CLINICAL TRIAL PROTOCOL

Open-label, Dose-escalation Trial to Evaluate the Safety and Pharmacokinetics of GEN1046 in Japanese Subjects With Advanced Solid Malignancies

Short Title: GEN1046 Safety and PK in Subjects With Advanced Solid Malignancies

Protocol Number:	GCT1046-02
Sponsor Name:	Genmab*
Regulatory Agency Identifier Number(s)	NCT04937153
Investigational Medicinal Product (IMP):	GEN1046 (DuoBody®-PD-L1x4-1BB)
Development Phase:	1
Protocol Approver**	**Name** PPD, MD **Title** PPD
Protocol Date and Version:	23-Sep-2020 (Original Protocol, v1.0) 09-Dec-2020 (Amendment 1, v2.0) 27-May-2021 (Amendment 2, v3.0) 21-Feb-2022 (Amendment 3, v4.0) 23-Mar-2023 (Amendment 4, v5.0) 13-Dec-2023 (Amendment 5, v6.0) 30-Aug-2024 (Amendment 6, v7.0)

*Genmab is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Genmab trials may vary, such as, but not limited to Genmab A/S or Genmab US, Inc. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the following sponsor information page.

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

SPONSOR INFORMATION PAGE

The information on this page can be updated without amending the protocol.

Sponsor information for Japan	Genmab US, Inc. 777 Scudders Mill Road Plainsboro, New Jersey 08536 United States of America

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STATEMENT OF COMPLIANCE

GCP Compliance

This trial will be conducted in compliance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP), ICH GCP E6(R2), standards stipulated in Article 14, Paragraph 3 and Article 80-2 of the "Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices," Japanese Ministerial Ordinance on Good Clinical Practice for Drugs (J-GCP), Principles of the Declaration of Helsinki, and applicable regulatory requirements. Generally, the priority is given to J-GCP for definitions of terminology and other minor differences between J-GCP and ICH GCP.

Confidentiality Statement

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ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
1Q3W	1 dose (once) every 3 weeks
1Q3W×2	1 dose (once) every 3 weeks for 2 occasions
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBc	antibody to hepatitis B core antigen
anti-HBs	antibody to hepatitis B surface antigen
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the concentration-time curve
β-hCG	beta-human chorionic gonadotropin
BOIN	Bayesian optimal interval
BOR	best overall response
C1D1	Cycle 1 Day 1
CD	cluster of differentiation
CI	confidence interval
C_{max}	maximum concentration
CNS	central nervous system
CPI	checkpoint inhibitor
CR	complete response
CRF	case report form
CRO	contract research organization
CRS	cytokine release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	predose trough concentration
DCR	disease control rate
DEC	Dose Escalation Committee
DLT	dose-limiting toxicity
DOR	duration of response

Abbreviation	Definition
DUCT	drugs used in the clinical trial
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
FAS	full analysis set
Fc	fragment crystallizable
FcγR	IgG Fc receptor
FFPE	formalin-fixed paraffin-embedded
FIH	first-in-human
G-CSF	granulocyte-colony stimulating factor
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GLP	Good Laboratory Practice
GM-CSF	granulocyte/macrophage colony stimulating factor
HIV	human immunodeficiency virus
HLH	hemophagocytic lymphohistiocytosis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
iCPD	immune confirmed disease progression (according to iRECIST)
IEC	independent Ethics Committee
IFNγ	interferon gamma
IgG	immunoglobulin G
ILD	interstitial lung disease
IMP	Investigational Medicinal Product
irAE	immune-related adverse event
IRB	Institutional Review Board
iRECIST	immune Response Evaluation Criteria in Solid Tumors
IRR	infusion-related reaction
IV	intravenous(ly)
J-GCP	Japanese Ministerial Ordinance on Good Clinical Practice for Drugs
KL-6	Krebs von den Lungen-6
LSLV	last subject last visit

Abbreviation	Definition
mAb	monoclonal antibody
MOA	mechanism of action
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
ORR	objective response rate
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PK	pharmacokinetic(s)
PR	partial response
PS	performance status
PT	prothrombin time
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RO	receptor occupancy
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCCHN	squamous cell carcinoma of the head and neck
sCD25	soluble interleukin-2 receptor
SCr	serum creatinine
SD	stable disease
SFU	safety follow-up visit
SUSAR	suspected unexpected serious adverse reaction
$T_{1/2}$	half-life
TEAE	treatment-emergent adverse event
TIL	tumor-infiltrating lymphocytes
T_{max}	time of maximum concentration
TNF	tumor necrosis factor
ULN	upper limit of normal
WOCBP	woman of childbearing potential

PROTOCOL AMENDMENTS

Protocol/Amendment No; Version	Date
Original Protocol; v 1.0	23 Sep 2020
Amendment 1; v 2.0	09 Dec 2020
Amendment 2; v 3.0	27 May 2021
Amendment 3; v 4.0	21 Feb 2022
Amendment 4; v 5.0	23 Mar 2023
Amendment 5; v 6.0	13 Dec 2023
Amendment 6; v 7.0	30 Aug 2024

Amendment 6 (30 Aug 2024)

Overall Rationale for Global Amendment 6:

To remove nonessential PK, ADA, and biomarker sampling requirements to reduce the burden for the subject remaining on trial.

The full list of amendment changes is summarized below. Changes included in the summary of changes table have been incorporated in the trial synopsis as applicable.

List of Changes in the Protocol and Their Rationales

Section No. and Name	Description of Change	Brief Rationale
Title Page	Changed name and title of Sponsor's protocol approver.	Change in Responsible Medical Officer.
1 Visit Assessment Schedule; Table 1-2 PK and ECG Sampling	Added footnote 6 indicating that with implementation of Amendment 6, PK sampling is not required from Cycle 5 onward (before infusion and end of infusion time points), or at treatment discontinuation, SFU, or UNS visits.	Removed nonessential PK, ADA, and biomarker assessments to reduce the burden for the subject remaining on trial.
1 Visit Assessment Schedule; Table 1-3 Immunogenicity (ADA) Sampling	Added footnote 3 indicating that with implementation of Amendment 6, immunogenicity sampling is not required from Cycle 3 onward, or at treatment discontinuation, SFU, or UNS visits.	
1 Visit Assessment Schedule; Table 1-4 Biomarker Sampling	Updated footnotes 2 and 3 to indicate that for adverse events, cytokines/chemokines (soluble factors) should only be assessed at the site's local laboratory following implementation of Amendment 6. Added footnote 4 indicating that with implementation of Amendment 6, tumor biopsies at UNS visits and cytokine/chemokine sampling from Cycle 4 onward are not required.	
2.3.5 Summary of Clinical Trials	Updated number of subjects treated with GEN1046 across trials as of 01 Apr 2024.	Aligned with data from current GEN1046 IB.

Section No. and Name	Description of Change	Brief Rationale
2.3.6 Benefit-Risk Assessment	Removed common adverse reactions associated with pembrolizumab and referred to current Japanese package insert.	Revised to simplify text and ensure alignment with package insert.
4.3 Dose and Schedule Rationale	Updated the data cut-off date	Aligned with data from current GEN1046 IB.
6.5.2 Pembrolizumab	Changed the reference safety information for pembrolizumab from "Summary of Product Characteristics (SmPC)" to "Japanese package insert."	Changed to the label of the applicable country for DUCT.
7.3.1 Immune-Related Adverse Events; 7.3.3.2 Hemophagocytic Lymphohistiocytosis	Added "For infections ongoing at the time of dosing, consider dose delay until resolution."	Clarification regarding dosing during ongoing infection.
7.3.1 Immune-Related Adverse Events, Table 7-1 Dose Modification and Management of Immune-Related Adverse Events	For pneumonitis, updated "grade 2" to "grade 1 or 2."	Aligned with other GEN1046 trials
7.3.3.1 Cytokine Release Syndrome	Added note that subjects with grade 3 CRS that improves to grade 1 or resolves within 48 hours do not have to permanently discontinue trial treatment.	Clarification to align with other GEN1046 trials.
7.3.3.2 Hemophagocytic Lymphohistiocytosis	Added information about overlapping features of hyperinflammatory syndromes and treatment guidance.	Clarification to align with other GEN1046 trials.
9.7 Biomarker Investigations	Added a sentence indicating biomarker samples will be collected as specified in Table 1-4.	Clarification to ensure alignment with current biomarker sampling schedule and assessments.
10.3.3 Pregnancy	Inserted language about reporting pregnancy and use of the pregnancy reporting form.	Inserted to align with safety language in current protocol template.
10.3.4 Timelines for Reporting	Revised language about mechanisms of reporting SAEs and pregnancy.	Revised to align with safety language in current protocol template.
10.6 Warnings and Precautions	Revised language indicating how relevant safety information will be communicated.	Revised to align with safety language in current protocol template.
11.3.1 Full Analysis Set	Modified FAS definition text to clarify "at least" 1 dose of trial treatment is required.	Clarification to accurately represent the FAS.
11.4.2 Treatment Exposure and Medications	Title of section revised from "Treatments" to "Treatment Exposure and Medications."	Clarification to better represent the content.
11.4.3.1 Adverse Events	Revised the definition of the on-treatment period.	Clarification to precisely describe the AE summary approach.

Section No. and Name	Description of Change	Brief Rationale
Throughout the protocol	Administrative changes and minor updates were made.	Administrative changes and for clarification of text.

TRIAL SYNOPSIS

Title	Open-label, Dose-escalation Trial to Evaluate the Safety and Pharmacokinetics of GEN1046 in Japanese Subjects With Advanced Solid Malignancies
Short Title	GEN1046 Safety and PK in Subjects With Advanced Solid Malignancies
Clinical Phase	Phase 1
Purpose and Rationale	The GCT1046-02 trial is designed to evaluate the safety and pharmacokinetics (PK) of GEN1046 as monotherapy or in combination with pembrolizumab in Japanese subjects with all non-central nervous system (CNS) solid tumors in order to permit extrapolation of the results to the ongoing global trials. As of the data cut-off date of the current edition of the Investigator's Brochure (IB) (01 Apr 2024), a total of 558 subjects have been dosed with GEN1046 in the 3 ongoing trials: 429 subjects in trial GCT1046-01 (61 in the dose escalation part and 368 in the dose expansion part), 18 subjects in trial GCT1046-02, and 111 subjects in trial GCT1046-04. Refer to the current version of the IB for preliminary data. Subjects in the dose escalation part of the GCT1046-01 trial received GEN1046 doses ranging from 25 mg to 1200 mg 1 dose every 3 weeks (1Q3W), and the maximum tolerated dose (MTD) was not reached. As of the data cut-off date, doses ranging from 25 mg to 1200 mg administered 1Q3W were safe and generally well tolerated. Based on the results of the ongoing FIH trial and the recommendation from the Pharmaceuticals and Medical Devices Agency, the starting dose for the GCT1046-02 trial was determined to be 15 mg 1Q3W. The GEN1046 + pembrolizumab combination is currently being investigated in the GCT1046-04 trial. The trial included an initial safety run-in with the objective to assess the safety and tolerability of the combination in 11 subjects before opening the randomized phase of the trial. Based on the totality of data from the safety run-in of GCT1046-04, both the trial steering committee and the Safety Committee assessed the safety profile of the GEN1046 + pembrolizumab dosing regimen to be acceptable and endorsed opening of the randomized part of the trial in January 2023. GCT1046-02: The initial dose level (ie, 15 mg) in the dose escalation part will be evaluated using an accelerated titration design. The accelerated titration design minimizes the number of Japanese subjects exposed to subtherapeutic doses of GEN1046. Based on the available PK and pharmacodynamic data from the GCT1046-01 trial, optimal clinical activity with GEN1046 appears to occur in the range of 80 to 140 mg 1Q3W for initial response, while higher doses may be beneficial for sustaining anti-tumor response through inhibition of the programmed death-ligand 1 (PD-L1)/ programmed cell death protein 1 interaction with higher PD-L1 receptor occupancy. Thus, the 4 subsequent dose levels of 50 mg, 140 mg, 400 mg, and 800 mg will be evaluated using a 3+3 design which is deemed appropriate and is a well-established trial design for evaluating novel therapeutic agents. The GEN1046 + pembrolizumab combination cohort (GEN1046 100 mg 1Q3W + pembrolizumab 200 mg 1Q3W) can be initiated once the GEN1046 140 mg monotherapy dose level has been declared safe (ie, no dose-limiting toxicities [DLTs] at the end of the DLT evaluation period). Given that GEN1046 and pembrolizumab are immunomodulatory agents, no significant ethnic difference in absorption, distribution, metabolism, or excretion is expected between Japanese and non-Japanese subjects. The results of the GCT1046-02 trial in Japanese subjects will be compared to the results of the GCT1046-01 trial in non-Japanese subjects to confirm consistency of PK, safety, tolerability, and identify potential ethnic differences in the dose-response relationship/PK-pharmacodynamic activity.

Objectives and Endpoints	**OBJECTIVES**	**ENDPOINTS**
	Primary Objectives	**Primary Endpoints**
	• Evaluate the safety and tolerability of GEN1046 administered as monotherapy or in combination with pembrolizumab • Determine dose-limiting toxicity (DLT) profile of GEN1046 administered as monotherapy or in combination with pembrolizumab • Assess PK of GEN1046 administered as monotherapy or in combination with pembrolizumab	• Adverse events (AEs) and safety laboratory parameters • DLT • PK parameters: area under the concentration-time curve (AUC), maximum concentration (C_{max}), time of C_{max} (T_{max}), predose trough concentrations (C_{trough}), and half-life ($T_{1/2}$), as applicable
	Secondary Objectives	**Secondary Endpoints**
	• Evaluate immunogenicity of GEN1046 administered as monotherapy or in combination with pembrolizumab	• Anti-drug antibody (ADA) response
	Exploratory Objectives	**Exploratory Endpoints**
	• Assess pharmacodynamic activity of GEN1046 administered as monotherapy or in combination with pembrolizumab	• Immune modulation biomarkers (cytokines associated with immune effector function such as interferon gamma [IFNγ])
	• Evaluate anti-tumor activity of GEN1046 administered as monotherapy or in combination with pembrolizumab	• Based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 per investigator assessment: o Confirmed objective response rate (ORR) o Disease control rate (DCR) o Duration of response (DOR)
Trial Design	This is an open-label, single-country, multicenter, phase 1 dose escalation trial to assess the safety, tolerability, and PK of GEN1046 as monotherapy or in combination with pembrolizumab. The trial will be conducted in Japanese subjects with advanced or metastatic solid tumors. In the dose escalation part, 5 dose levels of GEN1046 are planned: 15 mg, 50 mg, 140 mg, 400 mg, and 800 mg. Dose level cohorts will be enrolled sequentially. In the GEN1046 + pembrolizumab combination cohort, 100 mg GEN1046 + 200 mg pembrolizumab will be administered. GEN1046 and pembrolizumab will be administered as intravenous (IV) infusions every 21 days (ie, 1Q3W). Subjects will be monitored for DLTs during the first treatment cycle (21 days). The dose escalation will begin with an accelerated phase consisting of a single subject dosed at 15 mg (Dose Level 1), consistent with well-established accelerated titration designs. If a DLT occurs, the single-subject cohort may be expanded with up to 2 additional DLT-evaluable subjects. Dose Levels 2, 3, 4, and 5 will be evaluated using a 3+3 dose escalation design. The enrollment into the combination cohort will be guided by a decision table derived from a bayesian optimal interval (BOIN) design with a target toxicity rate of 0.3. Initially, at least 3 DLT-evaluable subjects and no more than 4 DLT-evaluable subjects will be assessed. Depending on the assessment of these subjects, up to an additional 6 subjects may be enrolled.	

	In the dose escalation part, continuous hospitalization is required for the DLT evaluation period (ie, subjects must be hospitalized from prior to GEN1046 dosing on Day 1 of Cycle 1 until Day 21 of Cycle 1). Subjects may be hospitalized longer at the discretion of the treating physician. At the time of hospital discharge, the subject must have phone accessibility and reside near a health care facility, and thus be able to contact their health care provider or seek medical attention immediately, if needed. In the combination cohort, hospitalization is required in Cycle 1 from Day 1 to Day 3 and the subject can be discharged on Day 4 if there is no safety concern and if the subject has phone accessibility and resides near a health care facility, and thus will be able to contact their health care provider or seek medical attention immediately, if needed. Once all subjects at a dose level in the dose escalation part have completed the DLT evaluation period, the Dose Escalation Committee (DEC) will review all available relevant safety, clinical, PK, and biomarker data and make a recommendation for the next dose level. Dose escalation will be determined taking into account all safety information, including non-DLT AEs. This recommendation is then reviewed by the Safety Committee before making a final decision. Similarly, the DEC and Safety Committee will review all available clinical data for the combination cohort and evaluate the safety of combining GEN1046 and pembrolizumab. Efficacy will be assessed by on-treatment imaging every 9 weeks (±7 days) until disease progression is assessed by the investigator, the start of new anti-cancer therapy, withdrawal of consent, or death, whichever occurs first.
Population and Sample Size	• Approximately 16 to 39 subjects are planned to be treated. • Approximately 2 to 3 sites are planned in Japan.
Inclusion Criteria	Each subject must fulfill all the following criteria to be treated in the trial. • Subject must sign an informed consent form indicating that he or she understands the purpose of and procedures required for the trial and is willing to participate in the trial, prior to any trial related assessments or procedures. • Subject must have a histologically confirmed non-CNS solid tumor that is metastatic or unresectable and for whom there is no available standard therapy likely to confer clinical benefit; or a subject who is not a candidate for such available therapy and for whom, in the opinion of the investigator, experimental therapy with GEN1046 or GEN1046 in combination with pembrolizumab may be beneficial. • Subject must be ≥20 years of age. • Asian race and Japanese ethnicity. • Subject must have measurable disease according to RECIST 1.1 • Subject must have Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤1. • Subject must have organ and bone marrow function as follows: a. Bone marrow/hematological function: i. Absolute neutrophil count (ANC) ≥1.5×10^9/L ii. Hemoglobin ≥9.0 g/dL iii. Platelet count ≥100×10^9/L b. Liver function: i. Total bilirubin ≤ upper limit of normal (ULN) ii. Alanine aminotransferase (ALT) ≤1.5×ULN iii. Aspartate aminotransferase (AST) ≤1.5×ULN iv. Albumin ≥30 g/L

	c. Coagulation status: i. Prothrombin time (PT)/International normalized ratio ≤1.5 ii. Activated partial thromboplastin time (aPTT) ≤1.5×ULN Note: Subjects receiving anticoagulant therapies should have the PT and aPTT within the therapeutic range of intended use of anticoagulants. d. Renal function: Glomerular filtration rate (GFR) ≥45 mL/min/1.73 m², according to the abbreviated Modification of Diet in Renal Disease equation: GFR = 186 × (SCr – 1.154) × (age – 0.203), where SCr, the serum creatinine level, is expressed in mg/dL; multiply the result by 0.742 if the subject is female. • A woman of childbearing potential (WOCBP) (postmenopausal or permanently sterilized is considered as not having reproductive potential) must agree to use adequate contraception during the trial and for 6 months after the last trial treatment administration. Adequate contraception is defined as highly effective methods of contraception. • A WOCBP must have a negative serum pregnancy test (beta-human chorionic gonadotropin) or urine pregnancy test at screening. • A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the trial and for 6 months after the last dose of trial treatment. • A man who is sexually active with a WOCBP and has not had a vasectomy must agree to use a barrier method of birth control, ie, condom with a partner using an adequate contraception, and must also not donate sperm during the trial and for 6 months after receiving the last dose of trial treatment. • Subject must provide a tumor tissue sample (formalin-fixed paraffin-embedded blocks/slides) from archival tissue or fresh biopsy collected before Cycle 1 Day 1, preferably derived from advanced disease stage.
Exclusion Criteria	Any potential subject who meets any of the following criteria will be excluded from being treated in the trial: • Subject has uncontrolled intercurrent illness, including but not limited to: a. Ongoing or active infection requiring IV treatment with anti-infective therapy that has been administered less than 2 weeks prior to first dose or any ongoing systemic inflammatory condition requiring further diagnostic work-up or management during screening. b. Symptomatic congestive heart failure (Grade III or IV as classified by the New York Heart Association, unstable angina pectoris or cardiac arrhythmia. c. Uncontrolled hypertension defined as systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg, despite optimal medical management. d. Ongoing or recent (within 1 year) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments, which may suggest risk for immune-related adverse events (irAEs). ***Note: The following conditions are not exclusionary:*** Residual hypothyroidism that required only hormone replacement or psoriasis that does not require systemic treatment. e. History of grade 3 or higher irAEs that led to treatment discontinuation of a checkpoint inhibitor (CPI) should be excluded. A subject with irAEs below grade 3 that led to discontinuation should be discussed with the sponsor. f. Prior history of myositis, Guillain-Barré syndrome, or myasthenia gravis of any grade.

	g. History of chronic liver disease or evidence of hepatic cirrhosis. h. Evidence of interstitial lung disease. i. History of non-infectious pneumonitis that has required steroids; or currently has pneumonitis. j. History of organ allograft (except for corneal transplant) or autologous or allogeneic bone marrow transplant, or stem cell rescue within 3 months prior to the first dose of trial treatment. k. Serious, non-healing wound, skin ulcer (of any grade), or bone fracture. • Any history of intracerebral arteriovenous malformation, cerebral aneurysm, new (younger than 6 months) or progressive brain metastases or stroke. a. Transient ischemic attack >1 month prior to screening is allowed. b. A subject with brain metastases must not be undergoing acute corticosteroid therapy or steroid taper. Chronic steroid therapy is acceptable provided that the dose is stable for the last 14 days prior to screening (≤10 mg prednisone daily or equivalent). c. A subject with CNS symptoms should undergo a computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain to exclude new or progressive brain metastases. Spinal cord metastasis is acceptable. However, subjects with spinal cord compression should be excluded. • Prior therapy: a. Radiotherapy: Radiotherapy within 14 days prior to the first dose of trial treatment. Palliative radiotherapy will be allowed. b. Treatment with an anti-cancer agent (within 28 days or after at least 5 half-lives of the drug, whichever is shorter), prior to trial treatment administration. Accepted exceptions are bisphosphonates (eg, pamidronate, zoledronic acid) and denosumab. c. Has received any investigational agent (including investigational vaccines) or used an invasive investigational medical device within 28 days before the planned first dose of trial treatment or is currently enrolled in an interventional trial. (***Note:*** A subject who is in the follow-up phase of an interventional trial may participate if the subject has not received the investigational agent within 28 days of the first dose of trial treatment.) d. Prior treatment with live, attenuated vaccines within 3 weeks prior to initiation of trial treatment. e. Chronic systemic immunosuppressive corticosteroid doses, ie, prednisone >10 mg daily (or equivalent) or a cumulative dose >150 mg prednisone (or equivalent) within 14 days before the first trial treatment administration. Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is permitted. f. Has received granulocyte colony stimulating factor or granulocyte/macrophage colony stimulating factor support 4 weeks prior to the first trial treatment administration or is chronically transfusion dependent. g. History of ≥ grade 3 allergic reactions to monoclonal antibody therapy as well as known or suspected allergy or intolerance to any agent given during the course of this trial. h. Discontinued treatment due to disease progression within the first 6 weeks of a CPI-containing treatment. i. Prior treatment with a 4-1BB (CD137) targeted agent.

