy attributed to non-specific uptake of the ADC in the peripheral nerves and subsequent release of MMAE, which disrupts microtubules and may cause neurodegeneration (Best et al. 2021). Patients will be monitored for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, neuropathic pain, or weakness. Patients who experience new or worsening peripheral neuropathy may require a dose delay, dose reduction, or discontinuation of GEN1107 as described in Section 5.6.

As with all biological products, there is the potential for the occurrence of IRRs. Allergic and/or hypersensitivity reactions may occur immediately as IRRs or may occur >24 hours after infusion of GEN1107 (Section 5.6.3). Patients will be closely monitored following GEN1107 administration and recommended management of IRRs is described in Section 5.6.2.

The effects of GEN1107 on embryogenesis, reproduction, and spermatogenesis in humans are unknown. Adequate and effective contraception must be used during and after GEN1107 treatment.

2. OBJECTIVES

Specific objectives and corresponding endpoints for the study are summarized in Table 2.

Table 2: Objectives and Corresponding Endpoints

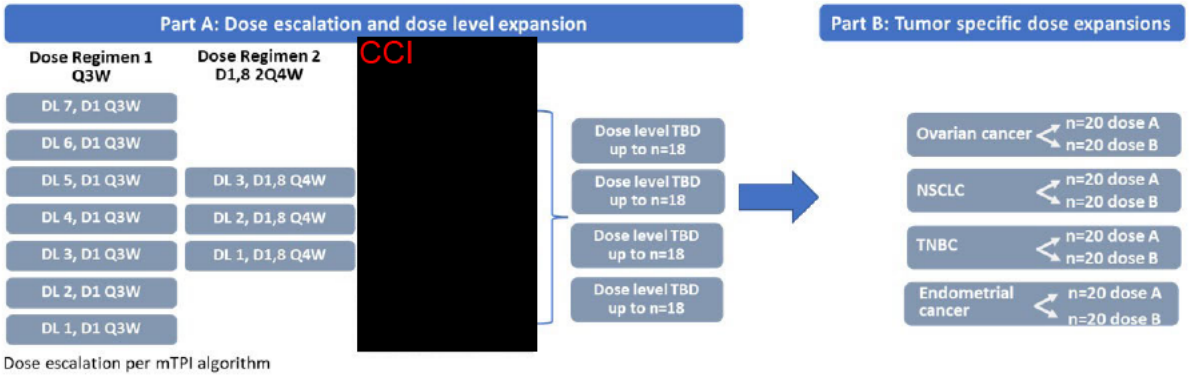
Primary Objectives	Primary Endpoints
• Evaluate the safety and tolerability of GEN1107 • Identify the MTD, if reached, and recommended dose for expansion of GEN1107	• Type, incidence, severity, and seriousness of AEs per the NCI CTCAE, Version 5.0, and per Appendix K for ocular toxicities, and relatedness of AEs • Type, incidence, and severity of laboratory abnormalities • Incidence of DLTs
Secondary Objectives	**Secondary Endpoints**
• Assess the antitumor activity of GEN1107 • Assess the PK of GEN1107 • Assess the immunogenic potential of GEN1107 • Evaluate preliminary antitumor activity based on CA-125 tumor marker levels in subjects with ovarian cancer	• ORR per RECIST, Version 1.1 • DCR • PFS • DOR • PK parameters for GEN1107 related analytes • Incidence of ADA • CA-125 response per GCIG criteria for ovarian cancer
Exploratory Objectives	• **Exploratory Endpoints**
• Evaluate efficacy of GEN1107 • Assess exploratory biomarkers in relation to antitumor activity, safety, pharmacodynamics, and resistance to GEN1107	• OS • Exploratory biomarkers of GEN1107-mediated and disease-related effects

Abbreviations: ADA=antidrug antibodies; AE=adverse event; DCR=disease control rate; DLT=dose-limiting toxicity; DOR=duration of objective response; GCIG= Gynecological Cancer Intergroup; MTD=maximum tolerated dose; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetics; RECIST=response evaluation criteria in solid tumors.

3. INVESTIGATIONAL PLAN

This is a global, open-label, multicenter Phase 1/2 study to evaluate the safety, tolerability, PK, and antitumor activity of GEN1107 in patients with advanced solid tumors. This study consists of 2 parts, Part A: dose escalation and dose level expansion, and Part B: tumor specific expansion. The study design is depicted in Figure 1.

Figure 1: Study Design Schema



Abbreviations: DL=dose level; mTPI=modified toxicity probability interval; NSCLC= non-small cell lung cancer; Q3W=every 3 weeks; Q4W=every 4 weeks; TBD=to be determined; TNBC= triple-negative breast cancer
Note: In Part A, up to 18 patients can be enrolled at a single dose level (9 patients in dose escalation and 9 patients in dose level expansion).
Dotted line indicates that the dose regimen may be evaluated based on accumulated data in the future.

3.1. Part A – Dose-escalation and Dose Level Expansion Cohorts

3.1.1. Dose-escalation Cohorts

GEN1107 will initially be administered on Day 1 of a 21-day cycle (Q3W) via IV infusion at the planned doses outlined in Table 3.

Table 3: Dose Escalation Schema for Q3W Regimen

GEN1107 Dose (mg/m^2)
8
15
30
45
60
75
90

The DEC may recommend investigation of lower or intermediate dose levels based on emerging clinical data.

Two alternative dosing regimens may also be investigated based on review of safety, antitumor activity, and PK data. In the first alternative dosing regimen (2Q4W, Dose Regimen 2) the dose would be administered on Day 1 and 8 of each 28-day cycle. CCI [redacted]

The 2Q4W regimen will be evaluated as the first alternative dosing regimen. The CCI [redacted] will be based on

review of safety, antitumor activity, and PK data from the Q3W and 2Q4W regimens evaluated in clinic.

Table 4: Dose Escalation Schema for 2Q4W regimen

GEN1107 Dose (mg/m^2)
30
40
50

The DEC may recommend investigation of additional (intermediate) dose levels based on emerging clinical data.

Dose-escalation cohorts

Dose escalation and identification of the MTD will be guided by mTPI method (Ji et al., 2010). A minimum of 1 DLT-evaluable patient will initially be enrolled into each of the first 2 dose level cohorts (8 and 15 mg/m^2 dose levels) with Dose Regimen 1. A minimum of 3 patients will be enrolled into each cohort if a qualifying event (a DLT or any ≥ Grade 2 related AE) occurs in the first 2 dose levels or when Dose level 3 is reached with Dose Regimen 1 and at all dose levels with Dose Regimen 2 and 3. In dose escalation, additional enrollment is allowed to ensure at least 3 DLT-evaluable patients.

3.1.2. Dose-escalation Decisions

The DLT evaluation period for each patient is based on data obtained during their first 21 days of treatment for the Q3W regimen and 28 days for the 2Q4W and CCI regimen. When the required number of patients complete the respective regimen's DLT period, the DEC will evaluate all available safety data and make a recommendation on whether dose escalation should proceed. The DEC will take into account DLTs or qualifying events occurring in additionally enrolled patients at the actual dose level during their review. The Safety Committee will be involved if there is a lack of DEC alignment.

The mTPI method uses a Bayesian statistical framework, and a beta-binomial hierarchical model to compute the posterior probabilities of 3 intervals that reflect the relative distance between the toxicity rate at each dose level to the target DLT rate. The DEC can recommend escalating to the next dose level, staying at the current dose level, or de-escalating to a lower dose level. If the recommendation is to stay at the current dose level, the minimum number of patients required will be guided by the mTPI algorithm. Dosing decision rules are determined for a target DLT rate of 25% with a 5% margin (Figure 2). The algorithm will stop if one of the following criteria is met:

- The maximum sample size has been achieved, or
- At least 6 patients have been treated at the presumed MTD (the decision can also be based on 5 subjects if no DLT has been observed on the respective dose level), or
- All doses explored appear to exceed the MTD

Figure 2: Decision Rules for Dose-escalation Based on the mTPI Method

	Number of enrollment at current dose level														
Number of DLT	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	D	S	S	S	E	E	E	E	E	E	E	E	E	E	E
2		DU	D	D	D	S	S	S	S	S	S	E	E	E	E
3			DU	DU	DU	D	S	S	S	S	S	S	S	S	S
4				DU	DU	DU	DU	D	S	S	S	S	S	S	S
5					DU	DU	DU	DU	DU	DU	D	S	S	S	S
6						DU	DU	DU	DU	DU	DU	DU	DU	S	S
7							DU	DU	DU	DU	DU	DU	DU	DU	DU
8								DU	DU	DU	DU	DU	DU	DU	DU
9									DU	DU	DU	DU	DU	DU	DU
10										DU	DU	DU	DU	DU	DU
11											DU	DU	DU	DU	DU
12												DU	DU	DU	DU
13													DU	DU	DU
14														DU	DU
15															DU

E = escalate to the next higher dose; D = de escalate to the next lower dose; DU = current dose is unacceptably toxic; S = stay at the current dose

Note: Target toxicity of 25% with equivalence interval of (20%, 30%). Prior distribution Beta(0.5, 0.5). To further enhance patient safety during dose escalation, the mTPI decision rule for 2 DLTs among 5 treated patients has been changed from "S" (stay) to "D" (de-escalate).

Patients who are not considered DLT evaluable may be replaced. De-escalation to a lower dose level may be performed at any time by the Sponsor in consultation with the DEC. The DEC may also recommend evaluation of intermediate dose levels not exceeding the MTD.

Additional patients may be enrolled at dose levels previously determined to be safe (after clearing the DLT criteria), up to a total of approximately 9 patients per dose cohort to obtain additional safety and tolerability information.

During dose escalation, if a patient tolerates at least 2 cycles of GEN1107 without achieving CR, additional treatment cycles at a higher dose level demonstrated to be safe may be administered at the discretion of the Investigator and upon approval by the Medical Monitor.

Patients enrolled during dose escalation may be selected based on their tumor types to inform Part B dose expansion decisions.

3.1.3. Dose-limiting Toxicity

DLTs will be graded according to NCI CTCAE, Version 5.0, except for ocular toxicities which will be graded per Appendix K. The DLT evaluation period is 21 days of treatment for the Q3W regimen and 28 days for the 2Q4W and CCI regimens. A DLT is defined as any of the following during the DLT evaluation period if considered not clearly and incontrovertibly due to the underlying disease or extraneous causes by either the Investigator or the Sponsor:

- Any death not clearly due to the underlying disease or extraneous causes
- ≥ Grade 3 non-hematologic toxicity, with the following exceptions:
  - Grade 3 fatigue lasting ≤7 days
  - Grade 3 nausea, vomiting, or diarrhea that resolves to Grade 2 or less within 72 hours with adequate supportive care
  - ≥ Grade 3 electrolyte or serum chemistry abnormality resolving within 72 hours, unless the patient has clinical symptoms in which case these abnormalities are considered DLTs regardless of duration
  - ≥ Grade 3 amylase/lipase elevation not associated with signs/symptoms of pancreatitis
- The abnormality indicative of drug-induced liver injury as defined by Hy's Law criteria in Section 7.1.13.8.
- Grade 4 anemia or Grade 3 anemia lasting >7 days (transfusions permitted)
- Grade 4 neutropenia lasting >7 days
- Grade 4 thrombocytopenia lasting >7 days, or ≥ Grade 3 thrombocytopenia with clinically significant bleeding
- Febrile neutropenia (ANC <1000/µL with a single oral temperature measurement of ≥ 38.3ºC [101ºF] or a temperature of ≥ 38ºC [100.4ºF] sustained over a 1-hour period)

Patients experiencing a DLT within the DLT evaluation period should discontinue GEN1107 immediately. If requested by the Investigator, a patient with a DLT may continue in the trial only after discussion with the sponsor. For this decision, a thorough benefit-risk assessment of the individual patient by the Investigator is required. If a patient experiences a toxicity that would have qualified as a DLT, but that occurs after the DLT evaluation period, the patient's benefit-risk must be thoroughly assessed and discussed with the sponsor. A consultation with the Safety Committee may be considered.

3.1.4. Part A Dose Level Expansion

If recommended by the DEC, up to 4 dose cohorts across dose regimens may be expanded up to a total of up to approximately 18 patients per dose level to obtain additional safety,

PK, PD, and activity data to estimate the optimal biological dose(s) and inform selection of the recommended expansion doses, to further support dose optimization in Part B. Patients enrolled at these dose levels may be selected based on their tumor types to inform Part B dose expansion decisions.

3.2. Part B – Tumor-specific Expansion

To further support dose optimization, Part B will be initiated at 2 or more expansion doses based on a comprehensive analysis of safety, tolerability, PK, PD, and antitumor activity data from Part A in up to 4 different tumor-specific cohorts of up to 40 patients per cohort, each cohort evaluating up to 2 dose levels. The dose expansions may be the MTD or a lower dose level from Part A and different dose levels may be selected for each expansion cohort. Patients in each cohort will be randomized with a 1:1 ratio to receive 1 of the dose expansions of GEN1107 (approximately 20 patients in each dose level). If the Safety Committee determines that only one dose level is appropriate for further testing for a particular tumor type, an initial 20 patients may be evaluated at that dose level. Additional dose levels may be tested based on the totality of available data. If supported by the risk-benefit profile, it is feasible to enroll approximately 20 additional patients after enrolling the initial 20 patients at a selected dose level.

Safety and antitumor activity will be continuously monitored throughout the study by the Sponsor. An ongoing, quarterly review of patient safety and SAEs will be conducted by the Safety Committee during Part B. After the initial 20 patients (approximately 10 patients in a dose level) are enrolled and randomized in each cohort, the Safety Committee will review the data and confirm whether enrollment should continue (to accrue a total of 20 patients in a dose level), based on the cumulative safety and activity data.

3.3. Duration of Treatment

Patients will continue to receive study treatment until the first instance of disease progression, unacceptable toxicity, Investigator decision, consent withdrawal, study termination by the Sponsor, pregnancy, or death. Patients may continue treatment with GEN1107 beyond RECIST 1.1 progression if they have Investigator-assessed clinical benefit, no rapid disease progression, tolerance to trial treatment, do not have threat to vital organs or critical anatomical sites (eg, central nervous system metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention, stable ECOG PS, and continuing treatment would not delay any intervention to prevent serious complications of disease progression. The decision should be discussed with the sponsor. If progression is confirmed on the next tumor assessment, GEN1107 should be discontinued.

3.4. Stopping Criteria

3.4.1. Enrollment Pause in Part A

If a patient death is considered related to GEN1107 by the Sponsor, enrollment will be paused at that dose level and all higher dose levels until:

- The case is reviewed by the DEC and Safety Committee (Section 3.6).
- The Sponsor has notified applicable regulatory authorities of the outcome of the safety assessment and justification for restarting enrollment in the affected cohorts. If necessary, according to local regulatory requirements, the Sponsor has received approval to resume enrollment.

3.4.2. Enrollment Halt for the Entire Study

Safety will be monitored throughout the study by the DEC and Safety Committee (in Part A) and by the Safety Committee (in Part B), with consideration for halting enrollment if the incidence and/or the severity of toxicity leads to a benefit-risk assessment that is unacceptable for the study population. The DEC and Safety Committee (in Part A) and the Safety Committee (in Part B) will consider whether to allow patients already receiving treatment to continue, to consider modifications to the protocol to continue enrollment, or to terminate the study.

If enrollment is halted due to safety concerns, enrollment can only restart after appropriate amendments and notifications of regulatory agencies with approval to resume as needed according to local regulatory requirements.

Enrollment in the entire study will be halted by the Sponsor if the overall benefit/risk is considered unfavorable.

3.5. End of Study

The end of trial is defined as the last date of data collection for the last subject in the trial globally.

The maximal study duration is either 3 years after the last patient's first treatment or until all patients have completed the end of treatment visit or started a new anticancer therapy or discontinued from the trial, whichever comes first. In addition, the Sponsor reserves the right to terminate the study earlier than the planned completion. For patients with a potential treatment benefit, patients may be eligible for continued treatment with Genmab IMP(s) by an extension protocol or as provided for by the local country's regulatory mechanism. However, Genmab reserves the unilateral right, at its sole discretion, to determine whether to supply Genmab IMP(s) and by what mechanism, after termination of the trial and before the product(s) is/are available commercially.

3.5.1. Estimated Study Duration for an Individual Patient

The estimated trial duration for an individual patient is approximately 19 months, consisting of a 28-day screening period, an estimated 24-week treatment period (the duration of

treatment may vary for each patient), and an estimated 12-month post-treatment survival follow-up period (the duration of follow-up may vary for each patient).

3.6. Dose Escalation Committee and Safety Committee

The DEC and Safety Committee will monitor the safety of GEN1107 throughout the study.

3.6.1. Dose Escalation Committee

The DEC will be chaired by the Sponsor's medical director (or delegate). Membership includes the Investigator(s) as well as the sponsor's clinical research scientist, safety physician, statistician, clinical pharmacologist, and other relevant stakeholders, as appropriate. The DEC will meet at regular frequency throughout the Dose Escalation part of the study. The schedule of DEC meetings will depend on the completion of DLT evaluation periods.

All available data, including but not limited to safety, PK, and pharmacodynamic data, covering the DLT evaluation period will be reviewed by the DEC. Cumulative data from treatment doses after the DLT period will also be monitored. If there is a lack of alignment by the DEC on the next dosing steps, the Safety Committee will be involved.

Further details are described in the DEC Charter.

3.6.2. Safety Committee

The Sponsor's Safety Committee is a cross-functional committee that evaluates the evolving safety profile of the product, supports assessment of the product's benefit/risk profile and recommends risk management strategies to ensure safety of patients who participate in Genmab sponsored clinical trials or patients treated with marketed Genmab drugs. The Safety Committee can also stop further enrollment if treatment-emergent toxicity is determined to result in an unfavorable change in patient benefit/risk. Enrollment may be temporarily held, if needed, for the Safety Committee to evaluate the emerging data.

Decisions will be communicated to investigators and decisions with the potential to affect patient safety (eg, unfavorable change in benefit/risk assessment) will be promptly communicated to investigators and health authorities, as required.

3.7. Discussion and Rationale for Study Design

Nonclinical pharmacology studies demonstrate the antitumor activity of GEN1107 and the potential for benefit for patients whose cancers express PTK7. Initial clinical development of GEN1107 will involve its evaluation in patients who have previously received standard therapies known to confer clinical benefit (unless ineligible to receive or refused to receive or therapy is unavailable in the region). The safety of GEN1107, including identification of the MTD, if reached, and the recommended expansion doses, will be characterized in dose escalation. Once dose escalation is complete in Part A, up to 4 dose level expansion cohorts across dose regimens of up to approximately 18 patients will be enrolled to further evaluate the safety, PK, and antitumor activity of GEN1107, including potential refinement of the expansion doses. Part B will evaluate the safety and antitumor activity of the expansion doses

from Part A in 4 disease-specific cohorts of patients, to further support dose optimization in dose expansion.

3.8. Rationale for Selection of Doses

The cynomolgus monkey was selected as a pharmacologically/toxicologically relevant species as GEN1107 cross-reacts with cynomolgus monkey PTK7 with similar affinity as human. In the GLP toxicology study in cynomolgus monkeys, the HNSTD of GEN1107 was determined to be CCI . The proposed starting dose for this FIH study was set using a safety factor CCI with the HNSTD. Using standard allometric scaling across species and converting to a body-surface area adjusted dose, the starting dose is 8 mg/m^2 Q3W.

GEN1107 has been administered on Day 1 of a 21-day cycle (Q3W) at the planned doses ranging from 8 to 60 mg/m^2 Q3W. CCI

To improve the safety profile, two alternative dosing regimens may be investigated based on review of the totality of available safety, antitumor activity, and PK data.

The 2Q4W regimen will be evaluated as the first alternative dosing regimen. The starting dose for 2Q4W regimen is 30 mg/m^2 CCI

The CCI will be based on review of safety, antitumor activity, and PK data from Q3W and 2Q4W regimens evaluated in clinic.

3.9. Blinding and Unblinding

Not applicable as this is an open-label study.

4. STUDY POPULATION

Patients must meet all of the enrollment criteria to be eligible for this study. Eligibility criteria may not be waived by the Investigator and are subject to review in the event of a good clinical practice audit and/or health regulatory authority inspection.

Investigators, in consultation with the sponsor's medical director (or delegate), must ensure enrollment criteria are met, and the eligibility review is completed. If a patient's status changes (including laboratory results or receipt of additional medical records) after screening but before the first dose of trial treatment is given, the Investigator must ensure the patient still fulfills all eligibility criteria prior to the first dose.

4.1. Inclusion Criteria

Per Protocol Amendment 2, the inclusion criteria 1 and 2 have been replaced by separate inclusion criteria for Parts A and B (see below). Inclusion criteria 3-9 remain the same for both Parts A and B.

