Official Protocol Title:	A Phase 2 Study of VLS-101 in Patients with Solid Tumors.
NCT number:	NCT04504916
Document Date:	September 20, 2022

Title Page

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Protocol Title: A Phase 2 Study of VLS-101 in Patients with Solid Tumors

Protocol Number: 002-04

Compound Number: MK-2140

Sponsor Name:

Merck Sharp & Dohme LLC
(hereafter called the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

NCT	04504916
IND	151470

Approval Date: 20 September 2022

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Sponsor Signatory

Typed Name: Title:	Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Title:	Date

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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 4	20-SEP-2022	Updated the MK-2140 (VLS-101) starting dose, study population inclusion criteria, and contraception language and revised the SAP.
Amendment 3	15-NOV-2021	Added ROR1 expression levels; updated with analysis per RECIST 1.1 as assessed by BICR; and added cohort-specific eligibility criteria.
Amendment 2	23-MAR-2021	Modified inclusion laboratory values; added Phase 1 clinical data; and adjusted visit windows.
Amendment 1	05-AUG-2020	Implement FDA-requested changes for inclusion criteria and study design.
Original Protocol	16-JUN-2020	Not applicable.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 04

Overall Rationale for the Amendments:

Updated the MK-2140 (VLS-101) starting dose, study population inclusion criteria, and contraception language and revised the SAP.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, Intervention Groups 4.3 Justification for Dose 4.3.1 Starting Dose for This Study 4.3.2 Maximum Dose/Exposure for This Study 6.1 Study Intervention(s) Administered, Table 3 6.6 Dose Modification (Escalation/Titration/Other)	Increased starting dose to 2.0 mg/kg from 1.75 mg/kg for most newly consented participants.	Dose updated from previous MTD to current RP2D now being used for all solid tumors.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	• Included de novo metastatic disease in the TNBC cohort • Clarified that in the NSCLC cohort, 2 prior lines of therapy applies to metastatic disease • Removed taxane exclusion for treatment of platinum-resistant disease in the ovarian cancer cohort • Expanded gastric cancer cohort to allow 2 lines of prior therapy and 1 additional line of HER2-directed monotherapy for participants with HER2+ disease and removed taxane exclusion from prior treatment • Expanded pancreatic cancer cohort to allow 2 lines of prior therapy and locally advanced disease	To allow more participants to be eligible for study treatment.
5.1 Inclusion Criteria 10.4.2 Contraception Requirements	Revised contraception requirements based on the half-life of MK-2140 (VLS-101) and updated contraceptive methods that are considered 'highly effective'.	To provide more clarity to contraception language.
9.7 Interim Analyses	Updated language in SAP regarding IA.	To clarify that totality of the data will be used to determine further action at IA.
Title Page 10.1.1 Code of Conduct for Clinical Trials	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.

Section # and Name	Description of Change	Brief Rationale
1.2 Schema, Figure 1 Study Design	Added figure to depict the study design.	To provide a concise overview of the study design.
1.3 Schedule of Activities	Updated SoA table to remove redundancy in footnotes for information present elsewhere in the protocol and clarified presentation.	To provide more clarity and ease of use.
1.3 Schedule of Activities 8.1.1 Informed Consent 8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research 8.1.9.1 Withdrawal From Future Biomedical Research	Added information on FBR consent and its withdrawal and that the requirement for consent for FBR is optional.	To maintain alignment and consistency.
6.1 Study Intervention(s) Administered, Table 3	Added lyophilized MK-2140 (VLS-101, zilovertamab vedotin) formulation.	To update MK-2140 (VLS-101, zilovertamab vedotin) product reference based on currently available formulation options.
4.2.1.6 Planned Exploratory Biomarker Research	Updated text to provide further detail for biomarker plan for the MK-2140 (VLS-101) program.	To reflect the biomarker plan for the MK-2140 (VLS-101) program unique to this particular study.
6.6 Dose Modification (Escalation/Titration/Other)	Clarified language regarding limitations on dosing delays.	To specify dosing delays due to AEs and unrelated medical procedures.

