PROTOCOL AND SUMMARY OF PROTOCOL AMENDMENTS

First-in-human, open-label, dose-escalation trial with expansion cohorts to evaluate safety of GEN1044 in subjects with malignant solid tumors

Protocol No.:	GCT1044-01
Sponsor Name:	Genmab*
Collaborator Name:	AbbVie
Clinical Research Organization:	[redacted]
EudraCT No.:	2019-003998-26
IND No.:	146815
NCT No.:	NCT04424641
IMP Name:	GEN1044 (DuoBody®-CD3x5T4)
Development Phase:	1/2a

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1 OVERVIEW OF PROTOCOL AMENDMENTS

Protocol/Amendment No; Version	Issue Date
Version 4.0 (incorporating protocol amendment 03)	30 Mar 2021
Version 3.0 (incorporating protocol amendment 02)	03 Apr 2020
Version 2.0 (incorporating protocol amendment 01)	10 Jan 2020
Version 1.0 (original protocol)	21 Nov 2019

2 SUMMARY OF PROTOCOL AMENDMENTS

The original protocol dated 21 November 2019 was amended 3 times. Amendments 1 and 2 were instituted before the first subject was enrolled. Brief summaries of the non-administrative changes are outlined in Table 1.

Table 1 Protocol Amendments

Number (date of internal approval)	Key details of amendment
1 (10 January 2020)	Removed duplicate hematology and biochemistry samples collected for analysis by the central laboratory.
	Added clarification on which laboratory tests were to be performed by the trial center's local laboratory and which were to be performed by a central laboratory.
2 (03 April 2020)	Incorporated Health Authority (Food and Drug Administration) feedback that recommended the following: • Modified the inclusion criteria for the prostate cohort, the squamous cell carcinoma of the head and neck cohort, and the non-small cell lung cancer cohort. • Relaxed the inclusion criteria to include subjects with moderate renal and hepatic impairment, given the expected low involvement of renal and hepatic pathway in the elimination of biological products such as GEN1044. • Excluded subjects with a marked baseline prolongation of QT/corrected QT interval (eg, repeated demonstration of a corrected QT interval >480 milliseconds (Common Terminology Criteria for Adverse Events Grade 1) using Fridericia's QT correction formula. • Collected additional PK sampling points after the priming dose, the first full dose on Day 8 in Cycle 1, as well as a dose at steady-state to adequately characterize the full PK profiles following single and multiple doses. Conducted population PK and covariate analysis of the effect by body weight on PK with emerging PK data. • Clarified that the dose administered beginning with Cycle 5 Day 1 would be the full dose (eg, 3 mg) administered on Days 1, 8, and 15 in previous cycles rather than a cumulative dose [redacted] every 21 days. • Modified the dose escalation plan for single-subject cohorts, so that any Grade ≥2 AE would trigger expansion to a 3-subject cohort. • Lowered the starting dose to 0.3 mg, which was predicted to result in a human maximum (peak) observed serum concentration more consistent with half maximal effective concentration values for cytotoxicity in pharmacology studies. • Revised the DLT criteria to: include any Grade ≥3 cytokine release syndrome event; include any Grade ≥4 ANC lasting >7 days, regardless of fever; exclude certain Grade ≥3 nonhematological events as DLTs. Corrected protocol Section 7.1 to reflect that Grade 4 absolute neutrophil count was <500. • Revised the protocol to permanently discontinue treatment for any DLT during the Dose Escalation part, and for any Grade 3 or 4 cytokine release syndrome event during Expansion. Provided dose modification guidelines for various toxicities (hematologic, gastrointestinal, hepatic, etc).

Number (date of internal approval)	Key details of amendment
	• Provided clinical treatment guidelines for cytokine release syndrome management.
	Added hepatitis B surface antigen to the required safety laboratory tests and modified exclusion criterion 10 to add a positive hepatitis B surface antigen result as exclusionary.
	Clarified various statistical sections, ie, define the Response Evaluable Set, described the best overall response analysis, clarified that the estimated disease control rate would be summarized in conjunction with the objective response rate.
3 (30 March 2021)	Adjusted the visit evaluation schedules (Table 1 and Table 5) to add: • Immune effector cell-associated encephalopathy score assessment. • AE and concomitant medications assessments at Cycle 2 Day 2. • A footnote to explain GEN1044 priming dose, intermediate dose(s), and full dose.
	Adjusted PK, antidrug antibody, and electrocardiogram sampling schedules to clarify on the PK sampling for better characterization and to clarify on the timing of triplicate electrocardiograms.
	Adjusted the biomarker schedules (Table 4 and/or Table 8) to: • Reduce the number of blood samples taken for cytokines; aligned cytokine sampling with PK sampling. • Add immune phenotyping and immune phenotyping (peripheral blood mononuclear cells) samples. • Add assessment of immune system activation including [redacted] • Clarified tumor biopsy requirements for Dose Escalation and Expansion parts.
	Clarified the Expansion endpoints for the exploratory objective for pharmacodynamics and potential biomarkers.
	Adjusted inclusion criteria to clarify on: • The number of prior systemic treatments allowed, by cancer type, for the Expansion. • Acceptable liver function for Dose Escalation and Expansion parts. • Tumor biopsy requirements for Dose Escalation and Expansion parts.
	Adjusted exclusion criteria to: • Add clarification that SARS-CoV-2 vaccination within 30 days prior to first GEN1044 was prohibited. • Add criterion that treatment with chimeric antigen receptor T cells within 30 days prior to first dose of GEN1044 was prohibited. • Clarify on allergic reactions.
	Added clarification that rescreening may only have been performed once.
	Updated the details on the management of cytokine release syndrome.

Number (date of internal approval)	Key details of amendment
	Added that SARS-CoV-2 vaccine administration during the DLT assessment period was prohibited
	Added clarification on the DLT period and DLT criteria for dose escalation as well as on the dose modification guidance and safety stopping criteria for the Dose Escalation and Expansion parts.
	Updated instructions for imaging scans and added clarification on postbaseline assessments per immune Response Evaluation Criteria in Solid Tumors and guidelines for prostate cancer assessment.
	Added clarifications on requirements for pregnancy testing and updated the tests to be performed by a central laboratory.
	Added clarifications on biomarker assessments and the requirements for tumor biopsy.
	Updated AEs of special interest section to include immune effector cell-associated neurotoxicity syndrome and added details for this in a new section as well as an appendix detailing management thereof.

Abbreviations: AE, adverse event; DLT, dose limiting toxicity; PK, pharmacokinetic.

3 REDACTED PROTOCOL VERSION 4.0, LATEST VERSION

CLINICAL TRIAL PROTOCOL

First-in-human, open-label, dose-escalation trial with expansion cohorts to evaluate safety of GEN1044 in subjects with malignant solid tumors

Protocol No.:	GCT1044-01
Sponsor Name:	Genmab*
Collaborator Name:	AbbVie
Clinical Research Organization:	[redacted]
EudraCT No.:	2019-003998-26
IND No.:	146815
IMP Name:	GEN1044 (DuoBody®-CD3x5T4)
Development Phase:	1/2a
Protocol Date and Version:	30 Mar 2021; v4.0 (Amendment 3) 03 Apr 2020; v3.0 (Amendment 2) 10 Jan 2020; v2.0 (Amendment 1) 21 Nov 2019; v1.0 (Original Protocol)

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SPONSOR INFORMATION PAGE

Sponsor information for countries in the European Economic Area, the United Kingdom and China	
Sponsor	Genmab A/S Kalvebod Brygge 43 1560 Copenhagen V Denmark
Sponsor information for all other countries	
Sponsor	Genmab US, Inc. 777 Scudders Mill Rd 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 principles of the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice, ICH GCP E6(R2), and applicable regulatory requirements.

Confidentiality Statement

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ABBREVIATIONS AND DEFINITIONS OF TERMS

1L	first line
2L	second line
5-FU	5-fluorouracil
ACC	adenocarcinoma
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
anti-HBc	antibodies to hepatitis B core antigens
anti-HBs	antibodies to hepatitis B surface antigens
aPTT	activated partial thromboplastin time
ASI	androgen synthesis inhibitor
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
ATC	Anatomical Therapeutic Chemical (Classification System)
AUC	area under the concentration-time curve
BLLOQ	below lower limit of quantitation
AUC_{0-t}	area under the concentration-time curve from time zero to timepoint t
AUC_{inf}	area under the concentration-time curve from time zero to infinity
AUC_{last}	area under the concentration-time curve from time zero to last quantifiable sample
BOIN	Bayesian Optimal Interval
BOR	best overall response
bsAb	bispecific antibody
BUN	blood urea nitrogen
C1D1	Cycle 1 Day 1
CI	confidence interval
C_{max}	maximum (peak) observed serum concentration
CNS	central nervous system
CPD	confirmed progressive disease
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CRF	case report form
CRO	contract research organization
CRPC	castrate-resistant prostate cancer
CRR	composite response rate
CRS	cytokine release syndrome
CT	computed tomography
[redacted]	[redacted]
CTCAE	Common Terminology Criteria for Adverse Events
CTR	clinical trial report
C_{trough}	predose trough concentration
CxDx	Cycle (number) Day (number)
CXR	chest x-ray
DCR	disease control rate
DDS	dose-determining set
DEC	Dose Escalation Committee

DILI	drug-induced liver injury
DL	dose level
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
dMMR	mismatch repair deficient
[redacted]	[redacted]
DOR	duration of response
EC_{50}	half maximal effective concentration
ECG	electrocardiogram
ECLIA	electrochemiluminescence immunoassay
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EGJ	esophagogastric junction
ER	estrogen receptor
FAS	full analysis set
Fc	fragment crystallizable
FcγR	Fc gamma receptor
FDA	Food and Drug Administration
FIH	first-in-human
FFPE	formalin fixed paraffin embedded
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GFR	glomerular filtration rate
GGT	gamma glutamyl transferase
GLP	Good Laboratory Practice
HBsAg	hepatitis B surface antigen
HCG	human chorionic gonadotropin
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HPV	human papillomavirus
IAS	immunogenicity analysis set
ICANS	immune effector cell-associated neurotoxicity syndrome
ICE	immune effector cell-associated encephalopathy
ICF	informed consent form
ICH	International Council on Harmonisation
iCPD	immune confirmed progressive disease
iCR	immune complete response
iDCR	immune disease control rate
iDOR	immune duration of response
IEC	independent Ethics Committee
IgG	immunoglobulin G
IFN-γ	interferon gamma
IL	interleukin
IMP	investigational medicinal product
INR	international normalized ratio
iORR	immune objective response rate
iPFS	immune progression-free survival
iPR	immune partial response

irAEs	immune-related adverse events
IRB	Institutional Review Board
iRECIST	immune Response Evaluation Criteria In Solid Tumors
IRR	infusion-related reaction
IRT	Interactive Response Technology
iSD	immune stable disease
iUPD	immune unconfirmed progressive disease
IV	intravenous
LDH	lactate dehydrogenase
LLOQ	lower limit of quantitation
mAb	monoclonal antibody
MABEL	minimal anticipated biological effect level
mBOIN	modified Bayesian Optimal Interval
MCH	mean corpuscular hemoglobin
MCHC	mean cell hemoglobin concentration
mCRPC	metastatic castrate-resistant prostate cancer
MCV	mean corpuscular volume
mDCR	modified disease control rate
mDOR	modified duration of response
MedDRA	Medical Dictionary for Regulatory Activities
MOA	mechanism of action
mORR	modified objective response rate
MPV	mean platelet volume
MRI	magnetic resonance imaging
MSI-H	microsatellite instability-high
NCI	National Cancer Institute
NOD-SCID	nonobese diabetic/severe combined immunodeficiency
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PAS	pharmacokinetic analysis set
PBMCs	peripheral blood mononuclear cells
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
PgR	progesterone receptor
PK	pharmacokinetic(s)
PO	per os (oral)
PR	partial response
PSA	prostate-specific antigen
PT	prothrombin time
Q1W	every week (weekly)
Q3W	every 3 weeks
RBC	red blood cell
RECIST	Response Evaluation Criteria In Solid Tumors
[redacted]	[redacted]
ROS	reactive oxygen species
ROS1	c-ros oncogene 1

RP2D	recommended phase 2 dose
rPFS	radiographic progression-free survival
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	Safety Committee
SCC	squamous cell carcinoma
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SFU	Safety Follow-up
SOC	standard of care
SUSAR	serious unexpected suspected adverse reactions
T3	triiodothyronine
$T_{1/2}$	elimination half-life
[redacted]	[redacted]
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
T_{max}	time to reach maximum (peak) serum drug concentration
TNBC	triple-negative breast cancer
TNF-α	tumor necrosis factor alpha
TNM	tumor nodes metastasis
TTR	time to response
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
WBC	white blood cell

PROTOCOL AMENDMENTS

DOCUMENT HISTORY	
Document	**Date**
Amendment 3, version 4.0	30 Mar 2021
Amendment 2, version 3.0	03 Apr 2020
Amendment 1, version 2.0	10 Jan 2020
Original Protocol, version 1.0	21 Nov 2019

Overall Rationale for Global Amendment 3:

1) For both Dose Escalation and the Expansion, intermediate dose(s) will be used between the initial priming dose of GEN1044 on C1D1 and the full dose of GEN1044. Based on available data, the DEC and Safety Committee will prospectively determine whether one or two intermediate doses will be used for a given dose level.
2) The "Dose Modifications and Safety Management Guidelines" and Statistics sections of the protocol have been updated.
3) Inclusion and exclusion criteria have been updated.

List of Changes in the Protocol and Their Rationale

Section No. and Name	Description of Change	Brief Rationale
Section 1	Reorganized Section 1. Section 1 is now called "Protocol Summary" • Section 1.1 Trial Synopsis • Section 1.2 Schema: Moved Figure 1 here (previously in Section 4) • Section 1.3 Schedule of Activities	Consistency with current Genmab protocol template.
Section 1.1, Trial Synopsis	Updated for consistency with changes elsewhere in protocol	Updated for consistency
Figure 1, Trial Design	• Minor update made to description of "Trigger for expansion to 3-subject cohorts": Changed "Grade ≥ 2 CRS (clinical symptoms)" to "Grade ≥ 2 AE during the DLT period." • Added definition of AE to footnote.	Corrected legend for consistency with text in protocol body; added definition of AE to footnote.
Table 1, Visit Evaluation Schedule – Dose Escalation Part; Table 5, Visit Evaluation Schedule – Expansion	• Added ICE Score Assessment • Added AE and Concomitant Medications assessments at C2D2 • Added footnote g regarding GEN1044 priming dose, intermediate dose(s), and full dose.	Added ICE Score Assessment. Added AE and concomitant medications assessments at C2D2. Added a footnote to explain trial drug priming dose, intermediate dose(s), and full dose.
Table 2, PK, ADA, and ECG Sampling – Dose Escalation Part; Section 9.3.4, Electrocardiograms	• Clarified PK sampling: ○ end of infusion +2 hr, removed C1D1 and C1D8 samples; added C1D15 and C2D1 samples. ○ end of infusion +4 hr sampling changed to +6 hr (+3hr); added C1D15 and C2D1 samples ○ 24 hr sample, added C1D16, C2D2, C5D2 samples, removed C5D1 sample ○ 72 hr sample, removed C1D11 and C5D1 samples, added C1D18, C2D4, and C5D4 samples. ○ added sample at C5D8 and C5D15 ○ removed 504 hr sample on C6D1	Clarification of PK sampling for better characterization of the PK profile. Removed 6 blood samples. Added 12 blood samples. Clarified timing of triplicate ECGs.

Section No. and Name	Description of Change	Brief Rationale
	• Clarified that triplicate ECGs should be performed within 20 minutes but at least 2 min apart	
[redacted]		
Section 3, Objectives and Endpoints	On Table "Expansion Part: Objectives and Endpoints": Clarified the endpoints for the exploratory objective "Assess pharmacodynamics and potential biomarkers of GEN1044"	Clarified the Expansion endpoints for the exploratory objective for pharmacodynamics and potential biomarkers
Section 4.1, Description of Trial Design; Section 4.2, Dose Escalation Part; Section 4.3, Expansion Part	Sections updated to reflect intermediate dose(s), and to clarify the priming dose and full dose.	Clarified GEN1044 priming dose, intermediate dose(s), and full dose.
Section 4.4, Planned Number of Subjects	Updated number of subjects.	Updated subject numbers to reflect that the number of subjects planned in Dose Escalation will be approximately 80 instead of approximately 58.
Section 5.1, Inclusion Criteria;	For Expansion only: Updated inclusion criteria 1 for uterine cancer, prostate cancer, esophageal cancer, TNBC, SCCHN, and NSCLC regarding the number of prior systemic treatments permitted. For Dose Escalation and Expansion: • Inclusion criterion 6: For clarification, under "acceptable liver function," removed the row "ALT and AST – any" result. • Inclusion criterion 11: Added "In case it is not feasible to meet the required criteria in escalation or expansion for fresh or archival tumor biopsy, the sponsor medical monitor's approval for enrollment is needed."	Clarification regarding the number of prior systemic treatments allowed, by cancer type, for the Expansion. Clarification of acceptable liver function for Dose Escalation and Expansion. Clarification of tumor biopsy requirements for Dose Escalation and Expansion.

Section No. and Name	Description of Change	Brief Rationale
Section 5.2, Exclusion Criteria	For Dose Escalation and Expansion: • Exclusion criterion 3: - Clarified that this criterion is for "Prior therapy and prophylaxis" - For 3d, changed wording to "~~Prior treatment~~ **Prophylaxis** with live, attenuated vaccines within 3 weeks prior to first dose of GEN1044**; or prophylaxis with the first and/or second injection of SARS-CoV-2 nucleic acid vaccine within 30 days prior to first dose of GEN1044**." - Added 3h: "**Treatment with chimeric antigen receptor T cell (CAR-T) therapy within 30 days prior to first dose of GEN1044**." • Exclusion criterion 6: Modified wording: "Has a ~~history of ≥ grade 2 CRS with other CD3-based bispecifics, or a~~ history of ≥ grade 3 allergic reactions to monoclonal antibody therapy as well as known or has known allergies, hypersensitivity, or intolerance to GEN1044 or its excipients (refer to the GEN1044 Investigator's Brochure)."	Added clarification that SARS-CoV-2 vaccination within 30 days prior to first GEN1044 is prohibited. Add criterion that treatment with CAR-T within 30 days prior to first dose of GEN1044 is prohibited. Clarified exclusion criterion regarding allergic reactions.
Section 5.3, Screening Failures	Clarified that rescreening may only be performed once.	Clarification that rescreening may only be performed once.
Section 6.1.2, Treatment Assignment	Added "intermediate dose(s)."	Added "intermediate dose(s)" for consistency with other protocol sections.
Section 6.2, Premedication Prior to GEN1044 Administration	Clarification of prophylactic premedication. Table title changed from "Premedication With Corticosteroids, Antihistamines, Antipyrexics" to "Mandatory CRS Prophylaxis" and table contents updated.	Clarification of prophylactic premedication.
Section 6.3, Dosages and Administration	Added cross-reference to Section 4.2, regarding when an overnight stay (24 hour in-hospitalization) is required.	Added cross-reference for improved clarity.
Section 6.5.2.1, Supportive Care for Cytokine Release Syndrome; Appendix 6, Management of Cytokine Release Syndrome	Clarified that use of mAb against IL-6 is at the investigator's discretion, and that repeated tocilizumab is defined as 3 doses within 24 hours. Updated cross-reference to Appendix 6 (now table instead of previous figure). Appendix 6: deleted Figure "Treatment Algorithm for Management of Cytokine Release Syndrome" and added Table "Management of Cytokine Release Syndrome"	Updated management of CRS.
Section 6.5.3, Prohibited Concomitant Therapy	Added that SARS-CoV-2 vaccine administration during the DLT assessment period is prohibited. Reminder added that sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.	Clarification that SARS-CoV-2 vaccinations are prohibited during the DLT assessment period.
Section 7, Dose Modifications and Safety Management Guidelines; Appendix 7, Dose Modification Guidelines for Specific Adverse Events	• Section 7.1, Dose-Limiting Toxicity ○ Updated to reflect DLT period in the event of either one or two intermediate doses. ○ Added a cross-reference to ICANS Section 10.4.2	Clarified DLT period and DLT criteria for Dose Escalation. Clarified dose modification guidance and safety stopping

Section No. and Name	Description of Change	Brief Rationale
	○ Clarified that the DMC does not assess grade ≥3 AEs that are nonserious. ○ Added the following to DLT criteria: ≥ grade 3 ICANS ○ Clarified the DLT criteria for grade 3 or 4 hematologic toxicities ○ Removed the following DLT criteria: - Grade 4 ANC lasting >7 days (regardless of fever) - A delay of >2 weeks in starting Cycle 2 due to a treatment-related toxicity. • Clarified dose modification guidance and safety stopping criteria for: ○ Section 7.2.1, Dose Escalation Part ○ Section 7.2.2, Expansion Part • Appendix 7, updated Table "Dose Modification Guidelines for Specific Adverse Events"	criteria for Dose Escalation and Expansion.
Section 9.2.1, Radiological Exam/Tumor Imaging	• Updated instructions for scans for Dose Escalation and for Expansion. • Section 9.2.1.2, Post-Baseline Imaging Assessments: Clarified that in the case of PD per RECIST v1.1, treatment and imaging assessments may continue in clinically stable (non-prostate cancer) subjects per iRECIST. • Section 9.2.1.3, iRECIST Assessment of Disease: Clarifications added. • Section 9.2.1.4, Guidelines for Prostate Cancer (Non-measurable Disease) Assessment: Clarifications added.	Updated instructions for scans. Clarified post-baseline assessments per iRECIST. Clarified guidelines for prostate cancer assessment.
Section 9.4.1, Clinical Safety Laboratory Tests	Added sentence to footnote b of Table: "A woman of childbearing potential must have a negative serum beta-hCG at screening. Subjects that are postmenopausal or permanently sterilized (see Appendix 1) can be considered as not having reproductive potential." Made the following changes in Section 9.4.1.1, Testing Performed by a Central Laboratory: • Cytokines **and chemokines** ○ Plasma and serum levels of cytokines **and chemokines** • Immune phenotyping [redacted]	Clarified requirements for pregnancy testing. Updated testing performed by a central laboratory.

Section No. and Name	Description of Change	Brief Rationale
Section 9.7, Biomarker Investigations	• [redacted] • [redacted]	[redacted]
Section 10.4, Adverse Events of Special Interest; Appendix 8, Recommended ICANS Management	• Section 10.4: o Added ICANS as an AESI. o Section 10.4.1, Cytokine Release Syndrome: o Changed Table title to "**Diagnosis and** Grading of CRS **in Adults** According to ASTCT Criteria" and added Fahrenheit conversion for temperature. o Added new section 10.4.2, Immune Effector Cell-Associated Neurotoxicity Syndrome, including Table. • Added new Appendix 8.	Updated AESI section. Added new ICANS section and appendix.
Section 11, Statistics; Appendix 9, Description of DLT Rates After Protocol Amendment 3	• The following clarifications were made: o Subjects in the Dose Escalation part will typically be analyzed according to the ~~dose level received (prime, full, full)~~ **assigned DL cohort.** o In the Expansion, primary safety and efficacy analyses will be conducted on all subject data ~~at the time~~ **at earliest when** all subjects who are still receiving trial treatment have at least 2 scans performed (such that the primary endpoint may be confirmed). • The following subsections were updated: o Section 11.1.7, Dose-Determining Analysis Set – Dose Escalation Part o Section 11.4, Treatments o Section 11.5.2, Primary Endpoint – Dose Limiting Toxicities o Section 11.5.3.2, Adverse Events o Section 11.5.3.5, Laboratory Abnormalities o Section 11.5.4, Statistical Hypothesis, Model, and Method of Analysis o Section 11.5.10.3, Duration of Response o Section 11.5.17, Exploratory Endpoint – Anti-tumor Activity Based on iRECIST o Section 11.6.19.5, Radiographic Progression-Free Survival • Section 11.7, Operating Characteristics: o Deleted Section 11.7.1, BOIN Operating Characteristics, including all tables and figures. o Section 11.7.2, Operating Characteristics for the Interim Analysis in Expansion Cohorts, was updated and was renumbered to be Section 11.7. • Added new Appendix 9, including new tables: o New Table "Dose-Determining Analysis Sets Comparison"	Clarifications and updates for consistency with other changes made in the protocol.

Section No. and Name	Description of Change	Brief Rationale
	○ New Table "Template for Describing DLT Rates"	
Section 15, References	References were updated to reflect new citations added in the body of the protocol.	Updated for consistency with citations in other sections of the protocol.
Appendix 2, RECIST (Version 1.1) Criteria Summary	Updated to improve clarity.	Updated to improve clarity.
Appendix 5, Prostate Cancer Clinical Trials Working Group 3 Recommendations – Assessment of Bone Lesions in Patients with Prostate Cancer	Updated to improve clarity. Added new Table "Prostate Cancer: Overall Combined PCWG3-Modified RECIST 1.1 Response"	Updated to improve clarity.
Title page; Sponsor Information Page; Statement of Compliance; Section 4.9, Trial Termination; Section 6.5, Concomitant Medications and Therapies; Section 6.7, Technical Complaint Handling; Section 8.1, Discontinuation of Trial Treatment; Section 8.2, Subject Discontinuation/ Withdrawal from the Trial; Section 8.3, Lost to Follow-up; Section 9.1, Demography and Baseline Assessments; Section 10, Safety Monitoring and Adverse Event Reporting; Section 12, Data Handling and Record Keeping; Section 13, Ethics; Section 14, Administrative Procedures; Appendix 1, Definition of Reproductive Potential and Contraception.	Updated language for consistency with current Genmab protocol template.	Updated for consistency with current Genmab protocol template.
Throughout the protocol	Minor editorial changes were made for clarity. Minor grammatical, formatting, or spelling changes were made; typographical errors were corrected.	Minor editorial changes were made for clarity. Minor grammatical, formatting, or spelling changes were made; typographical errors were corrected.