1. Updated per Protocol Amendment 2: for Part A, esophageal, GEJ, or gastric carcinoma; ESCC, and urothelial cancers (bladder, ureter, or renal pelvis) were removed (A.1). For Part B, additional detail was added (see B.1).
2. Updated per Protocol Amendment 2: for Part A, remains the same (A.2); for Part B, this information is incorporated into B.1.
3. Measurable disease at baseline as defined per RECIST, Version 1.1 (Eisenhauer et al., 2009)
4. Patients must be willing to provide a pre-treatment tumor specimen (archival or fresh biopsy samples). If a fresh biopsy is required, procedures more invasive than a core biopsy or significant risk procedures for which the procedure-associated absolute risk of mortality or major morbidity in the patient's clinical setting and specific institution is 2% or higher, should not be utilized.
5. Age 18 years or older at time of informed consent.
6. An ECOG performance status score of 0 or 1.
7. The following screening laboratory data are required. Patients cannot receive supportive care (transfusions or growth factors) for low platelets, neutrophils, or hemoglobin within 2 weeks prior to the screening laboratory assessment.
    - ANC ≥1500/µL, or ≥1000/µL for patients with benign ethnic neutropenia
    - Hgb ≥9 g/dL
    - Platelet count ≥100,000/ µL
    - Serum total bilirubin ≤1.5 × ULN or ≤3 × ULN for patients with Gilbert's disease
    - ALT and AST ≤3 × ULN (≤5 × ULN if there is evidence of hepatic involvement by malignant disease)
    - eGFR ≥50 mL/min, as calculated by either the CKD-EPI 2021 or CKD-EPI 2009 method

8. All toxicities related to prior anti-cancer radiotherapy, systemic therapy or surgical procedures must have recovered to baseline or Grade ≤ 1 based on the NCI CTCAE, Version 5.0 except alopecia, stable chronic changes due to radiation or surgery, endocrine-related toxicity due to checkpoint inhibitor treatment that can be corrected through hormone replacement therapy, and Grade 2 laboratory abnormalities that meet eligibility requirements. Grade ≤ 1 peripheral neuropathy is allowed.
9. The patient must provide written informed consent.

4.1.1. Part A

A.1. Patients must have pathologically confirmed diagnosis of one of the following tumor types:

- Ovarian cancer (must have high grade epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer including serous, endometrioid, and clear cell carcinomas, and excluding mucinous, low grade, and those with a sarcomatous or neuroendocrine element)
- Endometrial cancer (including endometrioid, serous, clear cell carcinomas, and carcinosarcoma, and excluding gastrointestinal mucinous type, low grade, mixed or undifferentiated carcinoma, and those with sarcomatous or mesonephric-like element)
- TNBC, ie, ER-negative, PR-negative, and HER2-negative breast cancer as determined by a CLIA-certified (or local equivalent) laboratory following ASCO-CAP guidelines.
- NSCLC

A.2. Patients must have metastatic or unresectable locally advanced, recurrent disease not amenable to further local therapy and must have previously received therapies known to confer clinical benefit (unless ineligible to receive or refused to receive or therapy is unavailable in the region). Patients with NSCLC with ALK, EGFR, proto-oncogene tyrosine-protein kinase ROS (ROS1), v-RAF murine sarcoma viral oncogene homolog B (BRAF), or any other known actionable genomic alterations, must have received treatment with at least one therapy appropriate to the genomic alteration. If a standard-of-care therapy is available that has not been administered, the reason that the therapy is not appropriate must be documented. Patients who have not received all available therapies known to confer clinical benefit may still be eligible and must be informed of alternative treatment options that might be advantageous to the patient.

4.1.2. Part B

B.1. Patients must have a histologically or cytologically confirmed metastatic or unresectable solid malignancy as specified below.

Cohort 1: Ovarian cancer

- Patients must have histologically or cytologically confirmed high grade serous ovarian cancer, primary peritoneal cancer, or fallopian tube cancer.
- Patients must have received 1 to 4 prior lines of therapy.
- Patients must have received prior treatment with the following therapies:
  - Platinum chemotherapy
  - Prior bevacizumab treatment is required unless the patient has a documented contraindication or due to precautions/intolerance
  - Patients with known or suspected deleterious germline or somatic BRCA mutations and who achieved a complete or partial response to platinum-based chemotherapy must have been treated with PARP inhibitor as maintenance treatment unless the patient is not eligible for treatment with PARP inhibitor
  - Mirvetuximab soravtansine, if appropriate and available in the enrollment region
  - Note the following (all patients):
    - Adjuvant ± neoadjuvant therapy is considered 1 line of therapy. Maintenance therapy (eg, bevacizumab, PARP inhibitors) will be considered part of the preceding line of therapy (ie, not counted independently).
    - Therapy changed due to toxicity in the absence of progression will be considered part of the same line (ie, not counted independently).
    - Hormonal therapy alone (ie, without chemotherapy) will not be counted as a separate line of therapy.
- Patients must have platinum-resistant disease:
  - Patients who have only had 1 line of platinum-based therapy must have received at least 4 cycles of platinum and must have either had a response (CR or PR) or had non-measurable disease at the start of platinum-based therapy and then progressed between >91 days and ≤183 days after the date of the last dose of platinum.
  - Patients who have received 2 to 4 lines of platinum-based therapy must have progressed on or within 183 days after the date of the last dose of platinum.

Cohort 2: TNBC

- Patients must have histologically or cytologically confirmed TNBC
- Patients for whom no designated SoC (eg, checkpoint inhibitors, PARP inhibitors, or antibody-drug conjugates) is available or appropriate and for whom single-agent chemotherapy is considered as the next line of treatment.
- Patients should have received prior antibody-drug-conjugate treatment, if ADC as SOC is available and appropriate.

- Patients must be refractory to or have relapsed after at least 2 prior and a maximum of 4 prior lines of cytotoxic therapy (including ADCs) or chemotherapy for locally advanced and unresectable or metastatic breast cancer, of which a minimum of one line of treatment was in the metastatic setting (these will qualify regardless of triple-negative status at the time they were given).
- Note the following (all patients):
    - Neoadjuvant/adjuvant therapy will qualify as 1 of the required prior regimens, if the development of locally advanced and unresectable or metastatic disease occurred within a 12-month period of time after completion of the neoadjuvant/adjuvant chemotherapy.
    - Prior antihormonal treatment for HR+ disease does not count against the total number of prior lines.

Cohort 3: Endometrial cancer

- Patients must have histologically or cytologically confirmed endometrial cancer (any subtype excluding neuroendocrine tumors or endometrial sarcoma).
- Patients must have received 1 to 3 prior lines of therapy in advanced, recurrent, or metastatic setting.
- Patients must have received prior platinum-based chemotherapy and a PD-(L)1 inhibitor.
- Note the following (all patients):
    - Prior induction plus maintenance is considered 1 line of therapy, even if parts of the treatment regimen (induction or maintenance) are interrupted and/or resumed at a later date, in the absence of disease progression while on active treatment.
    - A switch/change in regimen due solely to toxicity or patient preference (and not disease progression) is not considered a separate line of therapy.
    - Neoadjuvant and/or adjuvant chemotherapy, or radical concurrent chemoradiation count as a first line of prior systemic therapy if there is documented disease progression within 6 months of chemotherapy completion.

Cohort 4: NSCLC

- Patients must have a histologically or cytologically confirmed diagnosis of advanced (unresectable, recurrent and/or metastatic) NSCLC without actionable genomic alterations.
- Patients must have radiographically progressed on or after at least 1 (but no more than 3) prior lines of systemic therapy for unresectable and/or metastatic NSCLC including prior platinum-based therapy or alternative chemotherapy if platinum ineligible (eg, a gemcitabine-containing regimen).

- Patients must have received and progressed on or after prior treatment with a PD-1/PD-L1 inhibitor alone or in combination with platinum-based chemotherapy. To be considered to have progressed on or after prior treatment with a PD-1/PD-L1 inhibitor, patients should have either received this therapy in the advanced setting or have experienced disease progression during "maintenance" treatment following radical concurrent chemoradiation or in the adjuvant setting.
- Neoadjuvant and/or adjuvant chemotherapy, and/or radical concurrent chemoradiation counts as a first line of prior systemic therapy if there is documented disease progression within 6 months of chemotherapy completion.

4.2. Exclusion Criteria for Part A and Part B

1. Prior treatment with anti-PTK7 directed therapy.
2. Had progressive disease as best response while on treatment with an auristatin (eg, a vedotin or pelidotin)-based ADC as the most recent line of therapy.
3. Patients with primary platinum-refractory ovarian cancer, defined as a lack of response to or progression within 3 months after completing frontline platinum-containing therapy.
4. History of another malignancy within 3 years before the first dose of study drug, or any evidence of residual disease from a previously diagnosed malignancy. Exceptions are malignancies with a negligible risk of metastasis or death (eg, 5-year OS ≥90%), such as but not limited to, adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, breast ductal carcinoma in situ, or Stage I uterine cancer.
5. Known active central nervous system metastases, including carcinomatous meningitis. Patients with brain metastases may participate provided the metastases have been treated and are stable for at least 4 weeks prior to the first dose of study drug (repeat imaging during trial screening should be performed to ensure stability of brain metastases for ≥4 weeks), they have no new or enlarging brain metastases, and have discontinued corticosteroids prescribed for symptoms associated with brain metastases for at least 7 days prior to the first dose of study drug. Patients with a history of brain metastases, suspected new brain metastases, or a diagnosis of NSCLC or breast cancer should have a CT/ MRI scan of the brain at screening.
6. Patients with active or chronic corneal disorders, history of corneal transplantation, or any clinically significant corneal disease that prevents adequate monitoring of potential drug-induced keratopathy. Note: Patients with other active ocular conditions requiring ongoing therapy and/or monitoring must be discussed with the sponsor prior to enrollment.
7. Any uncontrolled viral, bacterial, or fungal infection within 2 weeks prior to the first dose of study drug. Routine antimicrobial prophylaxis is permitted.
8. Positive for HBsAg. Additional testing (eg, HBV core antibody, HBV surface antibody testing) should also be performed for patients with increased risk factors to exclude patients with recent or occult infections.

9. Active hepatitis C infection (positive by PCR or on antiviral therapy for hepatitis C within the last 6 months). Patients who have been treated for hepatitis C infection are permitted if they have documented sustained virologic response of at least 12 weeks.
10. Known HIV infection.
11. History of hepatic cirrhosis or autoimmune hepatitis or a history of drug-associated hepatitis within the past 2 years.
12. Additional information regarding transient ischemic attack is added per Protocol Amendment 2.
    12.1. Documented history of a cerebral vascular event (stroke), unstable angina, myocardial infarction, serious cardiac arrhythmia, or congestive heart failure with symptoms consistent with New York Heart Association Class III-IV within 6 months prior to the first dose of study drug. Transient ischemic attack >1 month prior to screening is allowed.
13. History of uncontrolled seizure disorders, clinically significant neurodegenerative disorders, including progressive peripheral neuropathy. Stable Grade ≤ 1 peripheral neuropathy is allowed.
14. Current ILD or pneumonitis or suspected ILD or pneumonitis that cannot be ruled out by imaging at screening.
15. Clinically significant autoimmune disease, either currently present or present within the previous 2 years, including current requirement for systemic immunosuppressive therapy equivalent to >10 mg/prednisone daily (local immunosuppressive therapy, such as inhaled or topical corticosteroids, is allowed).

16. Patients with hospitalization or clinical symptoms due to gastrointestinal obstruction within the past 3 months or radiographic evidence of gastrointestinal obstruction at the time of screening. Enrollment of patients who currently require parenteral nutrition must be discussed with the study medical monitor to determine eligibility.
17. Patients with pleural effusions or ascites requiring frequent thoracocentesis or paracentesis (more often than approximately every 4 weeks) for symptomatic management. Enrollment of patients with an indwelling peritoneal catheter must be discussed with the medical monitor to determine eligibility.
18. Prior antitumor treatments must have a washout period of 2 weeks for chemotherapy or therapy with small molecules and 4 weeks for antibody-based therapeutics prior to the first dose of study drug. If the underlying disease has progressed on treatment, a washout period of 2 weeks prior to the first dose of study drug is acceptable. Treatment with an investigational anticancer agent within 28 days or for systemic therapies within 5 half-lives of the drug, whichever is shorter, prior to trial treatment administration.
19. Use of strong CYP3A P450 inhibitors within 2 weeks prior to the first dose of study drug.
20. Radiotherapy or major surgery that is not completed 2 weeks prior to the first dose of study drug.
21. Patients of childbearing potential, unless under the following conditions:
    a Must have a negative serum pregnancy test (minimum sensitivity 25 mIU/mL or equivalent units of β-hCG) result within 2 weeks prior to the first dose of study drug. Patients with false positive results and documented verification that the patient is not pregnant are eligible for participation.
    b Must agree not to try to become pregnant starting at time of informed consent and continuing throughout the study and for at least 6 months after the final dose of study drug administration.
    c Must agree not to breastfeed or donate ova, starting at time of informed consent and continuing through 6 months after the final dose of study drug administration.
    d If sexually active in a way that could lead to pregnancy, must consistently use 2 highly effective methods of birth control starting at time of informed consent and continuing throughout the study and for at least 6 months after the final dose of study drug administration.
22. Patients who can father children, unless under the following conditions:
    a Must agree not to donate sperm starting at time of informed consent and continuing throughout the study period and for at least 6 months after the final study drug administration.
    b If sexually active with a person of childbearing potential in a way that could lead to pregnancy, must consistently use 2 highly effective methods of birth control starting at time of informed consent and continuing throughout the study and for at least 6 months after the final dose of study drug administration.
    c If sexually active with a person who is pregnant or breastfeeding, must consistently use 1 of 2 contraception options at time of informed consent and

continuing throughout the study and for at least 6 months after the final dose of study drug administration.

23. Known hypersensitivity to any excipient contained in the drug formulation of GEN1107.
24. Estimated life expectancy <12 weeks.
25. Other serious underlying medical condition that, in the opinion of the Investigator, would impair the patient's ability to receive or tolerate the planned treatment and follow-up.
26. Patients with a baseline QTcF of >480 ms.

4.3. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but do not meet the protocol-defined eligibility criteria (refer to Section 4.1 and Section 4.2) as assessed during screening. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to follow ICH guidelines, meet the CONSORT publishing requirements, and to respond to queries from health authorities. Minimal information to be documented includes demography, reason for screening failure (eg, eligibility criteria not met, patient withdrew consent, or other reasons), and any AEs related to a protocol mandated procedure (eg, tumor biopsy, CT scan), including washout or discontinuation of prior medications.

Individuals who screen fail may be rescreened once. Subjects who are rescreened are required to sign a new ICF. All eligibility criteria must be reassessed at the rescreening visit. Previous screening assessments (eg, scans, certain labs) may be used for rescreening purposes if still considered to be within the protocol required window for new planned date of C1D1.

4.4. Patients of Childbearing Potential or who can Father Children

A person of childbearing potential is anyone assigned female at birth who has experienced menarche and who has not undergone surgical sterilization (eg, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or has not completed menopause. Menopause is defined clinically as 12 months of amenorrhea in a person born female over age 45 in the absence of other biological, physiological, or pharmacological causes.

A person who can father children is anyone born male who has testes and who has not undergone surgical sterilization (eg, vasectomy followed by a clinical test proving that the procedure was effective).

4.5. Removal of Patients from Therapy or Assessment

The Sponsor or their designee must be notified if a patient is withdrawn from study treatment or follow-up. The reason(s) for withdrawal must be documented in the patient's medical records and CRF. In Part A dose escalation, patients who are considered not evaluable for DLT may be replaced. In Part A dose level expansion and Part B expansion, patients who discontinue from the study will not be replaced.

4.5.1. Discontinuation of Study Treatment

A patient's study treatment may be discontinued for any of the following reasons:

- Progressive disease
- AE
- Pregnancy
- Investigator decision
- Patient decision, non-AE (ensure that patients who stop treatment because of an AE are not included in this category)
- Study termination by Sponsor
- Other, non-AE

Patients who discontinue from study treatment will remain on study for follow-up unless they withdraw their consent.

4.5.2. Patient Withdrawal from Study

A patient may also be discontinued from the study for any of the following reasons:

- Patient withdrawal of consent
- Study termination by Sponsor
- Lost to follow-up
- Death
- Other

All patients who withdraw from trial participation should be followed for survival status (ie, whether the patient is alive or dead, and date of death). For example, medical records, national or local registries, and publicly available information as allowed per local regulation may be used to determine survival status. Patients may withdraw their consent to the data collection of survival status.

4.5.3. Lost to Follow Up

A patient will be considered lost to follow up if the patient repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible, counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls, and if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.

- Should the patient continue to be unreachable, the patient will be considered to have discontinued from the study.

5. TREATMENTS

5.1. Treatments Administered

GEN1107 is the IMP under study in this protocol.

The AMPs in this study include the required premedications (brimonidine tartrate eye drops and lubricating artificial tears). Refer to Appendix L for EU authorization status of IMPs and AMPs and other country-specific considerations.

Detailed information describing the preparation, administration, and storage of GEN1107 is provided in the IMP Manual.

5.2. Investigational Product

5.2.1. Description

The Investigational Product GEN1107 is supplied in 10-mL glass type I vials sealed with a 20 mm rubber stopper coated with a CCI copolymer film and topped with a 20 mm aluminum flip-off cap. Each vial contains 50 mg GEN1107 as a sterile, preservative-free, CCI .

GEN1107 is reconstituted with WFI, USP, or equivalent grade, for IV administration. Reconstituted GEN1107 is a CCI solution with no visible particulate matter.

Following reconstitution with CCI , a solution containing CCI GEN1107, CCI is produced. The pH is approximately CCI. The extractable volume is CCI .

5.2.2. Dose and Administration

Dosing is based on the patient's BSA calculated by the Mosteller's equation, based on assessments on Day 1 of each Cycle. Patients who have a BSA >2.2 m^2 will receive a dose based on BSA of 2.2 m^2. GEN1107 should be infused over a minimum of 30 minutes and the rate of infusion should not exceed 200 mL/hr. Detailed information describing the preparation, administration, and storage is provided in the Pharmacy Manual.

Patients in the dose-escalation phase will be required to undergo a 2-hour observation period on the day of the first 3 infusions following completion of the infusion. The infusion should be administered at a site properly equipped and staffed to manage anaphylaxis, should it occur. If the first 3 infusions are well tolerated, the observation period for subsequent infusions may be reduced to 1 hour.

GEN1107 must not be administered as an IV push or bolus. GEN1107 requires dilution prior to administration. A CCI must be used during IV administration. See the Pharmacy Manual for details.

GEN1107 should not be administered with other medications.

GEN1107 should be infused over a minimum of 30 minutes and the rate of infusion should not exceed 200 mL/hr.

See Section 5.6 for dose modifications and management of TEAEs.

The infusion site should be monitored closely for redness, swelling, pain, and infection during and at any time after administration. Patients should be advised to report redness or discomfort promptly at the time of administration or after infusion. Institutional guidelines will be followed for the administration of chemotherapy agents and precautions taken to prevent extravasation per institutional standards and as described in (Pérez Fidalgo et al., 2012; Polovich et al., 2014). Upon review of aggregate patient data, the DEC and/or Safety Committee may recommend or require a longer or shorter infusion duration.

5.2.2.1. Storage, Handling, and Accountability

Vials and solutions containing GEN1107 should be stored CCI in a controlled location accessible only to the pharmacist, the Investigator, or a duly designated person. GEN1107 vials and solutions should be stored protected from direct sunlight until the time of use. GEN1107 does not contain preservatives; therefore, reconstituted GEN1107 should be used within CCI.

Information on storage and handling of the reconstituted product is provided in the Pharmacy Manual. Reconstituted vials must not be shaken.

The Investigator or designee must maintain an accurate record of received, returned, and/or destroyed IMP and administration of study treatment to study patients in a drug accountability log/record. Drug accountability will be verified by the site monitor on a continuous basis and at the completion of the study.

When drug accountability has been verified by the site monitor, all expired/unused study IMP (eg, vials, capsules, prefilled syringes) can be destroyed or returned to the sponsor in accordance with the guidance in the IMP Manual.

Final drug accountability will be assessed at the end of the study (or at site closure, if applicable) in accordance with local regulations and guidelines.

5.2.3. Packaging and Labeling

GEN1107 is supplied in 10-mL type I glass vials labeled as “GEN1107”. Study drug labels will contain information to meet the applicable regulatory requirements. For further details, see the IMP Manual.

5.2.4. Preparation

Detailed drug preparation instructions are provided in the Pharmacy Manual.

5.3. Required Pre-medication and Post-medication

5.3.1. IRR

There are no required pre-infusion medications for GEN1107. Routine pre-medication for IRRs should not be administered prior to the first dose of study treatment. Patients who experience IRRs may receive pre-medications such as antihistamines (eg, diphenhydramine 50 mg IV or equivalent and famotidine 40 mg IV or equivalent), corticosteroids (eg, hydrocortisone 100 mg IV or equivalent), or antipyretics, such as acetaminophen (eg, 500 to 1000 mg PO) prior to subsequent doses of study drug. As clinical experience with GEN1107 infusions evolves, routine pre-medication prior to the first dose of study treatment may be instituted as recommended or required by the DEC and/or Safety Committee. For management of IRRs, see Section 5.6.2.