	j. Prior treatment with a T-cell agonist or an anti-cytotoxic T-lymphocyte-associated protein-4 targeted agent within 12 weeks prior to the initiation of treatment. • Toxicities from previous anti-cancer therapies that have not resolved to baseline levels or to grade 1 or less with the exception of alopecia, anorexia, vitiligo, fatigue, hyperthyroidism, hypothyroidism, and peripheral neuropathy. Anorexia, hyperthyroidism, hypothyroidism, and peripheral neuropathy must have recovered to ≤ grade 2. • Known past or current malignancy other than inclusion diagnosis, except for: a. Cervical carcinoma of Stage 1B or less. b. Non-invasive basal cell or squamous cell skin carcinoma. c. Non-invasive, superficial bladder cancer. d. Prostate cancer with currently undetectable prostate-specific antigen. e. Any curable cancer with a complete response of >2 years duration. • Known allergies, hypersensitivity, or intolerance to the trial treatment or its excipients. • Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments. • Has had major surgery (eg, requiring general anesthesia) within 4 weeks before screening, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the trial. **Note:** A subject with a planned surgical procedure to be conducted under local anesthesia may participate. • Known history of seropositivity for human immunodeficiency virus (HIV). • Subject is known to be hepatitis B positive (defined by a positive test for hepatitis B surface antigen [HBsAg] or antibodies to hepatitis B surface or core antigens [anti-HBs and anti-HBc, respectively]). Subjects immune due to vaccination or passive immunization due to immunoglobulin therapy can be included. • Known medical history or ongoing hepatitis C infection that has not been cured. • Substance abuse, medical, psychological, or social conditions that may interfere with the subject's participation in the trial or evaluation of the trial result. • Subject has been dosed before in this trial. • Female subject is pregnant, or breast feeding and cannot discontinue breast feeding for the duration of the trial or at least 6 months after the last trial treatment administration, or intends to conceive children within 6 months of ending trial treatment. • Subject in the combination cohort who has ongoing grade ≥2 sensory or motor neuropathy. • Subject in the combination cohort who has contraindications to the use of pembrolizumab per local prescribing information.
Trial Drug	In the dose escalation part, GEN1046 will be administered as an IV infusion over at least 60 minutes on Day 1 of each 3-week (21-day) treatment cycle. Dose levels planned are: 15 mg, 50 mg, 140 mg, 400 mg, and 800 mg.

	In the combination cohort, pembrolizumab will be administered first, followed by GEN1046 on Day 1 of each 3-week (21-day) treatment cycle. GEN1046 and pembrolizumab should be infused over at least 30 minutes and the GEN1046 infusion should begin at least 30 minutes after the end of the pembrolizumab infusion. Doses of GEN1046 and pembrolizumab will be 100 mg and 200 mg, respectively.
Statistics	The objectives and endpoints of the trial are stated above. There are no predefined hypotheses for this trial. The sample size is driven by the 3+3 design and prespecified dose levels (dose escalation part), and a decision table derived from a BOIN design with a target toxicity rate of 0.3 (combination cohort). Adverse events will be described using summary statistics. Summary tables will include only treatment-emergent adverse events. All AEs, deaths, and serious adverse events (including those from the pre- and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period will be flagged. Individual curves of plasma concentration of GEN1046, including information on actual dose, will be presented for all subjects. PK parameters may be calculated based on non-compartmental methods, depending on data availability. The PK parameters will be calculated separately for Cycle 1 and Cycle 3. ADA titers against GEN1046 will be listed and positive/negative host immune response to GEN1046 and optionally presence of neutralizing antibodies will be summarized (positive/negative). Biomarkers, such as PD-L1 and 4-1BB expression, peripheral immune cell populations, and cytokine measurements will be listed for all subjects who had samples collected and testing performed. Biomarker assessments will be summarized by time point using descriptive statistics. Results of biomarker analyses may be presented in a separate report. The best change in target lesions (maximal reduction in the sum of the diameters in the target lesions) at any time on trial will be reported using waterfall plots. Individual subject data listings and summaries of ORR, best overall tumor response, and DCR will be presented by cohort/indication and total. No formal interim analysis is planned for this trial.
GCP Compliance	This trial will be conducted in compliance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP), ICH GCP E6(R2), Japanese Ministerial Ordinance on Good Clinical Practice for Drugs, Principles of the Declaration of Helsinki, and applicable regulatory requirements.

1 VISIT ASSESSMENT SCHEDULE

Table 1-1 through Table 1-4 list all the assessments and indicate with an "X" the evaluations performed by visit.

- Table 1-1: Schedule of Activities
- Table 1-2: PK and ECG Sampling
- Table 1-3: Immunogenicity (ADA) Sampling
- Table 1-4: Biomarker Sampling

In addition to the fixed visits, it may be necessary to perform some of the assessments at unscheduled time points if deemed clinically necessary by the investigator. All data obtained from these assessments must be supported in the subject's source documentation.

Table 1-1 Schedule of Activities

Treatment Cycle (C)	Protocol Section	Screening	Cycle 1-2					Cycle 3 to Cycle 4			Cycle 5 onward	Treatment Discontinuation[1]	SFU1	SFU2	SFU3[17]	UNS
Day (d)/Week(w)		**≤21d prior to C1D1**	**1d**	**2d[19]**	**3d**	**8d**	**15d**	**1d**	**8d**	**15d**	**1d**	**-**	**30d after last dose**	**60d after last dose**	**90d after last dose**	**-**
Visit window				**-**	**+2d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±3d**	**-**	**+5d**	**±7d**	**±7d**	**-**
Informed consent	13.2.3	X														
Eligibility criteria	5.1, 5.2	X														
Demographics	9.1	X														
Medical history[2]	9.1	X[2]														
Height	9.3.2	X														
Body weight	9.3.2	X	X					X			X	X				
Physical examination	9.3.1	X	X			X[3]	X[3]	X	X[3]	X[3]	X[3]	X[3]	X			(X)[3]
Vital signs[4]	9.3.3	X	X	X		X	X	X	X	X	X	X	X			(X)
ECG in dose escalation part	9.3.4	X	Refer to Table 1-2 for details on ECG assessments in the dose escalation part													
ECG in combination cohort	9.3.4	X	X[15]					X[15]			X[15, 16]	X	X	X	X	(X)
CT/MRI scan	9.2, 9.2.1	X[5]	Every 9 weeks (±7 days) from C1D1 until disease progression[6]													
Chest X-ray	9.3.6	X	As clinically indicated[13]													
SpO_2	9.3.6	X	X					X			X					
ECOG PS	9.3.5	X	X[7]					X			X	X	X			(X)
Adverse events[2,8,18]	10	X[2,8]	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
Concomitant medication	9.1.4	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
GEN1046 administration	6		X					X			X					(X)
Pembrolizumab administration[14]	6		X					X			X					(X)
End of treatment	8											X				
Evidence of new anti-cancer treatment	6.4.2, 8.3											X	X	X	X	
Hematology	9.4	X[9]		X[10,11]		X[10]	X[10]	X[11]	X[10]	X[10]	X[11]	X[10]	X[10]	X[10]	X[10]	(X)
Biochemistry[20]	9.4	X[9]		X[10,11]		X[10]	X[10]	X[11]	X[10]	X[10]	X[11]	X[10]	X[10]	X[10]	X[10]	(X)
Coagulation factors	9.4	X[9]						X[11]			X[11]	X	X	X	X	
Endocrine	9.4	X[9,11,12]	X[11,12]					X[11,12]			X[11,12]					
Urinalysis	9.4	X[9]						X[11]			X[11]	X	X	X	X	(X)
Pregnancy test (serum or urine)	9.4	X[9]						X[11]			X[11]	X	X	X	X	(X)
Hepatitis B	9.4	X[9]										X				(X)
Hepatitis C	9.4	X[9]										X				
PK/ADA sampling	9.5, 9.6	Refer to Table 1-2 and Table 1-3 for details of PK/ECG sampling and ADA (immunogenicity) sampling														

Treatment Cycle (C)	Protocol Section	Screening	Cycle 1-2					Cycle 3 to Cycle 4			Cycle 5 onward	Treatment Discontinuation[1]	SFU1	SFU2	SFU3[17]	UNS
Day (d)/Week(w)		**≤21d prior to C1D1**	**1d**	**2d[19]**	**3d**	**8d**	**15d**	**1d**	**8d**	**15d**	**1d**	**-**	**30d after last dose**	**60d after last dose**	**90d after last dose**	**-**
Visit window				**-**	**+2d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±3d**	**-**	**+5d**	**±7d**	**±7d**	**-**
Tumor biopsy, biomarkers	9.7	Refer to Table 1-4 for detailed biomarker assessment schedule														

1Q3W=1 dose every 3 weeks; ADA=anti-drug antibody; AE=adverse event; C1D1=Cycle 1 Day 1; CT=computed tomography; D/d=day; DLT=dose-limiting toxicity; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; ICF=informed consent form; ILD=interstitial lung disease; irAE=immune-related adverse event; iRECIST=immune Response Evaluation Criteria In Solid Tumors; KL-6=Krebs von den Lungen-6; MRI=magnetic resonance imaging; PD=progressive disease; PI=principal investigator; PK=pharmacokinetic(s); PS=performance status; SpO_2=oxygen saturation; SAE=serious adverse event; SFU1=safety follow-up visit 1; SFU2=safety follow-up visit 2; SFU3=safety follow-up visit 3; TSH=thyroid-stimulating hormone; T3=total triiodothyronine; T4=free thyroxine; UNS=unscheduled visit; (X)=optional assessment at UNS visit.

1. If the subject shows PD or confirmed PD (as per iRECIST), starts new anti-cancer treatment, or discontinues trial treatment due to another reason, the Treatment Discontinuation visit should be performed as soon as possible after permanent discontinuation of trial treatment. Subjects in the combination cohort will receive pembrolizumab treatment in combination with GEN1046. Both GEN1046 and pembrolizumab should be discontinued. Subjects may only continue on GEN1046 or pembrolizumab monotherapy if approved by the sponsor's medical monitor. Subjects move into the safety follow-up period once both drugs have been discontinued.
2. Any medical condition (signs, symptoms, and diagnosis) occurring prior to first dose of trial treatment should be documented as medical history. Medical conditions that occur after the ICF is signed and prior to first dose of trial treatment should only be reported as AEs if they were assessed by the investigator to be caused by a protocol-mandated procedure (ie, tumor biopsy and/or CT scan), including washout or discontinuation of prior medications.
3. A physical examination should only be performed as indicated by the subject's symptoms, AEs, or other findings as determined by the investigator.
4. Temperature, blood pressure, and heart rate on trial treatment administration days. On days when trial treatment is not administered, vital signs only need to be obtained once any time during the visit.
5. All subjects will have a CT scan with contrast or MRI of thorax, abdomen, and pelvis during screening. If a CT scan or MRI has been performed within 21 days prior to visit C1D1 as part of standard procedure, it is acceptable as a screening scan for the trial. If there is suspicion of brain metastases, a CT scan or MRI of the head and neck will be performed within 21 days prior to the C1D1 visit. Scans that exceed the 21-day window may be used for trial enrollment with sponsor approval.
6. On-trial imaging will be performed every 9 weeks from the date of first dose (or more frequently if clinically indicated) until disease progression is assessed by the investigator, the start of new anti-cancer therapy, withdrawal of consent, or death, whichever occurs first. Imaging assessments should follow calendar days and should not be adjusted for delays in cycle starts. If imaging shows disease progression, then a subsequent imaging assessment may be performed within 4 to 7 weeks to confirm progression.
7. The C1D1 ECOG PS should not be performed if the screening ECOG PS was obtained within the previous 5 days.
8. Nonserious AEs and SAEs must be reported from the first dose of trial treatment until 60 days after the last dose of trial treatment. For subjects in the combination cohort, only SAEs, regardless of causality, will be reported from SFU2 through SFU3. After SFU3, only SAEs judged by the investigator to be related to trial treatment should be reported.
9. All laboratory tests at the screening visit must be obtained within 7 days of C1D1 (with the exception of hepatitis B and hepatitis C samples, which may be obtained at any point during the 21-day screening window).
10. Laboratory samples should be obtained for hematology and biochemistry on Day 2 (Cycle 1 only), Day 8, Day 15, Treatment Discontinuation, and at the safety follow-up visits.
11. Starting with Cycle 2, laboratory samples should be obtained on Day 1 of each cycle or up to 3 days before the dosing day.
12. TSH, T3, and T4 will only be measured at screening, C2D1, and on Day 1 of every even cycle thereafter.
13. Any additional testing such as KL-6, CT, and others to be performed, if clinically indicated and by PI decision based on ILD clinical guidelines (JSH-Guidelines, 2014) or similar.
14. The GEN1046 + pembrolizumab combination cohort (GEN1046 100 mg 1Q3W + pembrolizumab 200 mg 1Q3W) can be initiated once the GEN1046 140 mg monotherapy dose level has been declared safe (ie, no DLTs at the end of the DLT evaluation period).
15. On infusion days, ECG will be performed before infusion and at the end of infusion +2 hours (±15 minutes).
16. ECG must be obtained at Cycle 5, Cycle 7, and every 4 cycles thereafter.
17. SFU3 is only required for subjects in the combination cohort.
18. CCI [redacted]

19. Day 2 visit is only applicable for Cycle 1.
20. CCI [redacted]

Table 1-2 PK and ECG Sampling

Treatment Cycle (C)	Screening	Cycle 1					Cycle 2	Cycle 3					Cycle 5 to Cycle X[6]	Treatment Discontin-uation[6]	SFU1[6]	SFU2[6]	SFU3[5,6]	UNS[6]
Day (d)	**≤ 21d prior to C1D1**	**1d**	**2d**	**3d**	**8d**	**15d**	**1d**	**1d**	**2d**	**3d**	**8d**	**15d**	**1d**	-	**30d after last dose**	**60d after last dose**	**90d after last dose**	-
Visit Window				**+2d**	**±1d**	**±1d**	**+3d**	**±3d**		**+2d**	**±1d**	**±1d**	**±3d**		**+5d**	**±7d**	**±7d**	**-**
PK Sampling																		
Before infusion (on infusion days)		X	X[1]	X	X	X	X	X	X[1]	X	X	X	X[2,6]	X[6]	X[6]	X[6]	X[6]	X[3,6]
End of infusion (+15 minutes)		X					X	X					X[2,6]					
End of infusion +2 hours (±15 minutes)		X						X										
End of infusion +4 hours (±30 minutes)		X						X										
ECGs (in triplicate)[4]																		
Before infusion (on infusion days)	X	X						X						X	X	X		X[3]
End of infusion (+15 minutes)		X						X										

C1D1=Cycle 1 Day 1; D/d=day; ECG=electrocardiogram; PK=pharmacokinetic(s); SFU1=safety follow-up visit 1; SFU2=safety follow-up visit 2; SFU3=safety follow-up visit 3; UNS=unscheduled visit.

1. Time window for the Day 2 sample is 24±2 hours after the end of infusion on Day 1.
2. Cycle 5, Cycle 7, and every 4 cycles thereafter (Cycles 7, 11, 15, etc).
3. Optional at UNS visit.
4. Applies to GEN1046 monotherapy only: at each time point indicated, ECGs should be performed in triplicate.
5. SFU3 is only required for subjects in the combination cohort.
6. With implementation of Amendment 6, sample collection for PK assessments is not required for Cycle 5 and beyond, or at treatment discontinuation, SFU, or UNS visits.

Table 1-3 Immunogenicity (ADA) Sampling

Treatment Cycle	Cycle 1	Cycle 2	Cycle 3 to Cycle X[1,3]	Treatment Discontinuation[3]	SFU1[3]	SFU2[3]	SFU3[2,3]	UNS[3]
Day (d)/Week	**1d**	**1d**	**1d**	-	**30d after last dose**	**60d after last dose**	**90d after last dose**	-
Visit Window		**+3d**	**±3d**		**+5d**	**±7d**	**±7d**	-
Before Infusion (on infusion days)	X	X	X[1,3]	X[3]	X[3]	X[3]	X[3]	(X)[3]

ADA=anti-drug antibody; D/d=day; SFU1=safety follow-up visit 1; SFU2=safety follow-up visit 2; SFU3=safety follow-up visit 3; UNS=unscheduled visit; (X)=optional assessment at UNS visit.

1. Cycle 3, Cycle 5, Cycle 7, and every 4 cycles thereafter (Cycles 7, 11, 15, etc).
2. SFU3 is only required for subjects in the combination cohort.
3. With implementation of Amendment 6, sample collection for ADA assessments is not required for Cycle 3 and beyond, or at treatment discontinuation, SFU, or UNS visits.

Table 1-4 Biomarker Sampling

Treatment Cycle (C)	Screening	Cycle 1				Cycle 2		Cycle 3		Cycle 4 onward[4]	Treatment Discontinuation	UNS
Day (d)	**≤ 21 days prior to Visit C1D1**	**1d**	**2d**	**3d**	**8d**	**1d**	**8d**	**1d**	**8d**	**1d**	-	-
Visit Window				**+2d**	**±1d**	**+3d**	**±1d**	**±3d**	**±1d**	**±3d**	-	-
Tumor Biopsy[1]	X[1]											(X)[1,4]
Cytokines, chemokines (soluble factors)[2]		X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2,4]		(X)[2, 3]

C1D1=Cycle 1 Day 1; CRS=cytokine release syndrome; D/d=day; irAE=immune-related adverse event; FFPE=formalin-fixed paraffin-embedded; UNS=unscheduled visit; (X)=optional assessment at UNS visit.

1. All subjects must provide an FFPE tumor tissue sample from a fresh tumor biopsy or the most recent archival tissue (aspirates are not acceptable) collected before C1D1, preferably derived from advanced stage disease and taken after failure/stop of last prior treatment. Details to the preparation of slides and number of slides to be prepared will be described in the lab manual. Optional tumor biopsies may be collected if subjects have unscheduled biopsies or tumor tissue resection during the course of the trial.
2. Cytokine samples on C1D1 will be taken at baseline (predose) and on Day 2, Day 3, Day 8 corresponding to the time of predose. The time window for the Day 2 sample is 24 ± 2 hours after the end of infusion on Day 1. In Cycle 2 and Cycle 3, cytokine samples will be taken at Day 1 (predose) and at Day 8. From Cycle 4 onward, cytokine samples will be taken at Day 1 (predose). CCI
3. CCI
4. With implementation of Amendment 6, tumor biopsies at UNS visits and sample collection for cytokines/chemokines for Cycle 4 onward are not required.

2 INTRODUCTION

2.1 Introduction to GEN1046

GEN1046 is a bispecific antibody that induces activation of T cells through conditional 4-1BB stimulation, which is dependent on simultaneous binding to programmed death-ligand 1 (PD-L1). In addition, the PD-L1-specific arm of GEN1046 functions as a classical immune checkpoint inhibitor (CPI) by blocking the programmed cell death protein 1 (PD-1)/PD-L1 axis, also in the absence of 4-1BB binding. GEN1046 is being jointly developed by Genmab and BioNTech for the treatment of solid malignant tumors. GEN1046 is generated using Genmab's proprietary DuoBody® technology (Labrijn et al., 2013; Labrijn et al., 2014). Structurally, GEN1046 is similar to a conventional immunoglobulin G (IgG)1 molecule, with the exception of 4 amino acids in the fragment crystallizable (Fc) region that have been altered to allow generation of a stable bispecific molecule and to silence Fc-mediated effector functions. The capacity to bind the neonatal Fc receptor is preserved, providing for the relatively long plasma half-life that is typical for IgG1 molecules.

Conventional 4-1BB-targeting antibodies are typically dependent on direct agonist activity, or agonist activity through Fc γ receptor (FcγR)-mediated antibody crosslinking (Chin et al., 2018). The Fc domain of GEN1046 was engineered to silence interactions with FcγR and the complement factor C1q, thereby preventing 4-1BB agonist activity through FcγR-mediated crosslinking of membrane-bound GEN1046 and cytotoxic activity through FcγR-mediated effector functions and complement-mediated cytotoxicity. Thereby, 4-1BB agonist activity by GEN1046 is conditional; it is dependent on simultaneous binding of GEN1046 to both 4-1BB and PD-L1. In conclusion, GEN1046-mediated signaling of 4-1BB on activated T cells is strictly dependent on simultaneous binding of the PD-L1-binding arm (GEN1046 Investigator's Brochure [IB]).

2.2 Trial Rationale

There is a strong unmet medical need to develop new efficacious therapies for patients with advanced malignancies whose disease no longer responds to standard therapy. Although PD-1/PD-L1 inhibitors have been approved for several types of cancer, durable clinical responses are observed only in a limited number of patients and overcoming resistance remains a major challenge. Therefore, the combined targeted approach of a bispecific antibody may be necessary to improve the clinical benefits observed with anti-PD-(L)1 therapies.

The objectives of the GCT1046-02 trial are to investigate the safety, pharmacokinetics (PK), and pharmacodynamic activity of GEN1046 as monotherapy or in combination with pembrolizumab in Japanese subjects.