1 PROTOCOL SUMMARY

1.1 Trial Synopsis

Title	First-in-human, open-label, dose-escalation trial with expansion cohorts to evaluate safety of GEN1044 in subjects with malignant solid tumors	
Brief Title	Trial of safety of GEN1044 in subjects with malignant solid tumors	
Clinical Phase	1/2a	
Purpose and Rationale	There is a strong unmet medical need to develop new efficacious therapies for patients with advanced solid cancers whose disease no longer responds to currently available therapies. GEN1044 is a bispecific antibody that crosslinks CD3 expressed on T cells with 5T4 expressed on the cell surface on a variety of solid cancers. In immunohistochemistry studies performed at Genmab, 5T4 expression was confirmed in a variety of solid cancers, including non-small cell lung cancer (NSCLC) (both adenocarcinoma [ACC] and squamous cell carcinoma [SCC]), squamous cell carcinoma of the head and neck (SCCHN), uterine, prostate, esophageal, bladder and triple negative breast cancer (TNBC). GEN1044 induced T-cell mediated cytotoxicity in 5T4-expressing tumor cell lines derived from these indications upon co-culture with primary human T cells in vitro. Therefore, GEN1044 is a promising therapeutic agent for a wide range of 5T4-expressing solid cancers. Based on these pre-clinical results, this study will initiate with a dose escalation in order to identify the recommended phase 2 dose (RP2D). Upon completion of phase 1/Dose Escalation, the phase 2 Expansion cohorts will enroll subjects at the RP2D in the following indications were selected for the expansion cohorts: NSCLC (both ACC and SCC), SCCHN, uterine, prostate, esophageal, bladder cancer and TNBC. Additional tumor types may be selected for further investigation based on ongoing nonclinical research or based on preliminary efficacy signals generated in the dose escalation.	
Objectives and Endpoints (Dose Escalation Part)	**OBJECTIVES**	**ENDPOINTS**
	Primary: • Determine RP2D • Establish safety profile of GEN1044	 • Dose-limiting Toxicities (DLTs) • Adverse events (AEs) and safety laboratory parameters
	Secondary: Establish PK profile	 • PK parameters (clearance; volume of distribution; area under the concentration-time curve (AUC) from time zero to last quantifiable sample (AUC_{last}) and from time zero to infinity (AUC_{inf}); maximum (peak) observed serum drug concentration (C_{max}); time to reach maximum (peak) serum drug concentration (T_{max}); predose trough concentrations (C_{Trough}); and elimination half-life ($T_{1/2}$).
	• Evaluate immunogenicity of GEN1044	• Anti-drug antibody (ADA) response

	• Evaluate anti-tumor activity based on response assessment criteria (RECIST v1.1)	• Anti-tumor activity, ie, reduction in tumor size according to response assessment (RECIST v1.1): ○ Objective response rate (ORR) ○ Disease control rate (DCR) ○ Duration of response (DOR) ○ Time to response (TTR)
	Exploratory:	
	• Assess pharmacodynamics and potential biomarkers of GEN1044	• Immune system activation (eg, T-cell activation, cytokine production, [redacted]), expression of tumor targets (eg, 5T4, [redacted] and potential biomarkers)
	• Assess anti-tumor activity based on iRECIST	• Anti-tumor activity, ie, reduction in tumor size according to iRECIST ○ Immune ORR (iORR) ○ Immune DCR (iDCR) ○ Immune DOR (iDOR)
	• For prostate cancer subjects only: Assess anti-tumor activity based on Prostate Cancer Working Group 3 (PCWG3)-Modified Response Evaluation Criteria in Solid Tumors (mRECIST) 1.1	• Anti-tumor activity, ie, reduction in tumor size according to RECIST v1.1 modified by PCWG3 for bone lesions ○ Modified ORR (mORR) ○ Modified DCR (mDCR) ○ Modified DOR (mDOR) ○ Composite response rate (CRR)
	• For prostate cancer subjects only: Assess changes in prostate-specific antigen (PSA) from baseline	• PSA response • PSA progression
Objectives and Endpoints (Expansion Part)	**OBJECTIVES**	**ENDPOINTS**
	Primary:	
	• Evaluate anti-tumor activity	• ORR based on RECIST v1.1
	Secondary:	
	• Evaluate anti-tumor activity based on response assessment criteria (RECIST v1.1)	• Anti-tumor activity, ie, reduction in tumor size according to response assessment (RECIST v1.1): ○ DCR ○ DOR ○ TTR
	• Evaluate efficacy	• Progression free survival (PFS) • Overall survival (OS)
	• Further describe the safety profile of GEN1044	• AEs and safety laboratory parameter
	• Further describe the PK profile	• PK parameters (clearance; volume of distribution; AUC_{last} and AUC_{inf}; C_{max}; T_{max}; C_{Trough}; and $T_{1/2}$

	• Further describe the immunogenicity of GEN1044	• ADA response
	Exploratory:	
	• Assess pharmacodynamics and potential biomarkers of GEN1044	• Immune system activation (eg, T-cell activation and proliferation, cytokine production, [redacted] and [redacted]), expression of tumor targets (eg, 5T4, [redacted] and potential biomarkers), [redacted]
	• Assess anti-tumor activity based on iRECIST	• Anti-tumor activity, ie, reduction in tumor size according to iRECIST ○ iORR ○ iDCR ○ iDOR ○ iPFS
	• For prostate cancer subjects only: Assess anti-tumor activity based on Prostate Cancer Working Group 3 (PCWG3)-Modified Response Evaluation Criteria in Solid Tumors (mRECIST) 1.1	• Anti-tumor activity, ie, reduction in tumor size according to RECIST v1.1 modified by PCWG3 for bone lesions ○ mORR ○ mDCR ○ mDOR ○ CRR ○ rPFS
	• For prostate cancer subjects only: Assess changes in PSA from baseline	• PSA response • PSA progression
Trial Design	This is a first-in-human (FIH), open-label, multinational, multicenter phase 1/2a trial to evaluate the safety, PK, pharmacodynamics, and preliminary efficacy of GEN1044. GEN1044 will be administered as an IV infusion to a mixed population of subjects with solid tumors. The trial consists of 2 consecutive parts: a Dose Escalation (phase 1) and an Expansion (phase 2a). GEN1044 will be administered as via IV infusion weekly (Q1W) for the first 4 cycles (each cycle is 21 days), followed by every 3 weeks (Q3W), thereafter. Cycle 1 will consist of a priming dose, an intermediate dose, and a full dose. Alternatively, when necessary, Cycle 1 will consist of a priming and 2 intermediate doses, with the first full dose administered on Cycle 2 Day 1. The decision as to whether 1 intermediate dose or 2 intermediate doses will be used for a given cohort will be based on the recommendation of the DEC and confirmed by the Safety Committee. The full dose of GEN1044 will continue from Cycle 2 onwards. In the Dose Escalation part, subjects will be administered GEN1044 in escalating dose levels. In the Expansion part, subjects will be administered GEN1044 with the recommended dose from the escalation part. In both parts, subjects will continue to receive GEN1044 until any of the protocol-defined treatment discontinuation criteria are met. Different doses and schedules might be explored during the Dose Escalation and/or Expansion parts based on the data generated in the dose escalation. Efficacy will be assessed by on-treatment radiological exams/imaging every 6 weeks (±7 days) for 36 weeks, and every 12 weeks (±7 days) thereafter until PD as assessed by the investigator, the start of new anti-cancer therapy, withdrawal of consent, or death, whichever occurs first. For subjects with prostate cancer, efficacy will also be assessed by on-treatment bone scans every 6 weeks (+7 days) (or longer per local standards) for 24 weeks,	

	and every 12 weeks (±7 days) thereafter until PD, the start of new anti-cancer therapy, withdrawal of consent, or death, whichever occurs first.
Population	The multicenter, multinational trial population includes male and female subjects who are ≥18 years of age, with malignant solid tumors. Approximately 570 subjects will be screened to ensure approximately 400 subjects (80 in the Dose Escalation part, 320 in the Expansion part) are treated in the trial.
Key Inclusion Criteria	• Must be ≥18 years of age. • Must have measurable disease according to response assessment criteria relevant to the tumor type (eg, RECIST v1.1). • Must have an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score of 0-1 at Screening and on C1D1. • Subject must provide a tumor tissue sample during the screening period and prior to C1D1. 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. In case it is not feasible to meet the required criteria in escalation or expansion for fresh or archival tumor biopsy, the sponsor medical monitor's approval for enrollment is needed. • **Dose Escalation Part**: Subject with locally advanced or metastatic solid tumor(s) (excluding subjects with primary central nervous system [CNS] tumors), who has experienced disease progression while on standard therapy or is intolerant of, or not eligible for, standard therapy. • **Expansion Part:** Subject must have an advanced or metastatic, pathologically confirmed diagnosis of one of the following tumors: a. **Uterine Cancer:** Subject with advanced or metastatic uterine cancer (excludes uterine sarcoma, carcinosarcoma of uterus [including malignant mixed mullerian tumor], endometrial leiomyosarcoma and endometrial stromal sarcomas) for whom non-hormonal systemic therapy is required. Subject must have progressed on or after a prior systemic, platinum-based chemotherapy regimen administered for her advanced, recurrent, or metastatic disease. **Note:** Platinum-based regimens administered in the adjuvant or neoadjuvant setting are not included as a prior regimen. Subject should have received no more than 3 systemic regimens in the recurrent/metastatic setting. b. **Prostate Cancer:** Subject with advanced or metastatic, histologically-confirmed adenocarcinoma of the prostate. Subject must be castration resistant (defined as testosterone ≤50 ng/dL, or history of bilateral orchiectomy) and have progressed on at least 1 taxane-based chemotherapy regimen **AND** at least 1 androgen synthesis inhibitor (ASI) (eg, abiraterone, enzalutamide, apalutamide). Subject should have received no more than 4 systemic regimens in the recurrent/metastatic setting. c. **Esophageal Cancer:** Subject with locally advanced or metastatic adenocarcinoma or squamous cell carcinoma of the esophagus OR advanced/metastatic Siewert type I adenocarcinoma of the esophagogastric junction (EGJ), who progressed on or after at least 1 but no more than 3 prior lines of systemic treatment(s) for advanced disease. Subjects with HER2/neu positive esophageal cancer are required to have received treatment with an approved HER2/neu targeted therapy. d. **Triple Negative Breast Cancer (TNBC):** Subject with locally advanced or metastatic TNBC (defined as HER2-negative with <1% of tumor cell

nuclei immunoreactive for estrogen receptor (ER) and progesterone receptor per local assessment) who has progressed during or after at least 1 but no more than 3 systemic therapies (including a taxane in the metastatic or recurrent setting).

e. **Squamous Cell Carcinoma of the Head and Neck (SCCHN):** Subject with recurrent/metastatic squamous cell carcinoma of oral cavity, oropharynx, paranasal sinuses, nasal cavity, hypopharynx, or larynx. Subject must have received prior therapy with a platinum-based regimen **AND** anti-programmed cell death 1 (PD-1)/PDL1, if eligible for such therapy. Subject eligible to receive anti-epidermal growth factor receptor (EGFR) therapy must have received anti-EGFR therapy prior to study entry. Subject should have received no more than 3 systemic regimens in the recurrent/metastatic setting. **Note**: Prior therapy administered in the neoadjuvant or adjuvant setting is not considered a systemic regimen.

f. **Non-small Cell Lung Cancer (NSCLC)/ACC and NSCLC/SCC:** Subject with locally advanced or metastatic adenocarcinoma (ACC) or squamous cell carcinoma (SCC) of NSCLC must have experienced disease progression on or after his/her most recent systemic therapy for locally advanced or metastatic disease. Subject must have received prior therapy with a platinum-based regimen; a tyrosine kinase inhibitor (TKI) for the following mutations: anaplastic lymphoma kinase (ALK), c-ros oncogene 1 (ROS1) gene rearrangement or EGFR mutation; **AND** anti-PD-1/PDL1 if eligible for such therapy. Subject should have received no more than 3 systemic regimens in the locally advanced or metastatic setting. **Note**: Although the same criteria are relevant, NSCLC/ACC and NSCLC/SCC will be assessed in separate subject cohorts.

g. **Bladder Cancer**: Subject with locally advanced or metastatic urothelial carcinoma (of the bladder, ureter, urethra, or renal pelvis) who has disease progression during or following his/her most recent systemic therapy for locally advanced or metastatic disease. Subject must have a received prior therapy with a platinum-based regimen and anti-PD-1/PDL1 if eligible for such therapy. Subject should have received no more than 3 systemic regimens in the locally advanced or metastatic setting. **Note:** Prior therapy of neoadjuvant or adjuvant setting is not considered a systemic regimen.

For Both Dose Escalation and Expansion:

- Must have acceptable laboratory parameters according to the table below:

Parameter	Result
Acceptable renal function	GFR ≥30 mL/min (estimated using Cockcroft-Gault formula, see Appendix 4)
Acceptable liver function	
- Bilirubin	Total bilirubin ≤3.0×ULN[a]
Acceptable hematological status	
- Hemoglobin	≥5.6 mmol/L (9.0 g/dL)[b]
- ANC	≥1500/µL (1.5×10^9/L)
- Platelet count	≥100×10^9/L

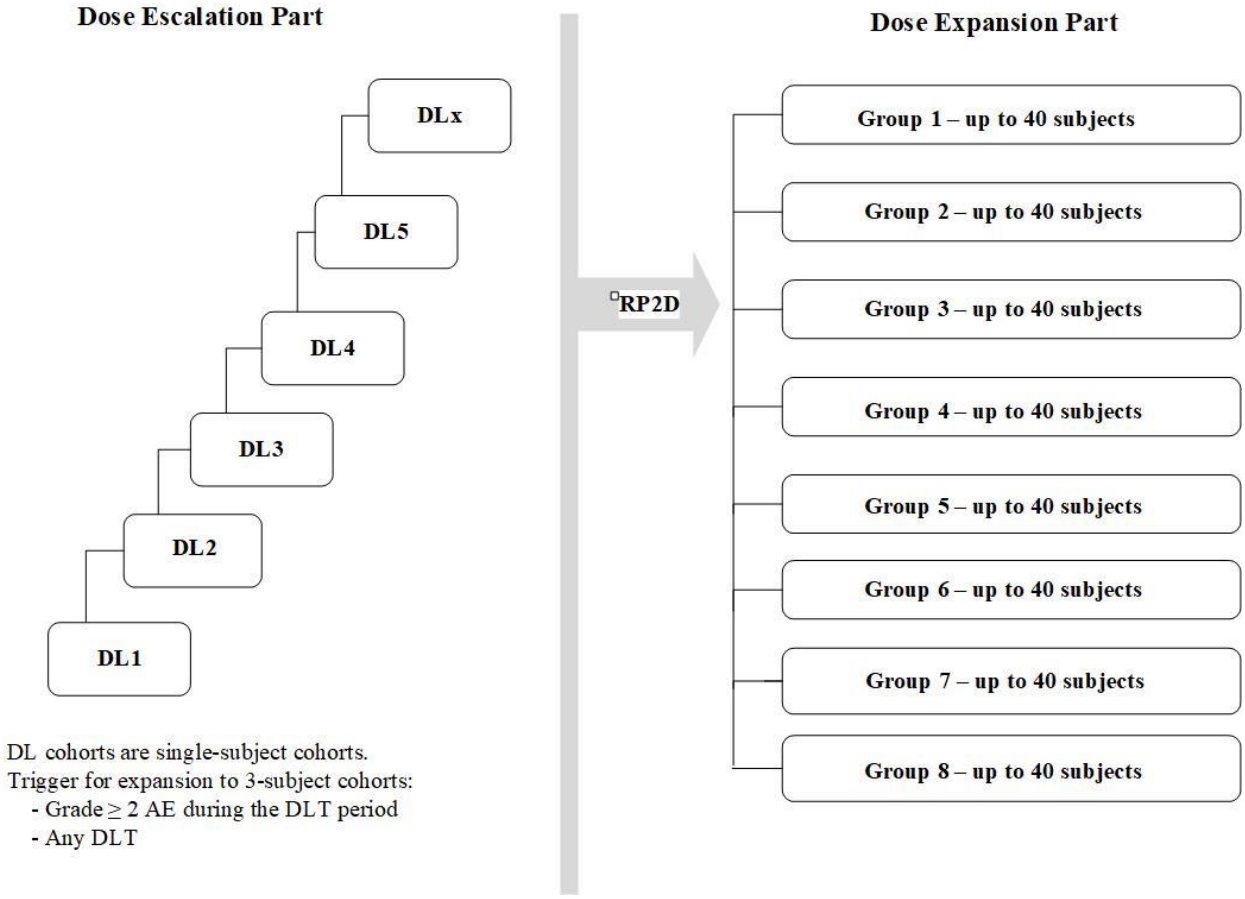
ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; GFR=glomerular filtration rate; ULN=upper limit of normal.
a. Except in subjects with Gilbert's syndrome, then direct bilirubin ≤2×ULN.
b. Must be met without erythropoietin dependency and without transfusion within 2 weeks prior to C1D1.

Key Exclusion Criteria	• Has an uncontrolled intercurrent illness, including but not limited to: o Ongoing or active infection requiring intravenous treatment with anti-infective therapy that has been administered less than 2 weeks prior to first dose. o Symptomatic congestive heart failure (grade III or IV as classified by the New York Heart Association), unstable angina pectoris or cardiac arrhythmia. o Has a marked baseline prolongation of QT/QTc interval (eg, repeated demonstration of a QTc interval >480 milliseconds (ms) (CTCAE grade 1) using Fridericia's QT correction formula. o Uncontrolled hypertension defined as systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg, despite optimal medical management. o 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:*** Childhood asthma that has resolved, residual hypothyroidism that required only hormone replacement or psoriasis that does not require systemic treatment. o Subjects with a history of grade 3 or higher irAEs that led to treatment discontinuation of a checkpoint inhibitor should be excluded. Subjects with irAEs below grade 3 that led to discontinuation should be discussed with the sponsor. o Subjects with a prior history of myositis, Guillain-Barré syndrome, or myasthenia gravis of any grade are excluded. o History of chronic liver disease or evidence of hepatic cirrhosis. o History of non-infectious pneumonitis that has required steroids, or currently has pneumonitis. o 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 GEN1044. o Serious, non-healing wound, skin ulcer (of any grade), or bone fracture. • Any history of intracerebral arteriovenous malformation, cerebral aneurysm, new (within the last 6 months) or symptomatic brain metastases or stroke. (Transient ischemic attack >1 month prior to screening is allowed.) • Subjects 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). • Subjects 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. • Known past or current malignancy other than inclusion diagnosis, except for o Cervical carcinoma of Stage 1B or less. o Non-invasive basal cell or squamous cell skin carcinoma. o Non-invasive, superficial bladder cancer.

	○ Prostate cancer with a current PSA level <0.1 ng/mL. ○ Any curable cancer with a complete response (CR) of >2 years duration. • Has a history of ≥ grade 3 allergic reactions to monoclonal antibody therapy as well as known or has known allergies, hypersensitivity, or intolerance to GEN1044 or its excipients. • Is a woman who is pregnant or breast-feeding.
IMP	GEN1044, IV administration
Efficacy Assessments	Efficacy assessments will include radiological/imaging assessments, bone scans (as applicable), prostate-specific antigen (PSA) results (as applicable), and survival status.
Safety Assessments	Safety assessments will include AEs, clinical laboratory assessments, physical examinations, vital signs, 12-lead electrocardiograms (ECGs), and ECOG-PS.
Other Assessments	Other assessments will include the evaluation of PK and immunogenicity samples, and the evaluation of biomarkers in blood, tumor biopsy [redacted]. [redacted]
Statistics	During the Dose Escalation part of the trial, the DLT rates will be presented to the DEC by each DL cohort and per each period-specific dose level, following a BOIN approach. The RP2D will be based on the accumulated DLT data, taking the totality of data into account. The primary endpoint in the Expansion cohorts is the ORR (ie, confirmed complete response or partial response per local review). Subjects eligible for an expansion cohort will be entered in a stage-wise fashion. For each stage, the "success" of the stage is predicted based on Bayesian methods given the ORR observed so far in the cohort. If the predictive probability of success is less than 10%, the cohort will not be further explored. AEs and safety laboratory parameters will be presented using summary statistics. Individual curves of concentration of GEN1044, including information on actual dose, will be presented for all subjects. PK parameters will be calculated based on non-compartmental methods. Summaries of objective response, best overall tumor response and disease control will be presented. PFS, OS and DOR will be summarized using survival analysis methods. The number of events may be small, and thereby limit use of the Kaplan-Meier methods to provide reliable information. In this case, descriptive statistics (eg, n, mean, standard deviation, median, minimum and maximum) will be presented.
GCP Compliance	This trial will be conducted in compliance with the protocol, principles of the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice, ICH GCP E6(R2), and applicable regulatory requirements.

1.2 Schema

Figure 1 Trial Design



AE = adverse event; DL = dose level, DLT = dose-limiting toxicity, RP2D = recommended phase 2 dose.

1.3 Schedule of Activities

Table 1 through Table 8 list all of the assessments and indicate with an "X" the evaluations performed by visit.

- Table 1: Visit Evaluation Schedule – Dose Escalation Part
- Table 2: PK, ADA and ECG Sampling – Dose Escalation Part
- Table 3: Vital Signs – Dose Escalation Part
- Table 4: Biomarker Table – Dose Escalation Part
- Table 5: Visit Evaluation Schedule – Expansion Part
- Table 6: PK, ADA and ECG Sampling – Expansion Part
- Table 7: Vital Signs – Expansion Part
- Table 8: Biomarker Table – Expansion Part

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 Visit Evaluation Schedule – Dose Escalation Part

Treatment Cycle (C)	Notes	Section Reference	Screening	Cycle 1									Cycle 2						
Day (d)/Week (wk)			**≤ 28d prior to C1 (1d)**	**1d**	**2d**	**4d**	**8d**	**9d**	**11d**	**15d**	**16d**	**18d**	**1d**	**2d**	**4d**	**8d**	**9d**	**11d**	**15d**
Visit window							**+1d**			**+1d**			**+2d**			**+2d**			**+2d**
Informed Consent		13.2.3	X																
Eligibility Criteria		5.1, 5.2	X																
Demographics		9.1.1	X																
Medical History		9.1.2 to 9.1.5	X																
Body weight		9.3.2	X																
Physical Examination	After Screening, perform exam only as indicated by subject's symptoms, AEs, or findings as determined by investigator.	9.3.1	X	X			X			X			X			X			X
Vital Signs	See Table 3 for GEN1044 dosing days. At Unscheduled visit, perform only as indicated by subject's symptoms, AEs, or findings as determined by investigator.	9.3.3	X	X			X			X			X			X			X
ICE Score Assessment	See Table 18.	10.4.2	X	X			X			X			X						
ECG	See Table 2	9.3.4	X																
Radiological Exam/Tumor Imaging	Imaging is calendar based. On-treatment imaging every 6 wks (±7d) for the first 36 wks (calculated from C1D1), then every 12 wks (±7d) until PD, start of new anti-cancer therapy, consent withdrawn, or death, whichever occurs first.	9.2.1	X[a]																
Whole-body Bone Scan	Subjects with prostate cancer. On-treatment scans every 6 wks (±7d) (or longer per local standards) for the first 24 wks(calculated from C1D1), then every 12 wks (±7d) until PD, start of new anti-cancer therapy, consent withdrawn, or death, whichever occurs first.	9.2.1	X																
ECOG-PS	Do not perform C1D1 ECOG-PS if within 5 days of Screening ECOG-PS. C1D1 ECOG-PS must be within 0-1 or subject cannot receive GEN1044. At Unscheduled visit, only if relevant.	9.3.5	X	X									X						

Treatment Cycle (C)	Notes	Section Reference	Screening	Cycle 1									Cycle 2						
Day (d)/Week (wk)			**≤ 28d prior to C1 (1d)**	**1d**	**2d**	**4d**	**8d**	**9d**	**11d**	**15d**	**16d**	**18d**	**1d**	**2d**	**4d**	**8d**	**9d**	**11d**	**15d**
Visit window							**+1d**			**+1d**			**+2d**			**+2d**			**+2d**
Adverse Events	See footnote "b." Report all AEs from first GEN1044 dose (C1D1) until 30 days after the last GEN1044 dose (ie, Safety Follow-up visit). After SFU only report suspected GEN1044-related SAEs.	10.1, 10.2	X[b]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Concomitant Medication		6.5, 9.1.4	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Premedication with Corticosteroids, Antihistamines and Antipyretics	Premedication is mandatory 30 to 120 minutes prior to first 3 administrations of GEN1044.	6.2, 6.5		X			X			X									
GEN1044 Administration[g]		6.3, 6.6		X			X			X			X			X			X
LABORATORY ASSESSMENTS																			
Hematology	At Unscheduled visit, only if relevant.	9.4	X[c]	X	X	X	X	X	X	X	X	X	X			X			X
Biochemistry	At Unscheduled visit, only if relevant.	9.4	X[c]	X	X	X	X	X	X	X	X	X	X		X	X		X	X
Coagulation factors	At Unscheduled visit, only if relevant.	9.4	X[c]										X						
Urinalysis	At Unscheduled visit, only if relevant.	9.4	X[c]																
Pregnancy test	At Unscheduled visit, only if relevant.	9.4	X[c]																
Hepatitis B	At Unscheduled visit, only if relevant.	9.4	X[c]																
T3, T4	At Unscheduled visit, only if relevant.	9.4	X[c]																
PK/ADA sampling	See Table 2	9.5, 9.6																	
Tumor biopsy, biomarkers	See Table 8	9.7																	
PSA	Subjects with prostate cancer; central lab	9.2.2	X[c]	X									X						
Serum testosterone	Subjects with prostate cancer; central lab	9.4.1	X[c]																

Table 1 Visit Evaluation Schedule - Dose Escalation Part (Continued)

Treatment Cycle (C)	Notes	Section Reference	Cycle 3 to Cycle 4			Cycle 5 to PD[f]			Treatment Discontin-uation visit	Safety Follow-up visit	Survival Follow-up	Unscheduled
Day (d)/Week (wk)			**1d**	**8d**	**15d**	**1d**	**8d**	**15d**	**-**	**30d after last dose**	**Every 12 wk after last dose**	
Visit window			**+3d**	**+1d**	**+3d**	**+3d**	**+3d**	**+3d**		**+14d**	**+7d**	
Body weight		9.3.2							X			
Physical Examination	After Screening, perform exam only as indicated by subject's symptoms, AEs, or findings as determined by investigator.	9.3.1	X	X	X	X	X[f]	X[f]	X	X		X
Vital Signs	See Table 3 for GEN1044 dosing days. At Unscheduled visit, perform only as indicated by subject's symptoms, AEs, or findings as determined by investigator.	9.3.3	X	X	X	X	X[f]	X[f]	X	X		X
ECG	See Table 2	9.3.4										
Radiological Exam/Tumor Imaging	Imaging is calendar based. On-treatment imaging every 6 wks (±7d) for the first 36 wks (calculated from C1D1), then every 12 wks (±7d) until PD, start of new anti-cancer therapy, consent withdrawn, or death, whichever occurs first.	9.2.1							X[d]			
Whole-body Bone Scan	Subjects with prostate cancer. On-treatment scans every 6 wks (+7d) (or longer per local standards) for the first 24 weeks (calculated from C1D1), then every 12 weeks (±7d) until PD, start of new anti-cancer therapy, consent withdrawn, or death, whichever occurs first.	9.2.1							X[d]			
ECOG-PS	At Unscheduled visit, only if relevant.	9.3.5	X			X			X	X		X
Adverse Events	See footnote "b." Report all AEs from first GEN1044 dose (C1D1) until 30 days after the last GEN1044 dose (ie, Safety Follow-up visit). After SFU, only report suspected GEN1044-related SAEs.	10.1, 10.2	X	X	X	X	X[f]	X[f]	X	X	X	X
Concomitant Medication		6.5, 9.1.4	X	X	X	X	X[f]	X[f]	X	X		X
Premedication with Corti-costeroids, Antihistamines and Antipyretics	Premedication is mandatory 30 to 120 min prior to first 3 administrations of GEN1044	6.2, 6.5										
GEN1044 Administration		6.3, 6.6	X	X	X	X						

Treatment Cycle (C)	Notes	Section Reference	Cycle 3 to Cycle 4			Cycle 5 to PD[f]			Treatment Discontin-uation visit	Safety Follow-up visit	Survival Follow-up	Unscheduled
Day (d)/Week (wk)			**1d**	**8d**	**15d**	**1d**	**8d**	**15d**	**-**	**30d after last dose**	**Every 12 wk after last dose**	
Visit window			**+3d**	**+1d**	**+3d**	**+3d**	**+3d**	**+3d**		**+14d**	**+7d**	
End of treatment	Perform Treatment Discontinuation visit as soon as possible after permanent GEN1044 discontinuation	8.1, 8.1.1							X			
Inquire if any new anti-cancer treatment		8.1.2							X	X	X	
Survival follow-up	Perform survival follow-up by telephone, email, or visit.	8.1.3, 9.2.3									X	
LABORATORY ASSESSMENTS												
Hematology	At Unscheduled visit, only if relevant.	9.4	X[e]			X[e]			X[e]	X[e]		X
Biochemistry	At Unscheduled visit, only if relevant.	9.4	X[e]			X[e]			X[e]	X[e]		X
Coagulation factors	At Unscheduled visit, only if relevant.	9.4							X[e]			X
Urinalysis	At Unscheduled visit, only if relevant.	9.4	X[e]			X[e]			X[e]			X
Pregnancy test	At Unscheduled visit, only if relevant.	9.4	X[e]			X[e]			X[e]			X
Hepatitis B	At Unscheduled visit, only if relevant.	9.4										X
T3, T4	At Unscheduled visit, only if relevant.	9.4										X
PK/ADA sampling	See Table 2	9.5, 9.6										
Tumor biopsy, biomarkers	See Table 4	9.7										
PSA	Subjects with prostate cancer; central lab	9.2.2	X[e]			X			X			X
Serum testosterone	Subjects with prostate cancer; central lab	9.4.1										

a. During Screening: All subjects will have a contrast CT of the chest/abdomen/pelvis; a non-contrast CT of chest and MRI of abdomen/pelvis, or chest x-ray as applicable for their respective tumor type. For subjects with SCCHN, head and neck imaging is also required; imaging of the pelvis is strongly recommended but not required. If a CT-scan or MRI has been performed within 28 days prior to visit Cycle 1 Day 1 as part of standard procedure, it is acceptable as a screening scan for the trial. If there is suggestion of brain metastases/tumors, a CT-scan or MRI of the head and neck will be performed within 28 days prior to the Cycle 1 Day 1 visit. A bone scan is required for subjects with prostate cancer.

b. Medical conditions occurring after ICF is signed and prior to first GEN1044 dose 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. Any medical history that worsens after the first dose of GEN1044 will be recorded as an AE. If the subject initiates new anti-cancer therapy within 30 days of the last dose of GEN1044, the SFU visit should be performed prior to starting new anti-cancer therapy. SAEs still ongoing after Safety Follow-up visit 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.

c. Obtain screening labs within 7 days of Cycle 1 Day 1 (exception: hepatitis B sample may be obtained earlier). Central lab: serum (beta-hCG) pregnancy, hepatitis B, T3, T4, serum testosterone, PSA; local lab: hematology, biochemistry, coagulation factors and urinalysis.

d. Radiological exam/tumor imaging and if applicable, bone scan, at Treatment Discontinuation visit unless performed within 28 days of last scheduled exam.

e. Starting with C3, obtain labs ≤3 days before D1. Central lab: PSA; local lab: hematology, biochemistry, coagulation factors, urine pregnancy test, and urinalysis.

f. Only collect during C5.

g. [redacted]

Table 2 PK, ADA and ECG Sampling – Dose Escalation Part

Treatment Cycle (C)	Notes	Section Reference	Screening	Cycle 1									Cycle 2						
Day (d)/Week (wk)			**≤ 28d prior to C1 (1d)**	**1d**	**2d**	**4d**	**8d**	**9d**	**11d**	**15d**	**16d**	**18d**	**1d**	**2d**	**4d**	**8d**	**9d**	**11d**	**15d**
Visit window							**+1d**			**+1d**			**+2d**			**+2d**			**+2d**
PK SAMPLING		9.5																	
Before Infusion (on infusion days)				X			X			X			X			X			X
End of infusion (+15 min)				X			X			X			X			X			X
End of infusion +2 hr (±15 min)										X			X						
End of infusion +6 hr (+3 hr)				X			X			X			X						
24 hr sample post end of infusion	Collect C1D2, C1D9, and C1D16 PK sample 24 ±2 hr after end of D1, D8 and D15 infusion, respectively. Collect C2D2 sample 24 ±2 hr after the end of C2D1 infusion.				X			X			X			X					
72 hr sample post end of infusion	Collect C1D4 and C1D18 PK sample 72 ±24 hr after end of D1 and D15 infusion, respectively. Collect C2D4 sample 72 ±24 hr after the end of C2D1 infusion.					X						X			X				
ADA SAMPLING		9.6																	
Before Infusion (on infusion days)				X									X						
ECGs		9.3.4																	
Before Infusion (on infusion days)	Triplicate ECGs, performed within 20 minutes but at least 2 min apart		X	X			X												
End of infusion (+15 min)	Triplicate ECGs, performed within 20 minutes but at least 2 min apart			X			X												

Table 2 PK, ADA, and ECG Sampling - Dose Escalation Part (Continued)

Treatment Cycle (C)	Notes	Section Reference	Cycle 3 to Cycle 4					Cycle 5 to PD					Treatment Discontin-uation visit	Safety Follow-up visit	Survival Follow-up	Unsched-uled
Day (d)/ Week (wk)			**1d**	**8d**	**9d**	**11d**	**15d**	**1d**	**2d**	**4d**	**8d**	**15d**	**-**	**30d after last dose**	**Every 12 wk after last dose**	
Visit window			**+3d**	**+1d**			**+3d**	**+3d**			**+3d**	**+3d**		**+14d**	**+7d**	
PK SAMPLING		9.5														
Before Infusion (on infusion days)	Optional at Unscheduled visits		X[a]	X[b]			X[b]	X[a]					X	X		X
End of infusion (+15 min)			X[a]	X[b]			X[b]	X[a]								
End of infusion +2 hr (±15 min)				X[b]				X[c]								
End of infusion +6 hr (+3 hr)				X[b]												
24 hr sample post end of infusion	C5 only: PK sample 24±2 hr after end of C5D1 infusion (ie, on C5D2)				X[b]				X[c]							
72 hr sample post end of infusion	C5 only: PK sample 72±24 hr after end of C5D1 infusion (ie, on C5D4)					X[b]				X[c]						
168 hr sample post end of infusion	C5 only: Collect PK sample 168+72 hr after end of C5D1 infusion (ie, on C5D8)										X[c]					
336 hr sample post end of infusion	C5 only: Collect PK sample 336+72 hr after end of C5D1 infusion (ie, on C5D15)											X[c]				
ADA SAMPLING		9.6														
Before Infusion (on infusion days)	Optional at Unscheduled visits		X[d]					X[d]					X	X		X

Treatment Cycle (C)	Notes	Section Reference	Cycle 3 to Cycle 4					Cycle 5 to PD					Treatment Discontin-uation visit	Safety Follow-up visit	Survival Follow-up	Unsched-uled
Day (d)/ Week (wk)			**1d**	**8d**	**9d**	**11d**	**15d**	**1d**	**2d**	**4d**	**8d**	**15d**	**-**	**30d after last dose**	**Every 12 wk after last dose**	
Visit window			**+3d**	**+1d**			**+3d**	**+3d**			**+3d**	**+3d**		**+14d**	**+7d**	
ECGs		9.3.4														
Before Infusion (on infusion days)	Optional at Unscheduled visits; if performed, ECG in triplicate, performed within 20 minutes but at least 2 min apart		X[e]													X
End of infusion (+15 min)			X[e]													

a. Collect PK samples at C3D1, C4D1, C5D1, C6D1, C7D1, then every 4 cycles thereafter on Day 1.
b. Only collect during C3.
c. Only collect during C5.
d. Collect ADA samples at C3D1, C5D1, C7D1, then every 4 cycles thereafter on Day 1.
e. Only to be collected for C3D1, not remaining cycles.