There are no required post-infusion medications for GEN1107.

5.3.2. Pre-medication and Ocular Therapy for Prevention of Ocular Toxicity

5.3.2.1. Ocular Vasoconstrictor Drops

Patients receiving GEN1107 are mandated to use a local ocular vasoconstrictor (brimonidine tartrate 0.2% eye drops or its equivalent) on each day of GEN1107 infusion..

- For example, with brimonidine tartrate 0.2% eye drops, 3 drops in each eye approximately 10 minutes prior to start of GEN1107 infusion and 2 subsequent administrations with approximately 8 hours apart between each administration are required.
- If the patient does not tolerate ocular vasoconstrictors due to adverse reactions, continued treatment with these may be stopped at the discretion of the Investigator and following discussion with the sponsor’s medical monitor.

5.3.2.2. Lubricating Artificial Tears

Patients receiving GEN1107 will be mandated to use lubricating artificial tears.

- Preservative-free lubricating artificial tears are required.
- Lubricating artificial tears will be self-administered as often as needed according to the package insert or instructions from the eye care provider from C1D1 to 30 days after last dose of GEN1107.
- Patients should be advised to wait at least 15 minutes after vasoconstrictor eye drop administration before instilling lubricating eye drops.

5.3.2.3. Other Preventive Therapies

Apply cold packs fully over the eyes following administration of the vasoconstrictor eye drops. Change cold packs as needed throughout infusion to ensure eye area remains cold during the entire infusion and 20 minutes after completion of infusion.

Patients should not wear contact lenses while being treated with GEN1107 from C1D1 to 30 days after last dose of GEN1107.

5.4. Concomitant Therapy

All concomitant medications, blood products, and radiotherapy will be recorded from Day 1 (pre-dose) through the safety reporting period. Any concomitant medications given for study protocol-related AEs should be recorded from the time of informed consent. A protocol-related AE is defined as an untoward medical event occurring resulting from a protocol mandated procedure.

5.4.1. Allowed Concomitant Therapy

The use of platelet and/or red blood cell supportive growth factors or transfusions, when applicable, is allowed. The use of colony-stimulating factors for the treatment of neutropenia per institutional practice is permitted during therapy.

Patients who require systemic immunosuppressive therapy equivalent to >10 mg/prednisone daily are not eligible for this study. Concomitant prednisone (or equivalent) may be used at a dose of ≤10 mg/day, or at higher physiologic replacement doses as applicable. High-dose corticosteroids may be used to manage hypersensitivity reactions (including pre-medication for known hypersensitivity reactions to contrast media used in radiographic assessments) or to treat other adverse events. Local immunosuppressive therapy, such as inhaled or topical corticosteroids, is allowed.

Supportive therapies for bone metastases, including bisphosphonates and RANK-ligand inhibitors are allowed; however, initiation of these therapies during the first cycle of study treatment should be avoided to prevent confounding the assessment of safety. Examples include alendronate (Fosamax), zolendronic acid (Reclast), risedronate (Actonel), and denosumab (Prolia).

The use of routine prophylactic antibiotics, when applicable, is allowed.

Study treatment may be interrupted by palliative radiotherapy not involving target lesions upon approval by the Medical Monitor.

Routine prophylaxis with vaccines is permitted (except during DLT observation period); it is recommended that any vaccines used contain only inactivated or non-living micro-organisms.

5.4.2. Prohibited Concomitant Therapy

Concomitant use with P-gp and/or strong CYP3A4 inhibitors may increase unconjugated MMAE exposure, which may increase the incidence or severity of adverse events. Use of strong inhibitors of CYP3A is prohibited (Appendix J) to minimize potential for increased MMAE exposure (FDA, 2023).

No other investigational drugs, immunosuppressive medications (>10 mg prednisone per day or equivalent), non-study systemic antineoplastic therapies, or growth factor and transfusion support are allowed within 2 weeks prior to the screening laboratory assessment. During the DLT period (Cycle 1), growth factor and transfusion support is discouraged unless medically indicated.

Patients may not receive other investigational drugs, immunosuppressive medications, radiotherapy, or systemic anti-neoplastic therapy during the study, except as specified in Section 5.4.1.

5.5. COVID-19 Management

National and institutional guidelines should be followed for the management of COVID-19 in patients with cancer, including local testing of patients who have been exposed or have symptoms of COVID-19. If the COVID-19 vaccine is administered, this should be captured as a concomitant medication for each date that the vaccine was administered. Adverse events that may result from vaccination should be documented. If possible, it is preferred that vaccinations are administered prior to initiation of the study, such that any toxicities that occur do not confound the safety characterization of GEN1107. If a patient tests positive for COVID-19 while on study, the Medical Monitor should be informed, and the event recorded as an AE. Asymptomatic patients may continue to receive study drug and be followed per local standard of care. If they become symptomatic, hold study drug. For symptomatic patients, hold study drug until they recover or return to baseline per local standard of care.

5.6. Dose Modifications and Management of Treatment-emergent Adverse Events

If a patient has a clinically significant, unresolved TEAE in Cycle 1 or beyond, the next cycle may be delayed for up to 14 days. Delays due to other reasons or lasting >14 days must be discussed with the medical monitor. Patients requiring a cycle delay >14 days due to an unresolved TEAE may be dosed in subsequent cycles at a reduced dose or the dosing frequency may be decreased with the approval of the study medical monitor. A CMP and CBC should be collected at least weekly during dose delays.

For patients receiving Day 1 and 8 2Q4W regimen, if toxicities occur on Day 8 of any cycle and require the dose to be held >5 days, then the dose must be eliminated, rather than delayed. If a patient only receives Day 1 and needs to skip Day 8, the patient could resume the next cycle as early as Day 22 (new Day 1), if the toxicity has resolved or returned to baseline by Day 22 (new Day 1).

For patients receiving CCI [redacted] regimen, if toxicities occur on CCI [redacted] of any cycle and require the dose to be held >3 days, then the dose(s) must be eliminated, rather than delayed. CCI [redacted]

In addition, study drug should be discontinued if any of the following criteria are met in the absence of other immediately apparent possible causes of these laboratory abnormalities, including but not limited to viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic:

- ALT and/or AST elevation >3 × ULN and total bilirubin >2 × ULN
- ALT and/or AST elevation >3 × ULN with the appearance of clinical symptoms of hepatic injury

Recommended dose modifications for study treatment-associated toxicity are summarized in Table 4, Table 5, and Table 6. Additional information on management of ocular toxicities, IRRs, allergic/hypersensitivity reactions, anaphylaxis, and overdose are provided in the sections that follow. Medical Monitor approval is required for continued study treatment after occurrence of a ≥ Grade 3 AE that is potentially associated with GEN1107. All dose reductions should be discussed with the sponsor's medical monitor.

Table 4: Recommended Dose Modifications for Potential GEN1107-associated Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Non-hematologic, **except** peripheral neuropathy and ocular toxicities (Section 5.6.1)	Continue at same dose level	Withhold dose until toxicity is ≤Grade 1 or has returned to baseline, then resume treatment at same dose level **Consider dose reduction for patients with recurrence despite best supportive care or in patients with Grade 2 AE lasting longer than 14 days**	Withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at same dose level **Consider to permanently discontinue for patients with recurrence despite best supportive care or in patients with Grade 3 AE lasting longer than 14 days.**	Withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then consider dose reduction to the next lower dose level[a] and resume treatment with Medical Monitor approval or discontinue at the discretion of the Investigator
Peripheral neuropathy	Continue at same dose level	Withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at a lower dose level	Permanently discontinue study drug	Permanently discontinue study drug
IRR; see Table 6	Consider pre-medication for subsequent GEN1107 treatment	Administer pre-medication for subsequent GEN1107 treatment. Consider slower infusion rate. If IRR recurs after the above measures, discuss with medical monitor whether to consider dose reduction to 1 dose level below current dose	Patients with an IRR that resolves to baseline or Grade 1 or lower within approximately 2 hours after intervention may continue GEN1107 with altered pre-medication, infusion rate, and/or reduced dose for subsequent infusions, if approved by the medical monitor OR Permanently discontinue from study treatment.	Permanently discontinue study drug
Hematologic	Continue at same dose level	Withhold until toxicity resolves to ≤Grade 1 or baseline, then	Withhold until toxicity resolves to ≤Grade 1 or baseline. **For neutropenia, strongly consider growth factor support**, then	Withhold dose until toxicity resolves to ≤Grade 1 or baseline. **Prophylactic growth factor support is required for all subsequent cycles.** If Grade 4 hematologic

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
		resume treatment at the same dose level.	resume treatment at the same dose level. **Prophylactic growth factor support should be strongly considered for subsequent cycles.**	toxicity recurs, consider dose reduction to the next lower dose level[a] and resume treatment with Medical Monitor approval, or discontinue at the discretion of the Investigator.
Toxicity	**Grade 3/Grade 4**			
Febrile neutropenia	Withhold dose until toxicity resolves to ≤Grade 1 (or to complete resolution of febrile neutropenia) or baseline. **Prophylactic growth factor support is required for all subsequent cycles.** If Grade 4 febrile neutropenia, consider dose reduction to the next lower dose level[a] and resume treatment with Medical Monitor approval, or discontinue at the discretion of the Investigator.			

Note: For patients at the lowest dose level, dose reduce by 50%. Discuss treatment delays of >14 days with the Medical Monitor.

[a] If toxicity recurs at Grade 3 or higher despite dose reduction, the dosing frequency may be decreased with medical monitor approval.

5.6.1. Ocular Toxicity

Specific ocular toxicities including corneal keratitis, conjunctivitis, iritis/uveitis, blurred vision, and serous detachment of retinal pigment epthielium will be graded per criteria listed in Appendix K, other ocular toxicities will be graded per NCI-CTCAE, Version 5.0.

Table 5: Recommended Dose Modifications for Potential GEN1107-associated Ocular Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Corneal keratitis	Dosing not interrupted	Delay dose until resolved to nonconfluent superficial keratitis, then maintain dose. Consider dose reduction for patients with recurrence despite best supportive care or in patients with Grade 2 lasting longer than 14 days.	Discontinue patient from study treatment.	Not applicable
Conjunctivitis	Dosing not interrupted	Delay dose until resolved to nonconfluent superficial punctate defects and mild vasodilation, then maintain dose. Consider dose reduction for patients with recurrence despite best supportive care or in patients with Grade 2 lasting longer than 14 days.	Discontinue patient from study treatment.	Not applicable
Iritis/Uveitis	Dosing not interrupted	Delay dose until resolved to Grade 0 or 1 and then maintain dose. Consider dose reduction for patients with recurrence despite best supportive care or in patients with Grade 2 lasting longer than 14 days.	Delay dose until resolved to Grade 0 or 1, then reduce dose to the next lowest dose level. Consider permanent discontinuation of patients with recurrence despite best supportive care or in patients with Grade 3 lasting longer than 14 days.	Discontinue patient from study treatment.

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Blurred vision	Dosing not interrupted	Delay dose until BCVA same as baseline or 20/40 whichever is worse, then maintain dose. Consider dose reduction for patients with recurrence despite best supportive care or in patients with Grade 2 lasting longer than 14 days.	Delay dose until BCVA same as baseline or 20/40 whichever is worse, then maintain dose. Consider permanent discontinuation of patients with recurrence despite best supportive care or in patients with Grade 3 lasting longer than 14 days.	Discontinue patient from study treatment.
Serous detachment of retinal pigment epithelium	Dosing not interrupted	Delay dose until detachment resolved to ≤Grade1, then maintain dose. Consider dose reduction for patients with recurrence despite best supportive care.	Delay dose until detachment starts to resolve, then reduce dose to the next lowest dose level. Consider permanent discontinuation of patients with recurrence despite best supportive care.	Permanently discontinue study drug.
Other ocular/corneal toxicities	Continue at same dose level	Withhold dose until evaluation by eye care provider and toxicity is ≤Grade 1 or has returned to baseline then resume treatment at current dose level. Consider dose reduction for patients with recurrence despite best supportive care or in patients with Grade 2 lasting longer than 14 days.	Withhold dose until evaluation by eye care provider and toxicity is ≤Grade 1 or has returned to baseline, then resume treatment at the next lowest dose level. Consider permanent discontinuation of patients with recurrence despite best supportive care or in patients with Grade 3 lasting longer than 14 days.	Permanently discontinue study drug.

5.6.2. Infusion-related Reactions

An IRR is defined as an adverse reaction to the infusion of pharmacological or biological substances that occurs within 24 hours of infusion. Infusion-related reactions may manifest as a combination of signs or symptoms including fever, rigors, flushing, itching, various types of rashes, urticaria, dyspnea, nausea, vomiting, back or abdominal pain, and/or hypotension (Kang and Saif, 2007).

All supportive measures consistent with recommended patient care should be given throughout the study according to institutional standards. Supportive measures may include extending the infusion time and/or administering medications for IRRs. It is recommended that patients remain in close proximity to a medical facility for 24 hours after administration of GEN1107 to enable prompt evaluation in case of a delayed IRR.

During the study, additional mitigation strategies may be explored to manage IRRs, as recommended by the DEC and/or Safety Committee. These mitigation strategies may include, but are not limited to, any of the following:

- Slowing, interruption, or other adjustments in the administration of GEN1107
- Potential pre-medication or post-medication for infusions, such as:
    - Antihistamines, such as diphenhydramine 50 mg IV or equivalent and famotidine 40 mg IV or equivalent
    - Antipyretics, such as acetaminophen 500–1000 mg PO, or ibuprofen 400-600 mg PO
    - Antiemetics, such as ondansetron
    - IV fluid support, such as normal saline
    - Anti-rigor medication, such as meperidine
    - Vasopressors
    - Corticosteroids, such as hydrocortisone 100 mg IV or equivalent or methylprednisolone 40 mg IV or equivalent

Recommendations for the management of IRRs are detailed in Table 6. The protocol will be amended if ≥ Grade 3 IRRs are seen in ≥20% of patients and the DEC and/or Safety Committee recommends pre-medication and/or modification of the infusion approach, as specified in Section 3.1.4.

Table 6: Management of Infusion-related Reactions

IRR Grade[a]			
Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Mild transient reaction: GEN1107 treatment interruption not indicated; intervention not indicated.	GEN1107 treatment interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 h	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.	Life-threatening consequences: urgent intervention indicated.
Treatment Recommendations			
Monitor vital signs more frequently as medically indicated until symptoms have resolved and patient is medically stable. Administer symptomatic treatment as medically indicated.	Hold GEN1107 treatment. Monitor vital signs more frequently until symptoms have resolved and subject is medically stable. Administer symptomatic treatment as medically indicated. If subject responds promptly and is medically stable in the opinion of the Investigator, GEN1107 may be continued at a slower rate.	Stop GEN1107 treatment. Institute additional medical management as indicated. Consider hospitalization.	Stop GEN1107 treatment immediately. Hospitalization.
Dose Modifications			
Consider pre-medication for subsequent GEN1107 treatment.	Consider pre-medication for subsequent GEN1107 treatment. Consider slower infusion rate. If IRR recurs after the above measures, discuss with medical monitor whether to consider dose reduction to 1 dose level below current dose.	Patients with an IRR that resolves to baseline or Grade 1 or lower within approximately 2 hours after intervention may continue GEN1107 with altered pre-medication, infusion rate, and/or reduced dose for subsequent infusions, if approved by the medical monitor. OR Permanently discontinue from study treatment.	Permanently discontinue from study treatment.

Abbreviations: IRR=infusion-related reaction; IV=intravenous; NSAIDS=non-steroidal anti-inflammatory drugs.
[a] Per NCI-CTCAE, Version 5.0

All Grade 3 IRR events (with onset either during infusion or within 24 hours after infusion) or hypersensitivity reaction (with onset occurring >24 hours after infusion) must be reported to the Sponsor or its designee immediately, regardless of relationship to GEN1107. All Grade 4 IRR events are SAEs and are to be reported within the SAE reporting timeframe of 24 hours via the standard SAE forms (Section 7.1.13.1.2).

5.6.3. Allergic/Hypersensitivity Reaction

Allergic/hypersensitivity reactions are characterized by adverse local or general responses from exposure to an allergen (NCI CTCAE, Version 5.0). Allergic/hypersensitivity reactions may occur immediately as IRRs or may occur >24 hours after infusion of GEN1107. The clinical presentation typically includes a combination of signs or symptoms including fever, rigors, flushing, itching, various types of rashes, urticaria, dyspnea, nausea, vomiting, back or abdominal pain and/or hypotension.

Allowed measures include dose modifications and concomitant medications.

5.6.4. Anaphylaxis

Anaphylaxis is a severe, life-threatening, generalized, or systemic allergic/hypersensitivity reaction. Anaphylaxis is characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with an acute onset of illness (minutes to several hours) with involvement of the skin and/or mucosa (eg, hives, pruritis, angioedema), respiratory compromise, (eg, dyspnea, bronchospasm, hypoxia), hypotension, syncope, and gastrointestinal symptoms (eg, pain, vomiting) (Roselló et al., 2017; Sampson et al., 2006).

If anaphylaxis occurs in a patient following study drug administration, GEN1107 should be immediately and permanently discontinued.

5.6.5. Intrapatient Dose Escalation

During dose escalation, if a patient tolerates at least 2 cycles of GEN1107 without achieving CR, additional treatment cycles at a higher dose level demonstrated to be safe may be administered at the discretion of the Investigator and upon approval by the Medical Monitor.

5.6.6. Management of Overdose

An overdose of GEN1107 is defined as administration of ≥20% of the intended dose. In the event of an overdose of GEN1107, study personnel should:

- Care for and medically stabilize the patient until there is no immediate risk of complications or death, if applicable. There is currently no known antidote for an overdose of GEN1107.
- Notify the Medical Monitor as soon as they become aware of the overdose, to discuss details of the overdose (eg, exact amount of GEN1107 administered, patient's BSA) and any AEs.
- Any AE associated with an overdose should be recorded on the AE eCRF with the diagnosis of the AE.

5.7. Treatment Compliance

Study drug administration will be performed by study site staff and documented in the source documents and the eCRF.

6. STUDY ACTIVITIES

6.1. Schedule of Events

Adverse events and concomitant medications will be recorded from Day 1 (pre-dose) through the 30 days after the last dose of GEN1107. Any protocol-related AEs/SAEs as well as any concomitant medications given for treatment of the AE should be recorded from the time of informed consent onward. A protocol-related AE is defined as an untoward medical event occurring resulting from a protocol mandated procedure.

SOE tables are provided in Appendix A, Appendix C, and Appendix E. Study activities are listed by visit in this section and descriptions of all study assessments are presented in Section 7.

6.2. Screening/Baseline Visit (Days –28 to 1)

Before performing any protocol-specific procedures that would not otherwise be done for a patient, a written and signed ICF must be obtained. Detailed timing of screening and baseline assessments are provided in Appendix A.

All patients will be requested to provide a pre-treatment tumor specimen (archival or fresh biopsy samples). If a fresh biopsy is required, procedures more invasive than a core biopsy or significant risk procedures for which the procedure-associated absolute risk of mortality or major morbidity in the patient's clinical setting and specific institution is 2% or higher, should not be utilized.

A CT/MRI of the brain should be done at Screening for all patients with a history of brain metastases, those suspected of new brain metastases, or those with a diagnosis of NSCLC or breast cancer.

Diagnostic-quality CT and/or MRI of the chest, abdomen, and pelvis (and neck if tumor involvement in this region is either documented or suspected), with IV contrast, should be performed unless medically contraindicated. Radiological scans performed prior to consent can be used for the purposes of the study if they have been performed as part of routine clinical practice and the patient consents for their medical records to be reviewed by the Sponsor or its designee.

Standard safety monitoring will be done. Patients will be asked to complete scheduled visits and assessments per the SOE (Appendix A, Appendix C, and Appendix E). Results of screening assessments should be reviewed against eligibility criteria to confirm that the patient meets all inclusion and exclusion criteria for the study.

If the patient meets all inclusion/exclusion criteria, contact the study Medical Monitor or its designee to obtain confirmation for enrollment and assignment of dose and cohort.

6.3. Treatment Visits

Cycle 1, Day 1 dosing must be completed within 7 days of enrollment approval, unless otherwise indicated.

Following Cycle 1 Day 1 patients will be asked to complete treatment visits per the SOE (Appendix A).

6.4. Response/Efficacy Visits

Antitumor activity will be assessed by radiographic imaging performed every 6 weeks (±4 days) for the first 6 months after the first dose of GEN1107, every 9 weeks (±4 days) from 6 to 12 months, and then every 12 weeks (±8 days) thereafter. Determination of antitumor activity and response will be based on objective response assessments as defined by RECIST Version 1.1. Objective responses (CR or PR) must be confirmed with repeat scans a minimum of 4 weeks to approximately 6 weeks after the first documentation of response.