2.3 Background

2.3.1 Target Disease

The patient population eligible for the GCT1046-02 trial are Japanese subjects with selected advanced and/or metastatic solid tumors who have failed available standard therapy or who are not candidates for standard therapy, and for whom experimental therapy with GEN1046 may be beneficial.

2.3.2 Current Treatment Options

Since the 1950s, patients with advanced and metastatic solid tumors have been treated with systemic chemotherapy, both as monotherapy and in combinations (DeVita and Chu, 2008). Chemotherapy can increase survival and at least maintain quality of life in many indications (Scheithauer et al., 1993). In general, at least 1 to 2 lines of standard chemotherapy regimens have shown efficacy in solid tumors; although, with very few exceptions, all patients' disease eventually progresses to death (Doi et al., 2019; Fizazi et al., 2015; Shibata et al., 2016; Steeg, 2016). Targeted small molecules and monoclonal antibodies (mAbs) were added to the therapeutic armamentarium in the late 1990s and early 2000s (Dervisis and Klahn, 2016), and the anti-PD-(L)1 antibodies have now demonstrated efficacy benefits in sensitive tumors, particularly those expressing PD-L1 or with high mutational burden (Betof Warner et al., 2020; Gong et al., 2018; Park et al., 2020). Nevertheless, some of the most common solid tumors are not impacted by the anti-PD-(L)1 mechanism alone, ie, most colorectal, HR^+ breast and prostate cancers, and primary or acquired resistance to immune checkpoint inhibition is an area of intense research interest (Nowicki et al., 2018). The immune CPIs have had the most impact of any systemic therapy for advanced disease to date, leading to durable complete responses (CRs) in a small percentage of patients with certain types of solid tumor (Betof Warner et al., 2020; Takano et al., 2019).

Most patients with advanced solid tumors now receive at least 2 lines of standard therapy, typically comprising a combination of chemotherapy, targeted therapy, and/or immunotherapy. However, once standard options have been exhausted, the recommendation is for patients to participate in a clinical trial, such as the present GCT1046-02 trial. This approach is endorsed by clinical guidelines of all major cancer societies (American Society of Clinical Oncology [ASCO], European Society for Medical Oncology [ESMO], Japanese Society of Medical Oncology [JSMO], and National Comprehensive Cancer Network [NCCN]).

2.3.3 Unmet Medical Need and Expected Benefit

There is a strong unmet medical need to develop new efficacious therapies for patients with advanced malignancies whose disease no longer responds to standard therapy.

Over recent years, clinical data have emerged on different mechanisms to activate the immune response against malignant cells. These observations have been rapidly advanced into effective immunotherapies. One successful strategy is to counteract immunosuppressive signals produced by cancer cells or cells in the tumor microenvironment (TME) with mAbs that target inhibitory receptors on immune effector cells (eg, PD-1) or their ligands (eg, PD-L1). Antibodies designed to block the inhibitory immune checkpoints, PD-1 or PD-L1, were first approved in melanoma and later in other types of cancers (Hodi et al., 2010; Ribas and Wolchok, 2018). However, durable clinical responses are observed only in a limited number of patients and overcoming resistance remains a major challenge. Therefore, the combined targeted approach of a bispecific antibody may be necessary to improve the clinical benefits observed with PD-1/PD-L1 monotherapy.

4-1BB is a costimulatory member of the tumor necrosis factor (TNF) receptor superfamily and is expressed on a variety of immune cells following activation, including T cells, dendritic cells (DC), and natural killer (NK) cells (Bartkowiak and Curran, 2015; Cheuk et al., 2004; Croft, 2009). Engagement of 4-1BB by its ligand leads to potentiation of effector immune responses (Bartkowiak and Curran, 2015). Crosslinking of 4-1BB by soluble 4-1BBL, 4-1BBL-expressing cells or agonist anti-4-1BB antibodies induces cytokine production, including interferon gamma (IFNγ) and TNF alpha (TNFα), prevents activation-induced cell death of T cells, and upregulates cytotoxic T-cell effector functions (Bartkowiak and Curran, 2015). In cancer patients, 4-1BB

expression on recently activated cluster of differentiation (CD)8^+ T cells has been used to identify tumor-antigen specific T cells in peripheral blood or tumor-reactive tumor-infiltrating lymphocytes (TIL) (Parkhurst et al., 2017; Wolfl et al., 2007; Ye et al., 2014), suggesting a role for 4-1BB in the anti-tumor immune response. Furthermore, combining 4-1BB agonists with PD-1 blockade has been shown to produce additive or synergistic antitumor activity in solid tumor models including both human TIL ex vivo and mouse in vivo models (Tolcher et al., 2017). Therefore, combined targeting of 4-1BB in addition to PD-L1 could provide a promising approach to boost anti-tumor immunity and to improve the clinical benefits observed with PD-1/PD-L1 monotherapy.

The mechanism of action (MOA) of GEN1046 is distinct from that of conventional PD-L1--blocking and 4-1BB -targeting IgG mAbs, as well as combination treatments thereof. Although the PD-L1-specific arm of GEN1046 functions as a classical CPI by blocking the PD-1/PD-L1 axis also in the absence of 4-1BB binding, the addition of a 4-1BB-stimulating arm further enhances T-cell activation. The unique MOA of GEN1046 supports the premise that GEN1046 is a promising therapeutic agent with potential anti-tumor activity in many different cancer types.

Rationale for GEN1046 and Pembrolizumab Combination

Pembrolizumab is a potent humanized immunoglobulin G4 monoclonal mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with both PD-L1 and PD-L2. Since 4-1BB is often co-expressed with PD-1 on CD8+ T cells, blockade of PD-1/PD-L1 as well as PD-1/PD-L2 signals and simultaneous costimulation through 4-1BB may synergize to enhance T-cell effector functions and improve the depth and duration of the response (Kim et al., 2020). Based on PK/pharmacodynamic modelling data, GEN1046 dose levels that favor peak trimer formation (crosslinking of GEN1046 to PD-L1 and 4-1BB) will result in greater 4-1BB activation, but only partial PD-L1 receptor occupancy (RO), whereas further increasing the dose of GEN1046 will favor higher PD-L1 RO at the expense of optimum 4-1BB activation. Combining GEN1046 at a dose that favors optimum 4-1BB conditional agonism with an agent that fully blocks the PD-1 interaction with both PD-L1 and PD-L2 may thus allow for more effective concurrent targeting of the 4-1BB and PD-1 pathways. In addition, PD-1 blockade will release free PD-L1 for binding to GEN1046, further promoting PD-L1–dependent 4-1BB conditional agonism. Therefore, the combination of conditional tumor and lymphatic tissue-targeted 4-1BB costimulation and complete PD-1 pathway blockade may synergize to enhance antitumor activity and improve clinical outcomes. This hypothesis is supported by nonclinical in vitro and in vivo animal studies showing that combination of GEN1046 or a mouse-reactive PD-L1x4-1BB bispecific antibody and a PD-1 inhibitor induced synergistic antitumor effects compared to each agent alone (Section 2.3.4).

2.3.4 Summary of Nonclinical Studies

A nonclinical pharmacology package demonstrating the potency and MOA of GEN1046 is available. GEN1046 binds to human PD-L1 and 4-1BB with affinity values in the high picomolar range. The MOA of GEN1046 is to induce activation of T cells through conditional 4-1BB stimulation which is dependent on simultaneous binding to PD-L1. In addition, the PD-L1-specific arm of GEN1046 functions as a classical immune CPI by blocking the PD-1/PD-L1 axis, also in the absence of 4-1BB binding. Thereby, GEN1046 enhances proliferation of activated $CD4^+$ and $CD8^+$ T cells and secretion of pro-inflammatory cytokines, primarily IFNγ.

The nonclinical safety program to support the first-in-human (FIH) trial with GEN1046 is also available and consists of in vitro studies using human cells and tissues (cytokine release assay,

hemolytic potential, plasma compatibility, and tissue cross-reactivity), and in vivo studies in cynomolgus monkeys (a non-Good Laboratory Practice [GLP] single-dose exploratory toxicity study; and in a 2 treatment-cycle GLP toxicity study with 1 dose every 3 weeks for 2 occasions [1Q3W×2], including safety pharmacology and local tolerance). The cynomolgus monkey was selected as the preferred toxicology species based on in vitro studies demonstrating that this is the only species where GEN1046 binds to both PD-L1 and 4-1BB.

In in vitro safety studies, GEN1046 was associated with cytokine release in a human whole blood model, although the median levels were generally low. These results suggest that GEN1046 represents a low risk for first-infusion reactions; however, there may be variability for individual donors. GEN1046 did not cause hemolysis and was also compatible with human whole blood and plasma at concentrations ≤500 µg/mL. In in vivo safety studies performed in cynomolgus monkeys, GEN1046 was well tolerated at dose levels up to CCI by intravenous (IV) infusion CCI. Overall, there were no adverse GEN1046-related changes in in-life parameters, macroscopic or microscopic changes, any sign of local intolerance and nothing was indicative of cytokine release syndrome (CRS). In limited safety pharmacology evaluations in the GLP toxicity study (electrocardiograms [ECGs]/heart rate, neurobehavioral), GEN1046 had no adverse effects. The no-observed-adverse-effect level (NOAEL)/highest non-severely toxic dose (HNSTD) for GEN1046 was considered CCI.

Nonclinical data supporting the combination of GEN1046 and pembrolizumab:

- The combination of GEN1046 with pembrolizumab enhanced CD8+ T-cell expansion and pro-inflammatory cytokine production in vitro compared to each agent alone (data on file).
- The combination of GEN1046 with pembrolizumab synergistically potentiated IFNγ release in an exhausted T-cell mixed lymphocyte reaction model in vitro (data on file).
- In the MC38 in vivo tumor model, a mouse-reactive PD-L1x4-1BB antibody combined with an antimouse PD-1 antibody induced more potent antitumor activity relative to each agent as monotherapy, significantly enhanced survival, and resulted in complete tumor regressions in the majority of mice tested compared to no complete tumor regressions seen with either single agent. This is suggestive of therapeutic synergy for the combination treatment. Importantly, the combination conferred protection against secondary tumor challenge, consistent with response durability and lasting immune memory in vivo (data on file).

For more comprehensive information related to the nonclinical studies for GEN1046, please refer to the IB.

2.3.5 Summary of Clinical Trials

The effect of GEN1046 in humans is currently being investigated in 3 ongoing trials:

- GCT1046-01, first-in-human trial across various solid tumors.
- The present trial, GCT1046-02, safety, tolerability, and PK in Japanese subjects.
- GCT1046-04, GEN1046 as monotherapy and in combination with pembrolizumab in second-line (or higher) non-small cell lung cancer.

As of the cut-off date of the current edition of the IB (01 Apr 2024), a total of CCI subjects have been dosed with GEN1046 in the 3 ongoing trials: CCI subjects in trial GCT1046-01 (CCI in the dose escalation part and CCI in the dose expansion part), 18 subjects in trial GCT1046-02, and CCI subjects in trial GCT1046-04. Refer to the current version of the GEN1046 IB for preliminary data.

Clinical Data Supporting the Combination of GEN1046 and Pembrolizumab:

The GEN1046 + pembrolizumab combination is currently being investigated in the GCT1046-04 trial. The trial included an initial safety run-in with the objective to assess the safety and tolerability of the combination in CCI subjects before opening the randomized phase of the trial. Based on the totality of data from the safety run-in of GCT1046-04, both the trial steering committee and the Safety Committee assessed the safety profile of the GEN1046 + pembrolizumab dosing regimen to be acceptable and endorsed opening of the randomized part of the trial in January 2023.

2.3.6 Benefit-Risk Assessment

Based on data from the ongoing clinical trials with GEN1046, treatment with GEN1046 monotherapy has overall been well tolerated. The most common related treatment-emergent adverse events (TEAEs) are immune-mediated hepatitis, malaise, anemia, and hypothyroidism (refer to the GEN1046 IB).

AEs associated with PD-L1-targeted therapy may be of immunologic etiology and are commonly referred to as irAEs. PD-L1-targeted therapy can usually continue in the presence of mild irAEs with close monitoring. However, moderate to severe irAEs have been reported and require close monitoring and proper management (Brahmer et al., 2018). A specific mitigation plan for handling of irAEs in this trial can be found in Table 7-1.

As referenced in the reference safety information section of the GEN1046 IB, immune-related adverse events (irAEs) like neutropenia, hepatic events, and decreased platelet count are anticipated reported events for the compound class considering its MOA and irAEs further corroborated with resolution upon treatment with immunosuppressants. Further details on potential risks, including the risk of hemophagocytic lymphohistiocytosis (HLH), and mitigation strategies of treatment with GEN1046 monotherapy or in combination can be found in Section 7.3.3 and in the most recent version of the GEN1046 IB. The sponsor's GEN1046 Safety Committee will continuously monitor subject safety throughout the trial as described in Section 10.7.

Pembrolizumab has a well-established safety profile both as first-line and second-line standard of care. Refer to the current Japanese package insert for pembrolizumab for additional details (KEYTRUDA JP Prescribing Information).

Both GEN1046 and pembrolizumab are immunomodulatory agents. Therefore, the most likely anticipated overlapping toxicities with GEN1046 and pembrolizumab include irAEs, fatigue, and IRR. Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) elevations will be closely monitored during the trial. However, the preliminary safety findings of the safety run-in of the GCT1046-04 trial suggest acceptable tolerability of GEN1046 in combination with pembrolizumab (data on file). Based on the nonclinical data available to date, published data from other human 4-1BB and PD-L1 mAbs, the established safety profile of pembrolizumab and the clinical data already generated in the GCT1046-01 and GCT1046-04 trials, exploration of GEN1046 as monotherapy and as combination therapy with pembrolizumab is regarded as justifiable and the benefit-risk ratio is considered acceptable in the proposed trial population.

3 OBJECTIVES AND ENDPOINTS

Objectives and related endpoints are described below (Table 3-1).

Table 3-1 Objectives and Endpoints

OBJECTIVES	ENDPOINTS
Primary Objectives	**Primary Endpoints**
• Evaluate the safety and tolerability of GEN1046 administered as monotherapy or in combination with pembrolizumab • Determine dose-limiting toxicity (DLT) profile of GEN1046 administered as monotherapy or in combination with pembrolizumab • Assess pharmacokinetics (PK) of GEN1046 administered as monotherapy or in combination with pembrolizumab	• Adverse events (AEs) and safety laboratory parameters • DLT • PK parameters: area under the concentration-time curve (AUC), maximum concentration (C_{max}), time of C_{max} (T_{max}), predose trough concentrations (C_{trough}), and half-life ($T_{1/2}$), as applicable
Secondary Objectives	**Secondary Endpoints**
• Evaluate immunogenicity of GEN1046 administered as monotherapy or in combination with pembrolizumab	• Anti-drug antibody (ADA) response
Exploratory Objectives	**Exploratory Endpoints**
• Assess pharmacodynamic activity of GEN1046 administered as monotherapy or in combination with pembrolizumab	• Immune modulation biomarkers (cytokines associated with immune effector function such as IFNγ)
• Evaluate anti-tumor activity of GEN1046 administered as monotherapy or in combination with pembrolizumab	• Based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 per investigator assessment: o Confirmed objective response rate (ORR) o Disease control rate (DCR) o Duration of response (DOR)

4 TRIAL DESIGN

4.1 Description of Trial Design

This is an open-label, single-country, multicenter, phase 1 dose escalation trial, to assess the safety, tolerability, and PK of GEN1046 as monotherapy or in combination with pembrolizumab. The trial will be conducted in Japanese subjects with advanced or metastatic solid tumors (as defined in the inclusion/exclusion criteria in Section 5.1 and Section 5.2, respectively).

GEN1046 monotherapy and GEN1046 + pembrolizumab combination therapy will be evaluated as outlined in Table 4-1.

In the GEN1046 monotherapy part, escalating GEN1046 dose levels will be administered sequentially.

The GEN1046 + pembrolizumab combination cohort (GEN1046 100 mg 1Q3W + pembrolizumab 200 mg 1Q3W) can be initiated once the GEN1046 140 mg monotherapy dose level has been declared safe (ie, no dose-limiting toxicities [DLTs] at the end of the DLT evaluation period) (Figure 4-1).

GEN1046 + pembrolizumab will be administered as IV infusions every 21 days (ie, 1Q3W) until 1 or more of the discontinuation criteria are met (Section 8.1). Assessments will be performed as detailed in the Schedule of Activities tables (Section 1).

Table 4-1 GEN1046 Monotherapy Dose Escalation Levels, and GEN1046 + Pembrolizumab Combination Therapy Levels

GEN1046 Monotherapy			
Dose Level	**GEN1046 Dose**	**Dose Regimen**	**Route of Administration**
1	15 mg	1Q3W	IV
2	50 mg	1Q3W	IV
3[1]	140 mg	1Q3W	IV
4	400 mg	1Q3W	IV
5	800 mg	1Q3W	IV
GEN1046 + Pembrolizumab Combination Therapy[2]			
	GEN1046/Pembrolizumab Dose	**Dose Regimen**	**Route of Administration**
	100 mg/200 mg	1Q3W	IV

1Q3W=1 dose every 3 weeks; DEC=Dose Escalation Committee; IV=intravenous; MTD=maximum tolerated dose.

1. If the MTD is reached, the DEC may propose a lower dose in between the previous dose level and the current MTD dose level (eg, if MTD is reached at 800 mg, a dose of 500 mg can be investigated; if MTD is reached at 140 mg, a dose of 100 mg can be investigated).
2. The GEN1046 + pembrolizumab combination cohort (GEN1046 100 mg 1Q3W + pembrolizumab 200 mg 1Q3W) can be initiated once the GEN1046 140 mg monotherapy dose level has been declared safe (ie, no DLTs at the end of the DLT evaluation period).

In the GEN1046 dose escalation part, 15 mg GEN1046 will be the starting dose level (refer to Section 4.3).

Subjects will be monitored for DLTs (see Section 7.1) during the first treatment cycle (21 days).

Once all subjects at a dose level in the dose escalation part have completed the DLT evaluation period, the Dose Escalation Committee (DEC) will review all available relevant safety, clinical, PK, and biomarker data, and will make a recommendation for the next dose level. Dose escalation will be determined taking into account all safety information, including non-DLT adverse events

(AEs). This recommendation is then reviewed by the Safety Committee before making a final decision (Section 10.7). Similarly, the DEC and Safety Committee will review all available clinical data for the combination cohort and evaluate the safety of combining GEN1046 and pembrolizumab (Section 10.7).

The dose escalation will begin with an accelerated phase consisting of a single-subject dosed at 15 mg (Dose Level 1), consistent with well-established accelerated titration designs (Le Tourneau et al., 2009; Simon et al., 1997). The single-subject cohort may be expanded with up to 2 additional DLT-evaluable subjects based on the criteria outlined below (See Section 11.3.2 for a definition of DLT-evaluable). Dose Levels 2, 3, 4, and 5 will be evaluated using a 3+3 dose escalation design. An overview of the trial design is provided in Figure 4-1 .

The following provides a description of the procedure for subject enrollment and guidelines for dose escalation decisions:

Dose Level 1

If the subject in Dose Level 1 meets any of the following criteria specified below, the dose level will be expanded to 3 subjects and will be evaluated with a standard 3+3 design before escalating to the 50 mg dose level:

- The subject experiences a DLT or based on the recommendation from the DEC and decision by the Safety Committee.
- The subject experiences an AE that fulfills at least 1 of the following criteria:
  - Any hematologic ≥ grade 3 drug-related toxicity with the exception of neutropenia or thrombocytopenia. For neutropenia or thrombocytopenia, the ≥ grade 3 drug-related toxicity must persist for more than 7 days.
  - Any non-hematologic ≥ grade 2 (laboratory and non-laboratory) drug-related toxicity including hepatotoxicity (transaminases and/or bilirubin).

Subsequent Dose Escalation Cohorts

Three subjects will be enrolled in each subsequent dose escalation cohort. Dose escalation will follow the rules of a 3+3 design:

- If no DLTs are observed in the first 3 subjects, the dose level will be determined safe, and 3 additional subjects will be enrolled in next higher dose level.
- If a DLT is observed in 1 of 3 DLT-evaluable subjects, an additional 3 subjects will be allocated to the same dose level.
- If ≥2 of 3, or ≥2 of 6 DLT-evaluable subjects experience a DLT, then the dose level is not safe and the previous dose level that is safe will be determined to be the maximum tolerated dose (MTD).
- If no DLT is observed in 3 DLT-subjects at the highest dose level to be explored, all dose levels are determined to be safe in Japanese subjects.

If the MTD is reached, the DEC may propose a lower dose in between the previous dose level and the current MTD dose level (eg, if MTD is reached at 800 mg, a dose of 500 mg can be investigated; if MTD is reached at 140 mg, a dose of 100 mg can be investigated).

GEN1046 + Pembrolizumab Combination Cohort

The DEC will evaluate the toxicities observed in the combination cohort during the first cycle (ie, the DLT period) and recommend to the Safety Committee whether to declare the safety of the combination regimen cleared or to expand the cohort by enrolling additional subjects based on the totality of the data in GCT1046-02 and emerging combination data from the global program.

The enrollment into the combination cohort will be guided by a decision table derived from a Bayesian optimal interval (BOIN) design with a target toxicity rate of 0.3. Initially, at least 3 and no more than 4 DLT-evaluable subjects will be assessed. Depending on the assessment of these subjects, up to an additional 6 subjects may be enrolled. Enrollment is dependent on the number of DLTs observed among DLT-evaluable subjects as outlined in Table 4-2. Subjects not evaluable for DLTs can be replaced at any time.