Table 3 Vital Signs – Dose Escalation Part

Notes	Section Reference	Time Point
	9.3.3	Pre-infusion (up to 30 min before infusion)
		15 min after start of infusion (±5 min)
If infusion lasts for more than 60 minutes, vital signs should be assessed every 15 minutes (± 5 minutes) for the remaining duration of the infusion		At the end of infusion (±5 min)
		30 min after end of infusion (±5 min)
		1 hour after end of infusion (±10 min)
		2 hours after end of infusion (±10 min)

Table 4 Biomarker Table – Dose Escalation Part

Table 4 Biomarker Table – Dose Escalation Part (Continued)

Table 5 Visit Evaluation Schedule – Expansion Part

Treatment Cycle (C)	Notes	Section Reference	Screening	Cycle 1									Cycle 2						
Day (d)/Week (wk)			**≤28d prior to C1 (1d)**	**1d**	**2d**	**4d**	**8d**	**9d**	**11d**	**15d**	**16d**	**18d**	**1d**	**2d**	**4d**	**8d**	**9d**	**11d**	**15d**
Visit window							**+1d**			**+1d**			**+2d**			**+2d**			**+2d**
Informed Consent		13.2.3	X																
Eligibility Criteria		5.1, 5.2, 9.4.2	X																
Demographics		9.1.1	X																
Medical History		9.1.2 to 9.1.5	X																
Body weight		9.3.2	X																
Physical Examination	Full physical exam at Screening. After Screening, perform exam only as indicated by subject's symptoms, AEs, or findings as determined by investigator.	9.3.1	X	X			X			X			X						X
Vital Signs	Full vital signs only at Screening; for subsequent visits, only temperature and blood pressure. See Table 7 for GEN1044 dosing days. At Unscheduled visit, perform only as indicated by subject's symptoms, AEs, or findings as determined by investigator.	9.3.3	X	X			X			X			X						X
ICE Score Assessment	See Table 18.	10.4.2	X	X			X			X			X						
ECG	See Table 6	9.3.4	X																
Radiological Exam/Tumor Imaging	See footnote "a" regarding Screening. Imaging is calendar based. On-treatment imaging every 6 wks (±7d) for the first 36 wks (calculated from C1D1), then every 12 wks (±7d) until PD, start of new anti-cancer therapy, consent withdrawn, or death, whichever occurs first.	9.2.1	X[a]																
Whole-body Bone Scan	Subjects with prostate cancer. On-treatment scans every 6 wks (±7d) for the first 24 wks (calculated from C1D1), then every 12 wks (±7d) until PD, start of new anti-cancer therapy, consent withdrawn, or death, whichever occurs first.	9.2.1	X																

Treatment Cycle (C)	Notes	Section Reference	Screening	Cycle 1									Cycle 2						
Day (d)/Week (wk)			**≤28d prior to C1 (1d)**	**1d**	**2d**	**4d**	**8d**	**9d**	**11d**	**15d**	**16d**	**18d**	**1d**	**2d**	**4d**	**8d**	**9d**	**11d**	**15d**
Visit window							**+1d**			**+1d**			**+2d**			**+2d**			**+2d**
ECOG-PS	Do not perform C1D1 ECOG-PS if within 5 days of Screening ECOG-PS. C1D1 ECOG-PS must be within 0-1 or subject cannot receive GEN1044. At Unscheduled visit, only if relevant.	9.3.5	X	X									X						
Adverse Events	See footnote "b." Report all AEs from first GEN1044 dose (C1D1) until 30 days after the last GEN1044 dose (ie, Safety Follow-up Visit). After SFU only report suspected GEN1044-related SAEs.	10.1, 10.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Concomitant Medication		6.5, 9.1.4	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Premedication with Corticosteroids, Antihistamines and Antipyretics	Premedication is mandatory 30 to 120 minutes prior to first 3 administrations of GEN1044	6.2, 6.5		X			X			X									
GEN1044 Administration[f]		6.3, 6.6		X			X			X			X			X			X
LABORATORY ASSESSMENTS																			
Hematology	At Unscheduled visit, only if relevant.	9.4	X[c]	X	X	X	X	X	X	X	X	X	X			X			X
Biochemistry	At Unscheduled visit, only if relevant.	9.4	X[c]	X	X	X	X	X	X	X	X	X	X		X	X		X	X
Coagulation factors	At Unscheduled visit, only if relevant.	9.4	X[c]	X									X						
Urinalysis	At Unscheduled visit, only if relevant.	9.4	X[c]																
Pregnancy test	At Unscheduled visit, only if relevant.	9.4	X[c]																
Hepatitis B	At Unscheduled visit, only if relevant.	9.4	X[c]																
T3, T4	At Unscheduled visit, only if relevant.	9.4	X[c]																
PK/ADA sampling	See Table 6	9.5, 9.6																	
Tumor biopsy, biomarkers	See Table 8	9.7	X																
PSA	Subjects with prostate cancer; central lab	9.2.2	X[c]	X									X						
Serum testosterone	Subjects with prostate cancer; central lab	9.4.1	X[c]																

Table 5 Visit Evaluation Schedule - Expansion Part (Continued)

Treatment Cycle (C)	Notes	Section Reference	Cycle 3 to Cycle 4			Cycle 5 to PD			Treatment Discontin-uation visit	Safety Follow-up visit	Survival Follow-up	Unsched-uled
Day (d)/ Week (wk)			**1d**	**8d**	**15d**	**1d**	**8d**	**15d**	**-**	**30d after last dose**	**Every 12 wk after last dose**	
Visit window			**+3d**	**+3d**	**+3d**	**+3d**	**+3d**	**+3d**		**+14d**	**+7d**	
Body weight		9.3.2							X			
Physical Examination	Full physical exam at Screening. After Screening, perform exam only as indicated by subject's symptoms, AEs, or findings as determined by investigator.	9.3.1	X	X	X	X			X	X		X
Vital Signs	See Table 7 for GEN1044 dosing days. At Unscheduled visit, perform only as indicated by subject's symptoms, AEs, or findings as determined by investigator.	9.3.3	X	X	X	X			X	X		X
ECG	See Table 6	9.3.4										
Radiological Exam/Tumor Imaging	Imaging is calendar based. On-treatment imaging every 6 wks (±7d) for the first 36 wks (calculated from C1D1), then every 12 wks (±7d) until PD, start of new anti-cancer therapy, consent withdrawn, or death, whichever occurs first.	9.2.1							X[d]			
Whole-body Bone Scan	Subjects with prostate cancer. On-treatment scans every 6 wks (+7d) for the first 24 wks (calculated from C1D1), then every 12 wks (±7d) until PD, start of new anti-cancer therapy, consent withdrawn, or death, whichever occurs first.	9.2.1							X[d]			
ECOG-PS	At Unscheduled visit, only if relevant.	9.3.5	X			X			X	X		X
Adverse Events	See footnote "b." Report all AEs from first GEN1044 dose (C1D1) until 30 days after the last GEN1044 dose (ie, Safety Follow-up Visit). After SFU, only report suspected GEN1044-related SAEs.	10.1, 10.2	X	X	X	X			X	X	X	X
Concomitant Medication		6.5, 9.1.4	X	X	X	X			X	X		X
Premedication with Corticosteroids, Antihistamines and Antipyretics	Premedication is mandatory 30 to 120 minutes prior to first 3 administrations of GEN1044.	6.2, 6.5										
GEN1044 Administration		6.3, 6.6	X	X	X	X						
End of treatment	Perform Treatment Discontinuation visit as soon as possible after permanent GEN1044 discontinuation.	8.1, 8.1.1							X			

Treatment Cycle (C)	Notes	Section Reference	Cycle 3 to Cycle 4			Cycle 5 to PD			Treatment Discontin-uation visit	Safety Follow-up visit	Survival Follow-up	Unsched-uled
Day (d)/ Week (wk)			**1d**	**8d**	**15d**	**1d**	**8d**	**15d**	**-**	**30d after last dose**	**Every 12 wk after last dose**	
Visit window			**+3d**	**+3d**	**+3d**	**+3d**	**+3d**	**+3d**		**+14d**	**+7d**	
Inquire if any new anti-cancer treatment		8.1.2							X	X	X	
Survival follow-up	Perform survival follow-up by telephone, email, or visit.	9.2.3									X	
LABORATORY ASSESSMENTS												
Hematology	At Unscheduled visit, only if relevant.	9.4	X[e]			X[e]			X[e]	X		X
Biochemistry	At Unscheduled visit, only if relevant.	9.4	X[e]			X[e]			X[e]	X		X
Coagulation factors	At Unscheduled visit, only if relevant.	9.4							X[e]			X
Urinalysis	At Unscheduled visit, only if relevant.	9.4	X[e]			X[e]			X[e]			X
Pregnancy test	At Unscheduled visit, only if relevant.	9.4	X[e]			X[e]			X[e]			X
Hepatitis B	At Unscheduled visit, only if relevant.	9.4										X
T3, T4	At Unscheduled visit, only if relevant.	9.4										X
PK/ADA sampling	See Table 6	9.5, 9.6										
Tumor biopsy, biomarkers	See Table 8	9.7										
PSA	Subjects with prostate cancer; central lab	9.2.2	X[e]			X			X			X
Serum testosterone	Subjects with prostate cancer; central lab	9.4.1										

a. During Screening: All subjects will have a contrast CT of the chest/abdomen/pelvis; a non-contrast CT of chest and MRI of abdomen/pelvis, or chest x-ray as applicable for their respective tumor type. For subjects with SCCHN, head and neck imaging is also required; imaging of the pelvis is strongly recommended but not required. If a CT-scan or MRI has been performed within 28 days prior to visit Cycle 1 Day 1 as part of standard procedure, it is acceptable as a screening scan for the trial. If there is suggestion of brain metastases/tumors, a CT-scan or MRI of the head and neck will be performed within 28 days prior to the Cycle 1 Day 1 visit. A bone scan is required for subjects with prostate cancer.

b. Medical conditions occurring after ICF is signed and prior to first GEN1044 dose 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. Any medical history that worsens after the first dose of GEN1044 will be recorded as an AE. If the subject initiates new anti-cancer therapy within 30 days of the last dose of GEN1044, the SFU visit should be performed prior to starting new anti-cancer therapy. SAEs still ongoing after Safety Follow-up visit 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.

c. Obtain screening labs within 7 days of Cycle 1 Day 1 (exception: hepatitis B sample may be obtained earlier). Central lab: serum (beta-hCG) pregnancy, hepatitis B, T3, T4, serum testosterone, PSA; local lab: hematology, biochemistry, coagulation factors and urinalysis.

d. Radiological exam/tumor imaging and if applicable, bone scan, at Treatment Discontinuation visit unless performed within 28 days of last scheduled exam.

e. Starting with C3, obtain labs ≤3 days before D1. Central lab: PSA; local lab: hematology, biochemistry, coagulation factors, urine pregnancy test, and urinalysis.

f. Subjects in cohorts receiving 1 interim dose will receive: A priming dose on C1D1; an intermediate dose on C1D8; and the first full dose on C1D15. Subjects in cohorts receiving 2 interim doses will receive: A priming dose on C1D1; intermediate doses on C1D8 and C1D15; and the first full dose on C2D1.

Table 6 PK, ADA and ECG Sampling – Expansion Part

Treatment Cycle (C)	Notes	Section Reference	Screening	Cycle 1									Cycle 2						
Day (d)/Week (wk)			**≤ 28d prior to C1 (1d)**	**1d**	**2d**	**4d**	**8d**	**9d**	**11d**	**15d**	**16d**	**18d**	**1d**	**2d**	**4d**	**8d**	**9d**	**11d**	**15d**
Visit window							**+1d**			**+1d**			**+2d**			**+2d**			**+2d**
PK SAMPLING		9.5																	
Before Infusion (on infusion days)				X			X			X			X			X			X
End of infusion (+15 min)				X			X			X			X			X			X
24 hr sample after end of infusion	Collect C1D2 and C1D9 PK sample 24 hr ±2 hr after end of D1 and D8 infusion, respectively.				X			X											
ADA SAMPLING		9.6																	
Before Infusion (on infusion days)				X									X						
ECGs		9.3.4																	
Before Infusion (on infusion days)	Single ECG		X																

Table 6 PK, ADA and ECG Sampling - Expansion Part (Continued)

Treatment Cycle (C)	Notes	Section Reference	Cycle 3 to Cycle 4			Cycle 5 to PD			Treatment Discontin-uation visit	Safety Follow-up visit	Survival Follow-up	Unscheduled
Day (d)/ Week (wk)			**1d**	**8d**	**15d**	**1d**	**8d**	**15d**	**-**	**30d after last dose**	**Every 12 wk after last dose**	
Visit window			**+3d**	**+3d**	**+3d**	**+3d**	**+3d**	**+3d**		**+14d**	**+7d**	
PK SAMPLING		9.5										
Before Infusion (on infusion days)	Optional at Unscheduled visits		X[a]			X[a]			X	X		X
End of infusion (+15 min)			X[a]			X[a]						
ADA SAMPLING		9.6										
Before Infusion (on infusion days)	Optional at Unscheduled visits		X[a]			X[a]			X	X		X
ECGs		9.3.4										
Before Infusion (on infusion days)	Optional at Unscheduled visits; single ECG if performed								X			X

a. Collect PK and ADA samples at C3D1, C5D1, C7D1, then every 4 cycles thereafter on Day 1.

Table 7 Vital Signs – Expansion Part

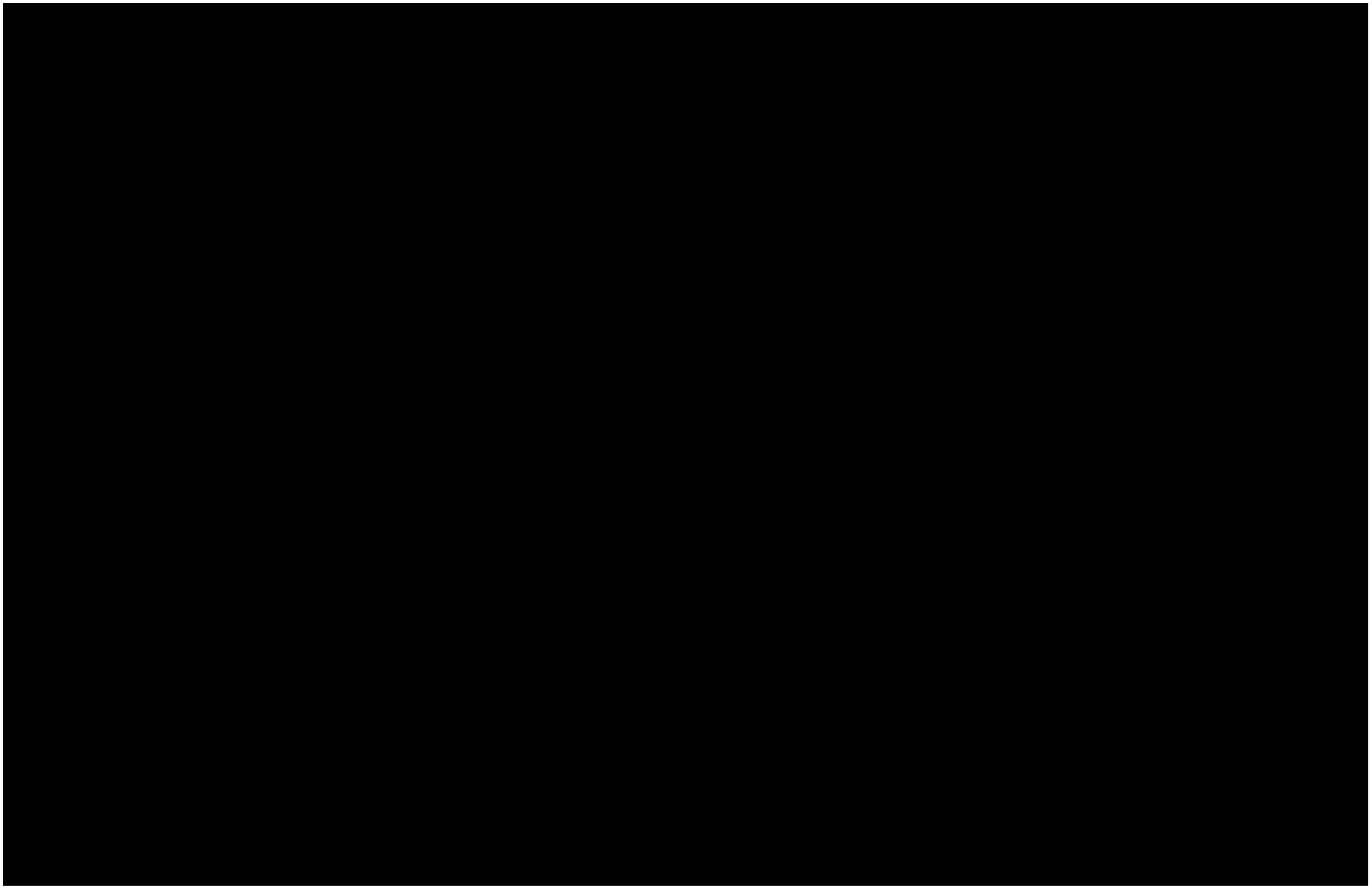
Notes	Section Reference	Time Point
	9.3.3	Pre-infusion (up to 30 min before infusion)
		15 min after start of infusion (±5 min)
If infusion lasts for more than 60 minutes, vital signs should be assessed every 15 minutes (± 5 minutes) for the remaining duration of the infusion		At the end of infusion (±5 min)
		30 min after end of infusion (±5 min)
		1 hour after end of infusion (±10 min)
		2 hours after end of infusion (±10 min)

Full vital signs should be collected at Screening only. On subsequent visits (Table 5), collect temperature and blood pressure measurements only.

Table 8 Biomarker Table – Expansion Part

[redacted]

Table 8 Biomarker Table – Expansion Part (Continued)



[redacted]

2 INTRODUCTION

2.1 Background

2.1.1 Overview of Diseases

2.1.1.1 Uterine Cancer

Uterine cancer is the most common type of gynecologic cancer and the fourth most common cancer among women in the US. In 2019, it is estimated that more than 61,800 women in the US will be diagnosed with uterine cancer, and that more than 12,100 deaths will occur (ASCO-Uterine, 2019). The majority of uterine cancers are endometrial cancers (adenocarcinoma). Although the 5-year survival rate for local uterine cancer is 95%, it drops to 69% for regional uterine cancer, and to only 16% for metastatic uterine cancer (ASCO-Uterine, 2019). There are limited treatment options for patients who progress on or after 1st line (1L) therapy. Patients typically receive single-agent chemotherapy with response rates of 7% to 13% (Fleming et al., 2004; Humber et al., 2007; Oaknin, 2019; Thigpen JT, 2004; Thigpen et al., 2004). Pembrolizumab was approved by the US FDA in 2017 for microsatellite instability-high (MSI-H) cancers including endometrial cancer (Marcus et al., 2019). The combination of pembrolizumab and lenvatinib was recently approved by the US FDA for patients who experience disease progression after prior systemic therapy and whose tumors are not MSI-H or mismatch repair deficient (dMMR).

2.1.1.2 Prostate Cancer

Aside from skin cancer, prostate cancer is the most common type of cancer among men. In 2019, it is estimated that more than 174,600 men in the US will be diagnosed with prostate cancer, and that more than 31,600 deaths will occur. Approximately 10% of patients manifest with advanced disease (ASCO-Prostate, 2019). Androgen-deprivation therapy is the main treatment option for advanced disease, however the disease typically progresses within 18 to 24 months to castrate-resistant prostate cancer (CRPC) (Frieling et al., 2015). More than 90% of patients with CRPC develop bone metastases (Frieling et al., 2015). For metastatic disease, the 5-year survival rate is 30% (ASCO-Prostate, 2019). In metastatic CRPC (mCRPC), frontline chemotherapy includes microtubule inhibition – where docetaxel is the standard of care (SOC) in combination with steroid (TAXOTERE, 2013). Other approved treatments for mCRPC include abiraterone acetate, denosumab, enzalutamide, cabazitaxel, radium-223, sipuleucel-T, and zoledronic acid (Frieling et al., 2015).

2.1.1.3 Esophageal Cancer

In the US, it is estimated that more than 17,600 new cases of esophageal cancer and 16,000 deaths will occur in 2019 (NCI-Esophageal, 2019). The 5-year survival for local esophageal cancer is 45%; this decreases to 24% for regional esophageal cancer, and only 5% for metastatic esophageal cancer (ASCO-Esophageal, 2019). Frontline chemotherapy includes tubulin inhibition in combination with platin plus 5-fluorouracil (5-FU) or irinotecan (mostly used in a relapsed setting). In a relapsed population, single agent tubulin inhibition is often used.

2.1.1.4 Triple-Negative Breast Cancer

Breast cancer is the most common cancer in women worldwide with approximately 1.7 million new cases diagnosed in 2012 (Ferlay et al., 2015). Triple-negative breast cancer (TNBC) accounts

for about 15% to 20% of breast cancers. TNBC tumors lack the expression of estrogen receptor (ER) and progesterone receptor, and do not show amplification of the human epidermal growth factor receptor 2 (HER2) gene. A more frequent association of TNBC has been found with African-American women, younger age, higher grade, more advanced stage at diagnosis, and is associated with breast cancer (BRCA) gene mutations (Abramson et al., 2015).

Anthracycline and taxane-based chemotherapy is the treatment of choice for patients with TNBC. Platinum-based chemotherapy has also been incorporated in the neoadjuvant and metastatic settings and despite high response rates with chemotherapy, median overall survival (OS) for women with metastatic TNBC is less than one year (Dent et al., 2007). Furthermore, patients with TNBC do not benefit from targeted therapies such as endocrine therapy or trastuzumab and no molecular targets have been identified (Santonja et al., 2018).

A high unmet medical need remains for women with metastatic TNBC, as this disease usually progresses rapidly following three to five lines of chemotherapy.

2.1.1.5 Squamous Cell Carcinoma of the Head and Neck

Head and neck cancers make up approximately 4% of cancers in the United States (ASCO-HN, 2019). It is estimated that over 65,400 cases will be diagnosed in 2019 and that more than 14,600 deaths will occur in 2019 (ASCO-HN, 2019).

Squamous-cell carcinoma of the head and neck (SCCHN) is a major cause of death with over 600,000 cases diagnosed annually worldwide. In 2018, approximately 64,690 people will develop oral cavity, pharyngeal, or laryngeal cancers in the US and an estimated 13,740 deaths will occur over the same period (NCCN, 2018). Head and neck cancers can arise in the oral cavity, pharynx, larynx, nasal cavity, paranasal sinuses, thyroid, and salivary glands. Tobacco use and alcohol greatly increase the risk of developing head and neck cancer. In addition, human papillomavirus (HPV) infection has a causal association with squamous cancers of the oropharynx (particularly tonsils and base of tongue) and recent evidence suggests that HPV may also be associated with increased risk of squamous cell carcinoma of the larynx (Chen et al., 2017). Patients with locally HPV-positive head and neck cancers have improved outcomes for response to treatment, progression-free survival (PFS), and OS as compared with HPV-negative tumors (Fakhry et al., 2008).

Treatment of head and neck cancers is complex and requires a multidisciplinary approach. The prognosis of patients with recurrent or metastatic SCCHN is generally poor with a median survival of approximately 6 to 12 months depending on patient's performance status and disease-related factors. First-line therapy for fit patients includes cetuximab with cisplatin or carboplatin plus 5-FU. The addition of cetuximab resulted in prolonged survival as compared with platinum and 5-FU alone (10.1 months vs. 7.4 months) as well as prolonged median PFS (3.3 months vs. 5.6 months) (Vermorken et al., 2008). Single-agent chemotherapy is recommended for patients with poorer performance status. In the past, the most widely used single agents included platinum compounds, taxanes, nab-paclitaxel, methotrexate, fluorouracil, and cetuximab (NCCN, 2018).

In the US and several other countries, the anti-programmed cell death protein 1 (PD-1) inhibitors, pembrolizumab and nivolumab, are approved for patients with progressive disease (PD) after platinum-containing chemotherapy. In one open-label phase 3 trial, 361 patients with recurrent SCCHN who had progressed within 6 months after platinum-based chemotherapy were randomized to nivolumab or standard single agent therapy (methotrexate, docetaxel, or cetuximab). Median OS was 7.5 months in the nivolumab group versus 5.1 months in the group

that received standard therapy and the response rate was 13.3% in the nivolumab group versus 5.8% in the standard-therapy group (Ferris et al., 2016). Similar efficacy was reported with pembrolizumab. While data from trials exploring the single agent activity of anti-PD-1s are encouraging, response rates remain low. Therefore, SCCHN remains an area of high unmet medical need and further opportunity exists to improve outcomes with novel treatment approaches.

2.1.1.6 Lung Cancer

Lung cancer remains the leading cause (23.5%) of death from cancer in the United States, with more than 228,000 new cases diagnosed and over 142,600 deaths estimated in 2019 (NCI-Lung, 2019). The most prominent risk factor associated with this disease is tobacco exposure (Chen et al., 2014; Derman et al., 2015). Treatments with curative intent for patients with early stage disease include surgery, chemotherapy, radiation therapy, or a combined modality approach.

Non-small cell lung cancer (NSCLC) represents 80% to 85% of all lung cancers. Within the subtypes of NSCLC, adenocarcinoma (ACC) represents approximately 40% of NSCLC and squamous cell carcinoma (SCC) represents approximately 25% to 30% of NSCLC (Brahmer et al., 2015).

1L treatment includes pembrolizumab monotherapy for those patients whose tumors express any level of programmed death-ligand 1 (PD-L1) (TPS ≥1%) (KEYNOTE 042 trial), high levels of PD-L1 (TPS ≥ 50%), or pembrolizumab in combination with a platinum doublet (KEYNOTE 189 trial, KEYNOTE 407 trial), regardless of PD-L1 score (KEYTRUDA, 2019; US-FDA, 2019). Patients ineligible to receive pembrolizumab, the SOC 1L treatment includes a platinum doublet. The chemotherapy regimens are dependent upon the underlying histology: non-squamous NSCLC patients are eligible to receive pemetrexed (Scagliotti et al., 2008) or anti-vascular endothelial growth factor (VEGF) antibodies including bevacizumab and ramucirumab (Johnson et al., 2004). Furthermore, patients whose tumors harbor oncogenic mutations including epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), c-ros oncogene 1 (ROS1), and BRAF are treated with the respective inhibitors.

Treatment options are limited after progression on 1L therapies, inclusive of an anti-PD1/PD-L1 therapy, and include combination chemotherapy or single agent chemotherapy.

2.1.1.7 Bladder Cancer

In the US, it is estimated that more than 80,400 new cases and more than 17,600 deaths will occur in 2019 (NCI-Bladder, 2019). Approximately 30% of patients manifest with advanced disease. The 5-year survival rate for local bladder cancer is 69%; this decreases to 35% for regional bladder cancer, and to only 5% for metastatic bladder cancer (ASCO-Bladder, 2019). As frontline chemotherapy treatment, tubulin inhibition is used in combination with platin or as a single agent therapy in a relapsed setting. Based on the phase 3 KEYNOTE-045 trial, pembrolizumab was approved as a second line (2L)+ therapy given significant improvements in OS and response rates as compared to investigator's choice chemotherapy (paclitaxel, docetaxel, or vinflunine) (KEYTRUDA, 2019; US-FDA, 2017). Treatment options are limited for those patients who progress on SOC 1L or 2L therapies, and include single agent chemotherapies.