Scanning frequency should be calendar based and does not depend on cycle visits. The schedule of response assessments should not be adjusted for dose delays, dose interruptions, or other reasons for changes in the timing of a patient's study activities.

Imaging should be conducted until any of the following reasons: disease progression, unacceptable toxicity, Investigator decision, consent withdrawal, study termination by the sponsor, pregnancy, or death, whichever comes first. For all tumor cohorts, imaging should also be performed whenever disease progression is suspected.

6.5. End of Treatment Visit (30 +7 Days After Last Dose of Study Drug)

An EOT visit should occur 30 +7 days after the last dose of GEN1107 unless delayed due to an AE or conducted earlier due to the start of another anticancer therapy. If EOT evaluations are completed less than 30 days after the last study treatment, the patient will be contacted 30 +7 days following the last treatment to assess any AEs. Patients will be asked to attend the EOT visit and complete the assessments per the SOE (Appendix A).

6.6. Follow-up (Every 12 Weeks ±1 Week)

A first follow-up visit will occur 12 weeks (±1 week) from the most recent prior response evaluation. Subsequent follow-up visits will be scheduled 12 weeks (±1 week) after the previous follow-up visit.

All patients who discontinue treatment with GEN1107 will remain on the study for follow-up and continue to be assessed for survival status and collection of first subsequent anticancer treatment information until 12 months post last dose of study drug or withdrawal of consent, death, or study closure, whichever occurs first.

Patients who discontinue treatment prior to disease progression will continue to be assessed for response for up to 12 months after EOT until PD is documented or a new therapy is initiated. Response will be assessed via diagnostic-quality CT and/or MRI of the chest, abdomen, and pelvis (and neck if documented or suspected involvement in this region), with IV contrast unless contraindicated.

Patients who have initiated a subsequent therapy will not be assessed for response but will be followed for survival.

6.7. End of Study/End of Follow-up

The date the patient met criteria for study discontinuation and the reason for study discontinuation will be recorded in the eCRF.

7. STUDY ASSESSMENTS

7.1. Description of Study Procedures

7.1.1. Informed Consent

Before the performance of any protocol-specific procedures that would not otherwise be done for a patient as part of standard of care, a written and signed ICF must be obtained from the patient.

7.1.2. Demographics and Medical History

The following demographic details will be collected at screening, where permitted by local regulations:

- Gender and sex assigned at birth
- Age at time of screening
- Race
- Ethnicity

Justification for the collection of race and ethnicity in all subjects

Clinical development of a drug requires an understanding of the optimal dose and/or exposure–effect relationship. To understand the relationship between exposure and safety/efficacy, PK of the drug needs to be characterized in a patient population, which includes quantitative characterization of IIV. Specifically, understanding of IIV at the population level can be achieved using population PK modelling, where the PK of a drug is characterized in the target patient population and IIV is investigated by assessing the effect of different covariates on PK parameters. Historically, race and ethnicity are important demographic variables contributing to IIV (Gill et al., 2016; Johnson, 1997; Johnson, 2000; Xie et al., 2001), and therefore this information will be helpful to assess the impact of exposure on safety and efficacy.

Patient medical history includes a thorough review of significant past medical history, current conditions, any treatment for prior malignancies and response to prior treatment, and any concomitant medications.

7.1.3. Physical Examination and Height

Physical examinations should include assessments of the following: abdomen, extremities, head, heart, lungs, neck, and neurological system, as well as weight at scheduled time points (Appendix A, Appendix C, Appendix E) during the study. Height will also be recorded at baseline; measurements of height obtained within the prior 12 months may be used.

Eyes should be examined by the Investigator and assessments should include a visual inspection of the eye orbit and conjunctiva and control of normal eye movement. The patient should be asked about any ocular symptoms (eg, itchy eyes, sticky eyelids, eye secretion, blurry vision etc.). In case of clinical findings, the patient must be referred to an ophthalmologist for assessment within 7 days, and before the next dose of study drug.

7.1.4. ECOG Performance Status

The grading scale for ECOG Performance Status is shown in Appendix G.

ECOG assessment will be completed according to the timepoints specified in Appendix A, Appendix C, and Appendix E.

7.1.5. Vital Signs

Vital signs measures are to include heart rate, blood pressure, respiratory rate, and temperature. Vital signs will be measured and recorded prior to the start of GEN1107 administration and at additional time points specified in Appendix A, Appendix C, and Appendix E.

7.1.6. Ophthalmology Tests

Patients will be referred to an eye care professional for an ophthalmic exam within 14 days prior to treatment initiation, within 7 days before Day 1 of Cycle 2 to Cycle 5, 7, and 9, as clinically indicated for subsequent cycles, and at the EOT visit. Baseline and interval exams include examination of both eyes and documentation of:

- BCVA
- Refraction
- Dilated slit lamp examination of the cornea, anterior chamber, and lens; Fluorescein staining and scoring using the Oxford scale or NEI scoring per local practice
- OCT of the nerve and macula
- Intraocular pressure

Patients who experience ocular TEAEs while on study will have complete ophthalmologic tests performed before Day 1 dosing for 4 subsequent treatment cycles.

7.1.7. Clinical Laboratory Tests

The laboratory assessments outlined in Table 7 will be performed by the local laboratories at scheduled time points (Appendix A, Appendix C, and Appendix E) during the study. Other safety tests may be conducted as clinically indicated, at the discretion of the Investigator.

Table 7: Clinical Laboratory Assessments

Category	Test
Glycemic control:	• fasting glucose • Hgb A1c
Serum chemistry:	• albumin • alkaline phosphatase • ALT • AST • blood urea nitrogen • calcium • carbon dioxide • creatinine • chloride • lactate dehydrogenase • phosphorus • potassium • sodium • total bilirubin
Blood hematology:	• red blood cell count • white blood cell count with 5-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), • absolute neutrophil count • platelet count • Hgb • hematocrit
Fasting lipid panel:	• total cholesterol • LDL • HDL • triglycerides
Pancreatic function:	• amylase • lipase
Coagulation:	• PT/aPTT/INR (aPTT is also acceptable)
Urinalysis:	• standard urinalysis (with reflexive microscopy for abnormal results)
Pregnancy:	• Baseline serum β-hCG pregnancy test for patients of childbearing potential. Post baseline urine pregnancy test is acceptable and any positive should be confirmed by serum.
Viral testing:	• HIV • Hepatitis B virus surface antigen • Hepatitis B virus core antibody • Hepatitis C virus rt-PCR
Biomarkers	• CA-125 (ovarian cancer and endometrial cancer with elevated CA-125 at baseline)

Abbreviations: ALT=alanine transaminase; aPTT=activated partial thromboplastin time; AST=aspartate transaminase; β-hCG= beta human chorionic gonadotropin; HDL=high-density lipoprotein; HIV=human immunodeficiency virus; Hgb=hemoglobin; Hgb A1c=hemoglobin A1c; INR=international normalized ratio; LDL=low-density lipoprotein; PCR=polymerase chain reaction; PT=prothrombin time

7.1.8. Electrocardiograms

Standard 12-lead safety ECGs will be conducted in triplicate for all patients at Screening, C1D1 (pre-dose), C3D1 (pre-dose), and EOT (Appendix A, Appendix C, and Appendix E).

All ECGs should be performed after the patient has been resting for at least 10 minutes prior to PK blood collections (Appendix A, Appendix C, and Appendix E).

Waiting periods between each ECG are not required. Electronic or paper copies of the tracings may be submitted to the Sponsor or its designee for possible central assessment.

7.1.9. Pregnancy Testing

For patients of childbearing potential, a serum β-hCG pregnancy test with sensitivity of at least 25 mIU/mL will be performed at baseline (D-14 to D1). After the first cycle, urine pregnancy tests may be performed within 7 days prior to Day 1 of each cycle and at the EOT visit and any positives should be confirmed by serum test. A negative pregnancy result is required before the patients may receive study drug. Pregnancy tests may also be repeated as requested per IRB/IEC or if required by local regulations.

7.1.10. Response/Efficacy Assessments

Tumor evaluation will be performed by CT, PET/CT scan (if diagnostic-quality CT scan included, and/or MRI scan of the chest, abdomen, and pelvis at the timepoints specified in Appendix A, Appendix C, and Appendix E. Imaging of the neck must also be obtained if there is documented or suspected involvement in this region. Scans must be of diagnostic quality, and IV contrast must be used unless medically contraindicated. For each assessed lesion, the same modality should be used throughout the duration of the study. For patients unable to tolerate contrast-enhanced CT assessments, MRI imaging is acceptable. MRI scans may not be appropriate to assess lung parenchymal lesions and CT without contrast enhancement is acceptable in such situations. If any other radiographic or disease assessment examination is conducted per standard of care, the assessment information will be collected in the eCRF.

In addition to radiographic tumor assessment, expression levels of CA-125 will be monitored for patients with ovarian cancer and patients with endometrial cancer who have elevated CA-125 at baseline. Blood collections for CA-125 should correspond as closely as possible with imaging visits. CA-125 should be assessed by the same laboratory throughout the study.

Patients' clinical data must be available for CRF source verification. Copies of tumor images must be made available for review by the Sponsor or its designee, and upon request for possible retrospective central review.

7.1.11. Pharmacokinetic, Immunogenicity, Pharmacodynamic, and Biomarker Assessments

The following paragraphs are relevant **only for patients in China**:

PK, ADA, and PD samples from patients in China will be shipped to the central laboratory, CCI [redacted], which is contracted by the Sponsor for storing and testing samples. The central laboratory will transport, store, and report samples as required and in a safe manner for study use only. The remaining samples will be destroyed in accordance with the standard destruction process after completion of testing in the laboratory. The testing labs for PK, ADA and PD are the following:

CCI [redacted]

[redacted]

CCI [redacted]

Tumor/slides samples for patients in China will be shipped to the central laboratory, CCI [redacted] which is contracted by Sponsor for storing and testing samples. The central laboratory will transport, store and report samples as required and in a safe manner for study use only. The remaining samples will be destroyed in accordance with the standard destruction process after completion of testing in the laboratory. The testing labs for tissue samples are the following:

CCI [redacted]

[redacted]

[redacted]

7.1.11.1. Pharmacokinetic and Immunogenicity Assessments

PK will be assessed based on GEN1107-related analyte concentrations measured at defined time points (Appendix B, Appendix D, and Appendix F).

Ac-MMAE, TAb, and u-MMAE concentrations in plasma will be determined using validated assays. The assays may include ELISA or LC-MS/MS, as well as other assays if further characterization is required. Analysis of GEN1107 ADC concentrations may be run in a subset of samples in an exploratory way using non-validated methods. Remaining PK samples will be archived for possible analysis of other GEN1107-related species.

A validated electrochemiluminescence assay will be used to assess levels of ADA against GEN1107 in serum. Samples will be archived for future ADA assessment including, but not limited to, neutralizing ADA assays.

7.1.11.2. Pharmacodynamic and Biomarker Assessments

Biomarker and pharmacodynamic biomarker assessments will be performed from tumor tissue and peripheral blood as outlined below. Exploratory, predictive, and prognostic biomarkers associated with response, resistance, or safety observations will be monitored before and during treatment with GEN1107. Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the trial, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the trial is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

7.1.11.2.1. Tumor Biopsies

To better understand relationships between pre-treatment tumor biological characteristics and patent outcome, submission of tumor tissue is required during the screening period (pretreatment) and are required for all patients. Samples for biomarker analyses will be collected as specified in Appendix B, Appendix D, and Appendix F. Detailed requirements

and instructions for tissue collection, processing and shipment are provided in the Laboratory Manual.
All patients must be willing to provide a pre-treatment tumor specimen (archival or fresh biopsy samples). In the absence of an archival tissue sample, a fresh biopsy is required. Procedures more invasive than a core biopsy or significant risk procedures for which the procedure-associated absolute risk of mortality or major morbidity in the patient's clinical setting and specific institution is 2% or higher, should not be utilized.

An optional fresh biopsy collected at time of radiographic disease progression may be provided for biomarker analyses, if clinically feasible and if the patient provides consent for this procedure.

Tumor samples will be tested for PTK7 expression via IHC assay. Additional biomarker analyses tumor specimens may include, but are not limited to, PTK7 RNA expression levels, PTK7 gene mutation or amplification, and established disease-specific biomarkers (eg, oncogenic driver mutations). Assays may include, but are not limited to, LC-MS/MS, IHC, and NGS of RNA and DNA to allow exploratory analyses for mechanisms of response and resistance.

7.1.11.2.2. Peripheral Blood Pharmacodynamic Biomarkers

The primary effects of GEN1107 on tumor cells may lead to changes in systemic biomarkers in the blood. Exploratory biomarker analyses in whole blood samples may be used to explore the relationship to clinical efficacy or mechanism of action of GEN1107. Biomarker assessments in the blood include, but are not limited to, protein expression analysis or cell-free nucleotide analysis. Protein levels involved in the mechanism of action of GEN1107 may be explored in order to characterize baseline levels in disease and monitor changes associated with treatment. Cell-free nucleotide analysis, including circulating tumor DNA, may be measured and analysis such as DNA mutations, copy number variations, and or rearrangements in genes may be performed to evaluate the association of such biomarkers with tumor burden, patient response, or disease biology.

Pharmacodynamic assessments will include, but not be limited to, disease burden monitoring, changes to target expression, and additional tumor-specific markers (eg, CCI [redacted]) or ctDNA. Correlative studies may be conducted to gain a better understanding of target-response relationship, predictive/prognostic biomarkers, MOA, resistance mechanisms, and pharmacodynamics of GEN1107.

7.1.11.2.3. Biospecimen Repository

In the US only, for patients who provide additional consent, remaining de-identified unused blood and/or tissue will be retained by Genmab and used for future research, including but not limited to the evaluation of targets for novel therapeutic agents, the biology of ADC sensitivity and resistance mechanisms, and the identification of biomarkers of ADCs. Blood and tissue samples donated for future research will be retained for a period of up to 25 years. If additional consent is not provided, any remaining biological samples will be destroyed after the study has been completed and all applicable regulatory obligations have been met.

7.1.12. Safety Assessments

Safety will be assessed through surveillance and recording of AEs including SAEs, recording of concomitant medications, ECOG, ECG, vital signs, and measurements of protocol-specified physical examination findings, ophthalmology tests, and clinical laboratory tests.

Safety findings will be monitored over the course of the study by the DEC/Safety Committee as described in Section 3.6.

7.1.13. Adverse Events

7.1.13.1. Definitions

7.1.13.1.1. Adverse Event

According to the ICH E2A guideline Definitions and Standards for Expedited Reporting, and 21 CFR 312.32, IND Safety Reporting, an AE is any untoward medical occurrence in a patient or clinical investigational patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

The following information should be considered when determining whether to record a test result, medical condition, or other incident on the AE eCRF:

- From the time of informed consent through the day prior to study Day 1, only study protocol-related AEs should be recorded. A protocol-related AE is defined as an untoward medical event occurring resulting from a protocol mandated procedure.
- All medical conditions present or ongoing pre-dose on study Day 1 that increase in NCI CTCAE grade (or for ocular toxicity, per grading in Appendix K) should be recorded.
- Medical conditions present or ongoing pre-dose on study Day 1 that worsen in severity, increase in frequency, become related to study drug, or worsen in any other way but do not meet the threshold for increase in CTCAE grade should be recorded.
- All AEs (regardless of relationship to study drug) should be recorded from study Day 1 (during and post-dose) through the end of the safety reporting period. Complications that occur in association with any procedure (eg, biopsy) should be recorded as AEs whether the procedure was protocol mandated.
- In general, an abnormal laboratory value should not be recorded as an AE unless it is associated with clinical signs or symptoms, requires an intervention, results in a SAE, or results in study termination or interruption/discontinuation of study treatment. When recording an AE resulting from a laboratory abnormality, the resulting medical condition, if known, rather than the abnormality itself should be recorded (eg, record “anemia” rather than “low Hgb”).

7.1.13.1.2. Serious Adverse Events

An AE should be classified as an SAE if it meets 1 of the following criteria:

Fatal:	The AE results in death.
Life threatening:	The AEs places the patient at immediate risk of death. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
Hospitalization:	The AE results in hospitalization or prolongs an existing inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent in the study or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization. Hospitalizations or prolonged hospitalizations for scheduled therapy of the underlying cancer or study target disease do not need to be captured as SAEs.
Disabling/ incapacitating:	An AE that results in a persistent or significant incapacity or substantial disruption of the patient's ability to conduct normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a patient exposed to the molecule or study treatment regimen before conception or during pregnancy.
Medically significant:	The AE does not meet any of the above criteria but could have jeopardized the patient and might have required medical or surgical intervention to prevent 1 of the outcomes listed above or involves suspected transmission via a medicinal product of an infectious agent. Potential DILI also is considered a medically significant event (see Section 7.1.13.8 for the definition of potential DILI.)

Abbreviations: AE=adverse event; DILI= drug-induced liver injury; SAE=serious adverse event

7.1.13.2. Adverse Event Severity

AE severity should be graded using the NCI CTCAE, Version 5.0, except for ocular toxicity, which should be graded per Appendix K.

AE severity and seriousness are assessed independently. "Severity" characterizes the intensity of an AE. "Serious" is a regulatory definition and serves as a guide to the Sponsor or its designee for defining regulatory reporting obligations (see definition for SAEs, above).

7.1.13.3. Relationship of the Adverse Event to Study Treatment

Medical judgment should be used to determine the likely relationship of the AE to the study drug considering all relevant factors including but not limited to relevant medical history, concomitant medical condition, concomitant medications.

Determination of relationship should also be based on evidence of temporal relationship, biologic plausibility, association/or lack of with the underlying disease and presence of a more likely cause.

The relationship of each AE to GEN1107 should be evaluated by the Investigator using the following criteria:

Related:	There is evidence to suggest a causal relationship between the drug and the AE, such as: • A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, hepatic injury, Stevens-Johnson Syndrome) • One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug (eg, tendon rupture)
Unrelated:	Another cause of the AE is more plausible (eg, due to underlying disease or occurs commonly in the study population), or a temporal sequence cannot be established with the onset of the AE and administration of the study treatment, or a causal relationship is considered biologically implausible

7.1.13.4. Procedures for Eliciting and Recording Adverse Events

Investigators and study personnel will report all AEs and SAEs whether elicited during patient questioning, discovered during physical examination, laboratory testing and/or other means by recording them on the eCRF and/or the SAE form, as appropriate.

7.1.13.4.1. Eliciting Adverse Events

An open-ended or non-directed method of questioning should be used at each study visit to elicit the reporting of AEs.

7.1.13.4.2. Recording Adverse Events

The following information should be recorded on the AE eCRF:

- Description including onset and resolution dates
- Whether it meets SAE criteria
- Severity
- Relationship to study treatment or other causality
- Outcome
- Action taken with study drug

7.1.13.4.3. Diagnosis vs. Signs or Symptoms

In general, the use of a unifying diagnosis is preferred to listing individual symptoms. Grouping of symptoms into a diagnosis should only be done if each component sign and/or symptom is a medically confirmed component of a diagnosis as evidenced by standard medical textbooks. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, report the individual symptom as a separate AE.

Important exceptions for this study are adverse reactions associated with the infusion of study drug. Record each sign or symptom as an individual AE in addition to the IRR term. If multiple signs or symptoms occur with a given infusion-related event, each sign or symptom should be recorded separately with its level of severity.

7.1.13.4.4. Recording Serious Adverse Events

For SAEs, record the event(s) on both the eCRF and an SAE form.

The following should be considered when recording SAEs:

- Death is an outcome of an event. The event that resulted in the death should be recorded and reported on both an SAE form and eCRF.

7.1.13.5. Overdose

All cases of overdose (as defined in Section 5.6.6), whether associated with an AE or not, must be reported to the sponsor within 24 hours of knowledge of the event (see additional details in Section 5.6.6).

7.1.13.6. Medication Errors

Medication errors (including infusion rate errors) and uses outside what is foreseen in the protocol, including misuse and abuse of trial treatment, whether associated with an AE or not, should be reported to the sponsor within 24 hours of knowledge of the event.

7.1.13.7. Pregnancy

7.1.13.7.1. Notification to Drug Safety

Complete a Pregnancy Report Form for all pregnancies that occur from the time of first study drug dose until 6 months after the last dose of GEN1107 including any pregnancies that occur in the partner of a study patient who is able to father a child. Only report pregnancies that occur in a patient's partner if the estimated date of conception is after the patient's first study drug dose. Email or fax to the Sponsor or its designee's Drug Safety Department within 24 hours of becoming aware of a pregnancy. All pregnancies will be monitored for the full duration; all perinatal and neonatal outcomes should be reported. Infants should be followed for a minimum of 8 weeks.

7.1.13.7.2. Collection of Data on the eCRF

All pregnancies (as described above) that occur within 6 months of the last dose of study drug(s) will also be recorded in the eCRF.

Abortion, whether accidental, therapeutic, or spontaneous, should be reported as an SAE. Congenital anomalies or birth defects, as defined by the "serious" criteria above should be reported as SAEs.