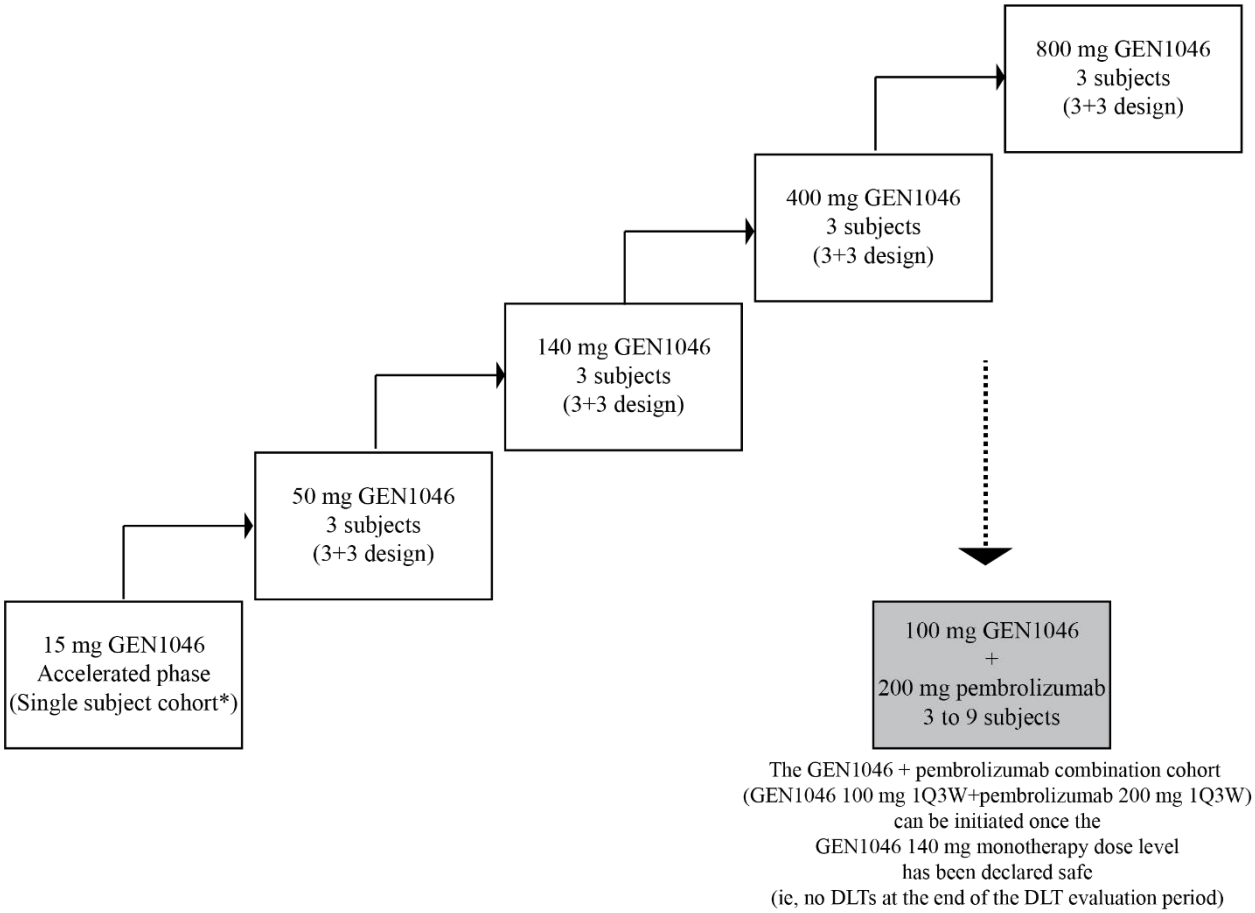
Table 4-2 Decision Guidelines Based on Number of Subjects With DLTs

Decision Based on Number of Subjects With DLTs (N_{DLT})	**Number of Subjects Evaluable for DLTs in the Combination Cohort**						
	3	**4**	**5**	**6**	**7**	**8**	**9**
Stop enrollment and declare combination safe, if $N_{DLT \leq}$	0	0	1	1	1	1	2
Continue enrollment, if $N_{DLT =}$	1	1	NA	2	2	2	3
Continue enrollment after Safety Committee approval, if $N_{DLT \geq}$	2	2	2	3	3	3	4
Consider stopping enrollment in agreement with Safety Committee, if $N_{DLT \geq}$	3	3	4	4	5	5	5

DLT=dose-limiting toxicity; NA=not applicable

Efficacy will be assessed by on-treatment imaging every 9 weeks (±7 days) until disease progression is assessed by the investigator, the start of new anticancer therapy, withdrawal of consent, or death, whichever occurs first.

Figure 4-1 Overview of the Trial Design (GEN1046 as Monotherapy or in Combination With Pembrolizumab)



* It will be mandatory to increase the 15 mg cohort size to 3 evaluable subjects if the single subject experiences:
- A DLT; or
- Any hematologic ≥ grade 3 drug-related toxicities with the exception of neutropenia or thrombocytopenia. For neutropenia or thrombocytopenia, ≥ grade 3 drug-related toxicity must persist for more than 7 days; or
- Any non-hematologic ≥ grade 2 (laboratory and non-laboratory) drug-related toxicity including hepatotoxicity (transaminases and/or bilirubin).

Note: In the dose escalation part, all dose levels above 15 mg will follow a 3+3 design.

4.1.1 Hospitalization: Cycle 1

In the dose escalation part, continuous hospitalization is required for the DLT evaluation period (ie, subjects must be hospitalized from prior to GEN1046 dosing on Day 1 of Cycle 1 until Day 21 of Cycle 1). Subjects may be hospitalized longer at the discretion of the treating physician. At the time of hospital discharge, the subject must have phone accessibility and reside near a health care facility, and thus be able to contact their health care provider or seek medical attention immediately, if needed.

In the combination cohort, hospitalization is required in Cycle 1 from Day 1 to Day 3 and the subject can be discharged on Day 4 if there is no safety concern and if the subject has phone accessibility and resides near a health care facility, and thus will be able to contact their health care provider or seek medical attention immediately, if needed.

In addition, as a routine precaution, all subjects must be observed during Cycle 1 and Cycle 2 on Day 1 for at least 4 hours after ending the infusion of GEN1046. For all subsequent cycles, subjects

must be observed for at least 2 hours after ending the infusion of GEN1046 (See Section 7.3.5 for additional details.)

4.1.2 Planned Number of Subjects

- Approximately 16 to 39 subjects are planned to be treated.
- Approximately 2 to 3 sites are planned in Japan.

4.1.3 Replacement of Subjects

- Any subject who withdraws from trial treatment before the completion of the DLT observation period for any reason other than a DLT (ie, is not evaluable for DLTs; refer to Section 7.1).
- Any subject who was enrolled in the trial but did not receive trial treatment.
- Any subject who has not received the full dose of trial treatment (ie, 90% to 110% of the planned dose) in the first cycle.

4.2 Trial Design Rationale

The GCT1046-02 trial is designed to evaluate the safety and PK of GEN1046 as monotherapy or in combination with pembrolizumab in Japanese subjects with all non-central nervous system solid tumors in order to permit extrapolation of the results to the ongoing global trials.

The initial dose level of GEN1046 (ie, 15 mg) in the dose escalation part will be evaluated using an accelerated titration design. The accelerated titration design minimizes the number of Japanese subjects exposed to subtherapeutic doses of GEN1046. Based on the available PK and pharmacodynamic data from the GCT1046-01 trial, optimal clinical activity with GEN1046 appears to occur in the range of 80 to 140 mg 1Q3W for initial response, while higher doses may be beneficial for sustaining anti-tumor response through inhibition of the PD-L1/PD-1 interaction with higher PD-L1 RO. All subsequent dose levels in the dose escalation part will be evaluated using a 3+3 design which is deemed appropriate and is a well-established trial design for evaluating novel therapeutic agents.

In the GEN1046 + pembrolizumab combination cohort, a BOIN-inspired design is used. It defines stopping guidelines based on the probability to exceed a predefined toxicity rate and provides a rational operational flexibility for the ongoing enrollment of subjects and safety evaluation.

Given that GEN1046 and pembrolizumab are antibody products, no significant ethnic difference in absorption, distribution, metabolism, or excretion is expected between Japanese and non-Japanese subjects. Results of a phase 1 trial in Japanese subjects indicated that the PK profile of weight-based pembrolizumab dosing in Japanese subjects with advanced solid tumors was generally similar to that of non-Japanese subjects with advanced solid tumors (Shimizu et al., 2016). Also, in the KEYNOTE-434 trial, the PK profile of 200 mg pembrolizumab 1Q3W in Japanese subjects was comparable with the historical PK profile for pembrolizumab in non-Japanese subjects (Doi et al., 2021).

The results of the GCT1046-02 trial in Japanese subjects will be compared to the results of the GCT1046-01 trial in non-Japanese subjects to confirm consistency of PK, safety, tolerability, and identify potential ethnic differences in the dose-response relationship/PK pharmacodynamic activity.

4.3 Dose and Schedule Rationale

GEN1046 Monotherapy

The GEN1046 dose selection in the escalation part was based on the experience from the FIH GCT1046-01 trial, where doses ranging from 25 mg to 1200 mg 1Q3W were evaluated in 61 subjects in the dose escalation part; safety, PK, and pharmacodynamic data were analyzed. As of the data cut-off date of 01 Apr 2024, doses from 25 mg to 1200 mg 1Q3W were considered safe and generally well tolerated.

Based on the results of the ongoing FIH trial and the recommendation from the Pharmaceuticals and Medical Devices Agency, the starting dose for the GCT1046-02 trial was determined to be 15 mg 1Q3W in the dose escalation part.

Based on PK/pharmacodynamic model predictions and available clinical data from the GCT1046-01 FIH trial, the optimal dose of GEN1046 that can provide higher trimer engagement is predicted to be in the range of 80 to 140 mg 1Q3W for initial response, while higher doses may be beneficial for sustaining anti-tumor response through inhibition of the PD-L1/PD-1 interaction with higher PD-L1 RO.

GEN1046 + Pembrolizumab Combination

In the combination cohort, subjects will receive GEN1046 100 mg 1Q3W in combination with pembrolizumab 200 mg 1Q3W.

GEN1046 100 mg 1Q3W was selected to be evaluated as monotherapy and in combination with pembrolizumab based on the following:

- Doses of 25 mg to 1200 mg 1Q3W that were evaluated in the dose escalation phase of the FIH trial were safe and generally well tolerated. The MTD was not reached.
- Preliminary evaluation of safety data showed no dose dependency, indicating there is no dose response with respect to frequency of AEs.
- Responses according to RECIST v1.1 were observed at GEN1046 doses of 80 mg to 200 mg 1Q3W in the dose escalation phase of the FIH trial. Additionally, responses were also observed in an expansion cohort with a dose of 100 mg 1Q3W.
- Consistent modulation of pharmacodynamic markers (proliferating [Ki67+] effector memory CD8+ T cells and total CD8+ T cells and increased levels of IFNγ and IP-10) was observed in peripheral blood at dose levels ≤200 mg. Reduced modulation of these endpoints was observed at higher dose levels (≥400 mg).
- The semi-mechanistic PK/pharmacodynamic model predicted a bell-shaped response for trimer formation, which peaked around 100 mg 1Q3W. To balance the trimer levels and target engagement with respect to PD-L1 RO, a dose of 100 mg 1Q3W was chosen that may provide optimum initial response to GEN1046.

The planned dose of pembrolizumab in the combination cohort is 200 mg 1Q3W, which is the approved dose in Japan. Based on the totality of data generated in the pembrolizumab development program, 200 mg 1Q3W is an appropriate dose of pembrolizumab for adults across all indications (KEYTRUDA JP Prescribing Information, 2024).

4.3.1 Rationale for Fixed GEN1046 Dosing

The FIH trial with GEN1046 was initiated with a fixed (flat) dose. A fixed dosing approach was favored to facilitate drug preparation without the need to calculate the dose, thus lowering the potential risk of dosing errors as compared with body weight-based dosing. In addition, fixed

dosing offered several advantages over weight-based dosing including better convenience and compliance, reduction of preparation time, and a reduced amount of drug waste. There are several examples of mAb-based therapeutics that have either been developed using a fixed dosing approach, or switched from body weight-based dosing to flat dosing either during clinical development or post-approval (Bai et al., 2012; Wang et al., 2009).

Furthermore, there is strong scientific rationale to support fixed dosing of GEN1046. Monoclonal antibodies typically distribute to the blood plasma and extracellular fluids only, which increase less than proportionally with an increase in body weight, and elimination takes place via proteolytic catabolism and intracellular degradation after binding to the target. Binding to the target is not related to body weight but mainly to tumor load, target expression levels in tumors versus endogenous expression, and affinity of the mAb. In addition, intracellular degradation of mAbs targeting antigens at the cell surface is also not likely to be body weight dependent. Minor effects of body size on distribution and elimination of mAbs do not typically support body size-based dosing. Published simulation studies comparing the performance of a body size-based and fixed dosing for several mAbs demonstrated that PK variability is expected to be similar between fixed and body size-based dosing (Bai et al., 2012; Wang et al., 2009).

4.4 End of Trial Definition

The trial is considered completed when the last subject completes the last visit (LSLV) or withdraws from the trial. However, the maximal trial duration is 3 years after the last subject's first treatment.

4.5 Trial Completion for an Individual Subject

A subject is considered to have completed the trial if the subject has completed the last scheduled trial contact (ie, the last safety follow-up [SFU] visit) shown in the Schedule of Activities (Table 1-1).

4.6 Treatment Discontinuation

Treatment should continue until the subject fulfills 1 of the treatment discontinuation criteria (see Section 8.1).

4.7 Trial Termination

The sponsor reserves the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of the sponsor.

In addition, the investigator may initiate trial-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. Reasons for the early closure of a trial site by the sponsor or investigator may include, but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the independent Ethics Committee (IEC)/Institutional Review Board (IRB) or local health authorities, the sponsor's guidance documents/trial plans, ICH GCP E6(R2), and applicable regulatory requirements.
- Inadequate recruitment of subjects by the investigator.
- Discontinuation of further GEN1046 development.

Following end of trial (see Section 4.4) or trial termination, the sponsor will make their best effort to provide post-trial access to GEN1046 for those ongoing trial subjects continuing to derive treatment benefit, in accordance with local laws and requirements.

5 TRIAL POPULATION(S)

5.1 Inclusion Criteria

Each subject must fulfill all the following criteria to be treated in the trial.

1. Subject must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the trial and is willing to participate in the trial, prior to any trial related assessments or procedures.

2. Criterion modified per Amendment 4.
   2.1 Subject must have a histologically confirmed non-central nervous system (CNS) solid tumor that is metastatic or unresectable and for whom there is no available standard therapy likely to confer clinical benefit; or a subject who is not a candidate for such available therapy and for whom, in the opinion of the investigator, experimental therapy with GEN1046 or GEN1046 in combination with pembrolizumab may be beneficial.

3. Subject must be ≥20 years of age.

4. Asian race and Japanese ethnicity.

5. Subject must have measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

6. Subject must have Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤1.

7. Subject must have organ and bone marrow function as follows:
   a. Bone marrow / hematological function:
      i. Absolute neutrophil count (ANC) $\geq 1.5\times10^9$/L
      ii. Hemoglobin ≥9.0 g/dL
      iii. Platelet count $\geq 100\times10^9$/L
   b. Liver function:
      i. Total bilirubin ≤ upper limit of normal (ULN)
      ii. Alanine aminotransferase (ALT) ≤1.5×ULN
      iii. Aspartate aminotransferase (AST) ≤1.5×ULN
      iv. Albumin ≥30 g/L
   c. Coagulation status:
      i. Prothrombin time (PT)/International normalized ratio ≤1.5
      ii. Activated partial thromboplastin time (aPTT) ≤1.5×ULN
      Note: Subjects receiving anticoagulant therapies should have the PT and aPTT within the therapeutic range of intended use of anticoagulants.
   d. Renal function:
      Glomerular filtration rate (GFR) ≥45 mL/min/1.73 m², according to the abbreviated Modification of Diet in Renal Disease equation:
      GFR = 186 × (SCr - 1.154) × (age - 0.203),
      where SCr, the serum creatinine level, is expressed in mg/dL; multiply the result by 0.742 if the subject is female.

8. Criterion modified per Amendment 4.
   8.1 A woman of childbearing potential (WOCBP) (postmenopausal or permanently sterilized is considered as not having reproductive potential) must agree to use adequate contraception during the trial and for 6 months after the last trial treatment administration. Adequate contraception is defined as highly effective methods of contraception (please refer to Appendix 1).

9. A WOCBP must have a negative serum pregnancy test (beta-human chorionic gonadotropin [β-hCG]) or urine pregnancy test at screening.

10. Criterion modified per Amendment 4.
    10.1 A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the trial and for 6 months after the last dose of trial treatment.

11. Criterion modified per Amendment 1.
    11.1 Criterion modified per Amendment 4.
    11.2 A man who is sexually active with a WOCBP and has not had a vasectomy must agree to use a barrier method of birth control, ie, condom with a partner using an adequate contraception (please refer to Appendix 1 for definition of adequate contraception), and must also not donate sperm during the trial and for 6 months after receiving the last dose of trial treatment.

12. Subject must provide a tumor tissue sample (formalin-fixed paraffin-embedded [FFPE] blocks/slides) from archival tissue or fresh biopsy collected before C1D1, preferably derived from advanced disease stage.

5.2 Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from being treated in the trial.

1. Criterion amended as per Amendment 5.

   1.1 Subject has uncontrolled intercurrent illness, including but not limited to:

   a. Ongoing or active infection requiring IV treatment with anti-infective therapy that has been administered less than 2 weeks prior to first dose or any ongoing systemic inflammatory condition requiring further diagnostic work-up or management during screening.
   b. Symptomatic congestive heart failure (Grade III or IV as classified by the New York Heart Association), unstable angina pectoris or cardiac arrhythmia.
   c. Uncontrolled hypertension defined as systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg, despite optimal medical management.
   d. Ongoing or recent (within 1 year) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments, which may suggest risk for irAEs. ***Note: The following conditions are not exclusionary:*** Residual hypothyroidism that required only hormone replacement or psoriasis that does not require systemic treatment.
   e. History of grade 3 or higher irAEs that led to treatment discontinuation of a CPI should be excluded. A subject with irAEs below grade 3 that led to discontinuation should be discussed with the sponsor.
   f. Prior history of myositis, Guillain-Barré syndrome, or myasthenia gravis of any grade.
   g. History of chronic liver disease or evidence of hepatic cirrhosis.
   h. Evidence of interstitial lung disease (ILD).
   i. History of non-infectious pneumonitis that has required steroids; or currently has pneumonitis.
   j. Criterion modified per Amendment 4.

      j1. History of organ allograft (except for corneal transplant) or autologous or allogeneic bone marrow transplant, or stem cell rescue within 3 months prior to the first dose of trial treatment.

   k. Serious, non-healing wound, skin ulcer (of any grade), or bone fracture.

2. Criterion modified per Amendment 1.

   2.1 Any history of intracerebral arteriovenous malformation, cerebral aneurysm, new (younger than 6 months) or progressive brain metastases or stroke.

      a. Transient ischemic attack >1 month prior to screening is allowed.
      b. A subject with brain metastases must not be undergoing acute corticosteroid therapy or steroid taper. Chronic steroid therapy is acceptable provided that the dose is stable for the last 14 days prior to screening (≤10 mg prednisone daily or equivalent).
      c. A subject with CNS symptoms should undergo a computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain to exclude new or progressive brain metastases. Spinal cord metastasis is acceptable. However, subjects with spinal cord compression should be excluded.

3. Criterion modified per Amendment 1.

   3.1 Criterion modified per Amendment 4.

   3.2 Prior therapy:

      a. Radiotherapy: Radiotherapy within 14 days prior to the first dose of trial treatment. Palliative radiotherapy will be allowed.

b. Treatment with an anti-cancer agent (within 28 days or after at least 5 half-lives of the drug, whichever is shorter), prior to trial treatment administration. Accepted exceptions are bisphosphonates (eg, pamidronate, zoledronic acid) and denosumab.
c. Has received any investigational agent (including investigational vaccines) or used an invasive investigational medical device within 28 days before the planned first dose of trial treatment or is currently enrolled in an interventional trial. (***Note:*** A subject who is in the follow-up phase of an interventional trial may participate if the subject has not received the investigational agent within 28 days of the first dose of the trial treatment.)
d. Prior treatment with live, attenuated vaccines within 3 weeks prior to initiation of trial treatment.
   Chronic systemic immunosuppressive corticosteroid doses, ie, prednisone >10 mg daily (or equivalent) or a cumulative dose >150 mg prednisone (or equivalent) within 14 days before the first trial treatment administration. Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is permitted.
e. Has received granulocyte-colony stimulating factor (GCSF) or granulocyte/macrophage colony stimulating factor (GM-CSF) support 4 weeks prior to the first trial treatment administration or is chronically transfusion dependent.
f. History of ≥ grade 3 allergic reactions to mAb therapy as well as known or suspected allergy or intolerance to any agent given during the course of this trial.
g. Discontinued treatment due to disease progression within the first 6 weeks of a CPI-containing treatment.
h. Prior treatment with a 4-1BB (CD137) targeted agent.
i. Prior treatment with a T-cell agonist or an anti-cytotoxic T-lymphocyte-associated protein-4 targeted agent within 12 weeks prior to the initiation of treatment.

4. Toxicities from previous anti-cancer therapies that have not resolved to baseline levels or to grade 1 or less with the exception of alopecia, anorexia, vitiligo, fatigue, hyperthyroidism, hypothyroidism, and peripheral neuropathy. Anorexia, hyperthyroidism, hypothyroidism, and peripheral neuropathy must have recovered to ≤ grade 2.

5. Known past or current malignancy other than inclusion diagnosis, except for:
   a. Cervical carcinoma of Stage 1B or less.
   b. Non-invasive basal cell or squamous cell skin carcinoma.
   c. Non-invasive, superficial bladder cancer.
   d. Prostate cancer with currently undetectable prostate-specific antigen.
   e. Any curable cancer with a CR of >2 years duration.

6. Criterion modified per Amendment 4.
   6.1 Known allergies, hypersensitivity, or intolerance to the trial treatment or its excipients.

7. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

8. Has had major surgery (eg, requiring general anesthesia) within 4 weeks before screening, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the trial. **Note:** A subject with a planned surgical procedure to be conducted under local anesthesia may participate.

9. Known history of seropositivity for human immunodeficiency virus (HIV).

10. Criterion modified per Amendment 1.
    10.1 Subject is known to be hepatitis B positive (defined by a positive test for hepatitis B surface antigen [HBsAg] or antibodies to hepatitis B surface or core antigens. Subjects immune due to vaccination or passive immunization due to immunoglobulin therapy can be included.