2.1.2 Introduction to GEN1044

The tumor-associated antigen 5T4 is broadly expressed across a wide range of solid cancers (Southall et al., 1990; Stern and Harrop, 2017). GEN1044 (DuoBody-CD3x5T4) is a bispecific

antibody that induces $CD4^+$ and $CD8^+$ T-cell activation, cytokine production and T-cell mediated cytotoxicity of 5T4-positive tumor cells by crosslinking cluster of differentiation 3 epsilon (CD3ε) on T cells and 5T4 on tumor cells. GEN1044 is being developed as a therapeutic agent for the treatment of solid cancers known to express 5T4.

GEN1044 is generated using Genmab's proprietary DuoBody® bispecific antibody platform (Labrijn et al., 2013; Labrijn et al., 2014). Structurally, GEN1044 is similar to conventional immunoglobulin G-1 (IgG1) molecules, with only a few amino acids difference in the fragment crystallizable (Fc) domain allowing for the generation of the bispecific antibody (F405L/K409R). In general, DuoBody molecules show biochemical characteristics comparable to monoclonal IgG1 molecules, normal neonatal Fc receptor (FcRn) binding and in vivo stability typical for IgG1 antibodies (Labrijn et al., 2013; Labrijn et al., 2014). In addition, the IgG Fc domain of GEN1044 was engineered to silence Fc-mediated effector functions by introduction of 3 point mutations (L234F/L235E/D265A [FEA]).

The preclinical anti-tumor activity of GEN1044 in vitro and in vivo (summarized in Section 2.1.3) and the expression of 5T4 across a wide range solid cancers support the premise that GEN1044 is a promising therapeutic agent with potential anti-tumor effect in many different cancer types.

2.1.3 Summary of Nonclinical Studies

A nonclinical data package, consisting of nonclinical pharmacology and toxicology studies in vitro and in vivo, is available for GEN1044.

GEN1044 showed binding to human CD3ε and 5T4 with affinities (K_D values, dissociation constants) of 310 nM and 2.9 nM, respectively, as determined by biolayer interferometry. Furthermore, GEN1044 showed dose-dependent binding to 5T4-expressing tumor cell lines of different cancer indications, including uterine, prostate, esophageal, breast, head and neck, lung and bladder cancer.

GEN1044 induced T-cell mediated cytotoxicity of 5T4-expressing tumor cell lines derived from different solid cancer indications in vitro, including uterine, prostate, esophageal, breast, head and neck, lung and bladder cancer. T-cell mediated cytotoxicity was dependent on binding to both CD3 and 5T4, as control antibodies monovalently binding only to CD3 or 5T4 did not induce any cytotoxicity. Furthermore, GEN1044 was shown to induce $CD4^+$ and $CD8^+$ T-cell activation and production of inflammatory cytokines, eg, interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), interleukin (IL)-1β, IL-2, IL-6, IL-8, and IL-10, in vitro in co-cultures of T cells and 5T4-expressing cell lines. [redacted]

GEN1044 showed anti-tumor activity in a 5T4-expressing xenograft model by subcutaneous coengraftment with human peripheral blood mononuclear cells (PBMCs) in nonobese diabetic/severe combined immunodeficiency (NOD-SCID) mice in vivo. Furthermore, GEN1044 showed anti-tumor activity in a 5T4-expressing xenograft model in $CD34^+$ hematopoietic stem cell humanized mice in vivo, which was associated with peripheral blood PD markers, such as T-cell activation and cytokine production.

The preclinical anti-tumor activity of GEN1044 in vitro and in vivo and the expression of 5T4 across a wide range of solid cancers support the premise that GEN1044 is a promising therapeutic agent with potential anti-tumor effect in many different cancer types.

The nonclinical safety program with GEN1044 consists of in vitro studies using human cells (cytokine release assay, hemolytic potential and plasma compatibility), and in vivo studies in cynomolgus monkeys. The cynomolgus monkey was selected as the preferred toxicology species based on comparable target binding affinities between human and cynomolgus monkey, and comparable pharmacological activity of GEN1044 in human and cynomolgus monkey primary T cells in vitro.

[redacted]

The FIH dose selection takes into account the mechanism of action (MOA) of GEN1044 and is based on a minimum anticipated biologic effect level (MABEL) estimated using in vitro non-clinical data and interspecies scaling and modeling (see Section 4.6).

For more comprehensive information related to the nonclinical studies for GEN1044, refer to the Investigator's Brochure.

2.1.4 Summary of Clinical Trials

This will be the first administration of GEN1044 in humans; therefore, no clinical experience is available. Refer to the GEN1044 Investigator's Brochure for additional background details.

2.2 Rationale

There is a strong unmet medical need to develop new efficacious therapies for patients with advanced solid cancers whose disease no longer responds to currently available therapies.

Over recent years, different mechanisms to activate the immune response against malignant cells have been explored, some of which were rapidly translated into effective cancer immunotherapies. One successful strategy is to redirect T cells towards tumor cells in a manner that is independent of their T-cell receptor specificity using CD3 bispecific antibodies (CD3 bsAb) that artificially crosslink CD3 on T cells with a tumor-associated antigen (TAA) on tumor cells. Simultaneous binding of CD3 bsAbs to T cells and TAA-positive tumor cells was shown to induce cytotoxic synapse formation and target cell kill without the need for specificity of the T-cell receptor for a peptide-MHC complex (Offner et al., 2006; Zhou et al., 2017). In humans, effective regression of advanced stage hematological malignancies has been reported upon treatment with the CD3xCD19 bispecific T-cell engager (BiTE) blinatumomab, which has been approved and marketed (Goebeler and Bargou, 2016; Przepiorka et al., 2015). Whereas a considerable number of CD3 bispecific antibodies (bsAbs) are currently in development for the treatment of hematological cancers, the number of CD3 bsAbs undergoing clinical evaluation in solid cancers is small. The CD3xEpCAM

rat-mouse hybrid antibody catumaxomab was approved for the treatment of malignant ascites (Linke et al., 2010), but marketing authorization was withdrawn in June 2017 at the manufacturer's request due to the company's insolvency. A handful of trials assessing the clinical safety and preliminary efficacy of CD3 bsAbs in solid tumors are currently enrolling, yet clinical efficacy remains to be established. Therefore, other opportunities need to be explored for targeting solid cancers with a CD3 bsAb approach.

5T4 is a TAA with expression on the membrane of tumor cells across a wide range of solid cancer indications and limited expression in normal tissues (Southall et al., 1990; Stern and Harrop, 2017), making it is a promising target for the development of anti-cancer therapeutics. Although different investigational 5T4-targeting cancer therapies are currently in preclinical and clinical development, no 5T4-targeting antibodies have been approved for the treatment of cancer thus far (Harrop et al., 2019; Shapiro et al., 2017). GEN1044 is a novel CD3x5T4 bsAb to be taken into clinical development.

In immunohistochemistry studies performed at Genmab, 5T4 expression was confirmed in a variety of solid cancers, including NSCLC (both ACC and SCC), SCCHN, uterine, prostate, esophageal, bladder and TNBC. GEN1044 induced T-cell mediated cytotoxicity in 5T4-expressing tumor cell lines derived from these indications upon co-culture with primary human T cells in vitro. Therefore, GEN1044 is a promising therapeutic agent for a wide range of 5T4-expressing solid cancers. Based on these pre-clinical results, this study will initiate with a Dose Escalation in order to identify the recommended phase 2 dose (RP2D). Upon completion of phase 1/Dose Escalation, the phase 2 Expansion will enroll subjects at the RP2D in the following indications selected for the expansion cohorts: NSCLC (both ACC and SCC), SCCHN, uterine, prostate, esophageal, bladder cancer and TNBC. Additional tumor types may be selected for further investigation based on ongoing nonclinical research or based on preliminary efficacy signals generated in the dose escalation.

A major obstacle that has limited the broad application of T-cell recruiting bispecific antibodies thus far is the constitutive induction of T-cell mediated responses when the therapeutic antibody contains an active IgG Fc domain (Harwood et al., 2017). Fc gamma receptor (FcγR) binding by the active Fc domains can induce off-target T-cell activation through FcγR-mediated antibody crosslinking, which can potentially lead to cytokine release syndrome (CRS) and cytokine storms (Harwood et al., 2017). GEN1044 contains an inert IgG1 Fc backbone that does not bind FcγRs or complement component C1q, thereby preventing secondary Fc-mediated crosslinking. In conclusion, GEN1044 was designed to induce potent and target-specific toxicity in 5T4-expressing tumors.

2.3 Benefit-Risk Assessment

The tumor-associated antigen 5T4 is broadly expressed across a wide range of solid cancers, while expression on normal cells is limited (Southall et al., 1990; Stern and Harrop, 2017). GEN1044 (DuoBody-CD3x5T4) is a bispecific antibody that induces $CD4^+$ and $CD8^+$ T-cell activation, cytokine production and T-cell mediated cytotoxicity of 5T4-positive tumor cells by crosslinking CD3ε on T cells and 5T4 on tumor cells. GEN1044 showed anti-tumor activity in several humanized mouse models including cell line- and patient-derived xenograft models. Crosslinking of CD3 and 5T4 by GEN1044 may have therapeutic benefits, as monovalently binding only to CD3 or 5T4 did not induce any T-cell mediated cytotoxicity in vitro.

GEN1044 is an investigational drug with safety data only available from nonclinical studies; no information is available regarding the adverse effects of GEN1044 in humans. Based upon the information to date, potential safety risks are based on the known MOA of GEN1044 in addition to nonclinical findings. Potential risks and mitigation strategies have been elaborated in separate sections of this protocol.

Available clinical safety data from other compounds that engage with T cells suggest that CRS is a frequent adverse event (AE). Cytokine release syndrome results in a defined constellation of symptoms including but not limited to chills, fever, and hypotension. Furthermore, the onset of this syndrome is acute and can be mitigated by 1) premedications including antipyretics and/or steroids, and/or 2) a priming dose, defined as a dose of the compound of interest less than the intermediate dose(s), "full" or subsequent doses. Mandatory short-term hospitalizations will further allow close observation of patients treated with GEN1044 during the time period during at which CRS may arise.

In addition to the above mitigation strategies against the potential risk of CRS, multiple safety groups including the Dose Escalation Committee (DEC), independent Data Monitoring Committee (DMC) and the sponsor Safety Committee (SC) will be reviewing data from this trial. Given the potential for enhanced benefit with limited and manageable toxicity indicates that GEN1044 should be administered in subjects of high unmet need including patients with solid malignancies who have progressed on all available SOC therapies and are otherwise ineligible to receive these. All subjects enrolled in this trial will be monitored by qualified health care professional(s) who will provide care and evaluate the subject's response to the trial drug, in terms of its safety and efficacy. In totality, the benefit-risk ratio is considered positive for this FIH, phase 1/2 trial of GTC1044-01. For more comprehensive information related to the nonclinical studies, potential safety aspects and the known and expected benefits/risks for GEN1044, refer to the Investigator's Brochure.

3 OBJECTIVES AND ENDPOINTS

Objectives and related endpoints are described in Table 9 (Dose Escalation) and Table 10 (Expansion).

Table 9 Dose Escalation Part: Objectives and Endpoints

Objectives	Endpoints
Primary	
• Determine recommended phase 2 dose (RP2D)	• Dose-limiting Toxicities (DLTs)
• Establish safety profile of GEN1044	• Adverse events (AEs) and safety laboratory parameters
Secondary	
• Establish PK profile	• PK parameters (clearance; volume of distribution; area under the concentration-time curve (AUC) from time zero to last quantifiable sample (AUC_{last}) and from time zero to infinity (AUC_{inf}); maximum (peak) observed serum drug concentration (C_{max}); time to reach maximum (peak) serum drug concentration (T_{max}); predose trough concentrations (C_{Trough}); and elimination half-life ($T_{1/2}$).
• Evaluate immunogenicity of GEN1044	• Anti-drug antibody (ADA) response
• Evaluate anti-tumor activity based on response assessment criteria (RECIST v1.1)	• Anti-tumor activity, ie, reduction in tumor size according to response assessment (RECIST v1.1): ○ Objective response rate (ORR) ○ Disease control rate (DCR) ○ Duration of response (DOR) ○ Time to response (TTR)
Exploratory	
• Assess pharmacodynamics and potential biomarkers of GEN1044	• Immune system activation (eg, T-cell activation, cytokine production, [redacted]), expression of tumor targets (eg, 5T4, [redacted] and potential biomarkers)
• Assess anti-tumor activity based on iRECIST	• Anti-tumor activity, ie, reduction in tumor size according to iRECIST ○ Immune ORR (iORR) ○ Immune DCR (iDCR) ○ Immune DOR (iDOR)
• For prostate cancer subjects only: Assess anti-tumor activity based on Prostate Cancer Working Group 3 (PCWG3)-Modified Response Evaluation Criteria in Solid Tumors (mRECIST) 1.1	• Anti-tumor activity, ie, reduction in tumor size according to RECIST v1.1 modified by PCWG3 for bone lesions ○ Modified ORR (mORR) ○ Modified DCR (mDCR) ○ Modified DOR (mDOR) ○ Composite response rate (CRR)
• For prostate cancer subjects only: Assess changes in prostate-specific antigen (PSA) from baseline	• PSA response • PSA progression

Table 10 Expansion Part: Objectives and Endpoints

Objectives	Endpoints
Primary	
• Evaluate anti-tumor activity	• Objective response rate (ORR) based on RECIST v1.1
Secondary	
• Evaluate anti-tumor activity based on response assessment criteria RECIST v1.1	• Anti-tumor activity, ie, reduction in tumor size according to response assessment criteria RECIST v1.1: ○ Disease control rate (DCR) ○ Duration of response (DOR) ○ Time to response (TTR)
• Evaluate efficacy	• Progression free survival (PFS) • Overall survival (OS)
• Further describe the safety profile of GEN1044	• Adverse events (AEs) and safety laboratory parameters
• Further describe the PK profile	• PK parameters (clearance; volume of distribution; area under the concentration-time curve (AUC) from time zero to last quantifiable sample (AUC_{last}) and from time zero to infinity (AUC_{inf}); maximum (peak) observed serum drug concentration (C_{max}); time to reach maximum (peak) serum drug concentration (T_{max}); predose trough concentrations (C_{Trough}); and elimination half-life ($T_{1/2}$).
• Further describe the immunogenicity of GEN1044	• Anti-drug antibody (ADA) response
Exploratory	
• Assess pharmacodynamics and potential biomarkers of GEN1044	• Immune system activation (eg, T-cell activation and proliferation, cytokine production, [redacted] and [redacted], expression of tumor targets (eg, 5T4, [redacted] and potential biomarkers), [redacted].
• Assess anti-tumor activity based on iRECIST	• Anti-tumor activity, ie, reduction in tumor size according to iRECIST ○ Immune ORR (iORR) ○ Immune iDCR (iDCR) ○ Immune DOR (iDOR) ○ Immune PFS (iPFS)
• For prostate cancer subjects only: Assess anti-tumor activity based on Prostate Cancer Working Group 3 (PCWG3)-Modified Response Evaluation Criteria in Solid Tumors (mRECIST) 1.1	• Anti-tumor activity, ie, reduction in tumor size according to RECIST v1.1 modified by PCWG3 for bone lesions ○ Modified ORR (mORR) ○ Modified DCR (mDCR) ○ Modified DOR (mDOR) ○ Composite response rate (CRR) ○ Radiographic progression-free survival (rPFS)
• For prostate cancer subjects only: Assess changes in prostate-specific antigen (PSA) from baseline	• PSA response • PSA progression

4 TRIAL DESIGN

4.1 Description of Trial Design

This is a first-in-human (FIH), open-label, multinational, multicenter phase 1/2a trial to evaluate the safety, PK, pharmacodynamics, and preliminary efficacy of GEN1044. GEN1044 will be administered as an IV infusion to a mixed population of subjects with solid tumors. The trial consists of 2 consecutive parts: a Dose Escalation (phase 1) and an Expansion (phase 2a).

In the Dose Escalation part, subjects will be administered GEN1044 according to dose levels outlined in Section 4.2. In the Expansion part, subjects will be administered GEN1044 with the recommended dose(s) from the escalation. GEN1044 will be administered via IV infusion weekly (Q1W) for the first 4 cycles (each cycle is 21 days), followed by every 3 weeks (Q3W), thereafter. Cycle 1 will consist of a priming dose, an intermediate dose, and a full dose. Alternatively, when necessary, Cycle 1 will consist of a priming and 2 intermediate doses, with the first full dose administered on Cycle 2 Day 1. The decision as to whether 1 intermediate dose or 2 intermediate doses will be used for a given cohort will be based on the recommendation of the DEC and confirmed by the Safety Committee (see Section 10.10).

In both parts, subjects will continue to receive GEN1044 until any of the protocol-defined treatment discontinuation criteria are met (refer to Section 8.1). Different doses and schedules might be explored during the Dose Escalation and/or Expansion parts based on the data generated in the dose escalation. Efficacy will be assessed by on-treatment radiological exams/imaging every 6 weeks (±7 days) for 36 weeks, and every 12 weeks (±7 days) thereafter until PD as assessed by the investigator, the start of new anti-cancer therapy, withdrawal of consent, or death, whichever occurs first. For subjects with prostate cancer, efficacy will also be assessed by on-treatment bone scans every 6 weeks (+7 days) (or longer per local standards) for 24 weeks, and every 12 weeks (±7 days) thereafter until PD, the start of new anti-cancer therapy, withdrawal of consent, or death, whichever occurs first. Response assessment criteria relevant to the tumor type (eg, RECIST v1.1 criteria) (Eisenhauer et al., 2009) will be used for response evaluation. Images may be submitted to a central imaging vendor if additional analyses are conducted.

For subjects in the Dose Escalation part who receive GEN1044 doses beyond the DLT evaluation period, all AEs corresponding to the definition of DLT (see Section 7.1) will be considered for the purpose of determining the RP2D. For the selection of the recommended dose for treatment of the Expansion cohorts and for further development, all drug-related AEs will be taken into consideration.

The concept of the design of the trial is shown in Section 1.2, Figure 1 . The Dose Escalation part will consist of dose-level (DL) cohorts. The Expansion part will consist of parallel cohorts, by type of cancer.

4.2 Dose Escalation Part

The rationale for the starting dose selection is provided in Section 4.6.

[redacted]

[redacted] The rationale behind implementation of intermediate dose(s) is to mitigate potential AEs (including CRS).

The DLT period will extend from the first dose on C1D1 until 7 days after the first full dose:

- [redacted]
- [redacted]

[redacted]

The planned doses are:

- a priming dose of 0.3 mg or higher,
- a full dose, [redacted]
- one, or potentially two, intermediate doses in-between the prime and full dose (if two intermediate doses are used the 1st will be lower than the 2nd). The DLT period will vary, depending on whether one or two intermediate doses are given (see above).

Higher dose levels might be explored depending on accrued data during the escalation part. All doses are fixed doses (not weight adjusted).

The FIH single-subject cohort is planned with a priming dose of 0.3 mg on C1D1, followed by a full dose of 3.0 mg on C1D8 and C1D15.

In the escalation part, the cohort sizes will start with single-subject cohorts. The trigger point to expand a 1-subject cohort into a 3-subject cohort is the observation of any of the following events:

- A grade ≥2 AE is observed within the DLT period.
- A DLT (see Section 7.1) is observed at any time within the DLT period.

That is, when any of these events occur in a 1-subject cohort, it is expanded by 2 additional subjects. When those subjects have completed their DLT period, the escalation model in Section 4.2.1 is initiated. If the single-subject cohorts reach the maximum dose level (beyond which no escalation is possible), it will be mandatory to expand that cohort size to 3 subjects.

In addition, in the single subject-cohort phase, the next cohort can start only once the DLT period for the previous dose level has been assessed and the next dose level is proposed by the DEC and endorsed by the SC. The DEC will recommend the dose level for the next cohort of subjects to the SC and this will need to be endorsed by the SC prior to using the recommended or higher dose in the next cohort dose level implementation. To supplement routine safety monitoring by the sponsor SC as outlined in this protocol, a DMC will monitor safety data for the trial on a quarterly basis or more frequently as determined by the sponsor. Additional details regarding the DEC, sponsor SC, and the DMC can be found in Section 10.9 and in Section 10.10.

If any single-subject DL cohort is expanded to a total of 3 subjects (based on the trigger point above being reached), all subsequent DL cohorts will initially have 3 subjects per cohort.

The next DL cohort, possibly including a higher full-dose level, can start only once the DLT period for the previous DL cohort has been assessed and the next full-dose level is proposed by the DEC and endorsed by the SC. Parallel cohorts may be initiated at any time, provided the full-dose level of the parallel cohort has already been safety-cleared by the SC and does not equal or surpass the full-dose level in the DL cohort under investigation. The DEC will recommend the full-dose level for the next cohort of subjects, including whether 1 or 2 intermediate doses should be given, to the SC and this will need to be endorsed by the SC prior to using the recommended or higher full-dose in the next cohort dose level implementation. The descriptive DLT tables provided to the DEC (see Appendix 9) will provide an overview of the DLT rates considering the whole DL cohort (as intended in the original protocol), and considering the individual period-specific dose level.

For any DL cohort that enrolls more than 1 subject, there will be a minimum of 24 hours between an individual subject's treatment infusion stop and a subsequent subject's treatment start in the same cohort, to account for any acute safety signals in each new dose level. The 24-hour treatment window between same-cohort subjects will not apply to backfilling cohorts enrolling subjects to be exposed to previously safety-cleared full dose levels.

An overnight stay (24 hours in-hospital observation) will be required for all subjects after administration of GEN1044 on Day 1 and Day 8 during Cycle 1 only and may be required for additional subjects and/or dose levels if recommended by the sponsor SC. If a second intermediate dose is implemented at C1D15, the sponsor may decide to require additional 24-hour hospitalization following this dose administration.

During treatment in the Dose Escalation part, safety assessments will be performed as indicated on Table 1. For the assessments of each cohort, the dose-limiting toxicities (DLTs) will be collected for the first treatment cycle, ie, a DLT evaluation period of 21 days from the priming dose (or 28 days if two intermediate doses are applied).

4.2.1 Escalation Model

A modified Bayesian Optimal Interval (mBOIN) design will be utilized to make recommendations at end of each DLT evaluation period (Liu, 2015). The target DLT rate is set to $\phi = 30\%$ with the assumptions that $\phi_1 = 0.6\phi$ is the highest sub-therapeutic DLT rate and $\phi_2 = 1.4\phi$ is the lowest DLT rate that has excessive toxicity. Under these assumptions, the thresholds that minimizes the decision error at end of each cohort are $\lambda_1 = 24\%$ and $\lambda_2 = 36\%$ (Liu, 2015).

Based on the accrued data (on each dose level) the mBOIN recommendations are supplied in Table 11.

Table 11 Modified BOIN Recommendations

	Total Number of DLT Evaluable Subjects Treated on a DL Cohort	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Recommendation Based on Total Number of DLTs on the DL Cohort	Escalate	0	0	≤1	≤1	≤1	≤1	≤2
	Remain	1	1	-	2	2	2	3
	De-escalate	2	2	2	3	3	3	4
	Terminate a dose level	3	≥3	≥3	≥4	≥4	≥4	≥5

DL=dose level; DLT=dose-limiting toxicity.

The DLT rate per each period-specific dose level may be provided to the DEC (supplementary to the DLT rate of the DL cohort) when the DEC is considering the dosing sequence of the next DL cohort. The mBOIN recommendation for the period-specific dose level may be interpreted in the context of Table 11 above (modified mBOIN recommendations). For example, the DLT rate of 3 mg when administered as priming dose will be provided, as will the DLT rate of 3 mg when provided as intermediate dose.

Given the different perspectives the different DLT rate estimates provide, the DEC will evaluate all available data to recommend the doses for the next DL cohort; the Safety Committee will make the final decision. A template for DLT reporting is provided in Appendix 9, Table 29.

4.2.1.1 Modifications to BOIN

The BOIN has the following general stopping rules:

i. Escalation stops if 80 subjects have already been dosed.

ii. Escalation stops if there are 9 subjects already treated on a DL cohort proposed by the DEC.

Dose Level Termination:

A potential drawback of the basic BOIN design is that, theoretically, a "very toxic" DL cohort could be investigated in multiple cohorts, if a neighboring DL cohort is not toxic. To avoid this problem, a dose level termination criterion is implemented (for DL cohorts with at least 3 DLT evaluable subjects): A DL cohort can no longer be investigated if an additional DLT-free cohort would lead to de-escalation.

Cohort Size:

In the standard titration part, it is allowed to estimate the DLT rate for the DL cohort if 1 subject is non-DLT evaluable and the remaining 2 subjects are DLT-evaluable, provided that neither of the 2 subjects experienced any grade ≥2 AE within the first 7 days of Cycle 1, or any DLT during the 21-day DLT period. (If a dose level has in total 2 subjects being DLT-evaluable and no DLTs are observed, the BOIN rule is to escalate.)

Also, over-recruitment by 1 subject is allowed, so that each 3-subject cohort may consist of 2 to 4 subjects who are evaluable for DLT.

It is noted that for 5 DLT evaluable subjects, the possibility to "remain" cannot be concluded. (The estimate DLT rate is 0%, 20%, 40%, 60%, 80% or 100%. No estimate within the limit of "remain": [24%, 36%].) In this case, the number of DLT evaluable subjects is brought up to 6 by an additional subject to regain this option.

In case a cohort had less than 3 DLT evaluable subjects, the next DL cohort (on the same dosing sequence) may be enlarged to bring the number of subjects on the dose level up to a multiple of 3.

Parallel Cohort(s) for Clinical Confirmation:

To better understand the safety, tolerability, PK, pharmacodynamics or anti-tumor activity, up to 7 additional subjects (ie, maximum total DL cohort size n=10) may be allocated in parallel to full-dose levels that are considered safe for such allocation (dose levels at or below the currently investigated full dose). In addition, new priming and/or intermediate dose levels may be investigated in a parallel cohort, provided its full-dose level does not exceed the most recent safety-cleared full-dose level. Any DLTs observed in a parallel DL cohort will be presented to the

DEC, and it will be up to the DEC to determine how these would impact the determination of the dose levels in the next cohort.

4.2.1.2 Describing Grade ≥2 CRS Occurring During the First 7 Days of Cycle 1

The incidence of grade ≥2 CRS occurring during priming dose will be supplemented to the DEC as descriptive statistics to determine the feasibility of the priming dose level from a CRS management perspective. The CRS event will only be used in the mBOIN model if it is a grade ≥3 CRS.

4.2.2 Other Dose Escalation/De-Escalation Procedures

The following provides a description of the procedures not directly associated with the BOIN as such, but that will impact subject accrual and provisions for dose escalation/de-escalation decisions.

1. After completion of the first full dosing of each DL cohort, based on the safety data and the BOIN, the sponsor SC will decide on the dose-level for the next cohort of subjects. Escalation to the next dose-level will not occur until all subjects needed for a specific DL cohort have passed the Cycle 1/DLT evaluation period.
2. The Dose Escalation part will be assessed in dose-level cohorts (DL cohorts); initially this will be in done in single-subject cohorts until the trigger point (see Section 4.2) is passed.
    - A single-subject DL cohort may be optionally expanded with up to 2 additional subjects for the purpose of obtaining additional safety, PK, pharmacodynamic, and biomarker data (ie, for a total of 3 subjects in that cohort).
3. A subject will be considered as evaluable for dose determination if they experience a DLT or meet the minimum treatment and safety evaluation requirements for the first cycle (refer to Section 7.1).

After completion of the DLT period for each DL cohort, the DEC and sponsor SC will review the data from the DLT period to propose the actual next dose level. Data to be reviewed will include but not be limited to all relevant safety, clinical, PK, biomarker data, and the next dose as suggested by the BOIN strategies.

The RP2D to be used for the Expansion part will be determined at the end of the Dose Escalation part by the DEC and sponsor SC, based on a review of the totality of data, including but not limited to efficacy, safety (including DLTs, AEs, safety laboratory values, and observations made after the end of the DLT evaluation period), biomarker and PK data, and dosing information.

4.3 Expansion Part

In the Expansion part, subjects will receive the RP2D dose(s) determined from the Dose Escalation part. Depending on the RP2D, this will be a priming dose of GEN1044 on C1D1, an intermediate dose on C1D8, and then either a second intermediate dose or full dose on C1D15. In case of the implementation of a second intermediate dose on C1D15, the subject will receive the first full dose on C2D1.

An overnight stay (24 hours in-hospital observation) will be required for all subjects after administration of GEN1044 on C1D1. For subjects experiencing CRS or ICANS following GEN1044 administration on C1D1, additional 24-hour hospitalization will be required after administration of GEN1044 on C1D8. As data accumulate, increased (or reduced) hospitalization

may be implemented for additional subjects and/or dose administrations if recommended by the sponsor.

Based on data available and if deemed appropriate, the expansion may be initiated before a possible maximum tolerated dose has been reached. Furthermore, different doses and schedules might be explored in the expansion cohorts. The aim of the expansion is to provide further data on the safety, tolerability, MOA, PK and anti-tumor activity of the selected dose/schedule.

Recruitment will be initiated in up to 8 parallel cohorts in different tumor types. Expansion cohorts may include disease subtypes, eg, uterine, prostate, esophageal, head and neck, NSCLC/ACC, NSCLC/SCC, bladder and TNBC. In each of the expansion cohorts, a non-binding and ongoing interim futility analysis will be conducted after about 20 subjects have at least 2 on-treatment scans (approximately 12 weeks). A maximum of 40 subjects may be recruited in each expansion cohort.

Further expansion cohorts in additional tumor types may be opened based on preliminary efficacy signals generated in the Dose Escalation part. The sponsor will determine the priority of opening the disease-specific expansion cohorts based the data obtained in the dose escalation.