7.1.13.8. Potential Drug-induced Liver Injury

Hy's Law can be used to estimate severity and the likelihood that a study drug may cause an increased incidence of severe hepatotoxicity.

The absence of hepatotoxicity in clinical trials provides a limited predictive value for potential DILI in the clinical setting(s) being studied. However, finding 1 Hy's Law case in clinical trials is ominous; finding 2 cases is highly predictive of a potential for severe DILI.

Definition

Briefly, potential Hy's Law cases include the following 3 components:

1. Aminotransferase (ALT and/or AST) elevation >3 × ULN

AND

2. Total bilirubin >2 × ULN, without initial findings of cholestasis (ie, elevated serum alkaline phosphatase),

AND

3. No other immediately apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

7.1.13.8.1. Reporting Requirements

Any potential Hy's Law case should be handled as an SAE and reported promptly to the Sponsor.

Reporting should include all available information and should initiate close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

7.1.13.8.2. Follow-up for Abnormal Laboratory Results Suggesting Potential DILI

In general, an increase of serum ALT or AST to >3 × ULN should be followed by repeat testing within 48 to 72 hours of serum ALT, AST, alkaline phosphatase, and total bilirubin, to confirm the abnormalities and to determine whether they are worsening.

Appropriate medical assessment should be initiated to investigate potential confounding factors and alternative causes of hepatotoxicity. During this investigation, consider withholding study drug.

Regional guidelines should be followed. Additional information is provided in FDA Guidance for Industry, DILI: Premarketing Clinical Evaluation, 2009.

7.1.13.9. Second Primary Malignancy

Second primary malignancy(ies) (not a metastasis of the cancer under trial), regardless of relatedness to trial treatment, must be reported as an SAE to the sponsor within 24 hours of knowledge of the event (at any time during or after the trial).

7.1.13.10. Reporting Periods for Adverse Events and Serious Adverse Events

The safety reporting period for all AEs and SAEs is from study Day 1 (pre-dose) through 30 days after the last dose of GEN1107. If an EOT visit is not possible, the safety reporting window is 30 days after last dose of study treatment or the decision to discontinue study drug, whichever is later. However, all study protocol-related AEs are to be recorded from the time of informed consent.

All SAEs that occur after the safety reporting period and are considered study treatment-related in the opinion of the Investigator should also be reported to the Sponsor.

SAEs will be followed until significant changes return to baseline, the event stabilizes (recovering/resolving), is no longer considered clinically significant by the Investigator, is assessed as chronic by the Investigator and all queries have been resolved, or the patient dies or withdraws consent.

All non-serious AEs will be followed through the safety reporting period with the exception of ocular TEAEs. Ocular TEAEs need to be followed until resolution, stabilization, or return to baseline. Certain additional non-serious AEs of interest may be followed until resolution, return to baseline, or study closure.

7.1.13.11. Serious Adverse Events Require Immediate Reporting

Within 24 hours of observing or learning of an SAE, Investigators are to report the event to the Sponsor or its designee, regardless of the relationship of the event to the study treatment. For initial SAE reports, available case details are to be recorded on the SAE form. At a minimum, the following should be included:

- Patient number
- Date of event onset
- Description of the event
- Study treatment, if known
- Investigator causality assessment

The completed SAE form must be emailed or faxed to the Sponsor or its designee's Drug Safety Department within 24 hours (see email or fax number specified on the SAE report form).

Relevant follow-up information should be submitted to the Sponsor or its designee as soon as it becomes available.

At a later date, the sites may be notified to start the reporting of SAEs to the sponsor via the EDC tool as a primary mechanism. In order to report pregnancies and if the EDC tool is unavailable to report SAEs, the site must use the respective paper report forms via secure transmission to ensure the event is reported within 24 hours following first knowledge of the event

Once the study has ended, if the Investigator learns of a second primary malignancy or a treatment-related SAE, the event should be reported using the paper forms via secure transmission.

7.1.13.12. Disease-Related Events/Outcomes and Other Events/Procedures Not Qualifying as Adverse Events or Serious Adverse Events

The following should not be reported as an AE or SAE:

- Events that are clearly consistent with the expected pattern of the underlying disease or its progression should not be recorded as AEs or SAEs.
    - That is, the terms “Disease Progression,” “Progression of Disease,” or “Malignant Disease Progression” and other similar terms should not be used to describe an AE or SAE. These data are captured as efficacy assessment data only.
        - In most cases, the expected pattern of progression will be based on the response criteria. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria.
        - Clinical symptoms may be reported as AEs or SAEs if the symptom cannot be determined as reasonably due to progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study.
- Hospitalization due solely to progression of the underlying cancer should not be reported as an SAE. See Section 7.1.13.1.2 for additional reasons when hospitalizations should not be reported as SAEs.
- Unrelated Procedures: Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, a medical condition for which an unscheduled procedure was performed should be reported if it meets the definition of an AE (eg, acute appendicitis should be reported as the AE and not the appendectomy).

7.1.13.13. Sponsor Safety Reporting to Regulatory Authorities

7.1.13.13.1. Reporting Requirements for Suspected Unexpected Serious Adverse Reactions

Investigators are required to report all SAEs to the Sponsor or its designee. The Sponsor or its designee will report all SAEs, including SUSARs, to regulatory authorities as required per local legislation or regulatory reporting requirements.

The sponsor has a legal responsibility to notify, as appropriate and according to local regulations, both the local health authority and other regulatory agencies about the safety of the product under clinical investigation. Prompt notification of SAEs by the Investigator to the sponsor is essential so that legal obligations and ethical responsibilities towards the safety of patients are met (Section 7.1.13.11).

The sponsor will ensure that all relevant information about SUSARs is documented and reported as soon as possible, but within a maximum of 15 calendar days (fatal or life-threatening SUSARs within a maximum of 7 calendar days) of first knowledge by the sponsor or designee, to the health authorities and/or to the IEC/IRB according to the applicable local regulatory requirements. Relevant follow-up information of SUSARs will be communicated subsequently within the required reporting timelines. The sponsor will submit SUSARs aggregated in line listings in periods as warranted by any local health authority.

The sponsor will also communicate relevant information on SUSARs with the investigators in predefined periods and according to local regulations.

The Investigator must be aware of reporting regulations/requirements for their local IEC/IRB. The clinical CRO will either supply the Investigator with the reports which should be passed on to the IEC/IRB or report directly to the IEC/IRB, depending on local regulations and agreement with the investigators. SUSARs aggregated in line listings will be distributed in periods as warranted by the IEC/IRB. The Investigator must review such safety information in a timely manner and signoff for the review as instructed by the sponsor, to document the awareness about the latest safety updates that may impact on the Investigator's responsibilities for patient care.

7.1.13.13.2. Regulatory Reporting Requirements for AMPs

Where an adverse event is suspected to be related only to an AMP, and does not result from a possible interaction with the IMP, safety reporting will be done by the sponsor in accordance with Chapter 3 of TITLE IX of Directive 2001/83/EC.

7.1.13.14. Annual Safety Reporting by Sponsor

The sponsor will submit a single Annual Safety Report for GEN1107. There are no other IMPs in this study.

7.2. Appropriateness of Measurements

The safety measures that will be used in this trial are considered standard procedures for evaluating the potential adverse effects of study medications.

Response will be assessed according to RECIST, Version 1.1, which are standardized criteria for evaluating response in solid tumors. The intervals of evaluation in this protocol are considered appropriate for disease management.

Immunogenicity is commonly assessed for biologics; therefore, standard tests will be performed to detect the possible presence of specific antibodies to GEN1107. PK assessments are also common in clinical studies to help characterize dose-exposure-response relationships.

8. DATA QUALITY CONTROL AND QUALITY ASSURANCE

8.1. Site Training and Monitoring Procedures

Prior to the enrollment of patients at the site, Sponsor or its designated clinical and medical personnel will review the following items with the Investigator and clinic staff:

- The protocol, study objectives, eligibility requirements, study procedures, registration, and withdrawal processes
- Current IB
- Recording and reporting AEs and SAEs
- Enrollment goals and study timelines
- The eCRF completion process and source documentation requirements
- Monitoring requirements
- IRB/IEC review and approval process
- Informed consent process
- Good clinical practice guidelines and related regulatory documentation requirements
- Key study team roles and responsibilities
- Investigational product storage, accountability, labeling, dispensing, and record keeping
- Patient coding and registration
- Study samples/specimen collection, handling, and shipping
- Protocol compliance
- Clinical study record keeping, document retention, and administrative requirements

Monitoring visits will occur periodically, with frequency dependent on the rate of enrollment and workload at each site. During monitoring visits, the Sponsor or its designee's representative will typically review regulatory documentation, eCRFs, source documentation, and investigational product storage, preparation, and accountability. The eCRFs will be reviewed for completeness, adherence to the provided guidelines, and accuracy compared to the source documents. The investigators must ensure that the monitor is allowed to inspect all source documents pertinent to study patients and must cooperate with the monitor to ensure that any problems noted during the trial are resolved. The Investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by Sponsor or its designated monitors and by quality assurance auditors, or representatives of regulatory authorities.

8.2. Data Management Procedures

The Sponsor or its designee will provide eCRF completion guidelines and training requirements for eCRF data entry.

Study-specific data management procedures will be maintained in the Clinical Data Management Plan.

8.3. Access to Source Data

The Investigator will permit the Sponsor or its designee's representatives to monitor the study as frequently as the Sponsor or its designee deems necessary to determine that protocol adherence and data recording are satisfactory. Appropriate measures to protect patient confidentiality are to be employed during monitoring. The eCRFs and related source documents will typically be reviewed in detail by the monitor at each site visit. Original source documents or certified copies are needed for review. This review includes inspection of data acquired as a requirement for participation in this study and other medical records as required to confirm that the information collected is correct. Other study records, such as correspondence with the Sponsor or its designee and the IRB/IEC and screening and drug accountability logs will also be inspected. All source data and study records must also be available for inspection by representatives of regulatory authorities and the IRB/IEC.

8.4. Accuracy and Reliability of Data

Steps to be taken to assure the accuracy and reliability of data include:

- The selection of qualified investigators and appropriate study centers.
- Review of protocol procedures with the investigators and associated personnel prior to the study.
- Periodic monitoring visits by the designated monitor(s).
- eCRFs will be reviewed for accuracy and completeness during monitoring visits to the study centers and/or by centralized monitoring. Any discrepancies will be resolved with the Investigator or designees as appropriate.

8.5. Quality Assurance Procedures

Representatives of the sponsor's clinical quality assurance department may visit the trial site at any time during or after completion of the trial to conduct an audit of the trial in compliance with regulatory guidelines and company policy. These audits will require access to all trial records, including source documents, for inspection and comparison with the eCRFs. Patient privacy must, however, be respected. The principal investigator and trial-site personnel are responsible for being present and available for consultation during routinely scheduled trial-site audit visits conducted by the sponsor or its designee(s).

Similar procedures for inspections may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this trial in support of a regulatory submission. The investigator should immediately notify the sponsor if

they have been contacted by a regulatory agency concerning an upcoming inspection. Regulatory inspectors must be allowed direct access to original medical records (source data/documents).

8.6. Data Handling and Record Keeping

8.6.1. Data Handling

It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor or its designee in the eCRFs and in all required reports. Data reported on the eCRF that is derived from source documents should be consistent with the source documents or the discrepancies should be explained.

Any change or correction to an eCRF will be maintained in an audit trail within the electronic data capture system. Data changes may only be made by those individuals so authorized. The Investigator should retain records of the eCRFs, changes and corrections, written and/or electronic.

8.6.2. Investigator Record Retention

The Investigator shall retain study drug disposition records and all source documentation (such as original ECG tracings, laboratory reports, in patient or office patient records) for the maximum period required by the country and institution in which the study will be conducted, or for the period specified by Sponsor, whichever is longer. The Investigator must contact the Sponsor or its designee prior to destroying any records associated with the study. If the Investigator withdraws from the study (due to relocation, retirement, etc.), the records shall be transferred to a mutually agreed upon designee, such as another Investigator or IRB/IEC. Notice of such transfer will be provided in writing to the Sponsor or its designee.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSIS METHODS

9.1. Determination of Sample Size

Up to approximately 280 patients are expected to be enrolled in this study. This number assumes that up to approximately 120 patients may be enrolled in Part A and up to an additional approximately 160 patients will be enrolled in Part B (up to approximately 40 patients in 4 tumor-specific expansion cohorts).

In Part B, after the initial 20 patients (approximately 10 patients in a dose level) are enrolled and randomized in each cohort, the Safety Committee will review the data and confirm whether enrollment should continue (to accrue a total of 20 patients in a dose level), based on cumulative safety and activity data.

No formal hypothesis testing is planned for the expansion cohorts in Part B. The sample size for expansion cohorts was determined based on the precision of the estimate. Table 8 provides the precision for various observed ORRs with a sample size of 20.

Table 8: Sample Size Calculations

Number of Responders	Observed ORR	95% CI[a]	80% CI[a]
8	40%	(19%, 64%)	(25%, 57%)
6	30%	(12%, 54%)	(17%, 47%)
4	20%	(6%, 44%)	(9%, 36%)

CI=confidence interval
[a] Based on the Clopper-Pearson method (Clopper and Pearson, 1934)

9.2. Efficacy Endpoint Definitions

Determination of antitumor activity and response will be based on objective response assessments as defined by RECIST Version 1.1.

9.2.1. Objective Response Rate

The ORR is defined as the percentage of patients achieving a PR or CR as assessed by the Investigator. Patients whose disease response cannot be evaluated per the response criteria will be scored as “not evaluable” for calculating the ORR. To be considered a cPR or cCR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. The CR rate is defined as the proportion of patients with a CR. Patients who cannot be assessed for response will be counted as not achieving a CR.

9.2.2. Disease Control Rate

The DCR is defined as the percentage of patients having SD or achieving a PR or CR (DCR=SD + PR + CR).

9.2.3. Progression-free Survival

PFS is defined as the time from the start of any study treatment to first documentation of disease progression or to death due to any cause, whichever comes first. Disease progression includes objective evidence of tumor progression or clinical progression per Investigator. PFS will be censored on the date of the last disease assessment documenting the absence of disease progression in patients who do not have disease progression and are still on study at the time of an analysis. PFS will also be censored at the date of the last disease assessment documenting absence of PD in patients who are given antitumor treatment other than the study treatment or are removed from the study prior to the documentation of tumor progression. Patients who do not have a tumor response evaluation after their first dose will be censored at 1 day.

9.2.4. Duration of Objective Response

DOR is defined as the time from the first documentation of an objective tumor response (CR or PR) to the first documentation of tumor progression or to death due to any cause, whichever comes first. DOR data will be censored, following the same rules as those outlined in PFS where applicable. Duration of response will be calculated for the subset of patients achieving an objective response.

9.2.5. Overall Survival

Overall survival is defined as the time from the start of any study treatment to the date of death due to any cause. Specifically,

OS = date of death - date of first dose of any study treatment +1.

Overall survival for patients who are alive at their date of last contact, including those lost to follow-up, will be censored at the date of last contact. If the last recorded date where a patient is known to be alive is the date of first dose of any study treatment, survival time will be censored on the date of first dose of any study treatment (ie, OS duration of 1 day).

9.2.6. Response Based on CA-125

For patients with ovarian cancer, a CA-125 response per the GCIG criteria (Rustin et al., 2011) is defined as a ≥50% reduction in CA-125 levels from baseline. The following must also apply:

- CA-125 levels must be ≥2.0 times the ULN within 2 weeks before starting treatment
- The CA-125 response must be confirmed and maintained for at least 28 days

The date of response corresponds to the date when the CA-125 level is first reduced by 50%. The CA-125 response rate is defined as the percentage of patients achieving a CA-125 reduction per the GCIG criteria during treatment. The CA-125 response rate will be calculated for the subset of applicable patients.

9.3. Statistical and Analytical Plans

The statistical and analytical plans presented below summarize the more complete plans to be detailed in the SAP. The SAP will be finalized prior to database lock. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

9.3.1. General Considerations

Tabular summaries will be presented by cohorts unless otherwise specified using descriptive statistics.

9.3.1.1. Randomization and Blinding

No blinding will be performed in this open-label study.

No randomization will be performed in Part A (dose escalation).

In Part B (tumor-specific expansion) of the study, patients in each cohort will be randomized with a 1:1 ratio to receive one of the expansion doses of PRO1107.

9.3.1.2. Adjustments for Covariates

Adjustments for covariates are not planned.

9.3.1.3. Handling of Dropouts and Missing Data

Missing data will not be imputed, except for AE dates, while calculating duration of events and TE status; details will be provided in the SAP. For time-to-event endpoints including PFS, patients who have no specified event will be censored at the time of the last adequate assessment of the endpoint(s). Additional details will be provided in the SAP.

9.3.1.4. Multicenter Studies

There are multiple centers in this study; however, it is not anticipated that any center will accrue enough patients to warrant an analysis by center.

9.3.1.5. Multiple Comparisons and Multiplicity

No multiple comparisons are planned, and no alpha adjustment is needed in this Phase 1 study.

9.3.1.6. Data Transformations and Derivations

Time variables based on 2 dates (eg, start date and end date) will be calculated as (end date – start date +1 [in days]) unless otherwise specified in the planned analysis section.

Baseline values used in all statistical analyses will be the most recent non-missing measurement prior to the first dose of GEN1107 unless otherwise specified in the analysis plan or the SAP.

9.3.1.7. Analysis Sets

9.3.1.7.1. All-treated Subjects Analysis Set

The ATS analysis set includes all patients who receive any amount of PRO1107. The ATS set will be used for the presentation of safety data and may be used for sensitivity analyses of efficacy endpoints.

9.3.1.7.2. DLT-evaluable Analysis Set

The DE analysis set includes all treated patients who either experienced a DLT or remained on study for the full DLT evaluation period.

9.3.1.7.3. Efficacy-evaluable Analysis Set

The EE analysis set includes all treated patients who had a baseline and at least 1 postbaseline disease assessment according to RECIST Version 1.1, or who had Investigator claim of clinical progression after the first dose of GEN1107.

9.3.1.7.4. PK-evaluable Analysis Set

The PKE analysis set includes all patients who receive any amount of GEN1107 and have at least one postbaseline concentration measurement.

9.3.1.8. Examination of Subgroups

For selected endpoints, exploratory, subgroup analyses may be conducted including but not limited to the following categories, as appropriate:

- Prior therapies
- Disease subtype
- Baseline PTK7 tumor expression level

Detailed statistical methodology will be provided in the SAP.

9.3.1.9. Timing of Analyses

The final analysis for this study will occur after all patients have completed their treatment and the follow-up period or following study termination by the Sponsor.

9.3.2. Patient Disposition

An accounting of study patients by disposition will be tabulated and the number of patients in each analysis set will be summarized. Patients who discontinue study treatment and patients who withdraw from the study will be summarized with reason for discontinuation or withdrawal.

9.3.3. Patient Characteristics

Demographics and other baseline characteristics will be summarized. Details will be provided in the SAP.

9.3.4. Treatment Exposure and Compliance

Duration of treatment will be summarized and listed.

Duration of treatment, number of cycles, total dose, and dose intensity will be summarized by dose level. Dose modifications will also be summarized. Dose intensity will be calculated and summarized. Details will be provided in the SAP.

9.3.5. Efficacy Analyses

The ORR (confirmed or unconfirmed), best response (including CR rate), DCR per Investigator will be summarized using the ATS set and the EE set. A two-sided 95% exact binomial CI will be calculated (Clopper and Pearson, 1934).

Time-to-event endpoints, such as PFS, OS, and DOR, will be estimated for the EE set using the Kaplan-Meier method and Kaplan-Meier plots will be provided. Medians will be calculated, where possible. The 95% CIs may also be calculated, as appropriate. Detailed methodology will be provided in the SAP.

9.3.6. Pharmacokinetic and Immunogenicity Analyses

Ac-MMAE), TAb, and u-MMAE concentrations will be summarized with descriptive statistics for each cohort and at each PK sampling timepoint using the PKE analysis set. PK parameters will be estimated from concentration-time data using noncompartmental analysis and summarized by descriptive statistics. As the data allow, the following PK parameters to be assessed include but are not limited to:

- AUC
- C_{eoi} or C_{max}
- T_{max}
- C_{trough}
- $t_{1/2}$
- V_z
- CL

The incidence of ADAs will be summarized using descriptive statistics by treatment group, including time to first ADA and titer of ADA against PRO1107. The relationship between ADA and PK will be evaluated. The relationship between ADA and PD, safety, and/or clinical outcome may also be explored. Archived samples confirmed positive for ADA may be explored later for neutralizing activity.

9.3.7. Biomarker Analyses

Relationships of biomarker parameters (eg, baseline values, absolute and relative changes from baseline) to efficacy, safety, and PK parameters may be explored. Correlations between pharmacodynamic assessments and PK parameters will be explored in concentration-QT plots and regression analysis. Relationships and associated data that are determined to be of interest may be summarized. Details will be described separately in the SAP or biomarker analysis plan.