11. Known medical history or ongoing hepatitis C infection that has not been cured.

12. Substance abuse, medical, psychological, or social conditions that may interfere with the subject's participation in the trial or evaluation of the trial result.

13. Subject has been dosed before in this trial.

14. Female subject is pregnant, or breast feeding and cannot discontinue breast feeding for the duration of the trial or at least 6 months after the last trial treatment administration or intends to conceive children within 6 months of ending trial treatment.

15. Subject in the combination cohort who has ongoing grade ≥2 sensory or motor neuropathy.

16. Subject in the combination cohort who has contraindications to the use of pembrolizumab per local prescribing information.

5.3 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but do not meet the protocol-defined eligibility criteria (refer to Sections 5.1 and 5.2). Minimal information to be documented includes demography, reason for screening failure (eg, eligibility criteria not met, subject withdrew consent, other reasons), and any serious adverse events (SAEs) or AE related to a trial assessment.

Individuals who do not meet the criteria for participation in this trial (screen failures) may be rescreened. The rescreening must be approved by the sponsor to ensure that the safety of the subject is not compromised. All eligibility criteria must be re-assessed at the re-screening visit.

The following screening assessments may be used for rescreening if performed ≤ 21 days prior to C1D1 or if approved by sponsor:

- CT, MRI scans
- Laboratory assessments: Endocrine, hepatitis B, hepatitis C, serum β-hCG

Screen failures may be rescreened only once. Subjects are required to sign a new ICF if updates have been made since signing the most recent ICF.

6 TREATMENT

6.1 Treatment Assignment or Randomization

6.1.1 Subject Numbering

After signing the ICF, subjects will be assigned a unique subject identification number before undergoing any screening procedure(s).

6.1.2 Treatment Assignment

This is an open-label trial; therefore, blinding of treatment will not be performed. Randomization will not be used in this trial.

Site personnel must contact the contract research organization (CRO) when a potential subject has been identified. If there is an opening, the site will be given approval to start the screening process. If there is no opening, the subject will be placed on a waiting list and the site will be alerted of next available opening.

6.2 Dosage and Administration

An overview of trial treatments by monotherapy or combination therapy is presented in Table 4-1. Trial treatment should be administered as described in Table 6-1 until 1 or more of the discontinuation criteria in Section 8.1 are met. It should be noted that the maximum treatment duration with pembrolizumab is 24 months. However, if at 24 months a subject is still being treated with the GEN1046 and pembrolizumab combination or with pembrolizumab alone, treatment duration may be extended if agreed to by the sponsor's medical officer. See Section 8.1 for details regarding discontinuation of 1 component of treatment in the combination cohort.

Table 6-1 Trial Treatment

Trial treatment name	GEN1046[a]	Pembrolizumab[a]
Dosage formulation	Concentrate for solution for infusion	
Dose (including schedule and cycle length)	Dose escalation part: Table 4-1 Combination cohort: 100 mg 1Q3W	Dose escalation part: NA Combination cohort: 200 mg 1Q3W
Route of administration	IV	
Dosing instructions	Dose escalation part: GEN1046 infusion over at least 60 minutes Combination cohort: Pembrolizumab will be administered first, followed by GEN1046. GEN1046 and pembrolizumab should be infused over at least 30 minutes and the GEN1046 infusion should begin at least 30 minutes after the end of the pembrolizumab infusion. Refer to the IMP manual for additional details.	
Packaging	CCI [redacted]	Pembrolizumab will be provided in a glass vial containing 4 mL (25 mg/mL).
Labeling	Trial treatment labels will contain information to meet the applicable regulatory requirements. For further details see the IMP manual.	

IMP=Investigational Medicinal Product: IV=intravenous(ly); 1Q3W=1 dose every 3 weeks.
a. Refer to the IMP manual for further details.

In the dose escalation part, subjects will be hospitalized during Cycle 1 as described in Section 4.1.1. In the combination cohort, hospitalization is required in Cycle 1 from Day 1 to Day 3 and the subject can be discharged on Day 4 if there is no safety concern and if the subject has phone accessibility and resides near a health care facility, and thus will be able to contact their health care provider or seek medical attention immediately, if needed, as described in Section 4.1.1.

As a routine precaution, subjects dosed with GEN1046 must be monitored during infusion and treated in an area with resuscitation equipment and emergency agents. All subjects must be observed during Cycle 1 and Cycle 2 on Day 1 for at least 4 hours after ending the infusion of GEN1046. For all subsequent cycles, subjects must be observed for at least 2 hours after ending the infusion of GEN1046.

Refer to the Investigational Medicinal Product (IMP) manual for additional information and stepwise guidance on dosage and administration. Detailed dose modification guidance is provided in Section 7. Refer to Section 6.4 for information regarding concomitant therapy.

6.3 Compliance

Trial treatment will be administered by site personnel to assure compliance with trial requirements.

The date, time, and injection site of each trial treatment administration will be recorded.

6.4 Concomitant Medications and Therapies

The subject must be told to notify the trial site about any new medications he/she takes after the start of the trial treatment. All medications (other than the trial treatment) and significant non-drug therapies (including physical therapy, herbal/natural medications, and blood transfusions) administered during the trial must be collected and reported.

6.4.1 Permitted Concomitant Medications and Therapies

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as “prohibited” (Section 6.4.2).

Concomitant medications are allowed to provide adequate care and may be given as clinically indicated. All concomitant medications should be recorded. Name, indication (reason for use) and dates of administration (start and end dates) of concomitant therapies will be documented. If parenteral nutrition is given during the trial, the individual components do not need to be specified in detail, indication as “parenteral nutrition” is sufficient. If a subject needs general anesthesia, it will be sufficient to indicate “general anesthesia” without specifying the details.

The sponsor’s medical monitor, or delegate, should be contacted if there are any questions regarding concomitant medication or prior therapy.

The trial site will supply supportive medication.

The following concomitant medication and therapies are permitted during the trial:

- Local palliative radiotherapy of non-target lesions.
- G-CSF and other hematopoietic growth factors may be used in the management of acute toxicity, when clinically indicated or at the investigator’s discretion. Note: Hematopoietic growth factors other than G-CSF are not approved in Japan for events associated with cancer chemotherapy.

- Prophylactic antibiotics are also permitted per institutional standard practice.
- Blood cell transfusion (erythrocytes and/or thrombocytes), if clinically indicated.
- Chronic erythropoietin, provided that no dose adjustment was made within 2 months before the first dose of GEN1046. Note: Erythropoietin is not approved in Japan for anemia associated with cancer chemotherapy.
- Steroid treatment is permitted as premedication before GEN1046 administration and/or to modulate symptoms of an irAE at the discretion of the investigator (refer to Section 7.3.1).
- Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency).
- Bisphosphonates (eg, pamidronate, zoledronic acid) and denosumab.
- Multivitamins, vitamin D, calcium, and supplements in prevention of weight loss.
- SARS-CoV-2 vaccine is generally permitted, including mRNA-based, protein-based, or nonreplicating viral vector-based vaccines. Please consider choosing an appropriate type of SARS-CoV-2 vaccine and consult with an infectious disease expert if desired. Please note, SARS-CoV-2 vaccine should not be administered during the DLT observation period.

6.4.2 Prohibited Concomitant Therapy

The following medications are prohibited during the trial (from the first dose of trial treatment):

- Any other investigational therapy.
- Any other anti-cancer therapy, eg, chemotherapy, immunotherapy, radiotherapy, or experimental therapy. Local palliative radiotherapy on non-target lesions is allowed, provided that the radiation field does not encompass a target lesion.
- Corticosteroid that exceeds a total daily dose of 10 mg of prednisolone or equivalent administered for more than 10 days unless for the management of AEs (excluding corticosteroids given as premedication).
- Herbal preparations or related over-the-counter (OTC) preparations containing herbal ingredients are not permitted during participation in the trial.
- Live attenuated vaccines while participating in the trial and for 3 months following the last dose of trial treatment. Note: Seasonal influenza vaccines are generally killed-virus vaccines and are permitted however, intranasal influenza vaccines are live-attenuated-virus vaccines and are not allowed.
- No dietary supplements are allowed during the trial period (except for multivitamins, vitamin D, calcium, and supplements in prevention of weight loss). The use of traditional medicines is not permitted.

If a subject receives any of these during the trial, the sponsor must be notified for evaluation of whether the subject can continue treatment in the trial.

6.5 Trial Treatment Information

6.5.1 GEN1046

6.5.1.1 Physical Description

GEN1046 – [redacted] formulated in [redacted], is a [redacted] solution supplied as a concentrate for solution for infusion to be diluted (at site) in [redacted].

6.5.1.2 Packaging

The drug product will be provided in a [redacted] glass vial containing [redacted] GEN1046 ([redacted]).

6.5.1.3 Labeling

GEN1046 labels will contain information to meet the applicable regulatory requirements.

6.5.1.4 Preparation, Handling, and Storage

GEN1046 must be stored at [redacted].

Refer to the IMP manual for additional guidance on trial treatment preparation, handling, and storage.

6.5.2 Pembrolizumab

Pembrolizumab will be supplied by the sponsor, and it will be used as Drugs used in the Clinical Trial (DUCT) other than test drug in this trial. The reference safety information for pembrolizumab is the Japanese package insert (KEYTRUDA JP Prescribing Information).

6.5.2.1 Physical Description

Pembrolizumab (KEYTRUDA®) infusion is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for IV infusion.

6.5.2.2 Packaging

Each glass vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, United States Pharmacopeia (USP).

6.5.2.3 Preparation, Handling, and Storage

Pembrolizumab must be stored at controlled temperatures ranging from 2°C to 8°C.

Refer to the IMP manual for additional guidance on trial treatment preparation, handling, and storage.

6.5.3 Drug Accountability

The head of the trial site/the investigator has overall responsibility for the study drug(s). Tasks will be delegated to a qualified designee (eg, the study drug manager) who is adequately trained in the protocol. This delegation must be documented in the applicable study delegation of an authority form.

The study drug(s) will not be dispatched to the trial site until the sponsor or designee has received all required documents from the trial site in accordance with relevant standard operating procedures. Upon receipt, the designee (the study drug manager) who is assigned by the head of the trial site is responsible for ensuring that all study drug(s) received at the trial site is inventoried and accounted for throughout the trial. A copy of the shipping documents must be maintained for the investigator's records.

After sufficient amount of the study drug(s) is shipped to the trial site, the designee (the study drug manager) will acknowledge receipt of the study drug(s), documenting shipment content and condition. Accurate records of all study drug(s) dispensed, used and/or destroyed must be maintained as detailed later in this section.

A qualified designee for the study drug(s) (the study drug manager) will supply the study drug(s) only to the investigator or staff in this trial who administers to the subject according to procedures set out in the protocol. The designee (the study drug manager) should keep a current record of the inventory and dispensing of all clinical supplies. All administered/dispensed study drug(s) will be documented in the subject's source and/or other study drug(s) records. The designee (the study drug manager) is also responsible for ensuring the retrieval of all trial supplies from subjects. Further guidance and information for the final disposition of unused study drug(s) or return after use are provided in the IMP manual for additional guidance on study drug(s) preparation, handling, and storage.

The sponsor or its representatives will be permitted access to review the supplies storage, distribution, and their records anytime.

6.5.4 Handling of Other Trial Treatment

Not applicable.

6.6 Technical Complaint Handling

A technical complaint is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A technical complaint may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of technical complaint information from trials are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of technical complaint information; all trials conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

6.6.1 Procedures

All initial technical complaints must be reported to the sponsor by the trial-site personnel within 24 hours after being made aware of the event.

If the defect is combined with an AE or SAE, the trial-site personnel must report the AE or SAE to the sponsor according to the AE and SAE reporting process and timelines (Section 10.3) in addition to reporting the technical complaint. A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

6.6.2 Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding technical complaint issues are listed on the contact information page(s), which will be provided as a separate document.

7 DOSE MODIFICATIONS AND SAFETY MANAGEMENT GUIDELINES

A DEC is set up for the trial. The DEC will review data from each dose level cohort and make a recommendation regarding dose escalation. The recommendation of the DEC has to be endorsed by the Safety Committee.

7.1 Dose-Limiting Toxicity

For the purpose of dose escalation, the DLT monitoring period will be 21 days (ie, Cycle 1). The occurrence of any of the toxicities outlined in Section 7.1 will be considered a DLT if assessed by the investigator to be at least possibly related to trial treatment. Toxicities clearly not related to trial treatment (eg, disease progression, comorbidity, etc) will not be considered a DLT. SAEs, nonserious ≥ grade 3 AEs and clinically significant abnormal lab values ≥ grade 3 **at least possibly related** to trial treatment will be collected and assessed for DLTs. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be used to grade the intensity of AEs, with the exception of CRS, which will be graded according to the American Society for Transplantation and Cellular Therapy (ASTCT) criteria described by (Lee et al., 2019).

DLT criteria are defined below:

- Grade 5 toxicity.

Hematological

- Grade 4 neutropenia (ie, ANC $<0.5\times10^9$ cells/L) lasting more than 7 days. ***Note:*** *Neutropenia requiring growth factor support will be considered a DLT.*
- Grade 3 and 4 febrile neutropenia (ie, ANC $<1.0\times10^9$ cells/L with a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than 1 hour). ***Note:*** *Neutropenia requiring growth factor support will be considered a DLT.*
- Grade 4 thrombocytopenia ($\leq25.0\times10^9$ platelets/L) for minimal duration of 7 days. ***Note:*** *Thrombocytopenia requiring the transfusion of thrombocytes will be considered a DLT.*
- Grade 3 and 4 hemorrhage associated with thrombocytopenia of ≥ grade 3 requiring platelet transfusion.
- Grade 4 anemia. ***Note:*** *Anemia requiring the transfusion of erythrocytes will be considered a DLT.*

Non-hematological

- Liver toxicity (transaminases and bilirubin elevations) defined as the following:
  - Grade 4 AST, ALT, or bilirubin elevation.
  - Grade 3 AST, ALT, or bilirubin elevation that does not recover to ≤ grade 1 within 14 days.
  - Concomitant grade ≥ 2 AST, ALT elevation, and 2×ULN bilirubin elevation.

  Note: *Transaminase (ALT or AST) and/or bilirubin ≥ grade 2 elevation must be checked 2×/week for up to 4 weeks.*
- Grade 3 nausea that does not respond to optimal antiemetic treatment within 7 days.
- Grade ≥3 vomiting that does not respond to optimal antiemetic treatment within 3 days.
- Grade ≥3 diarrhea that does not respond to optimal antidiarrheal treatment within 3 days.

- Grade 3 irAEs that do not improve to ≤ grade 1 within 7 days by appropriate care or with corticosteroids **except for**:
  - Grade 3 pneumonitis, which always qualifies as a DLT.
  - Grade 3 nephritis (defined as inflammation of the kidney affecting the structure associated with grade 3 creatinine increase) which always qualifies as a DLT.
- Any grade 4 irAE.
- Any other ≥ grade 3 non-hematological AE (including liver toxicities other than increases of transaminases and bilirubin), which occurs during the first GEN1046 treatment cycle ***excluding***:
  - Grade 3 CRS, which has improved to grade 1 or resolved within 48 hours.
  - Grade 3 fever (>40.0°C for ≤24 hours).
  - Grade 3 hypotension (resolving within 24 hours).
  - Grade 3 IRRs that resolve to ≤ grade 1 within 24 hours.
  - Non-hematological laboratory abnormalities that have no clinical consequence and resolve to ≤ grade 2 within 7 days (this also includes electrolyte abnormalities that respond to medical intervention).
  - Grade 3 fatigue when fatigue was present at baseline or that lasts for <14 days after the last administration of GEN1046.
  - Grade 3 anorexia when grade 2 anorexia was present at baseline or that lasts for <1 day after the last administration of GEN1046.
- A subject experiencing a DLT (an AE fulfilling the DLT criteria within the DLT period of 21 days) should discontinue trial drug immediately.

7.2 Dosing Modification Guidance and Safety Stopping Criteria

Decisions regarding dose modification of trial treatment should be made using clinical judgment, taking into account relatedness of the AE to the trial treatment and the subject's underlying condition.

GEN1046 and pembrolizumab are considered immune modulators and it is possible that irAEs may occur. AEs of a potential immunologic etiology (ie, irAEs) may be defined as an AE consistent with an immune phenomenon associated with drug exposure after all other etiologies have been eliminated. A mitigation plan for handling AEs, in particular for elevated liver laboratory parameters, irAEs, hyperinflammatory syndromes, and IRRs, has been prepared for this trial in order to closely monitor, dose-delay, or withdraw subjects based on AEs that may occur with PD-L1 and 4-1BB targeted agents (see Section 7.3 and Table 7-1 and Section 7.3.3).

If a subject experiences neutropenia or febrile neutropenia considered related to trial treatment, dose modification and supportive care guidance is provided in Table 7-2. For all other AEs considered related to trial treatment, general instructions for interruption and restarting of trial treatment are outlined in Table 7-3. AEs with clear alternative causality may be exempt from dose modification rules.

Trial treatment must be permanently discontinued in case of a dose delay of more than 21 days due to toxicity possibly related to trial treatment unless otherwise approved by the sponsor's medical monitor. No intra-subject dose de-escalation will be allowed.

Subjects in the combination cohort may only continue on GEN1046 or pembrolizumab monotherapy if approved by the sponsor's medical monitor.

7.3 Dose Modification for Specific Adverse Events

7.3.1 Immune-Related Adverse Events

AEs associated with GEN1046 or the combination of GEN1046 and pembrolizumab may have an immunologic etiology. These irAEs may occur shortly after the first dose or several months after the last dose of these treatments and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial data for GEN1046 and the prescribing information for pembrolizumab, irAEs in this trial are expected to be reversible and managed with drug delays, administration of corticosteroids, and/or other supportive care.

When trial interventions are administered in combination, attribution of an AE to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to the combination, to GEN1046 alone, or to pembrolizumab alone, for AEs listed in Table 7-1, both interventions must be held until resolution of the AEs according to the criteria in Table 7-1.

General Instructions:

Additional procedures or tests such as bronchoscopy, endoscopy, or skin biopsy may be included as part of the evaluation. CCI

- Based on the severity of irAEs, trial treatment should be withheld or permanently discontinued, and corticosteroids administered.
- For severe and life-threatening irAEs, an IV corticosteroid should be initiated first (under hospital admission). Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.
- It is important to exclude infections diligently at admission and to keep monitoring subject closely (eg, with vital signs, hematology, LFTs, procalcitonin, and inflammatory markers, including CRP and ferritin) on a daily basis to exclude potential new infections. Infections should be treated immediately and adequately per the local standard of care. For infections ongoing at the time of dosing, consider dose delay until resolution.
- If subject is receiving high-dose corticosteroids (eg, ≥2 mg/kg for ≥3 days), initiate broad-spectrum antibiotics covering nosocomial infections as well as antifungals (unless there are contraindications) due to the increased risk of infections during immunosuppression. Concurrent neutropenia may increase the risk of infection.
- Corticosteroid taper should be initiated for corticosteroid treatment doses of 0.5 mg/kg or higher upon irAE improving to grade 1 or lower and continue to taper over at least 4 weeks.
- GEN1046 or GEN1046 combination regimen may be resumed after the irAE has resolved in severity to grade 1 or 0. Note: Corticosteroid dose must be ≤10 mg/day before treatment is resumed. This includes premedication for GEN1046 (ie, prednisone 10 mg daily or equivalent).
- For subjects who have required steroid intervention for any irAE, premedication with corticosteroids is recommended in relation to GEN1046 administration for future dosing cycles

(ie, prednisone 10 mg daily or equivalent) starting on the dosing day just prior to GEN1046 administration and once daily the following 9 days (10 days in total). **For specific guidance on ALT/AST elevations, please refer to Table 7-1.** GEN1046 or GEN1046 combination regimen should be permanently discontinued:

  - If the AE does not resolve within 6 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day.
  - For any recurrence of ≥ grade 3 irAE with the exception of hypothyroidism.
  - If there is a dose delay of any trial treatment for any reason for more than 6 weeks from the intended date of dose.
- Subjects in the combination cohort may only continue on GEN1046 or pembrolizumab monotherapy if approved by the sponsor's medical monitor.

Specifically for pembrolizumab, there have been reports of cases of interstitial lung disease leading to death; therefore, subjects should be carefully monitored for early symptoms (shortness of breath, dyspnea, cough, etc.) and chest X-rays should be performed. If any abnormality is observed, administration should be discontinued, and appropriate measures such as corticosteroids administration should be taken (KEYTRUDA JP Prescribing Information).

Dose modification and toxicity management guidelines for irAEs associated with GEN1046 and the combination of GEN1046 and pembrolizumab are provided in Table 7-1.