In the Expansion part, a DMC risk-benefit analysis will be performed at pre-specified intervals as defined in the DMC Charter. The DMC and the sponsor SC will evaluate the safety profile with particular emphasis on any safety signals. Additional details regarding the DMC can be found in Section 10.9.

4.4 Planned Number of Subjects

- Up to approximately 80 subjects are planned to be treated in the Dose Escalation part.
- Up to approximately 320 subjects are planned to be treated in the Expansion part.
- In total, up to approximately 400 subjects are planned to be treated in the trial.
- Assuming an anticipated screen failure rate of 30%, approximately 570 subjects can be screened.

4.5 Trial Design Rationale

The first part of this trial is a FIH, open-label, dose escalation safety trial studying GEN1044 in subjects with different types of malignant solid tumors, to determine the safety profile of GEN1044.

In order to address the trial objectives in this FIH trial, a BOIN design was selected. Compared to standard 3+3 and accelerated titration designs, the chosen BOIN design provides more flexibility while safeguarding the subject's safety.

The second part of this trial is the expansion of tumor-specific cohorts for further investigation. The aim of the expansion is to provide further data on the safety, tolerability, PK, and anti-tumor activity of the selected dose in specific tumor types.

4.6 Dose and Schedule Rationale

The first-in-human (FIH) dose selection takes into account the MOA of GEN1044 (T-cell activation and T-cell mediated cytotoxicity of 5T4-expressing tumor cells through GEN1044-mediated crosslinking of CD3 and 5T4) and is based on estimation of the MABEL using in vitro nonclinical data.

[redacted]

4.6.1 Rationale for Fixed Dosing

An additional consideration for the development of GEN1044 is to initiate the FIH trial with fixed dosing instead of body weight-based dosing. A fixed dosing approach is desirable to facilitate drug preparation without the need to calculate the dose, per subject, thus lowering the potential risk of dosing errors as compared with body weight-based dosing. In addition, fixed dosing also offers 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 fixed 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 GEN1044. Monoclonal antibodies typically distribute to the blood plasma and extracellular fluids only, which increase less than proportionally with 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 monoclonal antibody. In addition, intracellular degradation of monoclonal antibodies 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 monoclonal antibodies 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).

4.7 End of Trial Definition

The trial is considered completed when the last subject dies or withdraws from the trial. However, the maximum trial duration is 5 years after the last subject's first treatment in the trial. The sponsor will ensure post-trial treatment for ongoing trial participants with a potential treatment benefit.

4.8 Treatment Discontinuation

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

4.9 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 investigational medicinal product (IMP) development

The sponsor may, based on available data, need to discontinue further development of GEN1044. If the development of the GEN1044 is discontinued and trial termination is necessary, the sponsor will make their best effort to provision post-trial access of GEN1044 for those ongoing trial participants with a potential treatment benefit, in accordance with local laws and regulations.

5 TRIAL POPULATION(S)

5.1 Inclusion Criteria

Each potential subject must fulfill all of the following criteria to be assigned to treatment in the trial.

For Dose Escalation:

1. Subject with locally advanced or metastatic solid tumor(s) (excluding subjects with primary central nervous system [CNS] tumors), who has experienced disease progression while on standard therapy or is intolerant of, or not eligible for, standard therapy.

For Expansion:

1. Criterion modified per Amendment 3.
   1.1 Subject must have an advanced or metastatic, pathologically confirmed diagnosis of one of the following tumors:

   a. **Uterine Cancer:** Subject with advanced or metastatic uterine cancer (excludes uterine sarcoma, carcinosarcoma of uterus [including malignant mixed mullerian tumor], endometrial leiomyosarcoma and endometrial stromal sarcomas) for whom non-hormonal systemic therapy is required. Subject must have progressed on or after a prior systemic, platinum-based chemotherapy regimen administered for her advanced, recurrent, or metastatic disease. **Note:** Platinum-based regimens administered in the adjuvant or neoadjuvant setting are not included as a prior regimen. Subject should have received no more than 3 systemic regimens in the recurrent/metastatic setting.

   b. **Prostate Cancer:** Subject with advanced or metastatic, histologically-confirmed adenocarcinoma of the prostate. Subject must be castration resistant (defined as testosterone ≤50 ng/dL, or history of bilateral orchiectomy) and have progressed on at least 1 taxane-based chemotherapy regimen AND at least 1 androgen synthesis inhibitor (ASI) (eg, abiraterone, enzalutamide, apalutamide). Subject should have received no more than 4 systemic regimens in the recurrent/metastatic setting.

   c. **Esophageal Cancer:** Subject with locally advanced or metastatic adenocarcinoma or squamous cell carcinoma of the esophagus OR advanced/metastatic Siewert type I adenocarcinoma of the esophagogastric junction (EGJ), who progressed on or after at least 1 but no more than 3 prior lines of systemic treatment(s) for advanced disease. Subjects with HER2/neu positive esophageal cancer are required to have received treatment with an approved HER2/neu targeted therapy.

   d. **Triple Negative Breast Cancer (TNBC):** Subject with locally advanced or metastatic TNBC (defined as HER2-negative with <1% of tumor cell nuclei immunoreactive for estrogen receptor (ER) and progesterone receptor per local assessment) who has progressed during or after at least 1 but no more than 3 systemic therapies (including a taxane in the metastatic or recurrent setting).

   e. **Squamous Cell Carcinoma of the Head and Neck (SCCHN):** Subject with recurrent/metastatic squamous cell carcinoma of oral cavity, oropharynx, paranasal

sinuses, nasal cavity, hypopharynx, or larynx. Subject must have received prior therapy with a platinum-based regimen **AND** anti-PD-1/PDL1, if eligible for such therapy. Subject eligible to receive anti-EGFR therapy must have received anti-EGFR therapy prior to study entry. Subject should have received no more than 3 systemic regimens in the recurrent/metastatic setting. **Note:** Prior therapy administered in the neoadjuvant or adjuvant setting is not considered a systemic regimen.

f. **Non-small Cell Lung Cancer (NSCLC)/ACC and NSCLC/SCC:** Subject with locally advanced or metastatic adenocarcinoma (ACC) or squamous cell carcinoma (SCC) of NSCLC must have experienced disease progression on or after his/her most recent systemic therapy for locally advanced or metastatic disease. Subject must have received prior therapy with a platinum-based regimen; a tyrosine kinase inhibitor (TKI) for the following mutations: anaplastic lymphoma kinase (ALK), c-ros oncogene 1 (ROS1) gene rearrangement or EGFR mutation; **AND** anti-PD-1/PDL1 if eligible for such therapy. Subject should have received no more than 3 systemic regimens in the locally advanced or metastatic setting. **Note**: Although the same criteria are relevant, NSCLC/ACC and NSCLC/SCC will be assessed in separate subject cohorts.

g. **Bladder Cancer**: Subject with locally advanced or metastatic urothelial carcinoma (of the bladder, ureter, urethra, or renal pelvis) who has disease progression during or following his/her most recent systemic therapy for locally advanced or metastatic disease. Subject must have a received prior therapy with a platinum based regimen and anti-PD-1/PDL1 if eligible for such therapy. Subject should have received no more than 3 systemic regimens in the locally advanced or metastatic setting. **Note:** Prior therapy of neoadjuvant or adjuvant setting is not considered a systemic regimen.

For Both Dose Escalation and Expansion:

2. Must be ≥18 years of age.
3. 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. Where required by local or country specific regulations, each subject must sign a separate informed consent form if he or she agrees to provide samples for [redacted]. [redacted] the subject is still eligible to participate in the trial.
4. Must have measurable disease according to response assessment criteria relevant to the tumor type (eg, RECIST v1.1 [see Appendix 2]).
5. Must have an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score of 0-1 (see Table 14) at Screening and on C1D1. **Note**: Do not perform C1D1 ECOG-PS if within 5 days of Screening ECOG-PS. C1D1 ECOG-PS must be within 0-1 or subject cannot receive GEN1044.

6. Criterion modified per Amendment 3.

   6.1 Must have acceptable laboratory parameters according to the table below:

Parameter	Result
Acceptable renal function	GFR ≥30 mL/min (estimated using Cockcroft-Gault formula, see Appendix 4)
Acceptable liver function	
- Bilirubin	Total bilirubin ≤3.0×ULN[a]
Acceptable hematological status	
- Hemoglobin	≥5.6 mmol/L (9.0 g/dL)[b]
- ANC	≥1500/μL (1.5×10^{9}/L)
- Platelet count	≥100×10^{9}/L

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; GFR = glomerular filtration rate; ULN = upper limit of normal.

a. Except in subjects with Gilbert's syndrome, then direct bilirubin ≤2×ULN.

b. Must be met without erythropoietin dependency and without transfusion within 2 weeks prior to C1D1.

7. A woman of reproductive potential must agree to use adequate contraception during the trial and for 4 months after the last GEN1044 administration. Adequate contraception is defined as highly effective methods of contraception (please refer to Appendix 1 for more information). In countries where 2 highly effective methods of contraception are required, both methods will be required for inclusion.
8. A woman (of childbearing potential) must have a negative serum (beta-human chorionic gonadotropin [beta-hCG]) at screening. Subjects that are postmenopausal or permanently sterilized (see Appendix 1) can be considered as not having reproductive potential.
9. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the entire trial, until 4 months after last treatment.
10. A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control, eg, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, and all men must also not donate sperm during the trial and for 4 months after receiving the last dose of GEN1044.
11. Criterion modified per Amendment 3.

    11.1 Subject must provide a tumor tissue sample during the screening period and prior to C1D1. 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. In case it is not feasible to meet the required criteria in escalation or expansion for fresh or archival tumor biopsy, the sponsor medical monitor's approval for enrollment is needed.

5.2 Exclusion Criteria

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

For Both Dose Escalation and Expansion:

1. Has an uncontrolled intercurrent illness, including but not limited to:
    a. Ongoing or active infection requiring intravenous treatment with anti-infective therapy that has been administered less than 2 weeks prior to first dose.
    b. Symptomatic congestive heart failure (grade III or IV as classified by the New York Heart Association), unstable angina pectoris or cardiac arrhythmia.
    c. Has a marked baseline prolongation of QT/QTc interval (eg, repeated demonstration of a QTc interval >480 milliseconds (ms) (CTCAE grade 1) using Fridericia's QT correction formula.
    d. Uncontrolled hypertension defined as systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg, despite optimal medical management.
    e. 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:*** Childhood asthma that has resolved, residual hypothyroidism that required only hormone replacement or psoriasis that does not require systemic treatment.
    f. Subjects with a history of grade 3 or higher irAEs that led to treatment discontinuation of a checkpoint inhibitor should be excluded. Subjects with irAEs below grade 3 that led to discontinuation should be discussed with the sponsor.
    g. Subjects with a prior history of myositis, Guillain-Barré syndrome, or myasthenia gravis of any grade are excluded.
    h. History of chronic liver disease or evidence of hepatic cirrhosis.
    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 GEN1044.
    k. Serious, non-healing wound, skin ulcer (of any grade), or bone fracture.
2. Any history of intracerebral arteriovenous malformation, cerebral aneurysm, new (within the last 6 months) or symptomatic brain metastases or stroke. (Transient ischemic attack >1 month prior to screening is allowed.)
    a. Subjects 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).
    b. Subjects 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 3.

   3.1 Prior therapy and prophylaxis:

   a. Radiotherapy: Radiotherapy within 14 days prior to first GEN1044 administration. 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 GEN1044 administration. Accepted exceptions are bisphosphonates (eg, pamidronate, zoledronic acid) and denosumab.

   c. Received any investigational agent (including investigational vaccines) or used an invasive investigational medical device within 28 days before the planned first dose of GEN1044 or is currently enrolled in an interventional trial.

      Note: Subjects who are in the follow-up phase of an interventional trial may participate if the subject has not received an investigational agent within 28 days prior to the first dose of GEN1044.

   d. Prophylaxis with live, attenuated vaccines within 3 weeks prior to first dose of GEN1044; or prophylaxis with the first and/or second injection of SARS-CoV-2 nucleic acid vaccine within 30 days prior to first dose of GEN1044.

   e. Chronic systemic immunosuppressive corticosteroid doses, ie, prednisone >10 mg daily or a cumulative dose >150 mg prednisone within 14 days before the first GEN1044 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. Received granulocyte-colony stimulating factor (G-CSF) or granulocyte/macrophage-colony stimulating factor support 4 weeks prior to first GEN1044 administration or is chronically transfusion dependent.

   g. Any prior therapy with a compound targeting CD3.

   h. Treatment with chimeric antigen receptor T cell (CAR-T) therapy within 30 days prior to first dose of GEN1044.

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 a current prostate-specific antigen (PSA) level <0.1 ng/mL.

   e. Any curable cancer with a complete response (CR) of >2 years duration.

6. Criterion modified per Amendment 3.

   6.1 Has a history of ≥ grade 3 allergic reactions to monoclonal antibody therapy as well as known or has known allergies, hypersensitivity, or intolerance to GEN1044 or its excipients (refer to the GEN1044 Investigator's Brochure).

7. Has any condition for which, in the opinion of the investigator or the sponsor, 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:** Subjects with planned surgical procedures to be conducted under local anesthesia may participate.

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

10. Known history/positive serology for hepatitis B (unless immune due to vaccination or resolved natural infection or unless passive immunization due to immunoglobulin therapy):

    a. Positive test for hepatitis B surface antigen (HBsAg) or for antibodies to hepatitis B core antigens (anti-HBc)

       and

    b. Negative test for antibodies to hepatitis B surface antigens (anti-HBs).

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. Has been dosed in this trial before.

14. Is a woman who is pregnant or breast-feeding.

15. Seizure disorder requiring therapy (such as steroids or anti-epileptics).

5.3 Screening Failures

Screening failures are defined as subjects who consent to participate in the clinical trial but do not meet the protocol-defined eligibility criteria (see Section 5.1 and Section 5.2). A minimal set of screening failure information is required to ensure transparent reporting of screening failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements. Minimal information includes demography, screening failure details, eligibility criteria, and any SAE. (Refer to definition of SAE [Section 10.1.2] and AE reporting [Section 10.2] for additional information.)

Individuals who do not meet the criteria for participation in this trial (screening failures) may be rescreened once. The rescreening must be approved by the sponsor to ensure that the safety of the subject is not compromised. Upon rescreening, all eligibility criteria must be re-assessed by the investigator. Results from assessments performed during the previous screening period are acceptable for rescreening purposes if performed within the specified time frame and the inclusion/exclusion criteria are met.

Upon rescreening, the subject must complete a full new screening visit and all eligibility criteria must be re-assessed at the rescreening visit. A new screening number will not be allocated to the subject at rescreening.

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

A subject will be assigned to IV administration of GEN1044 with a defined priming dose, intermediate dose(s), and defined subsequent full (fixed) doses (see Section 4.2 [Dose Escalation] and Section 4.3 [Expansion]).

For Dose Escalation part:

Subjects will be assigned to a DL cohort in the order in which they become eligible for treatment assignment, using a manual assignment method provided by the sponsor or its contract research organization (CRO). For the Dose Escalation, site personnel must contact the CRO when a potential subject has been identified. If there is an opening in the currently enrolling dose level, 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 the next available opening either in the currently enrolling dose level or at the next opened dose level.

Refer to the laboratory manual for additional information and stepwise guidance on enrollment procedures.

For Expansion part:

Subjects will be allocated to the appropriate expansion cohort (Expansion Cohorts 1 through 8), based on the type of cancer (see Section 4.3). For each group, subjects will be allocated in the order in which they become eligible for treatment assignment, using an interactive response technology (IRT) system. Refer to the laboratory manual for additional information and stepwise guidance on enrollment procedures.

6.2 Premedication Prior to GEN1044 Administration

The purpose of the prophylactic premedication is to mitigate risk and severity of infusion-related reactions (IRRs) and CRS. Premedication with corticosteroids, antihistamines, and antipyretics (Table 12) is mandatory 30 to 120 minutes prior to the first 3 administrations of GEN1044 in Cycle 1, ie, the first, second, and third administrations in the Dose Escalation part and in the Expansion part. If CRS ≥ grade 2 occurs following the third administration (C1D15), prophylactic premedication should be continued and administered at the fourth administration (C2D1) and onwards until CRS events do not occur. If a grade 1 CRS event or no CRS event occurs following the third administration (C1D15), then prophylactic premedication should not be administered for subsequent GEN1044 administrations.

Corticosteroid administration can be either IV or oral including pre-medication administration (Table 12) with the recommended dose or equivalent (Appendix 3).

Table 12 Mandatory CRS Prophylaxis

			Glucocorticosteroids	Antihistamines	Antipyretics
Cycle 1	1st GEN1044 administration	Day 01*	Prednisolone 100 mg IV†	Diphenhydramine 50 mg IV or PO (or equivalent)	Paracetamol (acetaminophen) 650 to 1000 mg PO (or equivalent)
	2nd GEN1044 administration	Day 08*	Prednisolone 100 mg IV†	Diphenhydramine 50 mg IV or PO (or equivalent)	Paracetamol (acetaminophen) 650 to 1000 mg PO (or equivalent)
	3rd GEN1044 administration	Day 15*	Prednisolone 100 mg IV†	Diphenhydramine 50 mg IV or PO (or equivalent)	Paracetamol (acetaminophen) 650 to 1000 mg PO (or equivalent)
Cycle 2	4th GEN1044 administration	Day 01*	Yes, if CRS ≥ grade 2 occurred following the 3rd GEN1044 administration at C1D15, administration of glucocorticosteroids is continued in Cycle 2 until no subsequent CRS develops.	Yes, if glucocorticosteroids are administered	Yes, if glucocorticosteroids are administered

* 30 minutes to 2 hours prior to administration of GEN1044.
† or equivalent, including oral dose.

6.3 Dosages and Administration

Trial treatment should be administered as described in Section 4.2 (Dose Escalation) and Section 4.3 (Expansion) until one or more of the discontinuation criteria in Section 8.1 are met:

- Cycles 1 through 4: Days 1, 8, and 15 (once weekly for a 21-day cycle)
- Cycles 5 and beyond: Day 1 (every 3 weeks for a 21-day cycle)

Refer to the preparation and administration guideline for additional information and stepwise guidance on dosage and administration.

Detailed dose modification guidance is provided in Section 7. Refer to Section 6.5 for information regarding concomitant therapy.

GEN1044 will be administered using IV infusion on Days 1, 8, and 15 of each 3-week (21-day) treatment cycle. GEN1044 will be administered as a fixed dose. In the Dose Escalation part, subjects will be administered GEN1044 according to dose levels outlined in Section 4.2. In the Expansion part, subjects will be administered GEN1044 with the recommended dose from the escalation.

As a routine precaution, subjects dosed with GEN1044 must be monitored during infusion and treated in an area with resuscitation equipment and emergency agents. For weekly dosing during Cycle 1 and Cycle 2, all subjects must be observed for at least 4 hours after ending infusion of GEN1044. For all subsequent cycles, subjects must be observed for at least 2 hours after ending infusion of GEN1044. See Section 4.2 for additional details regarding when an overnight stay (24 hours in-hospital observation) is required.

Refer to the administration and preparation guideline in the GCT1044-01 IMP Manual for additional guidance on trial drug preparation, handling, and storage.

6.4 Compliance

GEN1044 will be administered by site personnel to assure compliance with trial requirements.

6.5 Concomitant Medications and Therapies

The subject must be told to notify the trial site about any new medications (including over-the-counter or prescription medicines, vitamins, and vaccines) they take after the start of GEN1044. All medications (other than GEN1044) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the trial (ie, beginning with administration of the first dose of trial drug until 30 days after the last dose of trial drug) must be documented.

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as "prohibited" (Section 6.5.3).

6.5.1 Permitted Concomitant Medications and Therapies

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

- Local palliative radiotherapy on non-target lesions.
- G-CSF and other hematopoietic growth factors may be used in the management of acute toxicity, such as febrile neutropenia and ≥ grade 3 neutropenia, when clinically indicated or at the investigator's discretion. In case of recurring ≥ grade 3 neutropenia, use of growth factors is mandated.
- Blood cell transfusion, if clinically indicated.
- Multivitamins, vitamin D, calcium and supplements in prevention of weight loss.
- Prescribed medicinal cannabinoids as palliative therapy

6.5.2 Permitted Concomitant Therapy Requiring Caution and/or Action

Concomitant medications are allowed to provide adequate care and may be given as clinically indicated. All concomitant medication 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 Medical Officer should be contacted if there are any questions regarding concomitant medication or prior therapy.

The trial site will ensure supportive medication, eg, premedication, anti-viral medication, anti-IL-6R.

6.5.2.1 Supportive Care for Cytokine Release Syndrome

Rescue medication in terms of an antidote to reverse the action of GEN1044 is not available.

Potential side effects of GEN1044 have to be treated symptomatically.

For treatment of CRS subjects should receive supportive care according to Appendix 6 (Table 26) and local guidelines. The supportive care can include, but is not limited to:

- Infusion of saline
- Systemic glucocorticosteroid, antihistamine, antipyretic(s)
- Support for blood pressure (vasopressin, vasopressors)
- Support for low-flow and high-flow oxygen and positive pressure ventilation
- Monoclonal antibody against IL-6R, eg, IV administration of tocilizumab
- At investigator's discretion: Monoclonal antibody against IL-6 (siltuximab) or IL-1R (anakinra), if not responding to repeated tocilizumab (3 doses within 24 hours).

Blood product support, analgesics, skin and mouth care, etc, should be according to local guidelines and the investigator's discretion.

CRS should be graded according to Table 16 (see Section 10.4.1).

6.5.2.2 Growth Factors

The use of growth factors for neutropenia such as G-CSF will be allowed during treatment with GEN1044. In case of recurring grade 3 neutropenia, use of growth factors is mandated.

6.5.3 Prohibited Concomitant Therapy

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

- Any other anti-cancer therapy, eg, chemotherapy, immunotherapy, radiotherapy or experimental therapy. Local palliative radiotherapy on non-target lesions is allowed.
- Corticosteroid that exceed 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 or CRS therapy).
- Herbal preparations or related over-the-counter (OTC) preparations containing herbal ingredients are not permitted during participation in the trial.
- Anti-CD3 antibodies.
- Live attenuated vaccines while participating in the trial and for 3 months following the last dose of GEN1044. Note: Seasonal influenza vaccines are generally killed virus vaccines and are permitted however, intranasal influenza vaccines are live attenuated and are not allowed.
- SARS-CoV-2 vaccine administration during the DLT assessment period.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered. 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.

6.6 GEN1044 Information

6.6.1 Physical Description of GEN1044

The GEN1044 supplied for this trial is a liquid formulation provided at 10 mg/mL. It will be manufactured and provided under the responsibility of the sponsor.

6.6.2 Packaging

GEN1044 – 10 mg/mL is formulated as a concentrate for solution for infusion to be diluted (at the site) in GEN buffer diluent [redacted]

[redacted]. The drug product will be provided to the site/pharmacy in a glass vial containing 5 mL of GEN1044 (50 mg/vial).

6.6.3 Labeling

GEN1044 labels will contain information to meet the applicable regulatory requirements. For further details see the trial-specific preparation and administration guideline in the GCT1044-01 IMP Manual.

6.6.4 Preparation, Handling, and Storage

The preparation, handling and storage of GEN1044 are described in the GCT1044-01 IMP Manual. GEN1044 must be stored at controlled temperatures ranging from 2°C to 8°C (35.6°F to 46.4°F).

6.6.5 Drug Accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of trial treatment in a drug accountability log. Drug accountability will be verified by the field monitor during site visits and at the completion of the trial.

When drug accountability has been verified and a copy of the completed drug accountability log has been received by sponsor, the investigator will dispose all used and unused trial treatment and packaging in accordance with the guidance in the GCT1044-01 IMP Manual and local regulations.

6.6.6 Handling of Other Trial Treatment

Not applicable.

6.7 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.

6.7.1 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 SAE, the trial-site personnel must report the technical complaint to the sponsor according to the SAE reporting process and timelines (Section 10.5) in addition to reporting the technical complaint. A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

6.7.2 Contacting Sponsor Regarding Technical Complaints

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding technical complaint issues are listed on the sponsor contact page, which will be provided separately from the protocol.

7 DOSE MODIFICATIONS AND SAFETY MANAGEMENT GUIDELINES

7.1 Dose-Limiting Toxicity

The DLT evaluation period is defined as the period from the start of the first GEN1044 administration on C1D1 of the Dose Escalation part of the trial until 7 days after the first full dose. As described in Section 4.1, if a subject receives the priming dose on C1D1, one intermediate dose on C1D8, and the full dose starting on C1D15, the DLT period will be the first 21 days of Cycle 1 (Cycle 1 days 1 through 21). If a subject receives the priming dose on C1D1, the first intermediate dose on C1D8, the second intermediate dose on C1D15, and the first full dose on C2D1, the DLT period will be Cycle 1 up to and including C2D7 (ie, a total of 28 days). The DLT evaluation period may be adjusted for potential GEN1044 treatment delay as described in Section 11.1.7.

National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (NCI-CTCAE, 2017) will be used to assess toxicities/AEs, except for CRS and immune effector cell-associated neurotoxicity syndrome (ICANS) (see Section 10.4.1 and Section 10.4.2, respectively).

A DEC is set up for the study. The DEC will review data from each DL cohort and make a decision regarding dose escalation. That decision of the DEC has to be confirmed by the sponsor SC. The DMC will review data on a quarterly basis.

Events to be collected and assessed by the DMC for DLTs include: SAEs; AESIs where applicable; and clinically significant abnormal laboratory values (that are not already covered by a separate AE term).

The occurrence of any of the toxicities outlined in this section will be considered a DLT if assessed by the investigator to be at least possibly related to GEN1044. AEs clearly not related to the trial treatment (GEN1044) such as disease progression, environmental factors, unrelated trauma, etc, should not be considered a toxicity event.

The following will qualify for a DLT:

- ≥ Grade 3 CRS, graded according to American Society for Transplantation and Cellular Therapy (ASTCT) criteria (Lee et al., 2019) (see Section 10.4.1, Table 16).
- ≥ Grade 3 ICANS, graded according to the criteria specified in Table 17, Section 10.4.2.
- Any Grade 3 or 4 non-hematologic toxicity except for:
  - Grade ≥ 3 nausea/vomiting or diarrhea <72 hours with adequate anti-emetic and other supportive care
  - Grade ≥ 3 fatigue <1 week
  - Grade ≥ 3 electrolyte abnormality that lasts <72 hours, unless the patient has clinical symptoms, in which case all grade ≥3 electrolyte abnormality regardless of duration should count as a DLT
  - Grade ≥ 3 amylase or lipase elevation NOT associated with symptoms or clinical manifestations of pancreatitis does not need to be counted as a DLT
  - Laboratory abnormalities are excluded except for below:
    - Clinically significant medical intervention is required to treat the subject, OR
    - The abnormality leads to hospitalization, OR
    - The abnormality persists for >1 week, OR
    - The abnormality results in a drug-induced liver injury (DILI)
- Any Grade 3 or 4 hematologic toxicity, except for:

  - Grade ≥ 3 lymphocytopenia lasting ≤72 hours
  - Grade 3 thrombocytopenia not associated with impaired hemostasis, clinically significant bleeding or required platelet transfusion therapy
  - Grade ≥ 3 ANC lasting <7 days and without fever
- Grade 3 or grade 4 febrile neutropenia:
  - Grade 3 is defined as absolute neutrophil count (ANC) <1000/mm^3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour.
  - Grade 4 is defined as ANC <500/mm^3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated.
- Liver toxicity as defined by Hy's Law (FDA-Guidance, 2009) below:
  - Aminotransferase (ALT and/or AST) >3×ULN.
  - Total bilirubin >2×ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase).
  - No other reason can be found to explain the combination of increased ALT/AST and total bilirubin.
- Any treatment-related toxicity that causes the subject to discontinue treatment during Cycle 1.
- Any grade 5 toxicity.

7.2 GEN1044 Dose Modification Guidance and Safety Stopping Criteria

7.2.1 Dose Escalation Part

- In the event a subject experiences an AE that meets DLT criteria as outlined in Section 7.1, treatment must be permanently discontinued (unless the subject per investigator's discretion has recovered or is expected to recover and expected to benefit from continued treatment). GEN1044 should also be held for the following:
  - If platelet count <50×10^9/L, hold dose until platelet count is ≥50×10^9/L.
  - If febrile neutropenia <0.5×10^9/L, hold dose until neutrophil count is ≥0.5×10^9/L.
  - If hemoglobin is <8 g/dL (<5 mmol/L), hold dose until hemoglobin ≥8 g/mL (>5 mmol/L).
  - **Note**: Transfusion with blood products and/or administration with G-CSF is permitted if needed (see Section 6.5.2.2).
- During the trial, a planned dose of GEN1044 can be postponed for up to 6 weeks for an AE, whether it is considered drug-related or not; a delay of >6 weeks requires permanent discontinuation of treatment. The delay might be extended to 12 weeks after consultation with the sponsor medical monitor.
- First episodes of cytokine blockade-refractory grade 3 CRS or ICANS (see Section 10.4.1) lasting >72 hours require permanent discontinuation from trial treatment.
- First episodes of refractory grade 4 CRS or ICANS require permanent discontinuation from trial treatment.
- Refer to Appendix 7, Table 27, for dose modification guidelines for specific adverse events. For dose escalation, these rules will only apply after the DLT period.