9.3.8. Safety Analyses

Safety data will be summarized descriptively using the ATS set. Unless otherwise stated, descriptive summary statistics for continuous variables will include number of patients with available data (n), mean, SD, median, minimum, and maximum values. Descriptive summary statistics for categorical data will include number of patients with available data (n) and percentage of patients in each category. Additional details will be provided in the SAP.

9.3.8.1. Adverse Events

An overview of AEs will provide a tabulation of the incidence of TEAEs, treatment-related TEAEs, ≥ Grade 3 TEAEs, treatment-related ≥ Grade 3 TEAEs, TESAEs, treatment-related TESAEs, TEAEs leading to study treatment discontinuation, treatment-related TEAEs leading to study treatment discontinuation, TEAEs and treatment-related TEAEs leading to dose reduction and interruption, and deaths. AEs will be defined as TE if they are newly occurring or worsen following the first dose of study treatment.

AE coding will be based on MedDRA and AE grade will be based on NCI CTCAE, Version 5.0, except for ocular toxicity which will be graded per Appendix K.

All summaries of TEAEs will be tabulated by preferred term and treatment group. In the event of multiple occurrences of the same AE with the same preferred term in 1 patient, the AE will be counted once as the occurrence. TEAEs will also be listed and summarized by severity and relationship to study drug.

9.3.8.2. Dose-Limiting Toxicity

The observed number and proportion of patients experiencing DLTs will be reported for the dose-escalation part.

9.3.8.3. Deaths and Serious Adverse Events

SAEs will be listed and summarized in the same manner as all AEs. Events with a fatal outcome will be listed.

9.3.8.4. Clinical Laboratory Results

Shift tables (from baseline grade to the worst post-baseline grade) will be provided for selected laboratory tests. Summary statistics for selected laboratory tests may be tabulated as

appropriate by scheduled visit. Laboratory values will be listed with grade per NCI CTCAE, Version 5.0 and flagged when values are outside the normal reference range.

9.3.8.5. Other Safety Analyses

9.3.8.5.1. Vital Signs

Summary statistics and change from baseline and/or pre dose to post dose may be tabulated, where appropriate. Vital sign data will be listed by subject at all collection time points.

9.3.8.5.2. ECOG Status

Shifts from baseline to the best and worst post-baseline score may be tabulated. ECOG data will be listed by subject at all collection time points.

9.3.8.5.3. ECG

ECG data will be listed by subject at all collection time points.

9.4. Efficacy Monitoring in Expansion

Analysis for futility will be performed separately for each cohort after at least 10 patients of a given cohort have been treated and had at least one response assessment post-baseline. A Bayesian predictive probability (PPoS) approach is used to determine the futility criteria.

PPoS is the probability of achieving "success" should the cohort be continued to the 20 patients. Given the data observed at interim, a cohort is considered "success" if the predictive probability that the ORR exceeds the response rate of current standard of care (p0) is greater than 80%. If PPoS is less than 10%, stopping further enrollment may be considered. Table 9 shows any cohort futility bars (Lee and Liu, 2008) based on PPoS for monotherapy.

Table 9: Non-Binding Futility Boundaries in Expansion Part

Number of response evaluable subjects per dose level	First 10 subjects	Total 20 subjects
Any cohort	0	≤3

Number of responses as assessed by investigators (including those pending confirmation).

For the Bayesian modelling, the prior response rate is assumed to follow a beta distribution with hyperparameters of a0=p0, b0=1-p0.

Assume the null ORR p0=10%; set the alternative ORR is 30% or 40% according to Table 10. The likelihood for futility under p0, and to continue under an alternative (p1), are provided by evaluating the cumulative probability density function of the binomial distribution, and assuming that possible earlier crossing(s) of the futility boundary are ignored.

Table 10: Operating Characteristics in the Expansion Part

Underlying ORR	Pass Futility at n=10	Pass Futility at n=20
10%	65%	13%
30%	97%	89%
40%	99%	98%

The operating characteristics of the expansion part, as shown in Table 10, are derived by evaluating the cumulative probability density function of the binomial distribution. For example, if the underlaying ORR is 30%, there is a 97% chance of passing futility after the first 10 patients; and there is 89% chance of declaring the efficacy at 20 patients. A similar interpretation applies to other underlaying ORR (10% and 40%).

9.5. Planned Analyses

9.5.1. Interim Analysis

An interim analysis is not planned for this trial.

9.5.1. Primary Analysis

The primary analysis will be conducted shortly after all subjects have discontinued the trial or 1 year after the first dose of the last subject enrolled, whichever occurs first. At this time, a final data sweep will be performed to determine the survival status of previously discontinued subjects.

10. INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

This study will be conducted in accordance with the Note for Guidance on Good Clinical Practice (ICH Harmonised Tripartite Guideline E6 (R2); FDA CFR [21 CFR § 50, 56, 312]), Declaration of Helsinki (Brazil 2013), and all applicable regulatory requirements and national law(s) (eg, European regulation 536/2014 for clinical trials) in the country(ies) where the study takes place shall constitute the main reference guidelines for ethical and regulatory conduct.

10.1. Informed Consent

The Investigator is responsible for presenting the risks and benefits of study participation to the patient in simple terms using the IRB/IEC approved informed consent document and for ensuring patients are re-consented when the informed consent document is updated during the study, if required. The Investigator will ensure that written informed consent is obtained from each patient, by obtaining the signature and date on the informed consent document prior to performing any protocol evaluations or procedures.

10.2. Ethical Review

The Investigator will provide the Sponsor or its designee with documentation of the IRB/IEC approval of the protocol and the informed consent document before the study may begin at the investigative site(s). The name and address of the reviewing ethics committee are provided in the Investigator file.

The Investigator will supply the following to the investigative site's IRB/IEC:

- Protocol and amendments
- Informed consent document and updates
- Clinical IB and updates
- Relevant curricula vitae, if required
- Required safety and SAE reports
- Any additional submissions required by the site's IRB/IEC

The Investigator must provide the following documentation to the Sponsor or its designee:

- The IRB/IEC periodic (eg, quarterly, annual) re-approval of the protocol
- The IRB/IEC approvals of any amendments to the protocol or revisions to the informed consent document
- The IRB/IEC receipt of safety and SAE reports, as appropriate

10.3. Regulatory Considerations

This study will be conducted in accordance with the protocol and ethical principles stated in the applicable guidelines on good clinical practice, and all applicable local and/or regional laws, rules, and regulations.

10.3.1. Investigator Information

The contact information and qualifications of the Principal Investigator and sub-Investigators and name and address of the research facilities are included in the Investigator file.

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, ICH GCP E6(R2), and applicable regulatory and country-specific requirements.

10.3.2. Protocol Amendments, Deviations, and Study Termination

All protocol amendments must be issued by the sponsor and signed and dated by the Investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the patients. In such case, any changes to the protocol (except for changes to eliminate an immediate hazard to a study patient) must be approved by the Sponsor prior to seeking approval from the IRB/IEC, and documented as important protocol deviation, and subsequently incorporated in a protocol amendment. The amendment must be promptly submitted to the IEC/IRB and relevant competent authority.

The Investigator is responsible for enrolling patients who have met protocol eligibility criteria. Protocol deviations must be reported to the Sponsor or its designee and the local IRB/IEC in accordance with IRB/IEC policies.

The Sponsor may terminate the study at any time. The IRB/IEC must be advised in writing of study completion or early termination.

10.4. Data Protection

The investigator will ensure that the confidentiality of all patients' data will be preserved. In the eCRF or any other documents submitted to the sponsor/sponsor's representative, the patients will not be identified by their names, but by an identification code, which consists of an assigned number in the study. The confidential patient identification code and the signed ICF will be maintained by the investigator in strict confidence.

In relation to the collection and handling of data, including any personal data, potential risks to the patients have been assessed and adequate technical and organizational measures are implemented to ensure a level of security appropriate to the risk.

The security measures implemented entail among other things that:

- Access to data has been restricted so that access is only granted to authorized individuals.
- Data are only stored on information technology systems and networks that are protected against virus, malware, and unauthorized access.

- Data are backed-up at regular intervals. In case of a data breach, a clear allocation of roles and responsibilities for managing the data breach, including notifying affected patients and authorities, has been established in order to mitigate any adverse impact on the patients.

Additional technical security measures implemented include that:

- EDC data are encrypted when at rest.
- Data have been pseudonymized to the effect that only authorized individuals can link data to identified individuals.
- A data breach response plan has been established.

The collection and processing of personal data from patients enrolled in this study will be limited to those data that are necessary to fulfill the objectives and purposes of the study and as specifically defined in the protocol.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place, as detailed above. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of patients confidential.

The informed consent obtained from the patient explicit consent or description of other legal basis for the processing of personal data for the purpose of the study and for the investigator/institution to allow direct access to original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries, as specified in the ICF.

The patient has the right to request access to their personal data and the right to request rectification of any data that are not correct or complete by contacting the investigator. Reasonable steps will be taken by the investigator to respond to such a request, taking into consideration the nature of the request, the conditions of the study, the clinical study agreement including any other relevant agreement, and applicable laws and regulations. The investigator will inform and work together with the sponsor when handling such requests.

In case of a potential data breach of the personal data, the investigator will inform the sponsor immediately and will contain the breach from spreading, where possible. Investigator and sponsor will work together to assess the risk to the individuals concerned, based on the circumstances of the case, including which data was involved, what security measures were in place (for instance, if the data was encrypted or pseudonymized), who might have accessed the data, etc.)

Based on this assessment, the data breach might be reported to the relevant authorities and/or the individuals concerned. Mitigating actions will be taken to avoid this event from reoccurring.

10.5. Study Documentation, Privacy, and Records Retention

To protect the safety of patients in the study and to ensure accurate, complete, and reliable data, the Investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the Investigator will provide the Sponsor, its licensees and collaborators, applicable regulatory agencies, and applicable IRB/IEC with direct access to original source documents or certified copies.

Records containing patient medical information must be handled in accordance with local and national laws, rules, and regulations and consistent with the terms of the patient authorization contained in the informed consent document for the study (the Authorization). Care should be taken to ensure that such records are not shared with any person or for any purpose not contemplated by the Authorization. Furthermore, CRFs and other documents to be transferred to the Sponsor or its designee should be completed in strict accordance with the instructions provided by the Sponsor or its designee, including the instructions regarding the coding of patient identities.

In compliance with local and/or regional regulations, this trial may be registered, and trial results may be posted on public registries, such as ClinicalTrials.gov or CTIS.

10.6. Publication Policy

All information, including but not limited to information regarding GEN1107 or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the Investigator and not previously published, and any data, including exploratory research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The Investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent. CROs (contract research organizations) involved in the study are not permitted to publish without the sponsor's prior written approval.

The Investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of GEN1107 and thus may be shared as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical study to be used, the Investigator is obligated to provide the sponsor with all data obtained in the study.

Study patient identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the Investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines (Battisti et al., 2015; ICMJE, 2010; ICMJE, 2023) the sponsor in conjunction with any collaborative group(s), shall have the right to publish such primary (multicenter) data and information as per the prespecified and approved publication plan. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other

materials. If requested by the sponsor in writing, the Investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the Investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the current version of 'Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals' (ICMJE Recommendations), which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, given final approval of the final version, and agreed to be accountable for all aspects of the work.

10.7. Clinical Trial Agreement

Payments by the Sponsor or its designee to Investigators and institutions conducting the trial, requirements for Investigators' insurance, the publication policy for clinical trial data, and other requirements are specified in the clinical trial agreement.

11. LAY PROTOCOL SYNOPSIS

NOTE: The lay protocol synopsis supports public disclosure activities and is not meant for site/investigator use.

Protocol Title	A Phase 1/2 Study of PRO1107 in Patients with Advanced Solid Tumors	
Brief Title	PRO1107 in Patients With Advanced Solid Tumors	
Protocol Number	GCT1107-01 (PRO1107-001)	
Compound	GEN1107	
Regulatory Agency Identifier Number(s)	**EU CT No.**	Not available
	NCT No.	NCT06171789

Brief Summary

This phase 1/2 study will take place in multiple countries and aims to enroll up to 280 participants. The goal of the study is to test the safety and effectiveness of a new drug, GEN1107, in people with advanced cancers that have either spread or cannot be removed by surgery. The study will focus on cancers such as ovarian, endometrial, breast, lung, and other types that have stopped responding to standard treatments.

The study has two parts: the first part will determine the safest dose(s) and schedule(s) of GEN1107, and the second part will assess how well the drug works at that dose. Participants will receive GEN1107 via an intravenous (IV) infusion on different schedules, and the study will last as long as the treatment continues to benefit patients. The treatment duration will vary for each participant, depending on how their cancer responds to the drug.

Rationale

This study is testing a new drug called GEN1107, which belongs to a class of drugs called antibody-drug conjugates (ADCs). ADCs are special because they combine two elements:

- Antibody: This part acts attaches to a specific protein (called PTK7) on the surface of cancer cells.
- Toxin (chemotherapy drug): This part is delivered directly to the cancer cell once the antibody attaches, allowing it to kill the cancer cells while minimizing damage to healthy cells.

PTK7 is a protein that is expressed in many solid tumors . By targeting PTK7, GEN1107 may be able to stop or slow down cancer growth.

Objectives (Purpose) / Endpoints (Assessments)

Primary Objective	*Primary Endpoint*
The main purpose of this study is to find out if GEN11107 is safe to use in patients with advanced cancers. The researchers want to understand how well people tolerate the drug, and they aim to figure out the highest dose that can be given safely without causing severe side effects.	The main measurement for this study will be the safety of GEN1107. Researchers will look at: • The type, frequency, and severity of side effects (such as nausea, fatigue, or more serious problems) experienced by patients. • Whether these side effects are related to the drug or happen for other reasons. • They will also check for any dose-limiting toxicities (DLTs), which are side effects severe enough to prevent increasing the dose of the drug.
Secondary Objectives	*Secondary Endpoints*

The study also aims to explore whether GEN1107 has anti-cancer effects. This will be done by evaluating how well GEN1107 works in shrinking or controlling the growth of tumors. It will also aim to improve understanding how the body processes GEN1107 (pharmacokinetics), such as how long the drug stays in the body and how it is broken down.	The researchers will measure several factors to see how well the drug works and how it affects the body, including: • Tumor response: They will measure how many patients experience tumor shrinkage or see their cancer stop growing. • Disease control rate (DCR): This includes how many patients have their cancer controlled (tumor shrinkage or no growth) for a certain period. • Progression-free survival (PFS): This is how long patients live without their cancer getting worse. • Duration of response (DOR): For those whose tumors shrink, they will track how long this effect lasts. • Pharmacokinetics (PK): They will measure how GEN1107 moves through and is cleared from the body.
Study Population This study will include adults aged 18 or older with advanced solid tumors, such as ovarian, endometrial, breast, lung, and other types, who have already tried standard treatments that have either stopped working or are no longer an option. Participants must be in generally good health with adequate organ function and be willing to provide a tumor sample before starting the study. Certain patients, such as those who have previously received similar treatments or have uncontrolled cancer in the brain, will not be eligible to participate.	
Ethical Considerations Before joining the study, participants will be fully informed about the potential risks and benefits, and they can choose to stop participating at any time. All medical tests, such as scans and blood tests, are performed to ensure that the treatment is safe and to monitor its effectiveness. The study aims to provide valuable information on a new treatment option for advanced cancers, and the results could benefit not only current participants but also future patients. Throughout the study, participants' health and quality of life will be carefully considered, with medical professionals available to address any concerns that arise.	

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APPENDICES

Appendix A: Schedule of Events for Q3W Regimen

Category	Day	Screening/ Baseline	Enrollment	Every 21-day cycle			EOT	Follow-up
		D –28 to -1	Within 7D of 1st dose	D1	D8	D15	Within 30 days of last dose[a]	Every 12 wks[b]
	Visit window			± 2D[c]	± 2D	± 2D	+7D	± 1 wk
Screening/Baseline and Safety Assessments	Informed consent	X	Submit eligibility confirmation to Sponsor prior to treatment					
	Inclusion/Exclusion, medical history	X		X[d]				
	Submission of tumor-related sample (archived or fresh) to central lab[e]	X					X[f]	
	Brain CT or MRI[g]	X						
	Physical examination including weight[h]	X		X[i]			X	
	Height	X[j]						
	Vital signs	X		X[k]			X	
	Ophthalmologic evaluation[l]	X		X[l]			X	
	Electrocardiogram	X[m]		X[m]			X[m]	
	ECOG performance status	X		X[m]			X	
	CBC with differential[n]	X		X[i, o]	X[p]	X[p]	X	
	PT/PTT/INR *(aPTT also acceptable)*	X					X	
	Comprehensive metabolic panel[q]	X		X[i, o]	X[p]	X[p]	X	
	Fasting glucose	X						
	HgbA1c[r]	X		X[i, o]			X	
	Fasting lipid panel[s]	X						
	Amylase and lipase[r]	X		X[i, o]			X	
	HBV surface antigen, HBV core antibody, and HCV rt-PCR	X						

Category	Day	Screening/ Baseline	Enrollment	Every 21-day cycle			EOT	Follow-up
	Visit window	**D –28 to -1**	**Within 7D of 1st dose**	**D1**	**D8**	**D15**	**Within 30 days of last dose[a]**	**Every 12 wks[b]**
				± 2D[c]	± 2D	± 2D	+7D	± 1 wk
	Pregnancy test for patients of childbearing potential	X[t]		X[o, u]			X[u]	
	Urinalysis[v]	X					X	
	Concomitant medications	Related to study procedures[w]		Collect from D1 predose through 30 days post last dose				
	Adverse event collection							X[x]
Treatment	GEN1107 administration			X[c]				
Pre-medication and preventive ocular therapy	Vasoconstrictor Eyedrops[y]			X				
	Cold packs[z]			X				
	Lubricating Eyedrops[aa]			X[aa]				
PK/Immunogenicity/ Biomarker	Blood sample collection			See the table below for additional sample collection visits and details				
Response Assessment	PET or CT and/or MRI of chest, abdomen, pelvis (and neck if documented or suspected involvement in this region)	X[bb]		X[dd]			X[ee]	X[ff]
	CA-125 sample collection and assessment[z]	X[cc]		X[dd]			X[ee]	X[ff]
Survival Status, Collection of First Subsequent Therapy								X[gg]

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; CBC=complete blood count; D=day; CMP=comprehensive metabolic panel; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; HCV=hepatitis C virus; HDL=high density lipoprotein; Hgb=hemoglobin; LDL=low density lipoprotein; MRI=magnetic resonance imaging; PCR=polymerase chain reaction; PK=pharmacokinetics; PT/PTT/INR=prothrombin time/partial thromboplastin time/international normalized ratio; wk/wks=week(s); RNA=ribonucleic acid; UPC=urine protein/creatinine ratio.

a EOT evaluations should be obtained before the initiation of non-protocol therapy. If EOT evaluations are completed before 30 days following the last study treatment, conduct a phone screen 30 days following the patient's last study treatment to ensure that no changes in AE profile have occurred.

b Every 12 weeks from the most recent prior response evaluation until documentation of disease progression or initiation of a new therapy, and every 12 weeks from the prior follow-up visit thereafter.

c The ± 2-day window does not apply to Cycle 1 infusion.

d Day 1 review of Inclusion/Exclusion criteria, medical history required during Cycle 1 only.

e The most recent available archived tumor specimen collected within 24 months is requested for all enrolled patients. Screening archival tumor tissue specimen obtained outside the 24-month window or less than 10 slides available, may be allowed with Medical Monitor approval.

f For US patients only discontinuing treatment due to disease progression: if a tumor biopsy was performed per standard-of-care at the time of disease progression, submit sample of tumor specimen, if available.

g A CT/MRI of the brain should be done at Screening for all patients with a history of brain metastases, those suspected of new brain metastases, or those with a diagnosis of NSCLC or breast cancer.

h Physical examinations should include assessments of the following: abdomen, extremities, head, heart, lungs, neck, neurological system, weight, and eye exam. Eyes should be examined by the Investigator and assessment should include a visual inspection of the eye orbit and conjunctiva and control of normal eye movement. The patient should be asked about any ocular symptoms (eg, itchy eyes, sticky eyelids, eye secretion, blurry vision etc.). In case of clinical findings, the patient must be referred to an ophthalmologist for assessment within 7 days, and before the next dose of study drug.

i Assessments can be performed up to 3 days prior to dosing on Day 1 of each cycle.

j Height measured in the last 12 months may be used.

k Vital signs should be recorded pre-dose and within 10 minutes after completion of GEN1107 administration. Vital signs measures are to include heart rate, blood pressure, respiratory rate, and temperature.