Table 7-1 Dose Modification and Management of Immune-Related Adverse Events

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab/GEN1046	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 1 or 2	Withhold treatment until resolution to ≤ grade 1 and corticosteroid has been tapered.	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper. Add prophylactic antibiotics.	Monitor subjects for signs and symptoms of pneumonitis. Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment.
	Recurrent grade 2, grade 3, or grade 4	Permanently discontinue Note: Refer to Section 7.2 for more details regarding action with pembrolizumab/GEN1046.		
Diarrhea/colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper.	Monitor subjects for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood, or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). Subjects with ≥ grade 2 diarrhea suspecting colitis should consider GI consultation and endoscopy to rule out colitis. Subjects with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent grade 3 or grade 4	Permanently discontinue Note: Refer to Section 7.2 for more details regarding action with pembrolizumab/GEN1046.		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab/GEN1046	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
CCI				

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab/GEN1046	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
CCI				

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab/GEN1046	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
			CCI	
	Grade 4	Permanently discontinue	Immediately administer corticosteroids (initial dose of 2 mg/kg methylprednisolone IV or equivalent). Initiate broad-spectrum antibiotics covering nosocomial infections as well as antifungals (unless there are contraindications) if subject is receiving high-dose corticosteroids (eg, ≥2 mg/kg for ≥3 days). If no improvement is observed within 3 – 5 days despite methylprednisolone IV or equivalent, consider prompt treatment with immunosuppressive therapy (eg, mycophenolate mofetil at 500 mg every 12 hours, or azathioprine; discuss with medical monitor). **Infliximab should not be used.**	CCI

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab/GEN1046	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
			Initiate steroid taper over at least 4 weeks when improvement to ≤ grade 1.	
T1DM or hyperglycemia	New onset T1DM or grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold[a]	Initiate insulin replacement therapy for subjects with T1DM Administer antihyperglycemic treatment in subjects with hyperglycemia	Monitor subjects for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[a]		
Hyperthyroidism	Grade 2	Continue	Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue[a]		
Hypothyroidism	Grade 2, 3, or 4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per SoC	Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine levels or acute kidney injury	Grade 2	Withhold	Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological toxicities	Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 2, 3, or 4	Permanently discontinue	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab/GEN1046	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Skin toxicities	Grade 1 or 2	Continue treatment at the discretion of the investigator	Based on severity of the skin toxicity, consider administration of corticosteroids. Corticosteroid taper should be initiated upon irAE improving to grade 1.	Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold treatment until resolved to ≤ grade 1		
	Grade 4	Permanently discontinue		
All other irAEs[b]	Persistent grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event[c]		
	Recurrent grade 3 or grade 4	Permanently discontinue		

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CRS=cytokine release syndrome; CTCAE=Common Terminology Criteria for Adverse Events; GI=gastrointestinal; HLH=hemophagocytic lymphohistiocytosis; ir=immune related; IV=intravenous(ly); SoC=standard of care; T1DM=type 1 diabetes mellitus; ULN=upper limit of normal.

Note: Non-irAEs will be managed as appropriate, following clinical practice recommendations.

a. The decision to withhold or permanently discontinue GEN1046 or GEN1046 combination regimen is at the discretion of the investigator or treating physician. If control achieved or ≤ grade 2, GEN1046 or GEN1046 combination regimen may be resumed.
b. Refer to Section 7.3.3 for guidance regarding hyperinflammatory syndromes (CRS and HLH).
c. Events that require discontinuation include but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

7.3.2 Neutropenia and Febrile Neutropenia

Table 7-2 Dose Modification and Management of Neutropenia and Febrile Neutropenia

CTCAE Term	Toxicity Grade (CTCAE v5.0)	Dose Modification	Guidance for Management of AE
Neutropenia **or** **Febrile Neutropenia**	Grade 3 or Grade 4	Withhold treatment until resolution to ≤ grade 1	Administer colony-stimulating factors including G-CSF, pegylated G-CSF or GM-CSF according to Institutional standards. For Grade 3 or 4 neutropenia occurring in Cycle 1, grade 3 or 4 neutrophil count must be observed in 2 consecutive assessments at least 12 hours apart without improvement prior to administration of growth factors.

AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; G-CSF=granulocyte-colony stimulating factor; GM-CSF=granulocyte/macrophage colony stimulating factor.

7.3.3 Hyperinflammatory Syndromes

These include rare but potentially fatal irAEs syndromes of immune hyperactivation caused by cytokine release and a resulting systemic inflammatory response, like in CRS and HLH.

7.3.3.1 Cytokine Release Syndrome

Any event of CRS should be graded according to ASTCT criteria described by (Lee et al., 2019).

Trial treatment should be permanently discontinued for subjects with grade ≥3 CRS (except for grade 3 CRS which has improved to grade 1 or resolved within 48 hours). However, per protocol, subjects should continue safety follow-up until the subject withdraws from the trial or starts another course of systemic anti-cancer therapy.

Management of CRS should follow the established guideline (Varadarajan et al., 2020) or local standard of care, with supportive treatment controlling fever, hypotension, and hypoxia; and in more severe cases, with anti-IL-6R mAb (eg, tocilizumab), systemic steroids, and vasopressors.

7.3.3.2 Hemophagocytic Lymphohistiocytosis

HLH is an hyperinflammatory hyperferritinemic immune response syndrome driven by T cells and associated with a cytokine storm. Acquired, secondary HLH is the most common subtype in adults. HLH triggers include occult malignancy (mainly lymphoma), infections, and iatrogenic causes like immunotherapy with immune CPIs (La Rosée et al., 2019).

Hyperferritinemia should always prompt inclusion of HLH as differential diagnosis. If ferritin levels are increased above 500 µg/L, they should be monitored closely. Ferritin values characteristic of HLH in adults are often >7000 µg/L. However, any rapid increase in the ferritin level compared to baseline per clinical assessment should raise the index of suspicion (Hines et al., 2023). If HLH is suspected, elevated soluble IL-2 receptor (sCD25) has been reported as a diagnostic test for adult HLH and it is recommended to assess sCD25 locally (per local standard) together with fibrinogen, triglycerides, and D-dimer. Other features supporting an HLH diagnosis that are not part of the HLH-2004 criteria below include elevated liver transaminases, hyperbilirubinemia, hepatomegaly and elevated LDH (La Rosée et al., 2019).

The HLH-2004 diagnostic criteria can be a useful tool for assessing HLH diagnosis. According to this score, the diagnosis of HLH can be established if 5 of the following 8 criteria are fulfilled:

1. Fever
2. Splenomegaly
3. Cytopenias (affecting ≥2 of 3 lineages in the peripheral blood):
   a. Hemoglobin <90 g/L
   b. Platelets $<100 \times 10^9$ /L
   c. Neutrophils $<1.0 \times 10^9$ /L
4. Hypertriglyceridemia and/or hypofibrinogenemia:
   a. Fasting triglycerides ≥3.0 mmol/L (ie, ≥265 mg/dL)
   b. Fibrinogen ≤1.5 g/L
5. Hemophagocytosis in bone marrow or spleen or lymph nodes. No evidence of malignancy
6. Low or no NK cell activity (according to local laboratory reference)
7. Ferritin ≥500 µg/L
8. sCD25 (ie, soluble IL-2 receptor) ≥2400 U/mL

The diagnosis of HLH can also be established, if a molecular diagnosis consistent with HLH is fulfilled.

There may be overlapping features in the pathophysiology and presentation between hyperinflammatory syndromes. Furthermore, the HLH-2004 diagnostic criteria above were derived from children with primary HLH. Based on experience from the GEN1046 development program and similarities with the safety profile of CAR T cell therapies, it is recognized that pathology and hyperinflammatory processes observed with GEN1046 are distinct from primary HLH and more like immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (Hines et al., 2023). **It is therefore recommended to start treatment solely on a strong suspicion of "HLH-like syndrome," even if 5 of the 8 HLH-2004 diagnostic criteria are not met.**

The management of HLH should be tailored to control hyperinflammation and to treat identified disease triggers.

Treatment with high-dose corticosteroids (start dose 2 mg/kg IV) is the cornerstone of treatment. Early intervention with high-dose steroids alone may be successful in the treatment of HLH induced by immune checkpoint blockade (Sadaat and Jang, 2018; Takahashi et al., 2020). If no reversal of laboratory parameters (including ferritin and bilirubin increases) within 24 hours, pulsed corticosteroids, eg, 1000 mg/day for 3 days according to (Takahashi et al., 2020), should be initiated immediately. If no improvement within 24 to 48 hours from the initiation of corticosteroid pulse therapy, treatment with anakinra or JAK1/2 inhibitors should be added (Hines et al., 2023; Keenan et al., 2021). For refractory cases, etoposide (an element of the HLH-94 protocol) may be used. Dose and frequency adjustments are advised for adult patients (La Rosée et al., 2019).

Checklist for recommended management of suspected HLH:

- Withhold trial treatment and contact medical monitor (sponsor)
- Initiate corticosteroids IV immediately (as described above) under hospitalization, especially in case of signs of organ-specific irAEs
- Initiate supportive care, including intensive care monitoring, if indicated
- Consider referral to a hematologist

- It is important to exclude infections and to keep monitoring subject closely (eg, with vital signs, hematology, liver function tests, procalcitonin and inflammatory markers including CRP and ferritin) on a daily basis to exclude potential new infections. Infections should be treated immediately and adequately per the local standard of care. For infections ongoing at the time of dosing, consider dose delay until resolution.
- If subject is receiving high-dose corticosteroids (eg, ≥2 mg/kg for ≥3 days), initiate broad-spectrum antibiotics covering nosocomial infections as well as antifungals (unless there are contraindications) due to the increased risk of infections during immunosuppression. Concurrent neutropenia may increase the risk of infection.
- If the event is not improving within 24 to 48 hours from the initiation of corticosteroids pulse therapy, consider adding an immunosuppressive agent (ie, anakinra or JAK1/2 inhibitors).

7.3.4 Dosing Modification and Management of All Other Treatment-Related AEs

Table 7-3 Dose Modification and Management of All Other Treatment-Related AEs

CTCAE Grade/Severity	Hold Treatment (Y/N)	Timing for Restarting Treatment
Grade 1 or Grade 2	N	Continue treatment at the discretion of the investigator.
Grade 3 (Severe)	Y	Withhold treatment until resolution to ≤ grade 1 or baseline
Grade 4 (Life-Threatening)	Y	Permanent discontinuation except if approved by the sponsor's medical monitor. If continuing on treatment, toxicity must resolve to Grade 1 or baseline.

AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; N=no; Y=yes.

7.3.5 Infusion-Related Reactions

7.3.5.1 GEN1046

The following treatment guidelines are provided below for subjects who experience an IRR associated with administration of GEN1046.

- Grade 1: If an IRR grade 1 occurs, the infusion does not need to be interrupted and can be continued at the investigator's discretion at half the infusion rate under close medical supervision.
- Grade 2 or Grade 3: If a grade 2 or grade 3 IRR occurs, the infusion should be interrupted, and appropriate medical management instituted. The infusion may be re-started at the investigator's discretion at half the infusion rate under close medical supervision, if symptoms have resolved to ≤ grade 1 within an hour.
    - Subjects who have experienced prior grade 2 or grade 3 IRRs in the trial should be premedicated. Premedication to prevent IRR in subsequent infusions may be administered at the investigator's discretion according to local guidelines but preferably includes an antihistamine (eg, diphenhydramine 50 mg or equivalent antihistamine), acetaminophen/paracetamol (eg, acetaminophen 500 to 1000 mg or equivalent), and if considered necessary, subjects should receive corticosteroids at a suggested maximum dose of 100 mg prednisone or equivalent.
    - If the subject has a recurrent grade 3 IRR despite premedication, the infusion should be stopped, and the subject should be withdrawn from treatment.

- Grade 4: If anaphylaxis or grade 4 IRR occurs, administration of GEN1046 should be discontinued immediately and permanently, and appropriate medical therapy should be administered.

Please note:

- As a routine precaution, all subjects must be observed during Cycle 1 and Cycle 2 on Day 1 for at least 4 hours after ending the infusion of GEN1046. For all subsequent cycles, subjects must be observed for at least 2 hours after ending the infusion of GEN1046.
  - Subjects must be observed in an area with resuscitation equipment and emergency agents.
- At all times during GEN1046 infusion, immediate emergency treatment of an anaphylactic reaction according to institutional standards must be assured. In order to treat possible anaphylactic reactions, for instance, dexamethasone 10 mg and epinephrine in a 1:1000 dilution or equivalents should always be available along with equipment for assisted ventilation.
- All premedication must be recorded.

7.3.5.2 Pembrolizumab

Pembrolizumab may cause severe or life-threatening IRRs, including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab-associated infusion reactions are provided in Table 7-4.

Table 7-4 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE v5.0 Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	• Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	• **Stop infusion**. • Additional appropriate medical therapy may include but is not limited to: - IV fluids - Antihistamines - NSAIDs - Acetaminophen - Narcotics • Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. • If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise, dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose.	Subject may be premedicated 1.5 hrs (±30 minutes) prior to infusion of trial treatment with: - Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). - Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).

NCI CTCAE v5.0 Grade	Treatment	Premedication at Subsequent Dosing
	Subjects who develop grade 2 toxicity despite adequate premedication should be permanently discontinued from further causative trial treatment.	
Grades 3 or 4 **Grade 3:** Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilator support indicated	• **Stop infusion.** • Additional appropriate medical therapy may include but is not limited to: - Epinephrine. In cases of anaphylaxis, epinephrine should be used immediately. - IV fluids - Antihistamines - NSAIDs - Acetaminophen - Narcotics - Oxygen - Pressors - Corticosteroids • Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. • Hospitalization may be indicated. Subject is permanently discontinued from further causative trial treatment.	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 at http://ctep.cancer.gov.		

CTCAE=Common Terminology Criteria for Adverse Events; IV=intravenous(ly); NCI=National Cancer Institute; NSAID=nonsteroidal anti-inflammatory drug; PO=orally.

7.4 Safety Stopping Rules

Trial treatment should be discontinued due to safety concerns under the following conditions:

- If the subject experiences a treatment-related AE that meets the criteria for treatment discontinuation as specified in Table 7-1, Table 7-2, or Table 7-3.
- An AE that fails to resolve to ≤ grade 1 within 21 days due to a toxicity possibly related to trial treatment, unless otherwise approved by the sponsor's medical monitor.
- Treatment-related grade 4 or life-threatening AE, except with approval from the sponsor's medical monitor.
- Second occurrence of an IRR of ≥ grade 3 despite premedication prior to the 2nd infusion.
- First occurrence of anaphylaxis or a grade 4 IRR.

Please note:

- Regardless of the reason for discontinuation, the subject should be examined as soon as possible (refer to Section 8.1 for details regarding discontinuation of treatment).

8 DISCONTINUATION AND FOLLOW UP

8.1 Discontinuation of Treatment

A subject's trial treatment must be discontinued for any of the following reasons:

- Unacceptable AEs requiring treatment discontinuation *
- Subject non-compliance
- Sponsor decision
- Subject request to discontinue trial treatment*
- Pregnancy
- Clinical progression*
- Disease progression (according to response criteria, Section 9.2)
- Other

*Every effort should be made to continue imaging evaluations according to the trial protocol. When a subject discontinues trial treatment, the subject remains in the trial and is followed until meeting 1 of the reasons listed in Section 8.2.

If a subject's trial treatment must be discontinued before the end of the treatment regimen, this will not result in automatic withdrawal of the subject from the trial.

Subjects should, whenever possible, irrespective of the reason for discontinuation, be examined as soon as possible and the Treatment Discontinuation visit should be performed. If the Treatment Discontinuation visit coincides with a regularly scheduled cycle visit, the Treatment Discontinuation visit evaluations will supersede those of the regularly scheduled cycle visit. In addition, the subject will still be followed for the SFUs (see Section 8.3).

Subjects in the combination cohort should discontinue both GEN1046 and pembrolizumab treatment and may only continue on GEN1046 or pembrolizumab monotherapy if approved by the sponsor's medical monitor.

Trial treatment assigned to the withdrawn subject may not be assigned to another subject.

8.2 Withdrawal from the Trial

A subject will be withdrawn from the trial for any of the following reasons:

- Death
- Lost to follow-up
- Sponsor decision
- Subject withdrawal of consent from trial
- Other

When a subject withdraws before completing the trial, the reason for withdrawal is to be documented. If the reason for withdrawal from the trial is withdrawal of consent, then no additional assessments are allowed, but the sponsor may retain and continue to use any data collected before the subject withdrew consent.

8.3 Safety Follow-up Evaluations

Subjects discontinuing from treatment for any reason will have SFUs 30 days (+5 days) (ie, SFU1) and 60 days (±7 days) (ie, SFU2) after the subject receives the last dose of trial treatment. In addition, subjects in the combination cohort will have a third SFU visit 90 days (±7 days) (ie, SFU3) after the subject receives the last dose of trial treatment. Refer to Section 10.2 for the specific AE reporting requirements in each SFU period. If the subject initiates new anti-cancer treatment within the SFU period, the SFU should be performed prior to starting new anti-cancer treatment.

8.4 Lost to Follow-up

For subjects whose status is unclear because they fail to appear for trial visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the subject, family or family physician as agreed in the ICF and by documenting in the source documents steps taken to contact the subject, eg, dates of telephone calls, registered letters. A subject should not be considered lost to follow-up until due diligence has been completed (at a minimum, 3 documented attempts).

9 TRIAL ASSESSMENTS

9.1 Demography and Baseline Assessments

9.1.1 Demographics

Demographic details will be assessed at screening.

9.1.2 Diagnosis and Disease Status

A subject's history relating to the underlying disease, including primary diagnosis, date of diagnosis, as well as disease status at trial entry, will be documented at screening. The primary site of cancer and initial and current disease stage (Tumor Nodes Metastasis [TNM] staging system) will be recorded.

For disease status the following will be collected:

- PD-L1 status as per local assessment (if available)
- Deficient mismatch repair (dMMR) or microsatellite instability (MSI) status as per local assessment (if available)
- Non-small cell lung cancer subjects: tumor status with respect to EGFR mutations and ALK/ROS1 rearrangement as per local assessment (if available)
- Squamous cell carcinoma of the head and neck (SCCHN) and cervical cancer: Human papillomavirus (HPV) status as per local assessment (if available)

9.1.3 Medical History

All relevant past and all current medical conditions/diseases (signs, symptoms, and diagnosis) occurring prior to the first dose of trial treatment should be documented as medical history. Medical conditions that occur after the ICF is signed and prior to the first dose of trial treatment should only be reported as AEs if there were assessed by the investigator to be caused by a protocol-mandated procedure (ie, tumor biopsy and/or CT scan), including washout or discontinuation of prior medications.

Any medical history/current medical condition that worsens after the first dose of trial treatment will be documented as an AE. See additional reporting details in Section 10.2.

9.1.4 Concomitant Medication

Any medication or therapy (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements, and blood transfusions) other than the trial treatment is considered concomitant medication and must be recorded.

Relevant prior concomitant medication administered during the trial from 21 days prior to first dose of GEN1046 and up to the last SFU visit should be recorded.

The subject must be told to notify the investigational site about any new medications he or she takes after the start of trial treatment. The sponsor's medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

9.1.5 Prior Cancer Therapy and Surgery

Administration of prior anti-cancer therapies for the disease under study, including surgery, radiotherapy, chemo-radiotherapy, systemic treatment regimens etc, from the time of the initial diagnosis until enrollment in this trial will be documented.

In addition, the best response, reason for discontinuation, dates of administration, and progression should be reported for anti-cancer therapies.

9.2 Efficacy Assessments

All subjects will have a CT scan with contrast or MRI-scan of the thorax, abdomen, and pelvis performed during Screening. Head and neck imaging is also required for subjects with SCCHN. Imaging of the pelvis is not required for subjects with SCCHN but is strongly recommended.

If approved by the sponsor, an MRI may be obtained (eg, if a CT with iodinated contrast is contraindicated). If there is suspicion of brain metastases or tumors, a CT scan of the head and neck or MRI will be performed before inclusion.

Localized CT with contrast or MRI (with or without contrast; for sarcomas with contrast) must be acquired for assessment of lesions of the skeleton/extremities and head and neck if not visible on other images. At the discretion of the investigator and after approval of the sponsor, combined positron emission tomography (PET)/CT (eg, fluorodeoxyglucose [FDG]-PET) may be performed for tumor assessments as per RECIST 1.1, but only if the CT portion is of similar diagnostic quality to CT alone.

The same imaging modality and ideally the same scanner should be used throughout the trial to optimize the reproducibility of the assessment and preserve the accuracy of the assessment of response or progression. Chest X-rays and ultrasound should not be used to measure tumor lesions.

Up to 5 target lesions (maximum 2 per organ) will be defined at screening and these must be followed throughout the trial. A lesion from which a fresh biopsy has been taken during the trial cannot be a target lesion. Non-target lesions will also be assessed throughout the trial. Initial tumor imaging at screening must be performed within 21 days prior to the date of first dose. If a CT scan or MRI has been performed within 21 days prior to visit C1D1 as part of standard procedure, it is acceptable as a screening scan for the trial. If there is suspicion of brain metastases, a CT scan or MRI of the head and neck will be performed within 21 days prior to the C1D1 visit. Scans that exceed the 21-day window may be used for trial enrollment with sponsor approval. The site must review screening images to confirm the subject has measurable disease per RECIST 1.1.

On-trial imaging will be performed every 9 weeks (±7 days) from the date of first dose (C1D1) until disease progression is assessed by the investigator (unless the investigator elects to continue treatment according to Immune Response Evaluation Criteria in Solid Tumors [iRECIST]), the start of new anti-cancer therapy, withdrawal of consent, or death, whichever occurs first. Imaging assessments should follow calendar days and should not be adjusted for delays in cycle starts. If imaging shows disease progression, then a subsequent imaging assessment should be performed within 4 to 7 weeks to confirm progression.

The reading of the scans will be done by a local radiologist. Sites should attempt to maintain the same radiologist throughout the trial. Results from the radiology evaluations shall be recorded and a copy of the evaluation reports should be kept in the subject's file. RECIST 1.1 criteria will be used for secondary endpoint response evaluation (Eisenhauer et al., 2009). If the investigator elects

to apply iRECIST (Seymour et al., 2017), treatment should continue until progressive disease (PD) has been verified.

Stable disease (SD) should meet the minimum duration of 6 weeks from the start of treatment. Additional CT scans or MRI-scans may be performed at the investigators discretion to confirm response or new symptoms. Tumor imaging to confirm partial response (PR) or CR should be performed at least 4 weeks after the first indication of a response is observed. In this case, the investigator must choose the imaging technology based on the clinical indication.

9.2.1 iRECIST Assessment of Disease

iRECIST (Seymour et al., 2017) is based on RECIST 1.1 but has been modified to account for the unique response patterns observed with immunotherapy.

iRECIST disease progression should be confirmed at least 4 to 7 weeks after the first radiologic evidence of PD in clinically stable participants. Subjects who have unconfirmed disease progression may continue on trial treatment until progression is confirmed as long as the subject is clinically stable. Subjects who are clinically stable must meet the following criteria:

- Subject must have clinical benefit from continuation of GEN1046 treatment (as assessed by the investigator) and must not have rapid disease progression
- Subject is tolerating GEN1046 treatment
- Subject must have a stable ECOG status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications for disease progression (eg, CNS metastases requiring immediate treatment).