7.2.2 Expansion Part

- In the event a subject experiences a ≥ grade 2 AE considered drug-related, the GEN1044 dose should be held until the AE resolves to ≤ grade 1. Exceptions are:
  - Grade 2 CRS
  - Grade 2 ICANS
  - ≥ grade 2 fever attributed to CRS
  - ≥ grade 2 hypotension attributed to CRS
  - ≥ grade 2 hypoxia attributed to CRS,
  - ≥ grade 2 lymphocytopenia

  If drug is held for more than 12 weeks, the subject should be permanently discontinued from therapy.
- In cases of cytokine blockade-refractory grade 3 CRS or ICANS lasting >72 hours, GEN1044 must be permanently discontinued.
- In cases of grade 4 CRS or ICANS, GEN1044 must be permanently discontinued.
- In the event a subject experiences a second episode of the same AE at ≥ grade 3, except fever/hypotension/hypoxia attributed to CRS or lymphocytopenia, GEN1044 must be permanently discontinued.
- Refer to Appendix 7, Table 27, for dose modification guidelines for specific adverse events.

7.3 Management of Infusion-Related Reactions

Interrupt GEN1044 infusion for IRRs of any severity and institute medical management/supportive treatment as needed.

- For subjects with grade 1, 2, or 3 IRRs, once reaction symptoms resolve, resume the infusion at no more than half the rate at which the IRR occurred. If the subject does not experience any further IRR symptoms, infusion rate escalation may resume at increments and intervals as clinically appropriate.
- For a grade 4 IRR (life-threatening), permanently discontinue administration of GEN1044 and institute appropriate emergency care.

8 DISCONTINUATION, FOLLOW UP AND COMPLETION

8.1 Discontinuation of Trial Treatment

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

- Unacceptable AE requiring treatment discontinuation (see Section 10)*
- Subject non-compliance
- Sponsor decision
- Pregnancy
- Subject request to discontinue trial treatment*
- Clinical progression*
- Radiographic evidence of disease progression
- Other

* Imaging should continue to be performed until evidence of radiographic disease progression despite treatment discontinuation. When a subject discontinues trial treatment, he/she is to remain on study and are to be followed until death, initiation of subsequent therapy, or any other reason listed in Section 8.2.

To the greatest extent possible, subjects should be examined as soon as possible, and the treatment discontinuation visit should be performed, irrespective of the reason for discontinuation. If the treatment discontinuation evaluations coincide with a regularly scheduled cycle visit, the treatment discontinuation evaluations will supersede those of the regularly scheduled cycle visit. Subjects should be assessed for adverse events within 30 days of the last administration of trial drug.

8.1.1 Treatment Discontinuation and Safety Follow-up Visit

The treatment discontinuation visit should be performed as soon as possible after permanent discontinuation of trial treatment, and will include the assessments described in Table 1 (Dose Escalation) and Table 5 (Expansion).

The Safety Follow-up visit (SFU) should be performed 30 (+14 days) after the subject has received the last dose of trial treatment.

If the treatment discontinuation visit is completed ≥30 days after last dose (eg, if dosing has been on hold awaiting resolution on safety issues, as described in Section 7), then the discontinuation visit and Safety Follow-up visit can be merged and completed on the same day.

Data collected should be added to the AE eCRF and the concomitant medications eCRF.

8.1.2 Post-Trial Treatment Anti-Cancer Therapy Status

New anti-cancer therapy initiated after the last dose of trial treatment is to be reviewed. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30-day SFU visit should occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated, the subject will move into survival follow-up.

8.1.3 Survival Follow-up

Information about survival status and initiation of any new anti-cancer therapy should be collected every 12 weeks (±7 days) (or more frequently around the time of a database lock), beginning from the day of last trial treatment dose until death or withdrawal from trial. Survival follow-up can be

performed by telephone contact (the subject or a family member may give the requested information), email, or during a routine visit, if such a visit is scheduled for other reasons not related to this trial. This should be documented in the medical records. Information related to subsequent progression after initiation of new anti-cancer therapy or death from any cause, whichever comes first, is to be collected.

8.2 Subject Discontinuation/Withdrawal from the Trial

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

- Death
- Lost to follow-up (see Section 8.3)
- The investigator or sponsor believes (eg, that for safety or tolerability reasons (eg, adverse event) it is in the best interest of the subject to discontinue the trial intervention
- Subject withdraws consent
- Other

If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected or generated before such a withdrawal of consent. A subject may choose to discontinue from any future study assessments (eg, dosing, imaging, blood sampling) but agree to remain in the trial and to be followed for survival follow-up, without withdrawal of consent.

If a subject withdraws consent from the trial, he/she may request destruction of any samples (including those collected for biomarker testing) taken and not tested, and the investigator must document this in the site trial records. When a subject withdraws consent, the reason for withdrawal is to be documented in the source document. Trial drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced. The investigator and sponsor will make every effort to ensure subject data are followed for completion of all trial safety assessments including the SFU visit and survival follow-up (see Table 1 [Dose Escalation] and Table 5 [Expansion]) at the time of trial discontinuation.

8.3 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, etc. A subject should not be considered lost to follow-up until due diligence has been completed (at a minimum 3 documented attempts). Subjects lost to follow-up should be documented.

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 recorded. The following should be recorded at screening:

For disease status, the following should be collected:

The primary site of cancer and initial and current disease stage (tumor nodes metastasis [TNM] staging system) will be recorded at screening.

[redacted]

Additionally, if known, local assessed cancer-associated mutations, gene signatures and immune therapy prognostic targets may also be recorded.

9.1.3 Medical History

Any medical condition (signs, symptoms and diagnosis) occurring prior to first dose of trial drug should be documented in the source documents as medical history. Medical conditions that occur after the ICF is signed and prior to first dose of trial drug should only be reported as AEs if they were assessed by the investigator to be caused by a protocol-mandated procedure (eg, 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 drug will be documented as an AE. See additional reporting details in Section 10.

9.1.4 Concomitant Medication

The subject must be told to notify the investigational site about any new medications he or she takes after the start of the trial drug.

Any medication or therapy (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements, and blood transfusions) other than GEN1044 is considered concomitant medication and should be recorded in the eCRF.

Relevant prior concomitant medication given within 30 days prior to screening, during the screening period within 28 days prior to first dose of GEN1044, and all medication given from the first dose of GEN1044 and up to 30 days after the last dose of GEN1044 should be recorded.

During the post-treatment period after the SFU only new anti-cancer treatment will be collected.

The subject must be told to notify the investigational site about any new medications he or she takes after the start of the trial drug.

The 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 (including surgery, radiotherapy, chemotherapy, radiotherapy, systemic treatment regimens, etc) must be recorded. For prior anti-cancer therapies, the number of cycles, best response, and reason for discontinuation along with dates of administration and progression should be reported.

9.2 Efficacy Assessments

Efficacy assessments will be conducted as specified in the visit assessment schedules (refer to Table 1 [Dose Escalation] and Table 5 [Expansion]) and will include the following: radiological/imaging assessments, bone scans (as applicable), PSA results (as applicable), and survival status. All efficacy assessments should be conducted throughout the trial until disease progression or withdrawal of consent from trial participation.

9.2.1 Radiological Exam/Tumor Imaging

In the Dose Escalation and Expansion parts, the reading of the scans will be done by the investigator. Results from the radiology evaluations shall be recorded in the eCRF and a copy of the evaluation reports should be kept in the subject's file.

In the Expansion part, sites may be required to submit electronic copies of all scans on an ongoing basis to a centralized imaging CRO for independent review of tumor assessments. Images obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons, should be captured in the eCRF and submitted to the central imaging vendor.

The imaging process is described in a separate imaging guidance document. Tumor imaging should be performed by CT or MRI, unless otherwise indicated in the imaging guidance document. MRI should be used only when CT is contraindicated, for imaging of the CNS, or for certain anatomical regions (see imaging guidance document). The same imaging technique with respect to the modality and use of contrast should be used in a subject throughout the trial to optimize the visualization of existing and new tumor burden. Determination of measurable and non-measurable diseases based on response assessment criteria relevant to the tumor type (eg, RECIST v1.1 [Appendix 2]) will be conducted by the local site investigator during screening for assessment of subject eligibility and during the study for assessment of response.

9.2.1.1 Baseline Imaging Assessments

Baseline imaging assessments will be performed at screening within 28 days of start of treatment (Day -28 to Day -1 prior to Cycle 1 Day 1).

Any imaging assessments considered of adequate diagnostic quality already completed during the regular evaluation of the subject within 28 days prior to start of treatment, including before signing the main trial ICF, can be considered as the baseline images for this trial.

During screening, all subjects will have a contrast CT of the chest/abdomen/pelvis; a non-contrast CT of chest and MRI of abdomen/pelvis, or chest x-ray as applicable for their respective tumor type.

- 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 a CT-scan or MRI has been performed within 28 days prior to visit Cycle 1 Day 1 as part of standard procedure, it is acceptable as a screening scan for the trial.
- If there is suggestion of brain metastases/tumors, a CT scan or MRI of the head and neck will be performed within 28 days prior to the Cycle 1 Day 1 visit.
- A bone scan is required for subjects with prostate cancer.

The following assessments are required at screening:

Chest, Abdomen, and Pelvis CT or MRI scan

All subjects will have a CT or MRI scan of the abdomen and pelvis, and CT of the chest.

If a subject is known to have a contraindication to CT IV contrast media or develops a contraindication during the trial, a non-contrast CT of the chest plus a contrast-enhanced MRI (if possible) of the abdomen and pelvis should be performed.

It is strongly recommended that MRI is used for evaluation of lesion(s) present within an irradiated field. Tumors within a previously irradiated field will be designated as “non-target” lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy. Biopsy confirmation MAY be considered for either target or non-target lesions if the lesion(s) measures <30 mm or if the treating physician determines it is clinically indicated. If a biopsy is performed on a previously irradiated lesion, an MRI (or CT if MRI is contraindicated) should be obtained following the biopsy procedure and before the start of treatment for use as the baseline screening exam.

Chest x-rays (CXRs) and ultrasound should not be used to measure tumor lesions.

Chest X-ray

A CXR is acceptable at screening in lieu of a chest CT only if the local SOC does not support a chest CT and the CXR does not show evidence of metastases. Otherwise, a chest CT is required.

If the baseline CXR shows no evidence of metastatic disease, subsequent imaging should also be performed with CXR; however, a chest CT scan must be obtained upon identification of lesions after baseline.

If the baseline CXR shows evidence of metastatic disease, a CT of the chest must be obtained and followed for progression and response per the imaging schedule defined above.

Brain CT or MRI scan (if clinically indicated)

In order for subjects with previously treated brain metastases to be eligible to participate in the trial, documented stability by brain imaging over at least 4 weeks is required, and there must be confirmation of no new or enlarging brain metastases within 28 days of the first dose of trial treatment. If brain metastases are suspected at screening, brain MRI or CT scans should be completed. A contrast-enhanced brain MRI is preferred; however, if MRI contrast is contraindicated, then an MRI without contrast or CT with/without contrast is acceptable.

Whole-body Bone Scan

A bone scan is required for subjects with prostate cancer. For subjects with non-prostate cancer, a bone scan should be performed if clinically indicated.

For any subject with an elevated screening serum alkaline phosphatase level (1.5×ULN range), bone imaging (eg, bone scan or positron emission tomography [PET] scan) should be conducted to identify possible bone metastases. If bone metastases are identified that have not been imaged on the CT/MRI performed for baseline tumor imaging (Section 9.2.1.1), then additional baseline and all subsequent tumor imaging studies must include such lesions in the imaging field. A whole-body bone scan should be performed per institutional SOC (eg, Tc-99 bone scan, whole-body bone MRI, FDG-PET or NaF-PET). Combined PET/CT may be used only if the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of IV contrast media. At the discretion of the investigators, FDG-PET scans may be performed to document disease progression as per RECIST v1.1 (Eisenhauer et al., 2009).

CT or MRI Scan of Other Metastatic Sites (if clinically indicated)

If clinically indicated, CT or MRI of other areas (eg, neck) of disease, as appropriate, should be performed.

Measurable or Non-measurable Disease Assessment

The investigator or qualified designee should review screening images to confirm if the subject has measurable or non-measurable disease. Measurable disease is defined as ≥1 target lesion that can be accurately measured in ≥1 dimension. If using a CT with a slice thickness of <5 mm or MRI, non-lymph node lesions must measure ≥10 mm in the longest diameter and lymph nodes must measure ≥15 mm in the shortest diameter. Lymph nodes that measure <10 mm in the short axis are deemed “non-pathologic.” Lymph nodes that measure ≥10 mm but <15 mm should be classified as non-target lesions.

Any potentially measurable lesion that has been previously treated with radiotherapy should be considered as a non-measurable lesion. However, if a lesion previously treated with radiotherapy has clearly progressed since the radiotherapy, it can be considered a measurable lesion.

Table 13 Radiological Exam/Tumor Imaging Assessment Collection Plan

Procedure	Screening/Baseline	During Treatment/Follow-up
Chest, abdomen, and pelvis CT or MRI (with IV contrast enhancement)	Mandated	Mandated, every 6 weeks (±7 days) for 36 wks (calculated from C1D1), then every 12 weeks (±7d) until PD, start of new anti-cancer therapy, consent withdrawn, or death, whichever occurs first
Brain CT or MRI	If clinically indicated	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis
Whole-body bone scan	Prostate cancer: mandated. Non-prostate cancer: If clinically indicated	Prostate cancer: Mandated, every 6 weeks (+7 days) (or longer per local standards) for 24 weeks (calculated from C1D1), then every 12 weeks (±7 days) until PD, start of new anti-cancer therapy, consent withdrawn, or death, whichever occurs first Non-prostate cancer: If clinically indicated
Localized bone CT or MRI	For any lesions identified on the whole-body bone scan that are not visible on the chest, abdomen and pelvis CT or MRI	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis
CT or MRI of other metastatic sites (eg, neck)	If clinically indicated	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis

Note: CXR is acceptable at screening in lieu of a chest CT if the local SOC does not support a chest CT.

9.2.1.2 Post-Baseline Imaging Assessments

Imaging assessments as described in Table 13 should be performed at the time points specified using the same imaging modality used at baseline, irrespective of trial treatment interruption or actual dosing.

- Imaging assessments (CT/MRI) for response evaluation will be performed every 6 weeks (±7 days) after C1D1 during the first 36 weeks, and every 12 weeks (±7 days) thereafter, or more frequently if clinically indicated.
- For subjects with prostate cancer, bone scans will be performed every 6 weeks (+7 days) (or longer per local standards) during the first 24 weeks, and every 12 weeks (±7 days) thereafter.

Radiological/imaging assessments and bone scans should be scheduled using the first dosing date (C1D1) as the reference date (not the date of the previous tumor assessment) and should be respected regardless of whether treatment with trial treatment is temporarily withheld or unscheduled assessments performed. Radiological/imaging assessments and bone scans should continue until PD, the start of new anti-cancer therapy, the subject withdraws consent, or death, whichever occurs first. (In the case of PD per RECIST v1.1, treatment and imaging assessments may continue in clinically stable (non-prostate cancer) subjects per iRECIST; see below.)

Additional imaging assessments may be performed at any time during the trial at the investigator's discretion to support the efficacy evaluations for a subject. Clinical suspicion of disease progression at any time requires a physical examination and imaging assessments to be performed promptly rather than waiting for the next scheduled imaging assessment. Any imaging modalities, if obtained and clinically indicated to assess response or progression, must be entered in the electronic data capture (EDC) pages for evaluation of response or progression.

Each lesion that is measured at baseline must be measured by the same method and when possible, by the same local radiologist/physician throughout the trial so that the comparison is consistent. If an off-schedule imaging assessment is performed because progression is suspected, subsequent imaging assessments should be performed in accordance with the original imaging schedule.

For subjects with baseline measurable disease, objective response (eg, according to RECIST v1.1) should be confirmed by a repeat imaging assessment. Subjects who obtain a confirmation scan do not need to undergo the next scheduled tumor imaging if it is <4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

In subjects who discontinue trial treatment without evidence of radiographic disease progression, tumor imaging must be performed until evidence of radiographic disease progression. If previous tumor imaging was obtained within 4 weeks prior to the date of discontinuation, then tumor imaging at treatment discontinuation is not necessary.

9.2.1.3 iRECIST Assessment of Disease

iRECIST is based on RECIST v1.1 but has been modified to account for the unique response patterns observed with immunotherapy. In this trial, iRECIST will be evaluated as an exploratory endpoint (Seymour et al., 2017).

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 disease progression per RECIST v1.1, but unconfirmed disease progression per iRECIST (iUPD), 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 trial treatment (as assessed by the investigator) and must not have rapid disease progression
- Subject is tolerating trial treatment
- Subject must have a stable ECOG-PS 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 and are not required to have subsequent imaging to confirm PD.

If the subsequent imaging obtained 4 to 7 weeks after the initial assessment of unconfirmed PD confirms disease progression (iCPD), subjects should discontinue trial treatment. If the subsequent imaging shows iRECIST stable disease (iSD), iRECIST partial response (iPR), or iRECIST complete response (iCR), imaging should be continued every 6 weeks (±7 days) and the subject should continue on trial treatment.

9.2.1.4 Guidelines for Prostate Cancer (Non-measurable Disease) Assessment

Prostate Cancer Working Group 3 (PCWG3) criteria (Scher et al., 2016) (see Appendix 5) will be used to evaluate bone lesions (regardless of the soft tissue component), and PCWG3-modified RECIST 1.1 will be used to assess overall combined response. The assessment will be performed by the investigator/local radiologist. In case of discrepancy in response assessment between PCWG3 vs. RECIST 1.1, the designation of PD of either takes priority. If the bone scan per PCWG3 demonstrates anything other than PD, RECIST 1.1 response takes priority (Appendix 5, Table 25). For PCWG3, the flare window is defined as C1D1 through to the end of Week 12 (ie, ≤84 days post-first GEN1044 dose). Accordingly, the first on-treatment bone scan at Week 6 is defined as the flare scan and represents the flare baseline scan to which all subsequent bone scans should be compared (2+2 rule).

9.2.2 PSA Testing for Subjects with Prostate Cancer

Serum PSA levels will be checked at Screening, then on Day 1 of every 3-week treatment cycle and at the Treatment Discontinuation visit and SFU visit (see Table 1 [Dose Escalation] and Table 5 [Expansion]). All PSA testing will be performed by the central laboratory.

9.2.3 Survival Status

Survival status will be assessed every 12 weeks (±7 days) beginning from the last dose of trial treatment until the subject withdraws consent or death occurs, whichever occurs first. Survival status may be requested more frequently around the time of a database lock. This information can be given by the subject or a family member. Information may be obtained by any mechanism such as telephone, email, or visit. If either the subject or designated family member is not available for this assessment, the response should be entered as “lost to follow-up” (see Section 8.3).

9.3 Clinical Safety Assessments

9.3.1 Physical Examination

Full Physical Exam:

The investigator or qualified designee will perform a full physical examination according to SOC 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 GEN1044, report any new or worsening findings since the last assessment as AEs. The time points for full physical examinations are described in Table 1 (Dose Escalation) and Table 5 (Expansion).

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 [Dose Escalation] and Table 5 [Expansion]), the investigator or qualified designee will perform a symptom-directed physical examination as clinically indicated prior to GEN1044 administration. New or worsening findings since the last assessment should be recorded as AEs.

9.3.2 Body Measurements

Body weight (without overcoat and shoes) will be measured at the time points indicated in Table 1 (Dose Escalation) and Table 5 (Expansion) 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 3 and Table 7 for Dose Escalation and Expansion, respectively. On non-infusion days, vital signs should be assessed any time during the visit.

For the Expansion part:

Full vital signs should be collected at Screening only. On subsequent visits (Table 7), collect temperature and blood pressure measurements only.

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 2 (Dose Escalation) and Table 6 (Expansion). ECGs will be performed in accordance with the ECG manual issued by the vendor. The digital ECGs will be transmitted from the sites electronically to a central laboratory for a measurement of the cardiac intervals and morphologic assessment by a central cardiologist.

The corrected QT interval (QTc) will be calculated using Fridericia's formula:

$$QTc_F = \frac{QT}{\sqrt[3]{\frac{RR}{(1s)}}}$$

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 print out. In case of discrepancy between central and the investigator ECG readings, the central reading will be used for trial analysis purposes.

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 eCRF with the description and time of the occurrence.

If triplicate ECGs are required (see Table 2), they should be performed within 20 minutes but at least 2 minutes apart.

9.3.5 ECOG Performance Status

The ECOG-PS will be assessed by the investigator at the time points indicated in Table 1 (Dose Escalation) and Table 5 (Expansion).

The Screening and C1D1 ECOG-PS must be within 0-1 or the subject cannot receive GEN1044. 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 14).

Table 14 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.

Source: (Oken et al., 1982).

9.4 Clinical Laboratory Assessments

The tests to be performed are detailed in Table 15; central and local laboratories will be used for analyses. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

Laboratory values for biochemistry and hematology must be obtained and reviewed by the investigator prior to each GEN1044 administration to ensure the subject can be dosed according to the dosing instructions defined in the protocol.

Beginning with Cycle 3, local and central laboratory samples should be obtained on Day 1 of each cycle or up to 3 days before Day 1. Every effort should be made to obtain local and central labs on the same day. PSA analysis should be performed by the central laboratory. Hematology, biochemistry, coagulation factors, urine pregnancy, and urinalysis should be performed locally.

For AE reporting of laboratory test abnormalities refer to Section 10.2.2.

9.4.1 Clinical Safety Laboratory Tests

Analysis of the tests detailed in Table 15 will be performed according to the visit schedule outlined in Table 1 (Dose Escalation) and Table 5 (Expansion). **Note**: After laboratory results are available from the Dose Escalation part, the number of laboratory analytes (Table 15) in the Expansion part of the study may be reduced, if the sponsor determines not all these tests are needed.

The investigator must review all laboratory results, document this review, and record any clinically relevant changes including dose modifications or delays as an AE.

Table 15 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology (local laboratory)	Hematocrit Hemoglobin Mean platelet volume (MPV) Platelet Count RBC Count	RBC Indices: MCV MCH MCHC % Reticulocytes	WBC Count with Differential[a] Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Biochemistry (local laboratory)	Albumin	Blood Urea Nitrogen (BUN)	Gamma glutamyl transferase (GGT)	Phosphate
	Alanine aminotransferase (ALT)	Calcium	Glucose	Potassium Sodium
	Alkaline phosphatase	Chloride	Glycosylated hemoglobin	Total and direct bilirubin
	Amylase	C-reactive Protein	Lactate dehydrogenase (LDH)	Total protein
	Aspartate Aminotransferase (AST)	Creatinine (estimated GFR by Cockroft-Gault formula)	Lipase Magnesium	Uric acid
Coagulation factors (local laboratory)	Prothrombin time (PT)	International normalized ratio (INR)	Activated partial thromboplastin time (aPTT)	
Urinalysis (local laboratory)	Leukocytes	Protein	Urine pregnancy	
Other screening tests (central laboratory)	Serum beta-hCG[b] Hepatitis B testing: Antibodies to hepatitis B surface antigen (anti-HBs), antibodies to hepatitis B core antigens (anti-HBc), hepatitis B surface antigen (HBsAg) Triiodothyronine (T3) and thyroxine (T4)			
Additional tests for subjects with prostate cancer (central laboratory)	Prostate-specific antigen (PSA) Serum testosterone – at Screening only			

a. WBC differential in either absolutes or percents.
b. Serum (beta-human chorionic gonadotropin [beta-hCG]) should be collected at screening only; urine pregnancy tests may be conducted at other visits. A woman of childbearing potential must have a negative serum beta-hCG at screening. Subjects that are postmenopausal or permanently sterilized (see Appendix 1) can be considered as not having reproductive potential.

9.4.1.1 Testing Performed by a Central Laboratory

The following analyses will be performed at a central laboratory:

- Clinical laboratory tests:
  - Serum beta-hCG (at Screening only)
  - Triiodothyronine (T3) and thyroxine (T4) (at Screening only)
  - Hepatitis B testing (at Screening only): Anti-HBs, anti-HBc, and HBsAg
  - Serum testosterone, for subjects with prostate cancer (at Screening only)
  - Prostate-specific antigen (PSA), for subjects with prostate cancer
- PK
  - Serum levels of GEN1044
- Immunogenicity

  - Serum presence of antibodies against GEN1044 (ADAs)
- Tumor biopsy
  - Analysis of specimens
- Cytokines and chemokines
  - Plasma and serum levels of cytokines and chemokines
- Immune phenotyping
- [redacted]

9.4.2 Eligibility Assessment Based on Laboratory Results

Laboratory samples at the screening visit must be obtained within 7 days prior to Cycle 1 Day 1, with the exception of hepatitis B (which may be obtained earlier) to assess eligibility as follows:

- Hematology, biochemistry, serum (beta-hCG) pregnancy testing, and hepatitis B testing (see Table 15)
- Coagulation factors and urinalysis (see Table 15)
- Serum testosterone (for subjects with prostate cancer) (see Table 15)

Note: PSA should also be obtained for subjects with prostate cancer (see Section 9.2.2 and Table 15).

9.5 Pharmacokinetics

9.5.1 Pharmacokinetic Assessments

Venous blood samples will be collected for measurement of serum concentrations of GEN1044 as specified in Table 2 (Dose Escalation) and Table 6 (Expansion). The 24-hour clock time of each sample will be recorded.

Each serum sample will be divided into aliquots. Samples collected for analyses of serum concentration may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the trial period. Genetic analyses will not be performed on these serum samples. Subject confidentiality will be maintained.

Further details are included in the laboratory manual.

Depending on data availability, a population PK approach will be used to assess the PK of GEN1044 and the effect of baseline body weight and other covariates on the PK of GEN1044. A population PK report will be generated separately from the clinical trial report.

9.5.2 Analytical Procedures

Serum samples will be analyzed to determine concentrations of GEN1044 using validated methods.

9.6 Immunogenicity

9.6.1 Immunogenicity Assessments

Venous blood samples will be collected from all subjects for measurement of serum concentrations of ADAs at the time points specified in Table 2 (Dose Escalation) and Table 6 (Expansion). These samples will be tested by the sponsor or sponsor's designee. Serum samples will be screened for antibodies binding to GEN1044 and the titer of confirmed positive samples will be reported. Samples collected for ADAs to GEN1044 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. Genetic analyses will not be performed on these serum samples. Subject confidentiality will be maintained.

The detection and titer characterization of ADAs may be performed using validated, specific and sensitive electrochemiluminescence immunoassay (ECLIA) methods and the titer of confirmed positive samples may be reported. The analysis may 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 GEN1044 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 GEN1044.

Biomarker assessments will focus on:

1. Evaluating circulating chemokines, cytokines, and other soluble markers as a potential pharmacodynamic biomarker.
2. Evaluating the composition, activation, and proliferation of the peripheral immune cells as a potential predictive biomarker that can identify those subjects that will respond to GEN1044.

[redacted]

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

9.7.1 Biomarker Assessments in Tumor Samples

Biomarker analyses in the tumor sample obtained at baseline and during treatment may help confirm the MOA of GEN1044 and enable the identification of biomarkers predictive of response to GEN1044 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 by, for example, immunohistochemistry, [redacted]

Assessments will be performed at the time points outlined in Table 4 (Dose Escalation) and Table 8 (Expansion) 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 pharmacodynamic and predictive markers such as a) circulating cytokines, chemokines, and other soluble markers and b) immune cell composition, activation, and proliferation, [redacted] and to explore the relationship to efficacy or MOA of GEN1044.

Assessments will be performed at the time points outlined in Table 4 (Dose Escalation) and Table 8 (Expansion) in order to enable correlation analyses with response to treatment or disease progression.

9.7.3 [redacted]

[redacted]

[redacted]

9.7.4 Sample Collections

[redacted]

[redacted]

If it is determined at any time before trial completion that additional material is needed from a 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).

9.7.5 Additional Analysis

In addition to the biomarker analyses listed above, other biomarkers deemed relevant to gain further knowledge about the pathomechanism of the disease or about GEN1044 (ie, MOA, related effect, or safety of the drug) may be measured, based on newly emerging data from other ongoing trials and/or literature data. Biomarker samples may further be used for up to 5 years after the last subject's last treatment, to help address emerging issues and to enable the development of safer, more effective, and, ultimately, individualized therapy. Such analyses would be specific to research related to the trial drug or diseases being investigated by the sponsor.

Moreover, biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the trial, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the trial is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

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

9.8 [redacted]

[redacted]

9.9 Resource Utilization

Not applicable.

9.10 Subject Reported Outcomes

Not applicable.

10 SAFETY MONITORING AND ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established SOPs in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

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 adverse event 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
- Solely due to progression of the underlying cancer
- 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 a SAE given above is not an SAE.

10.1.3 Definition of Adverse Events of Special Interest

Adverse events of special interest (AESI) 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. AESIs are

defined on the basis of an ongoing review of the safety data. AESIs are discussed further in Section 10.4 and in the Investigator's Brochure.

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.

10.2 Reporting Period

This is trial-specific and defined in Section 10.2.1, Adverse Event Reporting. Events requiring immediate reporting are listed in Section 10.5.

10.2.1 Adverse Event Reporting

All AEs, whether serious or non-serious (see definitions in Section 10.1), will be documented from the first GEN1044 dose until 30 days after the last GEN1044 dose, as documented in the Schedule of Activities, Section 1.3.

As noted in Section 9.1.3, medical conditions (signs, symptoms, and diagnosis) that occur after the ICF is signed and prior to first GEN1044 dose 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.

For details regarding follow-up of AEs and SAEs, see Section 10.7.

10.2.2 Procedures for Recording and Reporting

All AEs, serious or non-serious, must be documented.

- The diagnosis/cause of an AE should be documented rather than the symptoms of the AE.
- If no diagnosis is available, then each sign and symptom should be documented as individual AEs.
- All AEs that occur during the AE reporting period must be documented, whether or not the event is considered treatment-related.
- All AEs should be documented and re-assessment made at each visit (or more frequently, if necessary).
- Final assessment of AEs must be performed by a medically qualified person.

Laboratory abnormalities that are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy, or require changes in trial treatment should be documented as an AE.