l Patients will be referred to an eye care professional for an ophthalmic exam within 14 days prior to treatment initiation, within 7 days before Day 1 of Cycle 2 to Cycle 5, 7, and 9, as clinically indicated for subsequent cycles, and at the EOT visit. Baseline and interval exams include examination and recording of BCVA/refraction/dilated slit lamp/OCT/intraocular pressure (refer to Section 7.1.6 for details). Patients who experience ocular TEAEs while on study will have complete ophthalmologic tests performed before Day 1 dosing for 4 subsequent cycles.

m Routine safety ECGs required at Screening, up to 3 days prior to dosing on Cycles 1 Day 1 and Cycle 3 Day 1, and EOT.

n The CBC with differential is to include, but is not limited to, the following tests: red blood cell count, white blood cell count with 5-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), absolute neutrophil count, platelet count, Hgb, and hematocrit. CBC should be collected at least weekly during dose delays.

o The results from all relevant clinical laboratory assessments must be reviewed prior to dosing.

p Day 8 and 15 CBC with differential and CMP are required during Cycles 1 through 3.

q The CMP is to include the following tests: albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen, calcium, creatinine, chloride, lactate dehydrogenase, phosphorus, potassium, sodium, and total bilirubin. CMP should be collected at least weekly during dose delays.

r HgbA1c, amylase, and lipase will be tested before dosing at every other cycle starting from Cycle 3.

s Fasting lipid panel includes the following tests: total cholesterol, LDL, HDL, and triglycerides.

t A serum β-hCG pregnancy test with sensitivity of at least 25 mIU/mL will be performed at baseline.

u After the first cycle, pregnancy tests may be performed up to 7 days prior to Day 1 of each cycle and at EOT. A negative pregnancy result is required before the patient may receive the study drug. Postbaseline urine pregnancy tests are acceptable, and any positives should be confirmed by serum testing.

v Reflexive microscopy required for abnormal urine analysis.

w From the time of informed consent.

x All SAEs that are considered study treatment-related in the opinion of the Investigator should be reported to the Sponsor. If ongoing after the EOT visit, ocular TEAEs need to be followed until resolution, stabilization, or return to baseline. Certain additional non-serious AEs of interest should continue to be assessed per the follow-up schedule until resolution, return to baseline, or study closure.

y Patients receiving GEN1107 are mandated to use a local ocular vasoconstrictor (brimonidine tartrate 0.2% eye drops or its equivalent) on each day of GEN1107 infusion. For example, with brimonidine tartrate 0.2% eye drops, 3 drops in each eye approximately 10 minutes prior to start of GEN1107 infusion and 2 subsequent administrations with approximately 8 hours apart between each administration are required.

z Apply cold packs fully over the eyes following administration of the vasoconstrictor eye drops. Change cold packs as needed throughout infusion to ensure eye area remains cold during the entire infusion and 20 minutes after completion of infusion.

aa Preservative-free lubricating artificial tears which will be self-administered as often as needed according to the package insert or instructions from the eye care provider from C1D1 to 30 days after last dose of GEN1107. Wait at least 15 minutes after vasoconstrictor eye drop administration before instilling lubricating eye drops.

bb Scans prior to consent are acceptable if performed within 28 days prior to first dose of study drug and patient consents for their medical records to be reviewed.

cc CA125 testing is required for patients with ovarian or endometrial cancer. Baseline CA-125 should be tested within 2 weeks before starting treatment. CA-125 will be tested every 6 weeks (±4 days) for the first 6 months after the first dose of GEN1107, every 9 weeks (±4 days) from 6 to 12 months, and then every 12 weeks (±8 days) thereafter. Tumor assessment according to GCIG criteria is required for ovarian cancer only. CA-125 response will be confirmed with repeat testing 4 to 6 weeks after the first documentation of response.

dd Tumor assessment according to RECIST v1.1. Tumor assessments will be performed every 6 weeks (±4 days) for the first 6 months after the first dose of PRO1107, every 9 weeks (±4 days) from 6 to 12 months, and then every 12 weeks (±8 days) thereafter. Objective responses (complete response [CR] or partial response [PR]) will be confirmed with repeat scans 4 to 6 weeks after the first documentation of response.

ee EOT response assessment not required if done within 4 weeks prior to EOT visit.

ff Follow-up response assessments not required after documented disease progression or initiation of first subsequent therapy.

gg Until 12 months post last dose of study drug or withdrawal of consent, death, or study closure, whichever occurs first.

Appendix B: Collection Timepoints for Pharmacokinetic, Immunogenicity, Biomarkers Blood Samples, and Tumor Biopsies for Q3W Regimen

Cycle	Cycle Day	Time	Window	Relative Time	Plasma for PK and Biomarkers	Serum for ADA and Biomarkers	Archived Tumor Specimen	Fresh Tumor Biopsy (FFPE)
Screening	-28 to 1	N/A	N/A	N/A			X[a]	X[a]
Cycles 1 and 3	Day 1	Pre-dose	Within 4 h	START of infusion	X[b]	X[b]		
		End of infusion	+15 min	END of infusion	X			
		2 h	± 30 min	END of infusion	X			
	Day 2	24 h	± 8 h	START of infusion	X			
	Day 4	72 h	± 24 h	START of infusion	X			
	Day 8	168 h	± 48 h	START of infusion	X			
	Day 15	336 h	± 48 h	START of infusion	X	X[c]		
Cycles 2, 4, and every 4th cycle thereafter (eg, Cycle 8, 12, etc.)	Day 1	Pre-dose	Within 4 h	START of infusion	X	X		
		End of infusion	Within 15 min	END of infusion	X			
End of Treatment					X	X		X[d]

Abbreviations: ADA=antidrug antibody; FFPE=formalin-fixed paraffin-embedded; PK=pharmacokinetics.

a All patients are requested to provide a pre-treatment tumor specimen (archival or fresh biopsy sample). Please submit the most recent available archived tumor specimen (preferably collected within 24 months provided it was collected after failure/stop of last prior treatment and before treatment with GEN1107. A tumor tissue sample acquired before last prior treatment requires sponsor approval on a case-by-case basis.) or fresh tumor biopsy sample, if archived tumor specimen is not available. Detailed instructions for tissue collection, processing and shipment are provided in the Laboratory Manual.

b. C1D1 pre-dose collection window for blood samples is 72h prior to start of infusion.

c Serum for ADA and biomarkers are required at C1D15 and not required at C3D15.

d For US patients only discontinuing treatment due to disease progression: if a tumor biopsy was performed per standard-of-care at the time of disease progression, submit sample of tumor specimen, if available.

Appendix C: Schedule of Events for 2Q4W Regimen

Category	Day	Screening/ Baseline	Enrollment	Every 28-day cycle				EOT	Follow-up
		D –28 to -1	Within 7D of 1st dose	D1	D8	D15	D22	Within 30 days of last dose[a]	Every 12 wks[b]
	Visit window			± 2D[c]	± 2D	± 2D	± 4D	+7D	± 1 wk
Screening/ Baseline and Safety Assessments	Informed consent	X	Submit eligibility confirmation to Sponsor prior to treatment						
	Inclusion/Exclusion, medical history	X		X[d]					
	Submission of tumor-related sample (archived or fresh) to central lab[e]	X						X[f]	
	Brain CT or MRI[g]	X							
	Physical examination including weight[h]	X		X[i]				X	
	Height	X[j]							
	Vital signs	X		X[k]				X	
	Ophthalmologic evaluation[l]	X		X[l]				X	
	Electrocardiogram	X[m]		X[m]				X[m]	
	ECOG performance status	X		X[m]				X	
	CBC with differential[n]	X		X[i, o]	X[p]	X[p]	X[p]	X	
	PT/PTT/INR *(aPTT also acceptable)*	X						X	
	Comprehensive metabolic panel[q]	X		X[i, o]	X[p]	X[p]	X[p]	X	
	Fasting glucose	X							
	HgbA1c[r]	X							
	Fasting lipid panel[s]	X							
	Amylase and lipase[r]	X							

Category	Day	Screening/ Baseline	Enrollment	Every 28-day cycle				EOT	Follow-up
	Visit window	**D –28 to -1**	**Within 7D of 1st dose**	**D1**	**D8**	**D15**	**D22**	**Within 30 days of last dose[a]**	**Every 12 wks[b]**
				± 2D[c]	± 2D	± 2D	± 4D	+7D	± 1 wk
	HBV surface antigen, HBV core antibody, and HCV rt-PCR	X							
	Pregnancy test for patients of childbearing potential	X[t]		X[o, u]				X[u]	
	Urinalysis[v]	X						X	
	Concomitant medications	Related to study procedures[w]		Collect from D1 predose through 30 days post last dose					
	Adverse event collection								X[x]
Treatment	GEN1107 administration			X[c]	X[c]				
Pre-medication and preventive ocular therapy	Vasoconstrictor eyedrops[y]			X	X				
	Cold packs[z]			X	X				
	Lubricating eyedrops[aa]			X[aa]					
PK/Immunogenicity/ Biomarker	Blood sample collection		See the table below for additional sample collection visits and details						
Response Assessment	PET or CT and/or MRI of chest, abdomen, pelvis (and neck if documented or suspected involvement in this region)	X[bb]		X[dd]				X[ee]	X[ff]
	CA-125 sample collection and assessment[z]	X[cc]		X[dd]				X[ee]	X[ff]
Survival Status, Collection of First Subsequent Therapy									X[gg]

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; CBC=complete blood count; D=day; CMP=comprehensive metabolic panel; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; HCV=hepatitis C virus; HDL=high density lipoprotein; Hgb=hemoglobin; LDL=low density lipoprotein; MRI=magnetic resonance imaging; PCR=polymerase chain reaction; PK=pharmacokinetics; PT/PTT/INR=prothrombin time/partial thromboplastin time/international normalized ratio; wk/wks=week(s); RNA=ribonucleic acid; UPC=urine protein/creatinine ratio.

a EOT evaluations should be obtained before the initiation of non-protocol therapy. If EOT evaluations are completed before 30 days following the last study treatment, conduct a phone screen 30–37 days following the patient's last study treatment to ensure that no changes in AE profile have occurred.

b Every 12 weeks from the most recent prior response evaluation until documentation of disease progression or initiation of a new therapy, and every 12 weeks from the prior follow-up visit thereafter.

c The ± 2-day window does not apply to Cycle 1 infusion.

d Day 1 review of Inclusion/Exclusion criteria, medical history required during Cycle 1 only.

e The most recent available archived tumor specimen collected within 24 months is requested for all enrolled patients. Screening archival tumor tissue specimen obtained outside the 24-month window or less than 10 slides available, may be allowed with Medical Monitor approval.

f For US patients only discontinuing treatment due to disease progression: if a tumor biopsy was performed per standard-of-care at the time of disease progression, submit sample of tumor specimen, if available.

g A CT/MRI of the brain should be done at Screening for all patients with a history of brain metastases, those suspected of new brain metastases, or those with a diagnosis of NSCLC or breast cancer.

h Physical examinations should include assessments of the following: abdomen, extremities, head, heart, lungs, neck, neurological system, weight, and eye exam. Eyes should be examined by the Investigator and assessment should include a visual inspection of the eye orbit and conjunctiva and control of normal eye movement. The patient should be asked about any ocular symptoms (eg, itchy eyes, sticky eyelids, eye secretion, blurry vision etc.). In case of clinical findings, the patient must be referred to an ophthalmologist for assessment within 7 days, and before the next dose of study drug.

i Assessments can be performed up to 3 days prior to dosing on Day 1 of each cycle.

j Height measured in the last 12 months may be used.

k Vital signs should be recorded pre-dose and within 10 minutes after completion of GEN1107 administration. Vital signs measures are to include heart rate, blood pressure, respiratory rate, and temperature.

l Patients will be referred to an eye care professional for an ophthalmic exam within 14 days prior to treatment initiation, within 7 days before Day 1 of Cycle 2 to Cycle 5, 7, and 9, as clinically indicated for subsequent cycles, and at the EOT visit. Baseline and interval exams include examination and recording of BCVA/refraction/dilated slit lamp/OCT/intraocular pressure (refer to Section 7.1.6 for details). Patients who experience ocular TEAEs while on study will have complete ophthalmologic tests performed before Day 1 dosing for 4 subsequent cycles.

m Routine safety ECGs required at Screening, up to 3 days prior to dosing on Cycles 1 Day 1 and Cycle 3 Day 1, and EOT.

n The CBC with differential is to include, but is not limited to, the following tests: red blood cell count, white blood cell count with 5-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), absolute neutrophil count, platelet count, Hgb, and hematocrit. CBC should be collected at least weekly during dose delays.

o The results from all relevant clinical laboratory assessments must be reviewed prior to dosing.

p Day 8, 15, and 22 CBC with differential and CMP are required during Cycles 1 through 3; Starting from Cycle 4, Day 8 CBC with differential is required.

q The CMP is to include the following tests: albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen, calcium, creatinine, chloride, lactate dehydrogenase, phosphorus, potassium, sodium, and total bilirubin. CMP should be collected at least weekly during dose delays.

r HgbA1c, amylase, and lipase will be tested before dosing at every other cycle starting from Cycle 3.

s Fasting lipid panel includes the following tests: total cholesterol, LDL, HDL, and triglycerides.

t A serum β-hCG pregnancy test with sensitivity of at least 25 mIU/mL will be performed at baseline.

u After the first cycle, pregnancy tests may be performed up to 7 days prior to Day 1 of each cycle and at EOT. A negative pregnancy result is required before the patient may receive the study drug. Postbaseline urine pregnancy tests are acceptable, and any positives should be confirmed by serum testing.

v Reflexive microscopy required for abnormal urine analysis.

w From the time of informed consent.

x All SAEs that are considered study treatment-related in the opinion of the Investigator should be reported to the Sponsor. If ongoing after the EOT visit, ocular TEAEs need to be followed until resolution, stabilization, or return to baseline. Certain additional non-serious AEs of interest should continue to be assessed per the follow-up schedule until resolution, return to baseline, or study closure.

y Patients receiving GEN1107 are mandated to use a local ocular vasoconstrictor (brimonidine tartrate 0.2% eye drops or its equivalent) on each day of GEN1107 infusion. For example, with brimonidine tartrate 0.2% eye drops, 3 drops in each eye approximately 10 minutes prior to start of GEN1107 infusion and 2 subsequent administrations with approximately 8 hours apart between each administration are required.

z Apply cold packs fully over the eyes following administration of the vasoconstrictor eye drops. Change cold packs as needed throughout infusion to ensure eye area remains cold during the entire infusion and 20 minutes after completion of infusion

aa Preservative-free lubricating artificial tears which will be self-administered as often as needed according to the package insert or instructions from the eye care provider from C1D1 to 30 days after last dose of GEN1107. Wait at least 15 minutes after vasoconstrictor eye drop administration before instilling lubricating eye drops.

bb Scans prior to consent are acceptable if performed within 28 days prior to first dose of study drug and patient consents for their medical records to be reviewed.

cc CA125 testing is required for patients with ovarian or endometrial cancer. Baseline CA-125 should be tested within 2 weeks before starting treatment. CA-125 will be tested every 6 weeks (±4 days) for the first 6 months after the first dose of GEN1107, every 9 weeks (±4 days) from 6 to 12 months, and then every 12 weeks (±8 days) thereafter. Tumor assessment according to GCIG criteria is required for ovarian cancer only. CA-125 response will be confirmed with repeat testing 4 to 6 weeks after the first documentation of response.

dd Tumor assessment according to RECIST v1.1. Tumor assessments will be performed every 6 weeks (±4 days) for the first 6 months after the first dose of PRO1107, every 9 weeks (±4 days) from 6 to 12 months, and then every 12 weeks (±8 days) thereafter. Objective responses (complete response [CR] or partial response [PR]) will be confirmed with repeat scans 4 to 6 weeks after the first documentation of response.

ee EOT response assessment not required if done within 4 weeks prior to EOT visit.

ff Follow-up response assessments not required after documented disease progression or initiation of first subsequent therapy.

gg Until 12 months post last dose of study drug or withdrawal of consent, death, or study closure, whichever occurs first.

Appendix D: Collection Timepoints for Pharmacokinetic, Immunogenicity, Biomarkers Blood Samples, and Tumor Biopsies for 2Q4W Regimen

Cycle	Cycle Day	Time	Window	Relative Time	Plasma for PK and Biomarkers	Serum for ADA and Biomarkers	Archived Tumor Specimen	Fresh Tumor Biopsy (FFPE)
Screening	-28 to 1	N/A	N/A	N/A			X[a]	X[a]
Cycles 1 and 3	Day 1	Pre-dose	Within 24 h	START of infusion	X[b]	X[b]		
		End of infusion	+15 min	END of infusion	X			
	Day 4	72 h	± 24 h	END of infusion	X			
	Day 8	Pre-dose	Within 24 h	START of infusion	X			
		End of infusion	+15 min	END of infusion	X			
	Day 12	72 h	± 24 h	START of infusion	X			
	Day 15	168 h	± 48 h	START of infusion	X			
	Day 22	336 h	± 48 h	START of infusion	X			
Cycles 2, 4, and every 2nd cycle thereafter (eg, Cycle 6, 8,10,12 etc.)	Day 1	Pre-dose	Within 24 h	START of infusion	X	X[c]		
		End of infusion	Within 15 min	END of infusion	X			
	Day 8	Pre-dose	Within 24 h	START of infusion	X			
		End of infusion	Within 15 min	END of infusion	X			
End of Treatment					X	X		X[d]

Abbreviations: ADA=antidrug antibody; FFPE=formalin-fixed paraffin-embedded; PK=pharmacokinetics.

a. All patients are requested to provide a pre-treatment tumor specimen (archival or fresh biopsy samples). Please submit the most recent available archived tumor specimen (preferably collected within 24 months provided it was collected after failure/stop of last prior treatment and before treatment with GEN1107. A tumor tissue sample acquired before last prior treatment requires sponsor approval on a case-by-case basis.) or fresh tumor biopsy sample, if archived tumor specimen is not available. Detailed instructions for tissue collection, processing and shipment are provided in the Laboratory Manual.
b. C1D1 pre-dose collection window for blood samples is 72h prior to start of infusion.
c. Serum for ADA and biomarkers: Cycles 2, 4, and every 4th cycle thereafter, ie, Cycles 4, 8, 12, etc.
d. For patients discontinuing treatment due to disease progression: if a tumor biopsy was performed per standard-of-care at the time of disease progression, submit sample of tumor specimen, if available.