Any clinically unstable subjects should be discontinued from trial treatment at the first occurrence of radiographic disease progression. Subjects that are clinically unstable are not required to have repeated imaging to confirm PD by iRECIST however, a confirmation of progression scan may be obtained at the investigator's discretion after consultation with the sponsor.

If repeat imaging shows iRECIST immune confirmed disease progression (iCPD), subjects will discontinue trial treatment. However, if the subject is deriving benefit after iCPD is observed, an exception to continue trial treatment must be approved by the sponsor's medical monitor. If repeat imaging shows iRECIST immune stable disease (iSD), iRECIST immune partial response (iPR), or iRECIST immune complete response (iCR), imaging should be continued every 9 weeks (±7 days) and the subject should continue on trial treatment. Subjects who have repeat imaging to confirm progression do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later.

9.3 Clinical Safety Assessments

9.3.1 Physical Examination

The investigator or qualified designee will perform a full physical examination according to standard of care during the screening period. Report any relevant findings as medical history. Report any medical conditions as an AE if they were assessed by the investigator to have been caused by a protocol-mandated procedure (ie, tumor biopsy and/or CT scan), including washout or discontinuation of prior medications. After the first dose of trial treatment, report any new or

worsening findings since the last assessment as AEs. The time points for full physical examinations are described in Table 1-1.

After the screening visit, a physical exam should only be performed as indicated by the subject's symptoms, AEs, or other findings as determined by the investigator.

Symptom-Directed Physical Exam:

For visits that do not require a full physical examination (see Table 1-1), the investigator or qualified designee will perform a symptom-directed physical examination as clinically indicated prior to trial treatment administration. New or worsening findings since the last assessment should be recorded as AEs.

9.3.2 Body Measurements

Height (in cm) will be measured at screening.

Body weight (without overcoat and shoes) will be measured at the time points indicated in Table 1-1 and rounded to the nearest kilogram.

9.3.3 Vital Signs

Vital signs, including temperature, blood pressure, and heart rate, should be measured with the subject in a supine or reclined position and recorded. Within each visit, preferably the same equipment shall be used for vital sign measurements. On infusion days, vital signs should be assessed at the time points indicated in Table 1-1. On non-infusion days, vital signs should be assessed any time during the visit.

9.3.4 Electrocardiograms

The ECGs will be recorded digitally at the sites by using the standard 12-leads at the time points outlined in Table 1-2. ECGs will be performed in triplicate.

An overall interpretation of the ECGs will be performed by the investigator, or the investigator may delegate this task to a cardiologist, if applicable. The investigator ECG interpretation must be done using the paper ECG reading from the ECG machine by signing and dating the printout.

For the ECG recordings, the subjects must be resting and in a supine or reclined position for at least 10 minutes. Any irregularity observed or occurring during the ECGs (eg, vomiting, cough) should either repeat the ECG or be annotated on the electronic case report form (eCRF) with the description and time of the occurrence.

9.3.5 ECOG Performance Status

The ECOG PS will be assessed by the investigator at the time points indicated in Table 1-1. The screening and C1D1 ECOG PS must be within 0-1 or the subject cannot receive trial treatment. However, the C1D1 ECOG PS should not be performed if the screening ECOG-PS was obtained within the previous 5 days. Performance status will be scored using the ECOG PS scale index (Table 9-1).

Table 9-1 ECOG Performance Status

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

ECOG=Eastern Cooperative Oncology Group.
Source: (Oken et al., 1982).

9.3.6 ILD Screening and Early Detection

For ILD screening and early detection following trial treatment initiation, the following tests will be performed.

- Oxygen saturation measurements should be performed at screening and on Day 1 in each cycle.
- Chest X-ray imaging will be added at screening. During the treatment period, chest X-ray imaging and/or CT scan are optional and may be performed if clinically indicated. If a CT scan is performed for efficacy evaluation, the result can be substituted.
- Any additional testing such as Krebs von den Lungen-6, CT, and others to be performed, if clinically indicated and by principal investigator decision based on ILD clinical guidelines (JSH-Guidelines, 2014) or similar.

9.4 Clinical Laboratory Assessments

The tests to be performed are detailed in Table 9-2 and will be collected according to the visit schedule outlined in Table 1-1. Central and local laboratories will be used for analyses.

The investigator must review all laboratory results, document this review, and record any clinically relevant changes including dose modifications or delays as an AE. For AE reporting of laboratory test abnormalities, refer to Section 10.2.4.

9.4.1 Local Laboratory Assessments

Local laboratory values for hematology, biochemistry and coagulation must be obtained within 7 days prior to the first dose of each subject (with the exception of hepatitis B which may be obtained earlier and reviewed by the investigator prior to the first dose to ensure that the subject is still eligible). For the subsequent doses, these laboratory values must be obtained within 3 days, preferably on the day prior to each trial treatment administration and reviewed by the investigator prior to each trial treatment administration to ensure the subject can be dosed in line with the dosing instructions as defined in Section 6.2.

Additional local laboratory values may be obtained at the discretion of the investigator and used for other clinical treatment decisions of the subject.

9.4.2 Central Laboratory Assessments

Central laboratory assessments include PK (Section 9.5), immunogenicity assessments (anti-drug antibodies [ADAs]) (Section 9.6), and biomarker samples (Section 9.7). Details on the collections,

shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

Table 9-2 Laboratory Assessments

Local Laboratory				
Test Category	**Parameters**			
Hematology	Platelet count Red blood cell (RBC) count Hemoglobin Hematocrit	RBC indices: Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) % Reticulocytes		White blood cell (WBC) count with differential:[1] Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Biochemistry	Albumin	Blood urea nitrogen (BUN)	Gamma-glutamyl transferase (GGT)	Phosphate
	Alanine aminotransferase (ALT)	Calcium	Glucose	Potassium
				Sodium
	Alkaline phosphatase (ALP)	Chloride	Glycosylated hemoglobin (HbA1C)	Total and direct bilirubin
	Amylase	C-reactive protein (CRP)	Lactate dehydrogenase (LDH)	Total protein
	Aspartate aminotransferase (AST)	Creatinine (and estimated GFR[2])	Lipase	Uric acid
			Magnesium	Ferritin[3]
Coagulation factors	Prothrombin time (PT)	International normalized ratio (INR)	Activated partial thromboplastin time (aPTT)	
Urinalysis	Leukocytes	Protein	Urine pregnancy test	
Endocrine	Thyroid-stimulating hormone (TSH)	Free thyroxine (T4)	Total triiodothyronine (T3)[4]	
Serology	• Hepatitis B surface antigen (HBsAg) and hepatitis B core and surface antibodies (HBcAb and HBsAb, respectively). • Hepatitis C virus (HCV) antibody. If positive serology, PCR for HCV RNA to be performed.			
Pregnancy Test	For female subjects with child-bearing potential, a serum or urine pregnancy test should be performed at screening.			
KL-6	If clinical indicated and by PI decision based on ILD clinical guidelines (JSH-Guidelines, 2014) or similar (see Section 9.3.6).			
Central Laboratories				
Test Category	**Notes**			
PK	Plasma levels of GEN1046 (Section 9.5)			
Immunogenicity	Serum presence of antibodies against GEN1046 (ADA) (Section 9.6).			
Biomarkers	Tumor tissue sample; whole blood samples (see Section 9.7).			

GFR=glomerular filtration rate; ILD=interstitial lung disease; KL-6=Krebs von den Lungen-6; PCR=polymerase chain reaction; PI=principal investigator; PK=pharmacokinetic(s); RBC=red blood cell; RNA=ribonucleic acid; WBC=white blood cell.

1. WBC differential required in absolutes; also provide differential in percentages if available.
2. GFR to be estimated at screening, using the Abbreviated Modification of Diet in Renal Disease formula (see Appendix 2).

3. Refer to Section 7.3.3.2 for additional analytes to monitor if HLH is suspected.
4. Free T3 is acceptable if considered local standard.

9.5 Pharmacokinetics

9.5.1 Pharmacokinetic Assessments

Venous blood samples will be collected for measurement of plasma concentrations of GEN1046 as specified in Table 1-2.

Samples will be used to evaluate the PK of GEN1046. Samples collected for analyses of plasma concentration may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the trial period. Subject confidentiality will be maintained.

Additional information about the collection, handling, and shipment of samples is included in the laboratory manual.

9.5.2 Analytical Procedures

Plasma samples will be analyzed to determine concentrations of GEN1046 using validated methods.

9.6 Immunogenicity

9.6.1 Immunogenicity Assessments

Venous blood samples will be collected for the determination of ADAs to GEN1046 in serum at the time points specified in Table 1-3.

Serum samples will be screened for ADAs to GEN1046 and the titer of confirmed positive samples will be reported. The detection and titer characterization of ADAs will be performed using validated, specific, and sensitive electrochemiluminescence immunoassay (ECLIA) methods and the titer of confirmed positive samples will be reported. Samples collected for ADAs to GEN1046 may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the trial period for further characterization of immunogenicity. Subject confidentiality will be maintained.

The analysis will be performed under the supervision of the sponsor at an assay CRO. Neutralization characterization of ADAs may be performed at sponsor laboratories using appropriate methods.

Further details are included in the laboratory manual.

9.6.2 Analytical Procedures

The detection and characterization of antibodies to GEN1046 will be performed using validated methods under the supervision of the sponsor.

9.7 Biomarker Investigations

Biomarker investigations in this trial will include both candidate predictive biomarkers that may predict drug response to the treatment, and pharmacodynamic biomarkers in order to confirm biological activity and the proposed MOA for GEN1046. Biomarker samples will be collected as specified in Table 1-4.

Biomarker assessments will examine subject biological features for:

- Evaluating circulating chemokines and cytokines as a potential pharmacodynamic biomarker of response.
- Evaluating tumor/target associated markers (ie, 4-1BB and PD-L1 expression) and tumor-infiltrating T-cell characteristics as a potential predictive biomarker that can identify those subjects that will respond to GEN1046.

All biomarker assessments will be performed at Genmab or laboratories designated by Genmab.

9.7.1 Biomarker Assessments in Tumor Samples

All subjects must provide a tumor tissue sample (FFPE blocks/slides) from archival tissue or fresh tumor biopsy (aspirates are not acceptable) collected at screening, preferably derived from advanced stage disease. Details as to the preparation of slides and number of slides to be prepared will be described in the laboratory manual. In case it is not feasible to meet the required criteria for fresh tumor biopsy in escalation or expansion, the sponsor's medical monitor's approval for enrollment is needed. If deemed necessary by the investigator, the subject may be called in for an unscheduled visit; optional tumor biopsies may be collected if subjects have unscheduled biopsies or tumor tissue resection during the course of the trial.

Biomarker analyses in the tumor sample obtained at baseline and during treatment may help confirm the MOA of GEN1046 and enable the identification of biomarkers predictive of response to GEN1046 or to further understand the biology of the various types of cancer under study. Potential mechanisms of tumor response and resistance as well as treatment-induced changes in the tumor immune microenvironment may be monitored.

Analytes will be evaluated via immunohistochemistry (IHC)/immunofluorescence (IF) assays. If this technology is unavailable or deemed insufficient, an equivalent platform will be used as an alternative. Assessments will be performed at the time points outlined in Table 1-4 in order to enable correlation analyses with response to treatment or disease progression.

9.7.2 Biomarker Assessments in Blood Samples

Biomarker assessments will be performed using whole blood samples to investigate potential pharmacodynamics of circulating cytokines, chemokines, or soluble factors in relationship to efficacy or MOA of GEN1046. Analytes will be evaluated via enzyme-linked immunoassay (ELISA)/multi-array formatted assays. If this technology is unavailable or deemed insufficient, an equivalent platform will be used as an alternative. Assessments will be performed at the time points outlined in Table 1-4 in order to enable correlation analyses with response to treatment or disease progression.

9.7.3 Sample Collections

Samples for biomarker analyses will be collected as specified in Table 1-4. A tumor biopsy sample must be submitted during the screening period. A fresh biopsy obtained during screening may be provided; if a fresh biopsy cannot be obtained, the most recent archival tissue can be submitted if acquired ≤6 months prior to C1D1. Details for the preparation of slides and number of slides to be prepared will be described in the lab manual.

If it is determined at any time before trial completion that additional material is needed from an FFPE tumor sample for the successful completion of the protocol-specified analyses, the sponsor

may request that additional material be submitted, if available. Also, based on emerging scientific evidence relating to a potential correlation between a biomarker and treatment efficacy or safety, the sponsor may request additional material from previously collected tumor samples, if available.

Details on the collection, processing, storage, and shipment of biomarker samples will be provided in separate documents (eg, sample handling sheets or laboratory manual).

9.7.4 DNA/RNA Research

Not applicable.

9.8 Resource Utilization

Not applicable.

9.9 Patient Reported Outcomes

Not applicable.

10 SAFETY MONITORING AND ADVERSE EVENT REPORTING

10.1 Adverse Event Definitions

10.1.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a clinical trial subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

AEs (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

10.1.2 Definition of Serious Adverse Events

An SAE is defined as an AE that meets 1 of the following criteria:

- Is fatal or life-threatening[1]
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, ie, defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above. Medical and scientific judgment must be exercised in deciding whether an AE is “medically significant.”
- Requires inpatient hospitalization or prolongation of existing hospitalization[2]

[1] The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

[2] Hospitalizations for the following reasons should not be reported as SAEs:

- Routine treatment or monitoring of the underlying disease, not associated with any deterioration in the condition
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the underlying disease and has not worsened since signing the informed consent
- Social reasons and respite care in the absence of any deterioration in the subject’s general condition
- Treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of an SAE given above is not an SAE.

10.1.3 Definition of Adverse Events of Special Interest

Adverse events of special interest (AESIs) are defined as events, serious or nonserious, which are of scientific and medical concern specific to the sponsor’s product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

No AESIs have yet been defined for treatment with GEN1046.

10.1.4 Definition of Infusion-Related Reactions

IRRs are defined as any AEs occurring during infusion or where the onset of the event occurs within 24 hours after the end of infusion.

Investigators should consider the clinical picture and isolated events, such as "Fatigue," occurring within 24 hours after the end of infusion and assess whether they do or do not constitute an IRR.

For IRRs the causality of the event should be judged as "related" by the investigator.

10.1.5 Immune-related Adverse Events

Symptoms of irAEs should be quickly detected and treated as early as possible to prevent irreversible effects for which careful monitoring and timely management should follow conventional standards. Treatments may include corticosteroids as per investigator's discretion, along with other immune suppressive agents as required (see Section 7.3.1).

10.2 Adverse Event Reporting

All AEs must be reported from first dose of trial treatment until 60 days after the last dose of trial treatment. For subjects in the combination cohort, only SAEs, regardless of casualty should be documented from SFU2 through SFU3. Medical conditions that occur after the ICF is signed and prior to the first dose of trial treatment should only be reported as AEs if they were assessed by the investigator to be caused by a protocol-mandated procedure (ie, tumor biopsy and/or CT scan), including washout or discontinuation of prior medications.

The investigator will use the NCI CTCAE version 5.0 (NCI-CTCAE, 2017) to describe the intensity of AEs, with the exception of CRS, which will be graded according to the ASTCT criteria described by (Lee et al., 2019). Changes in intensity of an ongoing AE should be assessed at each visit or more frequent if deemed necessary and should be reported.

SAEs still ongoing after the SFU(s) should be followed on a regular basis according to the investigator's clinical judgment until the event has been resolved or until the investigator assesses it as chronic and all queries have been resolved. Only SAEs judged by the investigator as related to trial treatment should be reported after the last SFU.

Note:

- Final assessment of AEs must be performed by a medically qualified person, ie, a medical doctor.
- All AEs that occur during the AE reporting period must be reported, whether or not the event is treatment-related.
- All AEs should be entered in the eCRF and assessment should be made at each visit (or more frequently, if necessary).

10.2.1 Pre-existing Condition

In this trial, a pre-existing condition (ie, a disorder that was present before the AE reporting period has started and noted on the medical history form) is not to be reported as an AE. If, however, a pre-existing condition worsens during the treatment period, the event must be reported as an AE.

10.2.2 Diagnosis

The diagnosis/cause of an AE should be recorded rather than the symptoms of the AE. If no diagnosis is available, each sign and symptom should be recorded as individual AEs.

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

10.2.3.1 Disease Progression or Death

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be reported 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 that 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 should be reported as an AE or SAE.
- Hospitalization due solely to progression of the underlying cancer should not be reported as an SAE. See Section 10.1.2, under the definition of SAE, for additional reasons when hospitalizations should not be reported as SAEs.

10.2.3.2 Unrelated Procedures

Diagnostic and therapeutic non-invasive 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, an acute appendicitis should be reported as the AE and not the appendectomy).

10.2.4 Laboratory Test Abnormalities

Laboratory abnormalities that are considered clinically significant, ie, induce clinical signs or symptoms, require concomitant therapy, or require changes in trial treatment should be documented as an AE. Whenever possible, a diagnosis, rather than a symptom should be provided (eg, acute renal insufficiency due to acute tubular necrosis). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the laboratory/test result as an additional event.

10.3 Events Requiring Immediate Reporting

10.3.1 Serious Adverse Events

SAEs must be reported from the investigational site to the sponsor no later than 24 hours following a) the subject's visit at which such AE was reported, noted or recognized; b) the principal

investigator's or any investigator personnel's receipt of the test results; or c) other information at, or from which, such development was reported, noted or recognized.

Grade 3 and grade 4 abnormal laboratory test results if deemed serious (see Section 10.1.2) must be reported as SAEs when these are assessed as clinically significant by the reporting investigator.

10.3.2 Overdose and Medication Errors

An overdose is defined as a subject receiving a dose of GEN1046 in excess of 10% of that specified in this protocol.

An overdose of pembrolizumab is defined as any dose of 1000 mg or greater.

All cases of overdose must be reported to the sponsor as protocol deviations within 24 hours of knowledge of the event.

Medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product, should be reported as protocol deviations to the sponsor within 24 hours of knowledge of the event.

All cases of overdose and medication errors must be recorded in the AE page of the eCRF, whether associated with an AE or not, within 24 hours after awareness.

Overdose, medication errors, misuse and abuse do not automatically make an AE serious, but if the consequences are serious, for example death or hospitalization, the event is serious and must be reported as an SAE.

Rescue medication to reverse the action of GEN1046 is not available. In case of overdose, medication errors, misuse and/or abuse of trial drug, subjects should be monitored closely for potential side effects of GEN1046 and receive supportive care according to local guidelines for the management of the potential side effects.

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

In the event of an overdose, the investigator should:

- Contact the sponsor's medical monitor immediately.
- Closely monitor the subject for any AE/SAE and laboratory abnormalities until GEN1046 can no longer be detected systemically.
- Obtain a serum sample for PK analysis if requested by the sponsor's medical monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose.

10.3.3 Pregnancy

Pregnancy is not allowed in this trial. However, if any pregnancy occurs during trial participation, the pregnancy must be reported using the pregnancy reporting paper form available in the investigator site file. Pregnant trial subjects must be withdrawn from treatment immediately, whereas male subjects may continue in the trial should pregnancy of female partners occur. In this case, a separate informed consent will be obtained from the female partner for collection of information regarding the pregnancy.

All reports of pregnancy, occurring during the trial or 6 months after the last dose of trial drug, in female subjects or partners of male subjects must be reported to sponsor or designee within 24 hours of learning of its occurrence. The pregnancy must be followed-up to determine outcome (including premature termination) and status of mother and child. The child must be followed at least to the age of 1 month. Pregnancy complications and elective terminations must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE. Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the trial and considered by the investigator as possibly related to trial treatment, must be promptly reported to sponsor or designee.

10.3.4 Timelines for Reporting

All SAEs, events of overdose and/or medication errors with trial treatment, and pregnancy must be reported to the sponsor within 24 hours after the trial site's awareness.

The primary mechanism for reporting an SAE to the sponsor is the EDC tool. In order to report pregnancies and if the EDC tool is unavailable to report SAEs, then 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 trial has ended, if the investigator learns of a treatment-related SAE, the event should be reported using the paper forms via secure transmission.

If the EDC system is down, the SAE, overdose and/or medication error must be reported from the trial site via:

- The Safety CRO email (GlobalSAEInbox@fortrea.com), or
- Fax (Japan – IDC: (81) 0061010 800-529-34043, Japan – KDDI: (81) 001010 800-529-34043, Japan - NTT: (81) 0033010 800-529-34043)

The Safety Reporting mailbox is available to receive reports 24 hours per day, 365 days per year. A safety reporting form or pregnancy form will be submitted to the Safety CRO by email/fax regardless of whether it is night, a weekend, or holiday, if the EDC is down.

10.4 Suspected Unexpected Serious Adverse Reactions

The sponsor has a legal responsibility to notify, as appropriate and according to local regulations, both the local regulatory 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 subjects are met.

The sponsor will ensure that all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSARs) is recorded and reported as soon as possible, but within a maximum of 15 days (fatal or life-threatening SUSARs within a maximum of 7 days) of first knowledge by the sponsor or designee, to the competent regulatory authorities and/or to the ethics committee according to the applicable local regulatory requirements. Relevant follow–up information of fatal or life-threatening SUSARs will be communicated subsequently within an additional 8 days. The sponsor will also communicate relevant information on SUSARs with the investigators, the head of the trial site and the IRB/IEC in predefined periods according to local regulations.

The investigator should be aware of local reporting regulations to the head of the trial site and the sponsor on all SAEs that occur at his/her site, and the head of the trial site will report to the

IEC/IRB. The investigator will respond to requests when the sponsor, the head of the trial site, or the IEC/IRB requires more information. The sponsor will supply the investigator and the head of the trial site and the IEC/IRB with the reports.

The sponsor will notify all investigators of the SUSAR in predefined periods according to local regulations.

10.5 Follow-Up on Adverse Events

All AEs should be followed until they are resolved, until the end of the safety follow-up period, or the start of new anti-cancer treatment, whichever comes first. However, all SAEs (independent of causality) still ongoing after the SFU must be followed on a regular basis, according to the investigator's clinical judgment, until the event has been resolved or until the investigator assesses it as chronic and all queries have been resolved.