- Whenever possible, a diagnosis should be provided (eg, anemia instead of low hemoglobin). 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.
- NOTE: A CTCAE grade 3 or 4 laboratory abnormality does not automatically indicate an SAE.

Disease-related events and outcomes not qualifying as AEs or SAEs are trial-specific and provided in Section 10.3.1.

10.3 Evaluation of Adverse Events

Severity

Toxicities will be graded for severity according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (NCI-CTCAE, 2017) to describe the intensity of AEs, except for CRS (see Section 10.4.1) and ICANS (see Section 10.4.2).

Relationship to the Investigational Medicinal Product

The investigator must assess whether or not the event is related to the trial drug. The relationship is to be judged using the following terms:

- Related
- Not related

If the relationship changes over time, the last judgment by the investigator should be reported. Relatedness has to be assessed and reported from the first time the event is being reported.

A suspected adverse reaction is one in which there is a reasonable possibility that the trial drug caused the AE; this means there is evidence to suggest a causal relationship between the trial drug and the AE (ie, considered related).

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

10.3.1.1 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 of progression that cannot be determined as reasonably due to progression of the underlying malignancy or do 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.

10.3.1.2 Unrelated Procedures

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. A medical condition for which an unscheduled procedure was performed, should

however be reported if it meets the definition of an AE (eg, an acute appendicitis should be reported as the AE and not the appendectomy).

10.4 Adverse Events of Special Interest

The following are considered AESIs:

- CRS, graded according to ASTCT criteria (Lee et al., 2019) (see Table 16).
- ICANS (Lee et al., 2019)

AESIs are to be entered in the eCRF and reported to the Safety CRO within 24 hours if they meet seriousness criteria or just entered in the eCRF within 72 hours if not serious.

10.4.1 Cytokine Release Syndrome

CRS will be graded according to the ASTCT grading for CRS (Lee et al., 2019) (Table 16):

Table 16 Diagnosis and Grading of Cytokine Release Syndrome in Adults According to ASTCT Criteria

CSR Parameter	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Fever[a]	≥38.0°C (100.4°F)	≥38.0°C (100.4°F)	≥38.0°C (100.4°F)	≥38.0°C (100.4°F)	Death due to CRS in which another cause is not the principal factor leading to this outcome
With hypotension[b]	None	Not requiring vasopressors	Requiring 1 vasopressor with or without vasopressin	Requiring ≥2 vasopressors (excluding vasopressin)	
And/or hypoxia[b]	None	Requiring low-flow (≤6 L/minute) nasal cannula or blow-by	Requiring high-flow (>6 L/minute) nasal cannula, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure ventilation[c] (eg, CPAP, BiPAP, intubation and mechanical ventilation)	

Note: Organ toxicities or constitutional symptoms associated with CRS may be graded according to CTCAE but they **do not influence CRS grading**.

a. Fever is defined as temperature ≥38.0°C (100.4°F) **not attributable to any other cause**, with or without constitutional symptoms (eg,, myalgia, arthralgia, malaise). In patients who have CRS receiving antipyretics, anti-cytokine therapy, and/or corticosteroids, such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

b. CRS grade is determined by the more severe event: hypotension or hypoxia **not attributable to any other cause**. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS. Both systolic blood pressure (SBP) and mean arterial pressure (MAP) are acceptable for blood pressure measurement. No specific limits are required, but hypotension should be determined on a case-by-case basis, accounting for age and the patient's individual baseline, ie, a blood pressure that is below the normal expected for an individual in a given environment.

c. Intubation of a patient without hypoxia for the possible neurologic compromise of a patent airway alone or for a procedure is not by definition grade 4 CRS.

Source: (Lee et al., 2019)

10.4.2 Immune Effector Cell-Associated Neurotoxicity Syndrome

ICANS is a complication associated with endothelial cell activation, increased blood-brain-barrier permeability, and influx of elevated cytokines into the cerebrospinal fluid following T-cell activating therapies. Previously, it was considered in aggregate with CRS, but is now treated as a separate entity owing to its distinct timing and response to intervention. Accordingly, it may occur concurrently with CRS or shortly after CRS symptoms subside (but rarely before). Subjects receiving GEN1044 should be monitored for ICANS to facilitate early recognition, grading, and management. Common clinical manifestations include confusion or delirium, expressive aphasia, headache, seizures, and altered level of consciousness, some of which may mimic findings in an elderly hospitalized patient with fever. ICANS will be graded according to the ASTCT grading for ICANS (Table 17), which comprises five neurotoxicity domains including the immune effector cell-associated encephalopathy (ICE) cognitive assessment score (Table 18) (Lee et al., 2019).

Table 17 Diagnosis and Grading of Immune Effector Cell-Associated Neurotoxicity Syndrome in Adults According to ASTCT Criteria

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
ICE score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)	Death due to ICANS in which another cause is not the primary factor leading to this outcome
Depressed level of consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma.	
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly (≤5 min) or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between.	
Motor findings‡	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis	
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging§	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or cranial nerve VI palsy, or papilledema, or Cushing's triad	

ICANS grade is determined by the most severe event among the five neurotoxicity domains, not attributable to any other cause. For example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.

* A patient with and ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

† Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

‡ Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

§ Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

Source: (Lee et al., 2019)

Table 18 The Immune Effector Cell-Associated Encephalopathy (ICE) Assessment Tool

Cognitive Domain	Task	Points
Orientation	Orientation to year	1
	Orientation to month	1
	Orientation to city	1
	Orientation to hospital	1
Naming	Naming 3 common objects (eg, point to clock, pen, button)	3
Following commands	Ability to follow simple commands, eg, "*Show me two fingers*" or "*Close your eyes and stick out your tongue*"	1
Writing	Ability to write a standard sentence, eg, "*Our national bird is the bald eagle*"	1
Attention	Ability to count backwards from 100 by 10	1
Maximum ICE Score		**10**

Note: If the patient is unarousable and unable to perform ICE assessment (ICE 0), then Grade 4 ICANS.
Source: (Lee et al., 2019)

See Appendix 8 for a diagram of recommended ICANS management.

10.5 Events Requiring Immediate Reporting

10.5.1 Serious Adverse Events

SAEs must be reported from the investigational site to the sponsor no later than 24 hours following:

- The subject's visit at which such AE was reported, noted, or recognized;
- The principal investigator's or any investigator personnel's receipt of the test results; or
- Other information from which such development was reported, noted, or recognized.

10.5.2 Overdose/Medication Errors

An overdose is defined as a subject receiving a dose of GEN1044 in excess of 10% of that specified in this protocol. All cases of overdose must be reported to the sponsor as protocol deviations within 24 hours of knowledge of the event (see additional details in Section 10.5.2.1).

Medication errors (including infusion rate errors) and uses outside what is foreseen in the protocol, including misuse and abuse of the product, should be reported within 24 hours of knowledge of the event.

10.5.2.1 Treatment of Overdose

Rescue medication to reverse the action of GEN1044 is not available. In case of overdose, medication errors, misuse and/or abuse of the trial drug, subjects should receive supportive care according to local guidelines and potential side effects of GEN1044 should be treated symptomatically.

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
- Consider plasmapheresis, in consultation with the sponsor.
- 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.

10.5.3 Pregnancy

Pregnancy is not allowed in this trial. However, if any pregnancy occurs during trial participation, the pregnancy must be reported.

All reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor within 24 hours of knowledge of the event. In the case of pregnancy in the partner of a male subject, a separate ICF will be obtained from the female partner for collection of information regarding the pregnancy.

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 the GEN1044 must be promptly reported to sponsor or designee.

Pregnant trial subjects must be withdrawn from treatment immediately, whereas male subjects may continue in the trial should pregnancy of female partners occur.

10.6 Regulatory Reporting Requirements for 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 (see Section 10.5.1).

The sponsor will ensure that all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSARs) is documented 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/IRBs according to the applicable local regulatory requirements. Relevant follow–up information of fatal or life-threatening SUSARs will be communicated subsequently within the required reporting timelines. The sponsor will also communicate relevant information on SUSARs with the investigators in predefined periods according to local regulations.

The investigator should be aware of local reporting regulations to the IEC/IRB. The safety CRO will either supply the investigator with the reports which should be passed on to the IEC/IRB or report directly to the IEC/IRB, depending on local regulations.

The sponsor will notify all investigators of the SUSAR.

10.7 Follow-Up of Adverse Events and Serious Adverse Events

All AEs must be followed until they are resolved, or until the safety follow-up visit(s), or the start of new anti-cancer treatment, whichever comes first.

All SAEs and GEN1044-related AESIs qualifying for immediate reporting that are ongoing at the safety follow-up visit should continue to be followed on a regular basis 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 drug should be reported after the safety follow-up period.

10.8 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 provided Investigator's Brochure. Additional safety information collected between Investigator's Brochure 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.

10.9 Data Monitoring Committee

A DMC will be established to ensure the continuing safety of the subjects enrolled in this trial. This committee will consist of at least 1 medical expert in the relevant therapeutic area; committee membership responsibilities, qualifications, and procedures will be documented in its charter.

10.10 Dose Escalation Committee and Safety Committee

The DEC will be chaired by the sponsor's Responsible Medical Officer (or delegate) and membership will include investigator(s), a sponsor clinical scientist, a safety physician, a statistician, a clinical pharmacologist, and other sponsor staff, as appropriate. The DEC will meet at regular frequency throughout the Dose Escalation part.

All available data, including but not limited to safety, pharmacokinetic, and pharmacodynamic data, covering the DLT evaluation period will be reviewed by the DEC. Cumulative data from subsequent treatment doses may also be monitored. Recommendations on dose escalation (or de-escalation) will be made by the DEC to the Safety Committee.

The Safety Committee will consider the recommendation made by the DEC and make the final decision regarding dose escalation (or de-escalation). The Safety Committee can also stop further enrollment if treatment-emergent toxicity is determined to result in an unfavorable change in subject benefit/risk. Enrollment may be temporarily held, if needed, for the Safety Committee to evaluate the emerging data.

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

11 STATISTICS

The Statistical Analysis Plan (SAP) will be developed and finalized before database lock and will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

All presentations will be done separately for the Dose Escalation part and the Expansion part. Subjects in the Dose Escalation part will typically be analyzed according to the assigned DL cohort. Subjects in the Expansion part will be analyzed according to their assigned expansion cohort.

The primary analyses will be timed as follows:

- **Escalation**: Primary safety and efficacy analyses will be conducted on all subject data at the end of the escalation.
- **Expansion**: The expansion part consists of parallel cohorts, wherein each expansion cohort may report its individual primary analysis. Primary safety and efficacy analyses will be conducted on all subject data at earliest when all subjects who are still receiving trial treatment have at least 2 scans performed (such that the primary endpoint may be confirmed).

11.1 Analysis Sets

The analysis sets are defined similarly for both escalation and expansion parts.

11.1.1 Full Analysis Set

The full analysis set (FAS) and safety set are defined in the same way and will comprise all subjects who receive at least 1 dose of trial drug.

11.1.2 Response Evaluable Set

The response evaluable set consists of all subjects who have baseline evaluable disease and at least 1 post-baseline disease assessment. It also includes subjects who die before the first response assessment; these subjects are treated as non-responders.

11.1.3 Safety Set

See the definition of the FAS.

11.1.4 Per-Protocol Set

Not applicable.

11.1.5 Pharmacokinetic Analysis Set

The pharmacokinetic analysis set (PAS) will include all subjects who receive at least 1 dose of trial drug and who provide at least 1 evaluable PK sample.

11.1.6 Immunogenicity Analysis Set

The immunogenicity analysis set (IAS) will include all subjects who receive at least 1 dose of trial drug, and have a baseline and at least 1 evaluable on-treatment ADA sample.

11.1.7 Dose-Determining Analysis Set – Dose Escalation Part

The dose-determining set (DDS), which is used to define the number of DLT evaluable subjects on a DL cohort, will include all FAS subjects in the escalation part who meet the exposure criterion (defined below) and have sufficient safety evaluations, or experience a DLT prior to the 2nd full dose administration. The DLT period will extend until 7 days after the first full dose (see Section 4.2).

A subject meets the exposure criterion if all doses, up to and including the 1st full dose, are administered in a timely fashion: In general, the individual doses should not be delayed more than 7 days. However, longer dose delays might be acceptable if the DEC considers the assessments still to be appropriate. The first full dose should be administered at latest by 30 calendar days after C1D1 (if one intermediate dose is administered), or by 38 calendar days after C1D1 (if two intermediate doses are administered), counting the day of first exposure as C1D1.

If there is a longer dose delay the subject is considered as non-DLT evaluable (as long as the reason for the dose delay, or the dose delay itself, is not classified as a DLT). DLTs occurring beyond the DLT period will be presented, but not contribute to the DLT rates for the DL cohort per mBOIN.

Subjects who do not experience a DLT will be considered to have sufficient safety evaluations if they have been observed for ≥21 days (or ≥28 days if 2 intermediate doses are applied) following the priming dose, and are considered by both the sponsor and investigators to have enough safety data to conclude that a DLT did not occur.

For a period-specific dose level (doses up to and including 1st full dose), a subject is considered as DLT evaluable if the dose was timely administered (ie, not delayed for more than 7 days) and had sufficient safety evaluations up to the subsequent dose administration to conclude if a DLT did occur or not. The relative DLT periods for priming and intermediate doses extend the planned timing of the subsequent dosing (ie, extends until 7 days after the dose administration). For the 1st full dose, it extends up to 7 days past drug administration. Appendix 9 provides a comparison of the DDS considerations and a template for the reporting of DLT rates.

11.2 Subject Disposition

Subject dispositions will be presented in flow diagrams in accordance with the current CONSORT statement.

11.3 Subject Demographics and Baseline Characteristics

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

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical history at baseline will be summarized by system organ class and preferred term, by cohort or expansion cohort, depending on part.

11.4 Treatments

The FAS will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure to GEN1044, the cumulative dose administered, and dose intensity (computed as the ratio of actual cumulative dose received and number of cycles initiated) will be summarized by means of descriptive statistics.

The number of subjects with dose adjustments and the reasons will be summarized, and all dosing data will be listed.

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

11.5 Analysis of Dose Escalation Part

11.5.1 Primary Objectives

The primary objectives are to:

- Determine the RP2D
- Establish the safety profile of GEN1044

11.5.2 Primary Endpoint – Dose Limiting Toxicities

The number of DLTs during the DLT period will be observed, as part of determining the RP2D.

The number treated per FAS, number of DLT evaluable subjects, number of DLTs, and DLT rate on each DL cohort will be tabulated.

11.5.3 Primary Endpoint – Adverse Events and Safety Laboratory Parameters

11.5.3.1 Analysis Set and Grouping for the Analyses

For all safety analyses, the FAS (which is identical to Safety Set) will be used.

The overall observation period will be divided into 3 mutually exclusive segments:

1. Pre-treatment period: from day of subject's informed consent to the day before first dose of trial medication
2. On-treatment period: from day of first dose of trial medication to 30 days after last dose of trial medication
3. Post-treatment period: starts when the on-treatment period ends.

11.5.3.2 Adverse Events

Summary tables for AEs will include only AEs that started or pre-existing AEs that worsened during the on-treatment period, ie, the treatment-emergent adverse events (TEAEs).

The incidence of TEAEs (new or worsening from baseline) will be summarized by system organ class and/or preferred term; intensity (based on grades of NCI-CTCAE version 5.0) for all TEAEs except for CRS (see Section 10.4.1) and for ICANS (see Section 10.4.2); type of TEAE; relationship to trial treatment.

SAEs, non-serious TEAEs, and AESIs during the on-treatment period will be tabulated.

All fatal TEAEs, and all deaths (both on-treatment and post-treatment deaths) will be summarized.

All TEAEs, 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 TEAEs and AESIs will be specified in the SAP.

11.5.3.3 Laboratory Abnormalities

Grading of laboratory values will be assigned as per NCI-CTCAE version 5.0; further details will be provided in the SAP. 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) (or other project-specific) classification to compare baseline to the worst on-treatment value.

11.5.4 Statistical Hypothesis, Model, and Method of Analysis

No formal statistical hypotheses are formulated in this trial. Any P-values will be considered as hypothesis-generating results to be considered for future trials.

11.5.5 Handling of Missing Values/Censoring/Discontinuations

The constraints of the DLT assessments is described in Section 4.2.2.

Imputation of missing or partially missing dates relating to adverse events will be detailed in the SAP.

Missing concentrations of laboratory parameters will be reported as is in data listings. Concentration values below the lower limit of quantitation (LLOQ, BLLOQ) will be handled as LLOQ/2 in summary statistics, and reported as is in data listings.

11.5.6 Supportive and Sensitivity Analyses

Not applicable.

11.5.7 Secondary Objectives

The secondary objectives are to:

- Establish the PK profile

- Evaluate immunogenicity of GEN1044, based on ADA response
- Evaluate anti-tumor activity (reduction in tumor size) based on response criteria relevant to the tumor type: ORR, DCR, DOR, and TTR.

11.5.8 Secondary Endpoint – Pharmacokinetics

The PAS will be used for the analyses presented in this section.

Individual curves of concentration of GEN1044, including information on actual dose, will be presented for all subjects. All available data will be shown in these figures. The following PK parameters may be calculated based on the availability of data using non-compartmental methods:

- clearance;
- volume of distribution;
- maximum (peak) observed serum drug concentration (C_{max});
- time to reach maximum (peak) serum drug concentration (T_{max});
- area under the concentration-time curve (AUC) from time zero to last quantifiable sample (AUC_{last}) and from time zero to infinity (AUC_{inf});
- time to reach maximum (peak) serum drug concentration (T_{max});
- predose trough concentrations (C_{Trough}); and
- elimination half-life ($T_{1/2}$).

If deemed applicable, compartmental modelling approaches to parameter estimation will be applied.

Descriptive statistics of PK endpoints will include arithmetic and geometric means, standard deviation, CV%, median, minimum and maximum.

11.5.8.1 Data Handling Principles

Missing concentration values will be reported as is in data listings. Concentration values that are BLLOQ will be handled as LLOQ/2 in summary statistics, and reported as is in data listings. Any missing PK parameter data will not be imputed.

11.5.9 Secondary Endpoint – Immunogenicity

The IAS will be used for the analyses presented in this section.

Titers of GEN1044 will be listed and positive/negative host immune response to GEN1044 and the presence of neutralizing antibodies (if assessed) 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, AUC, C_{max}), major safety signals (such as CTCAE ≥ grade 3) and efficacy information (eg, change in tumor size by CT scan or MRI) will be explored, if possible.

11.5.10 Secondary Endpoint – Evaluation of Anti-tumor Activity

11.5.10.1 Objective Response Rate

The confirmed objective response rate (ORR) is defined as the proportion of subjects with best overall response (BOR) of confirmed CR or confirmed PR (ie, “responders”), as per local review

and according to RECIST v1.1 (Eisenhauer et al., 2009). Repeat imaging may be performed no less than 4 weeks after the criteria for CR or PR is met to confirm the initial response.

An assessment of stable disease (SD) requires at least 5 weeks from C1D1 to scan date.

The BOR will be summarized in conjunction with the ORR. The estimated rates and the exact 2-sided 95% CIs (using the Clopper-Pearson method) will be summarized. Individual subject data listings will be provided.

11.5.10.2 Disease Control Rate

The disease control rate (DCR) is defined as the proportion of subjects with BOR of confirmed CR, confirmed PR, or SD as per local review and according to RECIST v1.1 (Eisenhauer et al., 2009).

The estimated DCR and the exact 2-sided 95% CIs (using the Clopper-Pearson method) will be summarized in conjunction with the ORR.

11.5.10.3 Duration of Response

Duration of response (DOR) only applies to subjects with a best overall response that is either confirmed CR or confirmed PR according to RECIST v1.1 based on tumor response data per local review. 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 due to any cause. Subjects continuing without progression or death due to underlying cancer will be censored at the date of their last adequate tumor assessment. In case of progression after ≥2 missed visits, censoring will be done at last adequate tumor assessment date.

DOR distribution will be estimated using the Kaplan-Meier method, and the survival curve, median and 95% CI of the median will be presented. If too few responders this analysis may be omitted. Individual subject data listings will be provided.

11.5.10.4 Time to Response

Time to response (TTR) is defined as the time from the date of C1D1 to the first documented response of either confirmed CR or confirmed PR. Date of initial response is used, not date of confirmation. CR and PR are based on tumor response data as per local review and according to RECIST v1.1 (Eisenhauer et al., 2009).

The TTR calculations are restricted to those subjects in the FAS with a confirmed PR or CR. TTR will be summarized and listed.

11.5.11 Supportive Analyses of Secondary Efficacy Objectives and Endpoints

Not applicable.

11.5.12 Other Safety Data

11.5.12.1 Vital signs

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

11.5.12.2 ECGs

12-lead ECGs including PR, QRS, QT, heart-rate-corrected QT intervals using Fridericia's correction (QTcF), and RR intervals will be obtained for each subject during the trial. ECG data will be read and interpreted centrally. Triplicate ECGs are planned for the Dose Escalation part.

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 cohort).

11.5.12.3 ECOG Performance Status

ECOG-PS will be summarized by visit and listed.

11.5.13 Supportive Analyses for Secondary Objectives

Not applicable.

11.5.14 Tolerability

Not applicable.

11.5.15 Exploratory Objectives

11.5.16 Exploratory Endpoint – Biomarkers

The exploratory biomarker assessments are intended to evaluate potential pharmacodynamic markers, and to identify markers predictive of response or resistance to GEN1044. Since this clinical trial is not designed to address specific biomarkers-related statistical hypotheses, the analysis of these data should be viewed as exploratory and hypotheses generating. Analyses may include how the peripheral T-cell activation and proliferation and cytokine release distributes between the type of responder groups. Descriptive analysis will be performed, and further details for additional analyses will be defined in the SAP. Results from exploratory biomarker assessments may be documented in separate reports.

Biomarkers, including pharmacodynamic markers, may be listed, tabulated, and plotted when deemed appropriate. Analyses may be stratified by clinical covariates or molecular subgroups using the appropriate statistical methods (eg, non-parametric or parametric, analysis of covariance [ANCOVA], proportional hazards regression or Kaplan-Meier methods) depending on the endpoint and the hypotheses. Baseline biomarker levels, or changes in biomarker levels, may be assessed for correlation with tumor response and other clinical endpoints to identify responsive or resistant subgroups, as well as biomarkers or pathways attenuated following treatment with GEN1044.

Additional analyses that may be performed after the completion of the end-of-trial clinical trial report (CTR) will be documented in separate reports. These analyses may include but are not limited to the meta-analysis of data from this trial combined with data from other trials or the analysis of biomarkers generated from samples collected during the trial but analyzed after the database lock and completion of the CTR. These analyses will be described in an addendum of the SAP, or in a stand-alone analysis plan document, as appropriate.

Planned analyses are based on the availability of clinically valid assays and may be deferred if emerging trial data shows no likelihood of providing useful scientific information.

11.5.17 Exploratory Endpoint – Anti-tumor Activity Based on iRECIST

Responses assigned using iRECIST (Seymour et al., 2017) have a prefix of "i" eg, "immune" complete response (iCR) or partial response (iPR), and unconfirmed progressive disease (iUPD) or confirmed progressive disease (iCPD) to differentiate them from responses assigned using RECIST v1.1. Similar nomenclature is used for immune stable disease (iSD), immune objective response rate (iORR), immune disease control rate (iDCR) and immune duration of response (iDOR).

The iRECIST endpoints are analyzed using the same statistical methodology and the results presented in the same way as for the corresponding RECIST v1.1 endpoints, eg, iORR should be analyzed and reported in the same way as ORR.

If too few responders are observed, this exploratory analysis may be omitted. iRECIST will not be evaluated in subjects with prostate cancer.

11.5.18 Exploratory Endpoint – Anti-tumor Activity and Changes in PSA - Prostate Cancer Subjects Only

This section defines the endpoints used to address the assessment of anti-tumor activity and changes in PSA for the prostate cancer subjects. Depending on number of prostate cancer subjects treated in the escalation part, the summaries of the prostate cancer-specific endpoints in the escalation part may be omitted.

11.5.18.1 Modified ORR

For the prostate cancer subjects the modified ORR (mORR) is defined as confirmed response in soft tissue (visceral or nodal disease), per RECIST v1.1 (Eisenhauer et al., 2009), with no evidence of bone progression according to the Prostate Cancer Working Group 3 (PCWG3) criteria. The mORR is defined as the proportion of subjects with either complete or partial response.

The estimated mORR and the exact 2-sided 95% CIs using the Clopper-Pearson method will be presented for the prostate cancer subjects. Individual subject data listings will be provided.

11.5.18.2 Modified DCR

Modified DCR (mDCR) is defined similar to the definition in Section 11.5.10.2, but based on the response modification defined in Section 11.5.18.1.

The estimate of the mDCR and the exact 2-sided 95% CIs using the Clopper-Pearson method will be presented the prostate cancer subjects. Individual subject data listings will be provided.

11.5.18.3 Modified Duration of Response

Modified DOR (mDOR) is defined as the time from CR or PR (based on the response modification defined in Section 11.5.18.1) to the date of rPFS (see definition in Section 11.6.19.5). Censoring rules as described in Section 11.5.10.3 will be applied.

The mDOR distribution will be estimated using the Kaplan-Meier method, and the survival curve, median and 95% CI of the median will be presented. Individual subject data listings will be provided.

11.5.18.4 Composite Response Rate

The composite response rate (CRR) is defined as a response per the modified RECIST v1.1 criteria *or* a PSA response (see Section 11.5.18.5).

The estimated CRR and the exact 2-sided 95% CIs using the Clopper-Pearson method will be presented for the prostate cancer subjects. Individual subject data listings will be provided.

11.5.18.5 Exploratory Endpoint - PSA Response

Complete PSA response is defined as a decline in PSA of ≥50% from baseline confirmed by a second PSA measurement 4 to 6 weeks later.

The PSA response rate defined as the proportion of subjects with a PSA response in the FAS will be reported with exact 2-sided 95% CIs using the Clopper-Pearson method. Individual subject data listings will be provided.

11.5.18.6 Exploratory Endpoint - PSA Progression

Disease progression by PSA is defined as an increase in the PSA concentration by ≥25% above nadir (or baseline, if PSA never decreased below the baseline), with an absolute increase in the PSA level by 2 ng/mL, confirmed by a second value 3 or more weeks later.

The rate of PSA progression, defined as the proportion of subjects with a PSA progression in the FAS will be reported with exact 2-sided 95% CIs using the Clopper-Pearson method. Individual subject data listings will be provided.

11.5.19 [redacted]

[redacted]

11.6 Analysis of Expansion Part

11.6.1 Primary Objective

The primary objective is to evaluate the ORR for each expansion cohort.

11.6.2 Primary Endpoint – Objective Response Rate

ORR will be analyzed as described in Section 11.5.10.1.

11.6.3 Statistical Hypothesis, Model, and Method of Analysis

No formal statistical hypotheses are formulated in this trial. Any P-values will be considered as hypothesis generating results to be considered for future trials.

The estimated ORR and the exact 2-sided 95% confidence intervals (CIs) using the Clopper-Pearson method will be presented for each expansion cohort. Individual subject data listings will be provided.

The maximal response (maximal reduction in the sum of the longest diameter in the target lesions) in target lesions at any time on trial will be reported using waterfall plots.

The results of the response as seen in the escalation part will be reported similarly.

11.6.4 Handling of Missing Values/Censoring/Discontinuations

Any subjects with missing information regarding response to treatment will be counted as non-responders. Treatment of intermediate missing scans will be detailed in the SAP.

11.6.5 Supportive and Sensitivity Analyses

Not applicable.

11.6.6 Secondary Objectives

The secondary objectives are to:

- Evaluate anti-tumor activity (reduction in tumor size) based on response criteria relevant to the tumor type: DCR, DOR, and TTR.
- Evaluate efficacy, based on PFS and OS.
- Further describe the safety profile of GEN1044, based on AEs and safety laboratory parameters
- Further describe the PK profile
- Further describe the immunogenicity of GEN1044, based on ADA response.

11.6.7 Secondary Endpoint – Evaluation of Anti-tumor Activity

11.6.7.1 Disease Control Rate

DCR will be analyzed as described in Section 11.5.10.2.

11.6.7.2 Duration of Response

DOR will be analyzed as described in Section 11.5.10.3.

11.6.7.3 Time to Response

TTR will be analyzed as described in Section 11.5.10.4.

11.6.8 Secondary Endpoint – Evaluation of Efficacy

11.6.8.1 Progression-free Survival

PFS is defined as the time from the date of C1D1 to the date of the first documented progression or death due to any cause. PFS will be assessed via local review according to RECIST v1.1 (Eisenhauer et al., 2009). PFS will be censored in accordance with Table C1 in Appendix C in the FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Non-small Cell Lung Cancer Drugs and Biologics (FDA-Guidance, 2015).

PFS will be analyzed in the FAS population. The PFS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians and 95% CIs of the medians will be presented for each expansion cohort.

11.6.8.2 Overall Survival

OS is defined as the time from date of C1D1 to date of death due to any cause. If a subject is not known to have died, then OS will be censored at the latest date the subject was known to be alive (on or before the cut-off date).

OS will be analyzed in the FAS population. The OS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians, first and third quartiles and 95% CIs of the medians will be presented for each expansion cohort.

11.6.9 Secondary Endpoint – Adverse Events and Safety Laboratory Parameters

11.6.9.1 Analysis Set and Grouping for the Analyses

See Section 11.5.3.1.

11.6.9.2 Adverse Events

See Section 11.5.3.2.

11.6.9.3 Laboratory Abnormalities

See Section 11.5.3.3.

11.6.10 Secondary Endpoint – Pharmacokinetics

PK will be analyzed as described in Section 11.5.8.

11.6.11 Immunogenicity

Immunogenicity will be analyzed as described in Section 11.5.9.

11.6.12 Supportive Analyses of Secondary Efficacy Objectives and Endpoints

Not applicable.