Appendix E: Schedule of Events for CCI Regimen

Category	Day / Visit window	Screening/ Baseline D –28 to -1	Enrollment Within 7D of 1st dose	CCI	EOT Within 30 days of last dose[a] +7D	Follow-up Every 12 wks[b] ± 1 wk
Screening/Baseline and Safety Assessments	Informed consent	X	Submit eligibility confirmation to Sponsor prior to treatment			
	Inclusion/Exclusion, medical history	X				
	Submission of tumor-related sample (archived or fresh) to central lab[e]	X			X[f]	
	Brain CT or MRI[g]	X				
	Physical examination including weight[h]	X			X	
	Height	X[j]				
	Vital signs	X			X	
	Ophthalmologic evaluation[l]	X			X	
	Electrocardiogram	X[l]			X[m]	
	ECOG performance status	X			X	
	CBC with differential[n]	X			X	
	PT/PTT/INR *(aPTT also acceptable)*	X			X	
	Comprehensive metabolic panel[q]	X			X	
	Fasting glucose	X				
	HgbA1c[r]	X				
	Fasting lipid panel[s]	X				
	Amylase and lipase[r]	X				
	Pregnancy test for patients of childbearing potential	X[t]			X[u]	
	Urinalysis[v]	X			X	

Category	Day	Screening/ Baseline	Enrollment	CCI	EOT	Follow-up
	Visit window	**D –28 to -1**	**Within 7D of 1st dose**		**Within 30 days of last dose[a]**	**Every 12 wks[b]**
					+7D	± 1 wk
	Concomitant medications	Related to study procedures[w]		Collect from D1 predose through 30 days post last dose		
	Adverse event collection			Collect from D1 predose through 30 days post last dose		X[x]
Treatment	GEN1107 administration					
Pre-medication and preventive ocular therapy	Vasoconstrictor Eyedrops[y]					
	Cold packs[z]					
	Lubricating Eyedrops[aa]			X[aa]		
PK/Immunogenicity/ Biomarker	Blood sample collection			See the table below for additional sample collection visits and details		
Response Assessment	PET or CT and/or MRI of chest, abdomen, pelvis (and neck if documented or suspected involvement in this region)	X[bb]			X[ee]	X[ff]
	CA-125 sample collection and assessment[z]	X[cc]			X[ee]	X[ff]
Survival Status, Collection of First Subsequent Therapy						X[gg]

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; CBC=complete blood count; D=day; CMP=comprehensive metabolic panel; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; HCV=hepatitis C virus; HDL=high density lipoprotein; Hgb=hemoglobin; LDL=low density lipoprotein; MRI=magnetic resonance imaging; PCR=polymerase chain reaction; PK=pharmacokinetics; PT/PTT/INR=prothrombin time/partial thromboplastin time/international normalized ratio; wk/wks=week(s); RNA=ribonucleic acid; UPC=urine protein/creatinine ratio.

a EOT evaluations should be obtained before the initiation of non-protocol therapy. If EOT evaluations are completed before 30 days following the last study treatment, conduct a phone screen 30–37 days following the patient's last study treatment to ensure that no changes in AE profile have occurred.

b Every 12 weeks from the most recent prior response evaluation until documentation of disease progression or initiation of a new therapy, and every 12 weeks from the prior follow-up visit thereafter.

c The ± 2-day window does not apply to Cycle 1 infusion.

d Day 1 review of Inclusion/Exclusion criteria, medical history required during Cycle 1 only.

e The most recent available archived tumor specimen collected within 24 months is requested for all enrolled patients. Screening archival tumor tissue specimen obtained outside the 24-month window or less than 10 slides available, may be allowed with Medical Monitor approval.

f For US patients only discontinuing treatment due to disease progression: if a tumor biopsy was performed per standard-of-care at the time of disease progression, submit sample of tumor specimen, if available.

g A CT/MRI of the brain should be done at Screening for all patients with a history of brain metastases, those suspected of new brain metastases, or those with a diagnosis of NSCLC or breast cancer.

h Physical examinations should include assessments of the following: abdomen, extremities, head, heart, lungs, neck, neurological system, weight, and eye exam. Eyes should be examined by the Investigator and assessment should include a visual inspection of the eye orbit and conjunctiva and control of normal eye movement. The patient should be asked about any ocular symptoms (eg, itchy eyes, sticky eyelids, eye secretion, blurry vision etc.). In case of clinically significant findings, the patient must be referred to an ophthalmologist for assessment within 7 days if possible, and before the next dose of study drug.

i Assessments can be performed up to 3 days prior to dosing on Day 1 of each cycle.

j Height measured in the last 12 months may be used.

k Vital signs should be recorded pre-dose and within 10 minutes after completion of GEN1107 administration. Vital signs measures are to include heart rate, blood pressure, respiratory rate, and temperature.

l Patients will be referred to an eye care professional for an ophthalmic exam within 14 days prior to treatment initiation, within 7 days before Day 1 of Cycle 2 to Cycle 5, 7, and 9, as clinically indicated for subsequent cycles, and at the EOT visit. Baseline and interval exams include examination and recording of BCVA/refraction/dilated slit lamp/OCT/intraocular pressure (refer to Section 7.1.6 for details). Patients who experience ocular TEAEs while on study will have complete ophthalmologic tests performed before Day 1 dosing for 4 subsequent cycles.

m Routine safety ECGs required at Screening, up to 3 days prior to dosing on Cycles 1 Day 1 and CCI Day 1, and EOT.

n The CBC with differential is to include, but is not limited to, the following tests: red blood cell count, white blood cell count with 5-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), absolute neutrophil count, platelet count, Hgb, and hematocrit. CBC should be collected at least weekly during dose delays.

o The results from all relevant clinical laboratory assessments must be reviewed prior to dosing.

p Day CCI CBC with differential and CMP are required during CCI ; Starting from CCI , Day CCI CBC with differential is required.

q The CMP is to include the following tests: albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen, calcium, creatinine, chloride, lactate dehydrogenase, phosphorus, potassium, sodium, and total bilirubin. CMP should be collected at least weekly during dose delays.

r HgbA1c, amylase, and lipase will be tested before dosing at every other cycle starting from CCI .

s Fasting lipid panel includes the following tests: total cholesterol, LDL, HDL, and triglycerides.

t A serum β-hCG pregnancy test with sensitivity of at least 25 mIU/mL will be performed at baseline.

u After the first cycle, pregnancy tests may be performed up to 7 days prior to Day 1 of each cycle and at EOT. A negative pregnancy result is required before the patient may receive the study drug. Postbaseline urine pregnancy tests are acceptable, and any positives should be confirmed by serum testing.

v Reflexive microscopy required for abnormal urine analysis.

w From the time of informed consent.

x All SAEs that are considered study treatment-related in the opinion of the Investigator should be reported to the Sponsor. If ongoing after the EOT visit, ocular TEAEs need to be followed until resolution, stabilization, or return to baseline. Certain additional non-serious AEs of interest should continue to be assessed per the follow-up schedule until resolution, return to baseline, or study closure.

y Patients receiving GEN1107 are mandated to use a local ocular vasoconstrictor (brimonidine tartrate 0.2% eye drops or its equivalent) on each day of GEN1107 infusion. For example, with brimonidine tartrate 0.2% eye drops, 3 drops in each eye approximately 10 minutes prior to start of GEN1107 infusion and 2 subsequent administrations with approximately 8 hours apart between each administration are required.

z Apply cold packs fully over the eyes following administration of the vasoconstrictor eye drops. Change cold packs as needed throughout infusion to ensure eye area remains cold during the entire infusion and 20 minutes after completion of infusion.

aa Preservative-free lubricating artificial tears which will be self-administered as often as needed according to the package insert or instructions from the eye care provider from C1D1 to 30 days after last dose of GEN1107. Wait at least 15 minutes after vasoconstrictor eye drop administration before instilling lubricating eye drops.

bb Scans prior to consent are acceptable if performed within 28 days prior to first dose of study drug and patient consents for their medical records to be reviewed.

cc CA125 testing is required for patients with ovarian or endometrial cancer. Baseline CA-125 should be tested within 2 weeks before starting treatment. CA-125 will be tested every 6 weeks (±4 days) for the first 6 months after the first dose of GEN1107, every 9 weeks (±4 days) from 6 to 12 months, and then every 12 weeks (±8 days) thereafter. Tumor assessment according to GCIG criteria is required for ovarian cancer only. CA-125 response will be confirmed with repeat testing 4 to 6 weeks after the first documentation of response.

dd Tumor assessment according to RECIST v1.1 and GCIC criteria (for ovarian cancer only). Tumor assessments and CA-125 testing will be performed every 6 weeks (±4 days) for the first 6 months after the first dose of PRO1107, every 9 weeks (±4 days) from 6 to 12 months, and then every 12 weeks (±8 days) thereafter. Objective responses (complete response [CR] or partial response [PR]) will be confirmed with repeat scans 4 to 6 weeks after the first documentation of response. CA-125 response will be confirmed with repeat testing 4 to 6 weeks after the first documentation of response.

ee EOT response assessment not required if done within 4 weeks prior to EOT visit.

ff Follow-up response assessments not required after documented disease progression or initiation of first subsequent therapy.

gg Until 12 months post last dose of study drug or withdrawal of consent, death, or study closure, whichever occurs first.

Appendix F: Collection Timepoints for Pharmacokinetic, Immunogenicity, Biomarkers Blood Samples, and Tumor Biopsies for CCI Regimen

Cycle	Cycle Day	Time	Window	Relative Time	Plasma for PK and Biomarkers	Serum for ADA and Biomarkers	Archived Tumor Specimen	Fresh Tumor Biopsy (FFPE)
Screening	-28 to 1	N/A	N/A	N/A			X[a]	X[a]
CCI								
End of Treatment					X	X		X[d]

Abbreviations: ADA=antidrug antibody; FFPE=formalin-fixed paraffin-embedded; PK=pharmacokinetics.

a. All patients are requested to provide a pre-treatment tumor specimen (archival or fresh biopsy samples). Please submit the most recent available archived tumor specimen (preferably collected within 24 months provided it was collected after failure/stop of last prior treatment and before treatment with GEN1107. A tumor tissue sample acquired before last prior treatment requires sponsor approval on a case-by-case basis.) or fresh tumor biopsy sample, if archived tumor specimen is not available. Detailed instructions for tissue collection, processing and shipment are provided in the Laboratory Manual.
b. C1D1 pre-dose collection window for blood samples is CCI prior to start of infusion.
c. Serum for ADA and biomarkers: cycles CCI .
d. For patients discontinuing treatment due to disease progression: if a tumor biopsy was performed for next treatment decision at the time of disease progression, submit sample of tumor specimen, if available.

Appendix G: Performance Status Scales Conversion

Karnofsky		ECOG	
Percent	**Description**	**Score**	**Description**
100	Normal, no complaints, no evidence of disease.	0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
90	Able to carry on normal activity: minor signs or symptoms of disease.		
80	Normal activity with effort; some signs or symptoms of disease.	1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
70	Cares for self, unable to carry on normal activity or to do active work.		
60	Requires occasional assistance but is able to care for most of his/her needs.	2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
50	Requires considerable assistance and frequent medical care.		
40	Disabled, requires special care and assistance.	3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
30	Severely disabled, hospitalization indicated. Death not imminent.		
20	Very sick, hospitalization indicated. Death not imminent.	4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally Confined to bed or chair.
10	Moribund, fatal processes progressing rapidly.		
0	Dead.	5	Dead.

Appendix H: Guidance on Contraception

For the purposes of this guidance, complete abstinence, if consistent with the patient's preferred lifestyle, is an acceptable form of contraception. Complete abstinence is defined as abstinence starting from the time of informed consent and continuing throughout the study and until the end of systemic exposure (at least 2 months after the final dose of GEN1107).

Acceptable methods for highly effective birth control (preventing conception)

Patients who are of childbearing potential[a] or whose partners are of childbearing potential[a] and who are sexually active in a way that could lead to pregnancy may choose any TWO of the following methods (please see acceptable combinations below):

- Hormonal methods of contraception (excluding progestin-only pills; method must be associated with inhibition of ovulation), unless contraindicated
- Intrauterine device with failure rate <1%
- Tubal ligation
- Vasectomy (at least 90 days from the date of surgery with a semen analysis documenting azoospermia)
- Barrier method (male or female condom with or without spermicide, cervical cap with or without spermicide, diaphragm with or without spermicide)[b]

a A person of childbearing potential is defined as anyone born female who has experienced menarche and who has not undergone surgical sterilization (eg, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or has not completed menopause. Menopause is defined clinically as 12 months of amenorrhea in a person born female over age 45 in the absence of other biological, physiological, or pharmacological causes.

b A barrier method should only be used with a highly effective birth control method that is not a barrier method. Barrier methods alone, including a double-barrier method, are not considered highly effective. contraceptive measures (see unacceptable methods of contraception).

Acceptable combinations of contraceptive methods:	
● Hormonal method and vasectomy	● Intrauterine device and barrier method
● Hormonal method and barrier method	● Tubal ligation and vasectomy

Acceptable methods for preventing secondary exposure to seminal fluid
Patients born male and who are sexually active with a pregnant or breastfeeding person must use the contraceptives in Option 1 or 2:

- Option 1: Male condom (with or without spermicide) and cervical cap
- Option 2: Male condom (with or without spermicide) and diaphragm

Unacceptable methods of contraception	
● Periodic abstinence	● Spermicide only
● No method	● Progestin-only pills
● Withdrawal	● Concomitant use of female and male condoms
● Rhythm	● Barrier methods alone, including double-barrier methods

Appendix I: New York Heart Association Classification

A Functional and Therapeutic Classification for Prescription of Physical Activity for Cardiac Patients

Class I: Patients with no limitation of activities; they suffer no symptoms from ordinary activities.

Class II: Patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.

Class III: Patients with marked limitation of activity; they are comfortable only at rest.

Class IV: Patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

On-line source: http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-HeartFailure_UCM_306328_Article.jsp

Appendix J: CYP3A Inhibitors

NOTE: Additional strong CYP3A inhibitors may become available while the clinical trial is ongoing. The following statements would apply to those medications in addition to those listed in the table below.

The systemic exposure of MMAE has not been characterized. Strong inhibitors of CYP3A are prohibited to minimize potential for increased MMAE exposure.

Strong CYP3A Inhibitors
boceprevir
clarithromycin
cobicistat
conivaptan
danoprevir and ritonavir
diltiazem
elvitegravir and ritonavir
grapefruit juice
idelalisib
indinavir and ritonavir
itraconazole
ketoconazole
lopinavir and ritonavir
nefazodone
nelfinavir
paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)
posaconazole
ritonavir
saquinavir and ritonavir
telaprevir
tipranavir and ritonavir
troleandomycin
voriconazole

Note: Any additional strong CYP3A inhibitors that are identified or become commercially available while the clinical trial is ongoing should also be closely monitored for adverse reactions.

Appendix K: Grading System for Ocular Toxicities

Adverse Reaction	Severity	Grade
Corneal Keratitis	Clear cornea, no epithelial defects	0
	Nonconfluent superficial keratitis	1
	Confluent superficial keratitis, a cornea epithelial defect, or 3-line or more loss in best corrected distance visual acuity.	2
	Corneal ulcer or stromal opacity or best corrected distance visual acuity 20/200 or worse.	3
	Corneal perforation.	4
Conjunctivitis	No vasodilation, no epithelial defects	0
	Nonconfluent superficial punctate defects, mild vasodilation	1
	Confluent superficial punctate staining, moderate to severe vasodilation.	2
	Conjunctival ulcer or neovascularization	3
Iritis/Uveitis	Clear anterior chamber	0
	Rare cell in anterior chamber	1
	1-2+ cell or flare in anterior chamber	2
	3+ Cell or Flare in anterior chamber	3
	Hypopyon	4
Blurred Vision	BCVA same as baseline BCVA	0
	BCVA worse than baseline but no worse than 20/40	1
	BCVA worse than baseline but no worse than 20/200	2
	BCVA 20/200 or worse	3
	No light perception	4
Serous detachment of retinal pigment epithelium	No detachment	0
	Detachment which starts to resolve at or within 2 weeks	1
	Detachment which does not start to resolve at or within 2 weeks	2
	Detachment which does not start to resolve within 2 months	3

Appendix L: Country-Specific Considerations

Drug Name	IMP or AxMP	EU Authorization Status
GEN1107	IMP	Unauthorized
Ocular vasoconstrictor, eg, brimonidine tartrate 0.2% eye drops or equivalent	AxMP	Authorized
lubricating artificial tears	AxMP	Authorized

Appendix M: Sample Storage and Destruction

Any sample collected according to the Schedule of Events (Appendix A, Appendix C, and Appendix E) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to trial patients. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the trial. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded before being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the trial. Results are stored in a secure database to ensure confidentiality. Exploratory biomarker research may also be performed to investigate and better understand solid tumors, the dose response and/or prediction of response to GEN1107, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained; but are not necessarily reported as part of this trial. Samples can be retained for up to 5 years after the last patient receives the first dose of trial treatment. Samples will be destroyed after the 5-year retention period. Since the evaluations are not expected to benefit the patient directly or to alter the treatment course, the results of any exploratory biomarker research are not placed in the patient's medical record and are not to be made available to the patient, members of the family, the personal physician, or other third parties, except as specified in the informed consent. The patient retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the patient, the investigator is to provide the sponsor with the required trial and patient number so that any remaining samples and any other components from the cells can be located and destroyed. However, information collected from samples before the request for destruction will be retained by Genmab. The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the patient through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The patient has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Section 10.4 for patient confidentiality.

Protocol Amendment Summary of Changes

Protocol Amendment 2 (13 Feb 2025)

The following **substantive** changes were made. Additional minor changes have also been incorporated throughout the protocol to provide clarity and consistency.

Section Number and Name	Description of Change	Brief Rationale
Global changes	Throughout the protocol, the trial number has been updated from PRO1107-001 to GCT1107-01 and the Investigational Product number has been updated from PRO1107 to GEN1107. SMC was replaced by DEC and/or Safety Committee, as appropriate.	To align with Genmab's Investigational Product and trial numbering schema, as well as nomenclature.
Global changes	Wording has been added to align with required wording for EU CTR compliance.	Allow for possible future enrollment in the EU.
Cover Page	Converted to Genmab template, updated study number to reflect Genmab study number, updated compound name to reflect Genmab compound description, added short (brief) title for EU CTR compliance, updated sponsor name, updated protocol approver, updated sponsor information, and updated the confidentiality statement	ProfoundBio was acquired by Genmab and for compliance with EU CTR requirements and protocol template alignment
Sponsor Information Page	Added	Protocol template alignment
Investigator Agreement	Updated	Protocol template alignment
Synopsis, Section 3.1, Section 3.8	Added 2 alternative dose regimens and relevant rationale	To identify the potential recommended expansion doses

Section Number and Name	Description of Change	Brief Rationale
Synopsis, Section 3.1.2, and Section 3.1.3	Updated information related to DLT evaluation	Updated for additional clarity.
Synopsis, Section 3.1.3, Section 5.6, Section 7.1.13.1, Section 7.1.13.2, Section 9.3.8.1, and Appendix K	To specify that ocular toxicities will be graded according to the criteria provided in a new table (included in Appendix K) as opposed to CTCAE.	To ensure appropriate monitoring of potential ocular toxicities per FDA recommendation.
Synopsis, Section 2	Objectives and endpoints updates to align with the updates to the protocol.	Protocol alignment.
Section 3.5	Added details for the end of the study.	Updated with appropriate details
Section 4.3	Added details for the screen failures.	Updated with appropriate details
Section 4.5.3	Added details for the lost to follow up.	Updated with appropriate details
Section 5.2.2	Added “Patients that have a BSA >2.2 m^2 will receive a dose based on BSA of 2.2 m^2.”	To reduce a potential risk of toxicity for patients with BSA higher than 2.2 m^2
Section 5.3.2, Appendix A, Appendix C, and Appendix E	To include pre-medication and preventive ocular therapy for mitigation of ocular toxicity	To reduce ocular toxicities observed in dose escalation

Section Number and Name	Description of Change	Brief Rationale
Section 5.6 and Section 5.6.1	To include specific dose modification guidance for ocular toxicities	To include more detailed guidance for ocular toxicities to better modify doses based on the terms and grading of the ocular AEs
Section 7.1.6, Appendix A, Appendix C, and Appendix E	To include more frequent ophthalmology tests for all patients and additional ones for patients who experience ocular TEAEs while on study	To implement robust monitoring of ocular toxicities
Synopsis, Section 1.4.5, Section 1.4.6, Section 1.4.7, and Section 4.1	Inclusion Criterion 1 (5th to 7th bullet deleted) has been deleted as follows: • ~~• Esophageal, gastroesophageal junction (GEJ), or gastric adenocarcinoma~~ • ~~• Esophageal squamous cell carcinoma (ESCC)~~ • ~~• Urothelial cancers (bladder, ureter, or renal pelvis)~~	To concentrate on tumor types which were indicated to be with relatively higher expression of PTK7 with translational data
Synopsis, Section 4.1	Added separate chapter of Inclusion Criterion for Part B, with the Inclusion Criteria 1 added to define homogeneous populations for the 4 tumor-specific expansion cohorts.	To have a homogeneous population for dose optimization in Part B
Synopsis, Section 4.2	Exclusion criterion: #2 Removed (Part B only) from "Had progressive disease as best response while on treatment with an auristatin (eg, a vedotin or pelidotin)-based ADC as the most recent line of therapy (Part B only)." #5 Added "(repeat imaging during trial screening should be performed to ensure stability of brain metastases for ≥4 weeks)" on top of "Patients with brain metastases may participate provided the	To extend the requirement to Part A to enroll patients with better chance of benefiting from study drug To have detailed requirement of brain scans to ensure enrollment of appropriate patients

Section Number and Name	Description of Change	Brief Rationale
	metastases have been treated and are stable for at least 4 weeks prior to the first dose of study drug". #12 Specified that "Transient ischemic attack >1 month prior to screening is allowed." #18 Added "Treatment with an investigational anticancer agent within 28 days or for systemic therapies within 5 half-lives of the drug, whichever is shorter, prior to trial treatment administration." on top of "Prior antitumor treatments must have a washout period of 2 weeks for chemotherapy or therapy with small molecules and 4 weeks for antibody-based therapeutics prior to the first dose of study drug. If the underlying disease has progressed on treatment, a washout period of 2 weeks prior to the first dose of study drug is acceptable."	To have detailed requirement of allowed and prohibited cerebral vascular events to ensure enrollment of appropriate patients To ensure appropriate wash-out of investigational anticancer agents
Synopsis, Section 3.1.4, Section 3.2, Section 3.6, Section 3.7, Section 9.1, Section 9.3.1.1	Increase of number of levels of dose-level expansion in Part A from 3 to 4, increase total number of patients for a dose level in Part A from 12 to 18, and adding 2 alternative dose regimens in Part A. Sample size of Part A increased from 54 to 120 and this change increases the overall planned enrollment from 134 patients to 280 patients.	To accommodate Part A sample size with the addition of alternative regimens and increased number and size of dose-level expansions
Synopsis, Section 7.1.11.2.2	The Biomarkers Assessments section has been updated with additional details of planned analyses and assays to be used.	Clarification.
Section 7.1.13	Sections 7.1.13.11 (added wording), 7.1.13.12 (new), and 7.1.13.13 (added wording) have additional information.	Clarification.
Appendix B, footnotes a and d	Table revised to clarify that PK samples collected within 15 minutes of the end of infusion will not be collected before the infusion ends.	To clarify the window for the end-of-infusion PK sample.
Appendix C, Appendix D, Appendix E, Appendix F	Added for the new dose regimens.	To clarify visits if a different dose regimen is used.