10.6 Warnings and Precautions

No evidence available at the time of the approval of this trial protocol indicated that special warnings or precautions were appropriate, other than those noted in the IB. Additional relevant safety information collected between IB updates will be communicated in the form of investigator notifications. This information will be included in the subject informed consent and should be discussed with the subject during the trial as needed.

10.7 Dose Escalation Committee and Safety Committee

Subject safety will be monitored throughout the trial by the DEC and the Safety Committee. The DEC will be chaired by the sponsor's medical monitor and membership will include at a minimum the trial principal investigators, members of the sponsor medical and safety departments, as well as additional staff as appropriate.

The DEC will meet after completion of DLT evaluation period (ie, 21 days) by subjects enrolled at each dose level in the dose escalation part. Dose escalation recommendations will be proposed by the DEC in conjunction with the participating investigators. The DEC will convene when all subjects at a dose level complete the DLT evaluation period to make a recommendation regarding further dose escalation. Similarly, the DEC and Safety Committee will review all available clinical data for the combination cohort and evaluate the safety of combining GEN1046 and pembrolizumab.

The Safety Committee is convened after each DEC meeting to evaluate the recommendations from the DEC and determine how to proceed. The Safety Committee will monitor all available treatment-emergent data to ensure subject safety. The Safety Committee is responsible for ensuring that participation in the trial is safe for trial subjects, evaluating the outcome of ongoing safety surveillance, evaluating outcomes of DEC meetings, performing benefit-risk assessments, and for ensuring that appropriate actions are taken when new safety issues emerge.

11 STATISTICS

The statistical analysis of the data collected in this trial is the responsibility of the sponsor. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. A Statistical Analysis Plan (SAP) with further details of the planned analyses will be developed and finalized before database lock.

11.1 Statistical Hypotheses

Objectives and endpoints of the trial are stated in Section 3. There are no predefined hypotheses for this trial.

11.2 Sample Size Determination

The sample size is driven by the 3+3 design and pre-specified dose levels.

11.3 Populations for Analyses

11.3.1 Full Analysis Set

The full analysis set (FAS) comprises all subjects to whom trial treatment has been assigned and who received at least 1 dose of trial treatment. For all safety analyses, the FAS will be used.

11.3.2 Dose-Determining Analysis Set

The dose-determining set includes all subjects from the FAS who are followed up for at least 21 days after the initial full dose (see Section 4.1.3) of trial treatment and including any subject who had a DLT within the first cycle. This will be used for evaluation of DLTs.

11.3.3 Pharmacokinetic Analysis Set

The pharmacokinetic analysis set includes all subjects who provide an evaluable PK profile. A profile is considered evaluable if the following conditions are satisfied:

- The subject receives at least 1 dose of trial treatment.
- The subject provides at least 1 PK parameter.

11.3.4 Other Analysis Sets

Not applicable.

11.4 Statistical Analyses

11.4.1 Subject Demographics and Baseline Characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively for the FAS.

Relevant medical histories and current medical history at baseline will be summarized by system organ class and preferred term.

11.4.2 Treatment Exposure and Medications

The FAS will be used for the analyses below.

The duration of exposure in months to trial treatment as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized by means of descriptive statistics using the FAS.

Concomitant medications and significant non-drug therapies prior to and after the start of trial treatment will be listed and summarized according to the anatomical therapeutic chemical (ATC) classification system.

11.4.3 Safety Analyses

For all safety analyses, the FAS will be used.

11.4.3.1 Adverse Events

Summary tables for AEs will include only AEs that started or worsened during the on-treatment period (from the first dose of trial treatment until 60 days [SFU2] or 90 days [SFU3] after the last dose of trial treatment for monotherapy or combination therapy cohorts, respectively, or until the start of new anti-cancer treatment, withdrawal of consent, or death, whichever occurs first), ie, the TEAEs.

The incidence of TEAEs (new or worsening from baseline) will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and/or preferred term, severity (based on grades of CTCAE, version 5.0, with the exception of CRS, which will be graded according to the ASTCT criteria described by (Lee et al., 2019)), and relationship to trial drug.

All AEs, including SAEs and AESIs, during the on-treatment period will be tabulated.

All deaths (on-treatment and post-treatment) will be summarized.

All AEs, deaths, and SAEs (including those from the pre- and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

Further summaries of AEs, including summaries of AESIs, will be specified in the SAP.

11.4.3.2 Clinical Laboratory Data

Grading of laboratory values will be assigned programmatically as per CTCAE version 5.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher.

For laboratory tests where grades are not defined by the CTCAE, results will be categorized as low/normal/high based on laboratory normal ranges.

The following summaries will be generated separately for hematology, and biochemistry tests:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE grades, if applicable, and the classifications relative to the laboratory normal ranges.

For laboratory tests where grades are defined by the CTCAE:

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each subject will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value.

For laboratory tests where grades are not defined by the CTCAE:

- Shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.

11.4.3.3 DLTs

DLTs will be listed.

11.4.3.4 Other Safety Data

ECGs

12-lead ECGs including PR, QRS, QT, QTcF, and RR intervals will be obtained for each subject during the trial. ECG data will be read and interpreted (locally).

Categorical analysis of QT/QTc interval data based on the number of subjects meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented. In addition, a listing of these subjects will be produced (by treatment group).

Vital signs

Data on vital signs will be tabulated and listed; notable values will be flagged.

11.4.4 Pharmacokinetic Parameters

Individual curves of plasma concentration of GEN1046 as monotherapy or in combination with pembrolizumab, including information on actual dose, will be presented for all subjects. All available data will be shown in these figures. Concentrations below the limit of quantitation will be set to the lower limit of quantification (LLOQ)/2.

PK parameters (Table 11-1) may be calculated based on non-compartmental methods, depending on data availability. The PK parameters will be calculated separately for Cycle 1 and Cycle 3.

Further exploratory analyses of PK data may be performed.

Table 11-1 Non-compartmental Pharmacokinetic Parameters

Parameter	Description
CL	The total body clearance of drug from the plasma
Vd	Volume of distribution
AUC_{21days}	The AUC from time zero to day 21 (mass × time × volume-1)
AUC_{inf}	The AUC from time zero to infinity (mass × time × volume-1)
AUC_{last}	The AUC from time zero to last quantifiable measurement
C_{max}	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration
C_{trough}	Predose concentration
T_{max}	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration
$T_{1/2}$	The elimination half-life associated with the terminal slope (λz) of a semi-logarithmic concentration-time curve

a. AUC=area under the concentration-time curve.

11.4.5 Immunogenicity Analyses

Anti-drug antibody titers against GEN1046 will be listed and positive/negative host immune response to GEN1046 and optionally presence of neutralizing antibodies will be summarized (positive/negative). The presence of PK concentrations above a certain threshold, that depends on

the drug tolerance of the ADA assay, at the same time as the ADA sample may make the ADA undetectable and hence render non-conclusive. The association between positive/non-positive ADA and PK (predose, area under the concentration-time curve [AUC], maximum concentration [C_{max}]), major safety signals (CTCAE ≥ grade 3) and efficacy information (change in tumor size by CT scan) will be explored.

11.4.6 Exploratory Analysis

11.4.6.1 Pharmacodynamic Activity of GEN1046 Administered as Monotherapy or in Combination With Pembrolizumab

Evaluate immune modulation biomarkers (cytokines associated with immune effector function such as IFNγ)

Biomarkers, such as PD-L1 and 4-1BB expression, peripheral immune cell populations, and cytokine measurements will be listed for all subjects who had samples collected and testing performed. Biomarker assessments will be summarized by time point using descriptive statistics.

Results of biomarker analyses may be presented in a separate report.

11.4.6.2 Anti-Tumor Activity of GEN1046 Administered as Monotherapy or in Combination With Pembrolizumab

Based on RECIST v1.1 (Eisenhauer et al., 2009) per the investigator's assessment:

- Confirmed objective response rate (ORR)
- Disease control rate (DCR)
- Duration of response (DOR)

The confirmed ORR is defined as the proportion of subjects with best overall response (BOR) of CR or PR, which is confirmed by subsequent tumor assessment according to RECIST 1.1. ORR will be calculated based on the FAS, and its exact 95% CI, calculated by the Clopper-Pearson method, will be presented overall and by dose level.

DCR is defined as the proportion of subjects with BOR of CR, PR, or SD, per RECIST 1.1. DCR will be calculated based on the FAS, and its exact 95% CI, calculated by the Clopper-Pearson method, will be presented overall and by dose level.

DOR applies to subjects whose BOR is confirmed CR or PR according to RECIST 1.1 based on tumor response data. The start date is the date of first documented response of CR or PR (ie, the start date of response, not the date when response was confirmed), and the end date is defined as the date of the first documented progression or death. Subjects continuing without progression or death will be censored at the date of their last adequate tumor assessment. DOR will be listed and summarized for all subjects in the FAS with confirmed BOR of CR or PR.

The BOR is the best response recorded from the start of the treatment until disease progression/recurrence (the smallest measurements recorded since the treatment started will be used as the reference for PD). Subjects with CR or PR are considered to have an objective response. Subjects with CR, PR or SD are considered to be in disease control. Subjects who are not evaluable (NE) are counted as non-responders.

The best change in target lesions (maximal reduction in the sum of the diameters in the target lesions) at any time on trial will be reported using waterfall plots.

Individual subject data listings and summaries of ORR, best overall tumor response, and DCR will be presented by cohort/indication and total.

11.4.7 Interim Analyses

No formal interim analysis is planned for this trial.

12 DATA HANDLING AND RECORD KEEPING

12.1 Source Documentation

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly documented at the trial site as a basis for standard medical care. Specific details required as source data for the trial will be reviewed with the investigator before the trial described in the monitoring guidelines (or equivalent) and captured in a source data verification log at site.

For each subject, the investigator must indicate in the hospital/medical source records that the subject participates in this trial and the date of obtaining the ICF. The records should document data on the condition of the subject at the time the subject is enrolled in the trial to enable verification of eligibility. Signed and dated ICFs will be stored and archived according to local requirements. In addition, the following information, at the minimum, will also be recorded in the hospital/medical source records for each subject:

- Subject's name and date of birth.
- Screening/treatment number.
- Trial identification.
- Confirmation of eligibility for participation in the trial, including diagnosis.
- Medical history.
- Date of each visit.
- Any assessment performed eg, results of safety and efficacy evaluations.
- Concomitant medications.
- Occurrence of any AEs/SAEs (including description and duration).
- Status of the subject at the end of trial.
- Reason for discontinuation/withdrawal, if applicable.

Any worksheets used to capture data to facilitate completion of the eCRF will become part of the subject's source documentation.

In addition to the source data in medical records, data may be recorded directly electronically (eg, ECGs, PROs, etc). Such data are considered source data, and are accessible by both the investigator and sponsor.

The author of an entry in the source should be identifiable.

Information included in the subject's hospital records may be subject to local regulations. If there is a discrepancy between local requirements and the protocol, local regulations should be followed.

12.2 Case Report Form Completion

Case report form (CRF) data will be transcribed into an EDC system by trial-site personnel from the source documents. Both EDC and other electronically captured trial data are transmitted in a secure manner to the sponsor within agreed upon time frames.

Data relating to the trial must be documented and reported in English. Trial site personnel must complete the CRF as soon as possible after the data are available and preferably within 5 days. Source data and the CRFs should be available for review at the next scheduled monitoring visit. All eCRF entries, response to queries, corrections, and alterations must be made by the investigator or other authorized trial-site personnel. The completed eCRF must be verified and approved by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form.

Corrections to the eCRF after data entry can be done as follows:

- Trial-site personnel can make corrections in the EDC tool at their own initiative or as a response to an auto query (generated by the EDC tool).
- The monitor can generate a query for resolution by the trial-site personnel.
- The sponsor or designee can generate a query for resolution by the trial-site personnel.

12.3 Data Quality Management

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate trial sites, review of protocol procedures with the investigator and trial-site personnel before the trial, periodic monitoring visits by the sponsor (or sponsor's delegate), and direct transmission of clinical laboratory data from a central laboratory, into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided to trial-site personnel before the first subject is dosed. The sponsor/CRO will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the trial database, the data will be reviewed for accuracy and consistency with the data sources.

12.4 Record Retention

In compliance with current J-GCP, ICH GCP E6(R2), the investigator/institution (and as applicable, the IRB/sponsor) will maintain all eCRFs and all source documents, as well as a source document location list, that support the data collected from each subject, as well as all trial documents as specified in Record Retention of Article 26, 34 and 41 of J-GCP, and ICH GCP guideline Section 8, Essential Documents for the Conduct of a Clinical Trial, and all trial documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained for 25 years after end of trial. These documents will be retained for a longer period if required by the applicable regulatory requirements. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the trial records, custody must be transferred to a qualified and trained person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any trial documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this trial, the investigator/institution must permit access to such reports.

13 ETHICS

13.1 Trial-Specific Design Considerations

Thorough scientific evaluation of any promising treatment before market authorization is an ethical requirement. In the continuing search for medications with improved efficacy and safety profiles, it is necessary to fully investigate and understand new products before public exposure.

This trial is being conducted to evaluate the safety and PK of GEN1046 as monotherapy or in combination with pembrolizumab in subjects with advanced solid malignancies. The results of this trial will provide useful information on GEN1046 as monotherapy or in combination with pembrolizumab. These data are also needed to assist in developing dosage adjustment guidance in future trials.

The total blood volume to be collected is considered to be within the normal range allowed for this subject population over the time frame of the trial.

As with all clinical and PK trials, there are risks associated with venipuncture and multiple blood sample collection. To avoid multiple venipunctures, which may cause additional discomfort, the use of IV indwelling catheters is permitted in this trial. The blood sample collection scheme was designed to collect the minimum number of blood samples that accurately and completely describe the PK of GEN1046. Additionally, there are medical risks related to obtaining fresh biopsies. To mitigate such risks, fresh biopsies in this trial are performed only where it is considered feasible, without a high risk of complications for the subject, based on the discretion of the investigator.

Potential subjects will be fully informed of the risks and requirements of the trial and, during the trial, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the trial is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential AEs of the trial, and provide their consent voluntarily will be enrolled.

13.2 Regulatory Ethics Compliance

13.2.1 Investigator Responsibilities

The investigator is responsible for ensuring that the trial is performed in accordance with the protocol, current J-GCP, current ICH guidelines on GCP, and applicable regulatory and country-specific requirements.

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the trial data are credible.

13.2.2 Independent Ethics Committee or Institutional Review Board

This trial will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or trial conduct), the ICF, applicable recruiting materials, and subject compensation

programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data, or trial conduct), the amendment and applicable ICF revisions must be submitted promptly to the head of the trial site. The head of the trial site will submit them to the IEC/IRB for review and approval before implementation of the change(s), unless the amendment is issued to eliminate immediate hazards to trial subjects.

Where applicable, interim reports on the trial and/or review(s) of trial progress will be submitted by the investigator to the head of the trial site, and then, the head of the trial site will seek the opinion of the IEC/IRB with respect to the appropriateness of continuing the trial at the trial site at least once a year when the duration of the clinical trial exceeds 1 year.

At the end of the trial, the investigator (or sponsor where required) will notify the head of the trial site about the trial completion, and the head of the trial site will notify the IEC/IRB and the sponsor.

13.2.3 Informed Consent

The ICFs that are used must be approved by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki 2013, current ICH guidelines, applicable regulatory requirements, and sponsor policy.

It is the personal responsibility of the investigator or an authorized member of the trial-site personnel to explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the trial, and any discomfort participation in the trial may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time without justifying the reason. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of their disease. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable laws or regulations. By signing the ICF, the subject is authorizing such access and agrees to allow their trial physician to re-contact the subject for the purpose of obtaining consent for additional safety evaluations, including scans, if needed.

The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the trial, consent should be appropriately documented by means of the subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

13.2.4 Privacy of Personal Data

The head of the trial site/the investigator will ensure that the confidentiality of the subjects' data will be preserved. In the eCRF or any other documents submitted to the sponsor/ sponsor's representative, the subjects will not be identified by their names, but by an identification code, which consists of an assigned number in the trial. The confidential subject identification code and the signed Informed Consent Documents 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 subjects 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 is only stored on IT systems and networks that are protected against virus, malware, and unauthorized access.
- Data is 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 subjects and authorities, has been established in order to mitigate any adverse impact on the subjects.

Additional technical security measures implemented include that:

- All data is encrypted when at rest.
- Data has 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 subjects enrolled in this trial will be limited to those data that are necessary to fulfill the objectives and purposes of the trial 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 subjects confidential.

The informed consent obtained from the subject (or his or her legally acceptable representative) includes explicit consent or description of other legal basis for the processing of personal data for the purpose of the trial and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for trial-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 subject has the right to request access to his or her 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 trial, the clinical trial 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.

13.2.5 Return of Exploratory Research Data to Subjects and Investigators

Exploratory biomarker research is not conducted under standards appropriate for the return of data to subjects or investigators. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

14 ADMINISTRATIVE PROCEDURES

14.1 Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. 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 subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the trial, the IRB (and IEC where required) only needs to be notified.

During the course of the trial, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (see contact information page[s] provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

14.2 Regulatory Documentation

14.2.1 Regulatory Approval/Notification

This protocol (and any amendment[s] where necessary) must be submitted to the appropriate regulatory authorities. A trial may not be initiated until all local regulatory requirements are met.

14.3 Subject Identification, Enrollment, and Screening Logs

The investigator agrees to assign a unique subject identification to protect the subject's identity and to permit easy identification of each subject during and after the trial. All reports and communications relating to the trial will identify subjects by the unique subject identifier and year of birth or age.

The investigator must complete a subject screening and enrollment log, which reports on all subjects who consent to be on trial, are screened, screen failed, including those who meet eligibility for inclusion in the trial. The subject identification log will be treated as confidential and will be filed by the investigator in the trial file. The screening and enrollment logs will be reviewed by the sponsor or designee for completeness.

14.4 Monitoring

The sponsor will use a combination of remote and on-site monitoring to monitor this trial. The sponsor or delegate will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a trial site visit log that will be kept at the trial site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and trial-site

personnel and are accessible for verification by the sponsor trial-site contact. If electronic records are maintained at the trial site, the method of verification must be discussed with the trial-site personnel. Where allowed in accordance with local regulations, eg, in the event of a national emergency, and in agreement with the investigator, remote source data verification or source data review may be performed.

The head of the trial site and the investigator must permit the monitor access to all source data, including electronic medical records and/or documents for the purpose of verifying that the data documented in the eCRF are consistent with the original source data. Findings from this review of eCRFs and source documents will be discussed with the trial-site personnel. The sponsor expects that, during monitoring visits, the relevant trial-site personnel will be available, the source documentation will be accessible, and a suitable environment will be provided for review of trial-related documents. The monitor will meet/talk with the investigator on a regular basis during the trial to provide feedback on the trial conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, appropriate trial-site personnel will be available to provide an update on the progress of the trial at the site.

14.5 On-Site Audits

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. Subject privacy must, however, be respected. The 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 designees.

Similar auditing procedures 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 he or she has been contacted by a regulatory agency concerning an upcoming inspection.

14.6 Publication

All information, including but not limited to information regarding GEN1046 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 biomarker research data, generated as a result of this trial, 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 trial and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the trial will be used by the sponsor in connection with the continued development of GEN1046, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical trials to be used, the investigator is obligated to provide the sponsor with all data obtained in the trial.

The results of the trial will be reported in a CTR generated by the sponsor and will contain eCRF data from all trial sites that participated in the trial and may include direct transmission of clinical laboratory data into the sponsor's database. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the trial will be used to determine a coordinating investigator. Results of exploratory biomarker analyses performed after the CTR has been issued will be reported in a separate report and will not require a revision of the CTR. Trial subject identifiers will not be used in publication of results. Any work created in connection with performance of the trial 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, 2016; ICMJE, 2018), the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish trial site-specific data after the primary data are published. If an investigator wishes to publish information from the trial, 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 trial designs and sub-trial approaches, secondary results generally should not be published before the primary endpoints of a trial have been published. Similarly, investigators will recognize the integrity of a multicenter trial by not submitting for publication data derived from the individual trial site until the combined results from the completed trial 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 trial publication.

Authorship of publications resulting from this trial will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the trial 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 .

14.7 Registration of Clinical Trials and Disclosure of Results

The sponsor will register and/or disclose the existence of and the results of clinical trials as required by law.

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APPENDICES

Appendix 1 Definition of Reproductive Potential and Contraception

In this trial, a woman is considered of childbearing potential (WOCBP), UNLESS they are post-menopausal or permanently sterile.

- A postmenopausal state is defined as no menses, in subjects > 45 years of age, for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in subjects not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Female subjects of reproductive potential must agree to use adequate contraception during the trial treatment and for 6 months after the last dose of trial treatment. Adequate contraception is defined as highly effective methods of contraception (Table 15-1). Birth control methods are considered highly effective if they have a failure rate of less than 1% per year, when used consistently and correctly.

Table 15-1 Highly Effective Methods of Contraception

1.1	• Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation Oral • Intrauterine device[1] • Intrauterine hormone-releasing system[1] • Bilateral tubal occlusion[1] • Vasectomized partner[1, 2] • Not engaging in sexual intercourse[3]
1	Contraception methods that in the context of this guidance are considered to have low user dependency.
2	Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of child-bearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success.
3	In the context of this guidance 'not engaging in sexual intercourse' is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments. The reliability of 'not engaging in sexual intercourse' needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Table adapted from 'Recommendations related to contraception and pregnancy testing in clinical trials.' Advisory non-binding guidance represented at the Clinical Trial Facilitation Group (CTFG) meeting in Rome 2014 (CTFG, 2014).

Appendix 2 Estimation of Glomerular Filtration Rate Using Abbreviated Modification of Diet in Renal Disease Formula

Glomerular filtration rate (GFR) may be estimated, according to the abbreviated Modification of Diet in Renal Disease equation:

$$GFR = 186 \times (SCr - 1.154) \times (age - 0.203)$$

where SCr, the serum creatinine level, is expressed in mg/dL; multiply the result by 0.742 if the subject is female.

INVESTIGATOR AGREEMENT

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

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

NOTE: The Coordinating Investigator section below is applicable only to the country-specific coordinating investigators within the EU.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(DD-Mmm-YYYY)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(DD-Mmm-YYYY)

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