11.6.13 Other Safety Data

11.6.13.1 Vital signs

See Section 11.5.12.1.

11.6.13.2 ECGs

See Section 11.5.12.2. Single ECGs are planned for the Expansion part.

11.6.13.3 ECOG Performance Status

See Section 11.5.12.3.

11.6.14 Supportive Analyses for Secondary Objectives

Not applicable.

11.6.15 Tolerability

Not applicable.

11.6.16 Exploratory Objectives

11.6.17 Exploratory Endpoint – Biomarkers

See Section 11.5.16.

11.6.18 Exploratory Endpoint – Anti-tumor Activity Based on iRECIST

See Section 11.5.17 where reference is made to iRECIST guideline (Seymour et al., 2017) and the exploratory endpoints iORR, iDCR and iDOR. In addition, the iPFS will be evaluated in the expansion cohorts, and presented similar to PFS, see Section 11.6.8.1. The event date for iPFS is the first date at which progression is met (provided that the progression is confirmed at the next assessment, with exceptions as described in Seymour et al., 2017) or date of death due to any cause, whichever comes first.

11.6.19 Exploratory Endpoint – Anti-tumor Activity and Changes in PSA – Prostate Cancer Subjects Only

See Section 11.5.18.

11.6.19.1 Modified ORR

See Section 11.5.18.1.

11.6.19.2 Modified DCR

See Section 11.5.18.2.

11.6.19.3 Modified Duration of Response

See Section 11.5.18.3.

11.6.19.4 Composite Response Rate

See Section 11.5.18.4.

11.6.19.5 Radiographic Progression-Free Survival

Radiographic progression-free survival (rPFS) is defined as the time from the date of C1D1 to the date of the first documented progression per PCWG3-modified RECIST v1.1 (see Appendix 5, Table 25), or death due to any cause, whichever occurs first.

rPFS will be analyzed in the FAS population. The rPFS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians and 95% CIs of the medians will be presented for the prostate cancer subjects.

11.6.19.6 PSA Response

See Section 11.5.18.5.

11.6.19.7 PSA Progression

See Section 11.5.18.6.

11.6.20 [redacted]

[redacted]

11.7 Operating Characteristics for the Interim Analysis in Expansion Cohorts

The maximum sample size for each expansion cohort is 40 subjects. In order not to expose subjects to non-efficacious doses, an ongoing and non-binding interim futility analysis will be conducted based on about the initial 20 subjects. The interim analysis will be conducted when (at minimum) 2 scans from these subjects in the expansion cohort have been locally reviewed. At this time point the confirmed ORR will be derived and used as endpoint in the futility analysis. Those subjects not yet confirmed (eg, last scan demonstrating a CR or PR) will be counted as SD (ie, non-responders). The analysis will be supplemented by secondary summaries of the response (at timing of futility analysis): ORR (based on unconfirmed responses), DOR, anti-tumor activity (changes from baseline in target lesion size), PFS, OS, summaries of PK concentrations and parameters, and safety assessments. The totality of the data will be evaluated by the sponsor SC, which decides on further recruitment into the expansion cohort.

The futility analysis will be based on a Bayesian predictive probability approach (Lee and Liu, 2008). By using predictive probabilities, it is possible to directly assess the outcome of the next stage, if continued to its end (Saville et al., 2014). Given the interim data, the predicted probability is a weighted average of posterior probabilities, as if calculated given the outcome at the end of the stage. The weights correspond to how likely each outcome is. The predictive probabilities may in fact be calculated at any time point.

At the end of the trial the *outcome* of interest, ie, the "*success criteria,"* is defined as the *posterior* probability that ORR exceeds p_0 is at least 70%. If the predicted probability of success at timing of interim is less than 10% the expansion cohort is judged futile.

The historical rates (p_0) are tabulated in Table 19. Based on these, the number of responders required at interim to continue are presented by indication in Table 20. In addition, given the prior response rate, the success criteria is translated into required number of responders.

The operating characteristics are based on 100000 simulations for each scenario and were programmed in R v3.5.1 using RStudio v1.2.1335 (R-Core-Team, 2018; RStudio-Team, 2018).

In this trial the prior response rate is modelled as Beta($1+p_0$,$1+[1-p_0]$), which can be thought of as updating a uniform (non-informative) prior with a fraction of a response (ie, p_0) from one subject.

The expansion cohorts are judged as successful (at n=20) under the target response rate. Assuming a historical response rate, the predictive probability of success (at n=20) fails to reach the 10% bar in about 12% to 24% of the cases.

Table 19 Response Rate Characteristics by Indication

Case	Indication	Historical response rate (p_0)
A	Head and neck, bladder, esophageal, TNBC	10%
B	NSCLC, prostate	15%
C	Uterine	35%

Table 20 Requirements on Number of Responders and Operating Characteristics

Case	Number of responders to achieve		Operating characteristics based on 100.000 simulations under true underlying ORR			
	Be judged as successful at n=20	A posterior probability of ORR that exceeds p_0 by at least 70% at final analysis	True ORR	Likelihood to not judge as successful at n=20	Likelihood that estimated ORR $\geq p_0$ if final analysis is reached	Likelihood that posterior probability of ORR exceeds p_0 by at least 70% at final analysis
A	≥1/20	≥5/40	10%	12%	64%	41%
			20%	1%	98%	93%
B	≥2/20	≥7/40	15%	18%	66%	46%
			30%	1%	99%	98%
C	≥6/20	≥16/40	35%	24%	69%	39%
			55%	1%	99%	98%

11.8 Sample Size Calculation

As there is no formal statistical hypothesis in this trial, there is no sample size calculation based on power calculations. The operating characteristics for the expansion cohorts are presented in Section 11.7. To characterize the 95% CIs of the ORR using the Clopper-Pearson method, Table 21 is provided. (The calculations are performed in SAS® v9.4.) This gives an impression of the increased precision in the estimate when eg, increasing the sample size from 20 to 40 for a range of ORRs of interest.

Table 21 95% Clopper-Pearson Confidence Limits for a Given Point Estimate (eg, ORR)

ORR point estimate	10%	15%	20%	30%	35%	55%
n=20	(1.2%; 32%)	(3.2%; 38%)	(5.7%; 44%)	(12%; 54%)	(15%; 59%)	(32%; 77%)
n=40	(2.8%; 24%)	(5.7%; 30%)	(9.1%; 36%)	(17%; 47%)	(21%; 52%)	(38%; 71%)

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
- Subject 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

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 sub-investigator 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 and ECG data from the ECG vendor into the sponsor's database. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided. 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 verified for accuracy and consistency with the data sources.

12.4 Record Retention

In compliance with ICH GCP E6(R2), the investigator/institution 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 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 pharmacokinetics of GEN1044 in subjects with various types of solid tumors. The results of this trial will provide useful information on the PK of GEN1044. These data are also needed to assist in developing dosage adjustment guidance in future trials.

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 GEN1044. 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.

13.1.1 Trial and Site Start and Closure

The first act of recruitment is the first subject screening visit and will be the trial start date.

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. Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial-site closure visit has been performed.

In addition, the investigator may initiate trial-site closure at any time, provided there is reasonable cause and sufficient notice is given to the sponsor 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 IEC/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 trial drug development. The sponsor may, based on available data, discontinue further development of GEN1044. Following trial termination, the sponsor will make their best effort to provision post-trial access to GEN1044 for those ongoing trial subjects with a potential treatment benefit, in accordance with local laws and requirements.

If the trial is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the trial of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

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, ICH GCP E6(R2), and applicable regulatory and country-specific requirements. This includes supervision of the trial and staff. Delegation of responsibilities should be to only qualified staff and should be documented. In case the investigator is unavailable (eg, on vacation), the investigator should assure that a qualified, trained deputy physician is available for medical care of the subjects. Handover of information must be ensured and documented. The investigator shall notify the sponsor of any serious breach of ICH GCP E6(R2), the protocol, or any regulation where required immediately.

13.2.1.1 Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and for 1 year after completion of the trial.

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 to the protocol (if applicable), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this written approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

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 IEC/IRB for review and approval before implementation of the change(s).

The IB and updates to the IB, unexpected SAEs where a causal relationship cannot be ruled out, serious breaches, serious non-compliance, annual written summaries of the trial status, and deviations to the protocol implemented to eliminate immediate hazards to the subjects must be submitted to the IEC/IRB.

Interim reports on the trial and/or review(s) of trial progress will be submitted by the investigator, where applicable, to the IEC/IRB at intervals stipulated in its guidelines.

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

13.2.3 Informed Consent Process

The ICFs that are used must be approved by the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The ICF should be in accordance with principles that originated in the Declaration of Helsinki 2013, ICH GCP E6(R2), 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 (or their legally acceptable representatives) 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, if needed.

The subject (or his/her legally acceptable representatives) will be given sufficient time to read the ICF and the opportunity to enquire about details of the trial prior to deciding whether to participate in the trial. After this explanation and before any trial-specific procedure is performed, consent should be appropriately recorded by means of either the subject's or their legally acceptable representative's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

Subjects (or his/her legally authorized representative) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA, and EU GDPR requirements, where applicable, and the IRB/IEC or trial center. The investigator or authorized person obtaining the informed consent must also sign and date the ICF. After having obtained the consent, a copy of the ICF must be given to the subject.

If the subject (or legally acceptable representative) is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject (or legally acceptable representative) is obtained.

A subject who is rescreened is not required to sign another ICF unless the subject's rights, risks regarding trial participation, or well-being has changed since the first ICF was obtained.

A separate ICF will be used for the required [redacted] component of the trial if required by local regulations.

13.2.4 Data Protection

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 ICF will be maintained by the investigator in strict confidence.

In relation to the collection and handling of data, including any personal data, potential risks to the 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 their 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 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 their personal data and the right to request rectification of any data that are not correct or complete by contacting the investigator. Reasonable steps will be taken by the investigator to respond to such a request, taking into consideration the nature of the request, the conditions of the 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 Dissemination of Clinical Trial Data

The results of the trial will be reported in a CSR generated by the sponsor and will contain data from all trial sites that participated in the trial as per protocol. Results of exploratory biomarker analyses performed after the CSR has been issued may be reported in a separate report and will not require a revision of the CSR.

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. Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (eg, change in the sponsor's Medical Monitor or contact information). 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 deviation from the protocol is unavoidable, the investigator or other physician in attendance will contact the sponsor (see the separate sponsor Contact Information page, which is provided separately from the protocol). Except in emergency situations, this contact should be made before implementing any deviations 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 documented in the eCRF and source documents will reflect any deviation 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) must be submitted to the appropriate regulatory authorities in each respective country, in accordance with local regulations. 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 complete a subject identification log to permit easy identification of each subject during and after the trial. This document will be reviewed by the sponsor trial-site contact for completeness.

The subject identification log will be treated as confidential and will be filed by the investigator in the Investigator Site file and will never be transferred to the sponsor or any third parties. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the trial will identify subjects by their subject number (or screening number if not enrolled).

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the trial.

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 monitoring visit will be made as soon as possible after enrollment (ie, the first subject has signed the ICF) 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 investigator must permit the monitor access to all source data, including electronic medical records, and/or documents with the purpose of verifying that the data recorded 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, 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 principal investigator and trial-site personnel are responsible for being present and available for consultation during routinely scheduled trial-site audit visits conducted by the sponsor or its designees.

Similar procedures for inspections may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this trial in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection. Regulatory Inspectors must be allowed direct access to original medical records (source data/documents).

14.6 Publication Policy

All information, including but not limited to information regarding GEN1044 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 or 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. CROs involved in the trial are not permitted to publish without the sponsor's prior written approval.

The investigator understands that the information developed in the trial will be used by the sponsor in connection with the continued development of GEN1044, 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 CSR generated by the sponsor and will contain data from all trial sites that participated in the trial. 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 for the CSR (eg, when a signature by a coordinating investigator is required). Results of exploratory biomarker analyses performed after the CSR has been issued will be reported in a separate report and will not require a revision of the CSR. 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, 2010; ICMJE, 2019), the sponsor in conjunction with any collaborative group(s), shall have the right to publish such primary (multicenter) data and information as per the pre-specified and approved publication plan. 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 current version of ‘Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals’ (ICMJE Recommendations) http://www.icmje.org/recommendations/), 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

It is the responsibility of Genmab to register the trial in an appropriate public registry according to applicable regulations (eg, www.ClinicalTrials.gov; a website maintained by the National Library of Medicine at the US National Institutes of Health; trial registration may occur in other registries in accordance with local regulatory requirements). A summary of the trial results is made publicly available in accordance with applicable regulatory requirements.

14.8 Liabilities and Insurance

The sponsor is responsible for taking out relevant clinical trial insurance in accordance with local law and regulations.

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ATTACHMENT 1 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 drug, 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)

Sponsor's Responsible Medical Officer:

Name (typed or printed): [redacted], MD, PhD

Institution: [redacted] Genmab

Signature: [redacted] Date: [redacted]

(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.

Appendix 1 Definition of Reproductive Potential and Contraception

In this trial, subjects are considered to have reproductive potential, unless they are postmenopausal 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.

All female subjects must agree not to donate eggs (ova, oocytes) for the purpose of assisted reproduction during the trial and for 4 months after receiving the last dose of GEN1044.

Female subjects of reproductive potential must agree to use adequate contraception during and for 4 months after the last GEN1044 administration. Adequate contraception is defined as highly effective methods of contraception (Table 22). 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 22 Highly Effective Methods of Contraception

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[1]:
  - Oral
  - Injectable
  - Implantable[2]
- Intrauterine device[2]
- Intrauterine hormone-releasing system[2]
- Bilateral tubal occlusion[2]
- Vasectomized partner[2, 3]
- Sexual abstinence[4]

1 Hormonal contraception may be susceptible to interaction with GEN1044, which may reduce the efficacy of the contraception method.
2 Contraception methods that, in the context of this guidance, are considered to have low user dependency.
3 Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the female subject of child-bearing potential (ie, the trial subject) and that the vasectomized partner has received medical assessment of the surgical success.
4 In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatment. The reliability of sexual abstinence 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, version 1.1. (CTFG, 2020).

Appendix 2 RECIST (Version 1.1) Criteria Summary

Response Evaluation Criteria in Solid Tumors (RECIST) 1.1	
Term	**Definition**
Complete response (CR)	All of the following: • Disappearance of all target and non-target tumor lesions AND • Reduction in short axis to <10 mm in all pathological target and non-target lymph nodes* AND • Normalization of tumor marker level (if applicable)
Partial response (PR)	≥30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive disease (PD)	At least one of the following: • ≥20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir; this includes the baseline sum if that is the smallest on study) AND an absolute increase of ≥5 mm in the sum of diameters OR • Unequivocal† appearance of 1 or more new lesion(s) OR • Unequivocal progression of non-target lesions‡
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters (nadir) while on study.

Note: A measurable lesion must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT scan (CT slice thickness no greater than 5 mm).

* When lymph nodes are included as target lesions, the sum of lesions may not reach 0 mm even if CR criteria are met, since a normal lymph node is defined as having a short axis <10 mm.

† Not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (healing or flare of pre-existing lesions).

‡ Modest increases in the size of one or more non-target lesions are not considered unequivocal progression.

From RECIST version 1.1 (Eisenhauer et al., 2009).

A response (CR or PR) will be considered confirmed if the following response assessment (4-6 weeks after the initial response) still shows response (CR or PR). In cases where the initial response is followed by SD, it will be considered as confirmed if the SD is later followed by PR or CR. For example, if a patient had PR in week 6, SD in week 12, and PR in week 18, this PR will be considered as confirmed.

Appendix 3 Corticosteroid Dose Equivalents

Steroid	Approximate Equivalent Dose	
Betamethasone	12 mg	Long-acting
Dexamethasone	15 mg	Long-acting
Methylprednisolone	80 mg	Intermediate-acting
Triamcinolone	80 mg	Intermediate-acting
Prednisone	100 mg	Intermediate-acting
Prednisolone	100 mg	Intermediate-acting
Hydrocortisone	400 mg	Short acting
Cortisone	500 mg	Short-acting

Appendix 4 Estimation of Glomerular Filtration Rate Using Cockroft-Gault Formula

Glomerular filtration rate (GFR) may be estimated using the Cockroft-Gault formula

$$GFR = \frac{(140 - age) \times weight \times F_S}{Serum\ Creatinine \times 72}$$

Units: GFR [mL/min], age [years], weight [kg], serum creatinine [mg/dl], F_S is a correction Factor for Sex: in males $F_S = 1$, in females $F_S = 0.85$

Appendix 5 Prostate Cancer Clinical Trials Working Group 3 Recommendations - Assessment of Bone Lesions in Patients with Prostate Cancer

Adapted from (Scher et al., 2016)

Assessment of bone disease will be done by whole-body radionuclide bone scan. A bone scan will consist of 5 regions including skull, thorax, spine, pelvis, and extremities. Radiographic progression for bone disease will be assessed using the PCWG3 recommendations (Scher et al, 2016).

Table 23 Standard Baseline Disease Imaging Assessment of the Bone (Prostate Cancer Only)

Assessment		
Imaging	Bone	^{99m}Tc-methylene diphosphonate (^{99m}TcMDP) bone scan: • Record bone lesions and sites of bone lesions

Source: From Table 2, Scher et al., 2016

Table 24 Criteria for Progression of Bone Lesions (Prostate Cancer Only)

Assessment		
Imaging	Bone	• Two new lesions • Confirm ambiguous results by other imaging modalities (eg, CT or MRI); note: only positivity on the bone scan defines metastatic disease to bone

Source: From Table 3, Scher et al., 2016

Table 25 Prostate Cancer: Overall Combined PCWG3-Modified RECIST 1.1 Response

RECIST 1.1 response	PCWG3 response	PCWG3-modified RECIST 1.1
PD	Any	PD
Any	PD	PD
Any (except PD)	PDu	PDu
NE	Non-PD, NED, or NE*	NE
SD	Non-PD, NED, or NE*	SD
Non-CR/Non-PD	Non-PD, NED, or NE*	Non-CR/Non-PD
PR	Non-PD, NED, or NE*	PR
CR	Non-PED or NE*	PR (if target lesions at baseline) *OR* Non-CR/Non-PD (if no target lesions at baseline)
CR	NED	CR
Any	Not evaluated	RECIST v1.1

NE=non-evaluable (scan quality, missing, etc); NED=no evidence of disease; PDu=unconfirmed disease progression.
* If the bone scan is entirely missing or was not done, and bone lesions were present at baseline, the overall combined PCWG3-modified RECIST 1.1 response is NE.

Appendix 6 Management of Cytokine Release Syndrome

Table 26 Management of Cytokine Release Syndrome

CRS Grade	Management
1	**Fever:** Patients with a new fever should be admitted to the hospital if not already. Investigate for infection and rapidly startup broad-spectrum antibiotics. Continuation of antibiotic therapy is recommended until any potential neutropenia resolves. Constitutional symptoms may be helped by NSAIDs. **Tocilizumab:** No*. **Steroids**: No.
2	**Fever:** As per grade 1. **Hypotension**: Immediate clinical evaluation and intervention is warranted. At the first confirmed decrease ≥20% from baseline systolic, diastolic, or mean arterial pressure or evidence of worsening perfusion, administer an IV fluid bolus (20 mL/kg up to 1 L). Consider a vasopressor and administer no later than after the 3rd IV fluid bolus due to the vasodilation and capillary leak associated with CRS. **Hypoxia**: Consider X-ray or CT-scan if hypoxic and/or tachypneic. Administer oxygen by low-flow nasal cannula (≤6 L/min) or blow-by. **Tocilizumab**: No* (yes, if the patient has comorbidities†). **Steroids**: No (consider, if the patient has comorbidities‡).
3	**Fever:** As per grade 1. **Hypotension**: Immediate clinical evaluation and intervention is warranted. Administer a vasopressor (norepinephrine), with or without vasopressin, as most patients with CRS have peripheral vasodilation. **Hypoxia**: Administer oxygen by high-flow nasal cannula (>6 L/min), facemask, non-breather mask, or Venturi mask. **Tocilizumab**: Yes†. **Steroids**: Consider‡.
4	**Fever**: As per grade 1. **Hypotension**: Immediate clinical evaluation and intervention is warranted. Administer at least 2 vasopressors, with or without vasopressin, as most patients with CRS have peripheral vasodilation. **Hypoxia**: Administer positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation). **Tocilizumab**: Yes†. **Steroids**: Yes‡.

* Consider earlier intervention in specific cases. For example, an elderly patient with prolonged (>72 hours) and/or very high (>40.5°C/104.9°F) fever may not tolerate the resulting sinus tachycardia as well as a younger patient, so tocilizumab may be indicated.

† Tocilizumab (anti-IL-6R mAb) remains the only first-line anti-cytokine therapy approved for CRS. If there is no improvement in symptoms within 6 hours, or if the patient starts to deteriorate after initial improvement, a second dose of tocilizumab should be administered along with a dose of corticosteroids. For patients being refractory to tocilizumab (3 administrations), additional cytokine blockade therapy such as siltuximab (anti-IL-6 mAb) or anakinra (anti-IL-1R mAb) may be considered. However, such use is anecdotal and has low level of evidence and, as such, is entirely at the discretion of the treating physician.

‡ Consider dexamethasone over methylprednisolone due to improved CNS penetration even in absence of neurotoxicity, as high-grade CRS is correlated with risk of concurrent or subsequent immune effector cell-associated neurotoxicity syndrome (ICANS). If concurrent ICANS is observed, dexamethasone should be preferred.

Source: (Varadarajan et al., 2020)

Appendix 7 Dose Modification Guidelines for Specific Adverse Events

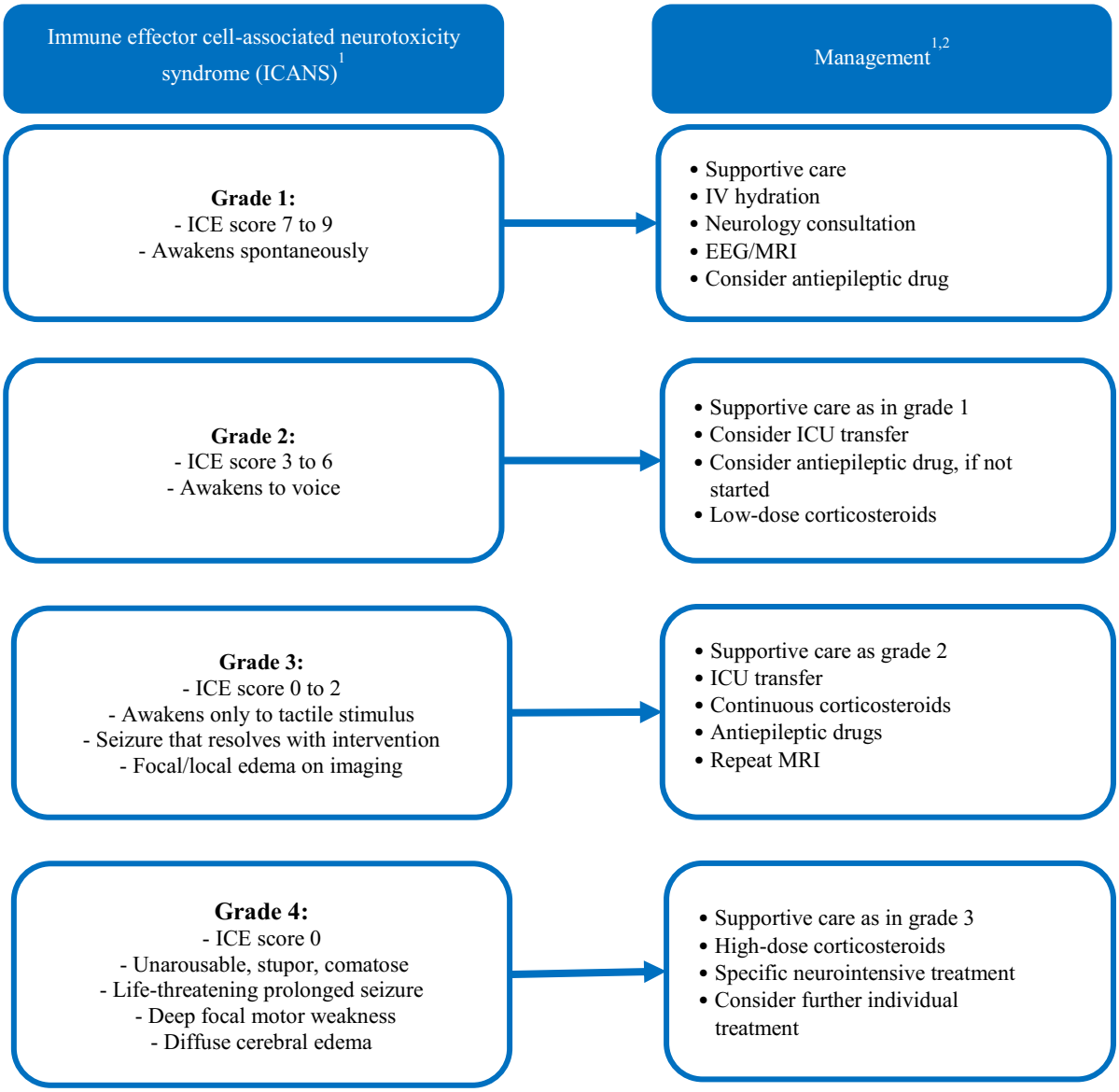
Table 27 Dose Modification Guidelines for Specific Adverse Events

System	Adverse Event(s)	Toxicity Grade or Condition (CTCAE v5.0)	Action to be Taken With GEN1044	Adverse Event Management
Immune system disorder	Cytokine release syndrome or ICANS	Grade 3 and cytokine blockade-refractory** for >72 hours	Permanently discontinue	
	CRS or ICANS	Grade 4	Permanently discontinue	
Hepatic	AST/ALT elevation or increased bilirubin	Grade 2; first occurrence	Withhold*	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper.
		Grade 2; second or following occurrence	Withhold*	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper.
		Grade 3; first occurrence	Withhold*	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper.
		Grade 3; second occurrence	Permanently discontinue	
		Grade 4; first occurrence (not recurrent)	Permanently discontinue	
Hematological	Platelet count decreased/ thrombocytopenia	Grade ≥3; first occurrence	Withhold*	Platelet infusions may be administered per institutional standards.
		Grade ≥3; second occurrence	Permanently discontinue	
	Neutropenia	Grade 2; first occurrence	Withhold*	Growth factors may be administered per institutional standards.
		Grade 2; second or following occurrence	Withhold*	Growth factors may be administered per institutional standards.
		Grade ≥3; first occurrence	Withhold*	Growth factors may be administered per institutional standards.
		Grade ≥3; second occurrence	Permanently discontinue	
	Febrile neutropenia	Grade ≥3; first occurrence	Withhold*	Growth factors may be administered per institutional standards.
		Grade ≥3; second occurrence	Permanently discontinue	

System	Adverse Event(s)	Toxicity Grade or Condition (CTCAE v5.0)	Action to be Taken With GEN1044	Adverse Event Management
Gastrointestinal	Nausea and/or vomiting >72 hours	Grade 2; first occurrence	Withhold*	Prophylactic administration of antiemetic therapy may be administered per institutional standards.
		Grade 2; second or following occurrence	Withhold*	Prophylactic administration of antiemetic therapy may be administered per institutional standards.
		Grade ≥3; first occurrence	Withhold*	Prophylactic administration of antiemetic therapy may be administered per institutional standards.
		Grade ≥3; second occurrence	Permanently discontinue	
	Diarrhea >72 hours	Grade 2; first occurrence	Withhold*	If the diarrhea is of immune-related etiology, administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.
		Grade 2; second or following occurrence	Withhold*	If the diarrhea is of immune-related etiology, administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.
		Grade ≥3; first occurrence	Withhold*	If the diarrhea is of immune-related etiology, administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.
		Grade ≥3; second occurrence	Permanently discontinue	
Other non-hematologic		Grade 3; first occurrence	Withhold*	
		Grade 3; recurrent	Permanently discontinue	
		Grade 4; first occurrence.	Permanently discontinue	

* GEN1044 can be resumed after AE has resolved to grade ≤1 and corticosteroid has been tapered. If GEN1044 is held for more than 12 weeks, the subject should be permanently discontinued from therapy.
** Including adequate and repeated treatment (3 doses within 24 hours) with anti-IL-6R mAb (tocilizumab).
Note: For dose escalation, these rules will only apply to the post-DLT period.

Appendix 8 Recommended ICANS Management



[1] Lee et al., 2019.
[2] Borrega Garcia et al., 2019.

Source: (Garcia Borrega et al., 2019; Lee et al., 2019)

Appendix 9 Description of DLT Rates After Protocol Amendment 3

Table 28 Dose-Determining Analysis Sets Comparison

DLT Consideration	Number FAS	Number DLT Evaluable	DLT Period	Comment
DL cohort	All those with at least 1 dose (ie, prime dose) administered	All those who meet the exposure criteria for the DL cohort, or experience a DLT during the DLT period	Up to 7 days past 1st full dose administration	Regardless of what individual dose that the DLT could be associated with, the DLT is attributed to DL cohort as such
Period-specific DLT rates	All those administered the period-specific dose	All those administered the period-specific dose in a timely fashion	Up to 7 days past dose administration	

Table 29 Template for Describing DLT Rates

DL Cohort (Dosing Sequences)	Number FAS	Number DLT Evaluable	Number DLTs	DLT Rate
*a/b/c** mg				
*a/b/c/d** mg				
*b/c/d** mg				
Supplementary DLT Rates for Period-Specific Dose Levels				
1st dose: *a* mg				
1st dose: *b* mg				
2nd dose: *b* mg				
2nd dose: *c* mg				
3rd dose: *c* mg				
3rd dose: *d* mg				
4th dose: *d* mg				

* prime/lower intermediate (/higher intermediate)/full dose numbered as: 1st dose/2nd dose/3rd dose OR 1st dose/2nd dose/3rd dose/4th dose.