Section # and Name	Description of Change	Brief Rationale
8.2.1.2 Tumor Imaging and Assessment of Disease	Clarified language regarding timing of study imaging.	To clarify that study imaging is to be based on calendar days rather than treatment cycles.
8 Study Assessments and Procedures	Clarified maximum amount of blood to be collected per the laboratory manual.	To provide further detail regarding amount of blood drawn from participants.
Throughout Document	With the transfer of protocol content from the VelosBio protocol template to the MSD protocol template, minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2 Study of VLS-101 in Patients with Solid Tumors

Short Title: A Phase 2 Study of VLS-101 in Patients with Solid Tumors

Acronym: MK-2140-002

Hypotheses, Objectives, and Endpoints:

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

In male and female participants with advanced/metastatic solid tumors:

[Will be populated by selections made in Section 3 Objectives and Endpoints]

Objectives	Endpoints
Primary	
• To document the proportion of study participants who achieve an objective tumor response per RECIST 1.1 as assessed by blinded independent central review (BICR)	• ORR, defined as the proportion of participants who achieve a confirmed CR or PR per RECIST 1.1 as assessed by BICR
Secondary	
• To document the proportion of study participants who achieve an objective tumor response per RECIST 1.1 as assessed by investigator • To characterize the duration of antitumor efficacy and to assess survival in participants receiving VLS-101 • To document the safety of VLS-101 • To evaluate the pharmacokinetic profile of VLS-101	• ORR, defined as the proportion of participants who achieve a confirmed CR or PR per RECIST 1.1 as assessed by investigator • Time to response (TTR), defined as the interval from the start of study therapy to the first documentation of objective tumor response • Duration of response (DOR), defined as the interval from the first documentation of objective tumor response to the earlier of the first documentation of disease progression or death from any cause

Objectives	Endpoints
	• Progression-free survival (PFS), defined as the interval from the start of study therapy to the earlier of the first documentation of disease progression or death from any cause • Time to treatment failure (TTF), defined as the interval from the start of study therapy to the earliest of the first documentation of disease progression, the permanent cessation of study drug due to an AE, or death from any cause • Overall survival (OS), defined as the interval from the start of study therapy to death from any cause • Type, frequency, severity, timing of onset, duration, and relationship to study drug of any treatment-emergent adverse events (TEAEs); laboratory abnormalities; serious adverse events (SAEs); or adverse events (AEs) leading to interruption, modification, or discontinuation of study treatment (referencing the NCI Common Terminology Criteria for Adverse Events [CTCAE], Version 5.0, for grading of the severity of AEs and laboratory abnormalities) • Derived total VLS-101, total antibody, and MMAE pharmacokinetic parameters (including, as appropriate for the analyte: C_{max} and AUC, as determined using noncompartmental methods)

Overall Design:

Study Phase	Phase 2
Primary Purpose	Treatment
Indication	Solid Tumors
Population	Male and female participants ≥18 years of age, with adequate performance status and organ function who have histologically or cytologically confirmed solid tumor with metastases that have progressed during or following previous treatment with established therapies
Study Type	Interventional
Intervention Model	Single Group This is a multi-site study.
Type of Control	N/A
Study Blinding	Unblinded Open-label
Blinding Roles	No Blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 42 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 30 participants per disease cohort will be allocated to complete the study as described in Section 9.1.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>
<table>
<tr><th>Intervention Group Name</th><th>Drug</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Admin-istration</th><th>Regimen/ Treatment Period/ Vaccination Regimen</th><th>Use</th></tr>
<tr><td>VLS-101 (MK-2140)</td><td>zilovertamab vedotin</td><td>2.0 mg/kg</td><td>Q2/3W</td><td>IV Infusion</td><td>Q2/3W until 1 discontinuation criterion is met</td><td>Test product</td></tr>
<tr><td colspan="7">IV=intravenous; Q2/3W=repeated 3-week cycles with a drug infusion on Day 1 and Day 8 of each cycle</td></tr>
</table>
</td></tr>
<tr><td>Total Number of Intervention Groups/ Arms</td><td>6 tumor-specific cohorts</td></tr>
<tr><td>Duration of Participation</td><td>Each participant will participate in the study for approximately 1-2 years from the time the participant provides documented informed consent through the final contact. After a screening phase of 28 days, each participant will receive assigned intervention until disease progression is radiographically documented per modified RECIST 1.1, unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator’s decision to discontinue the participant, noncompliance with study treatment or procedure requirements or administrative reasons requiring cessation of treatment, or withdrawal of consent.

After the end of treatment, each participant will be followed for the occurrence of AEs for 30 days.

All participants will be followed for OS until death, withdrawal of consent, or end of the study.</td></tr>
</table>

Study Governance Committees:

Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
Study governance considerations are outlined in Appendix 1.	

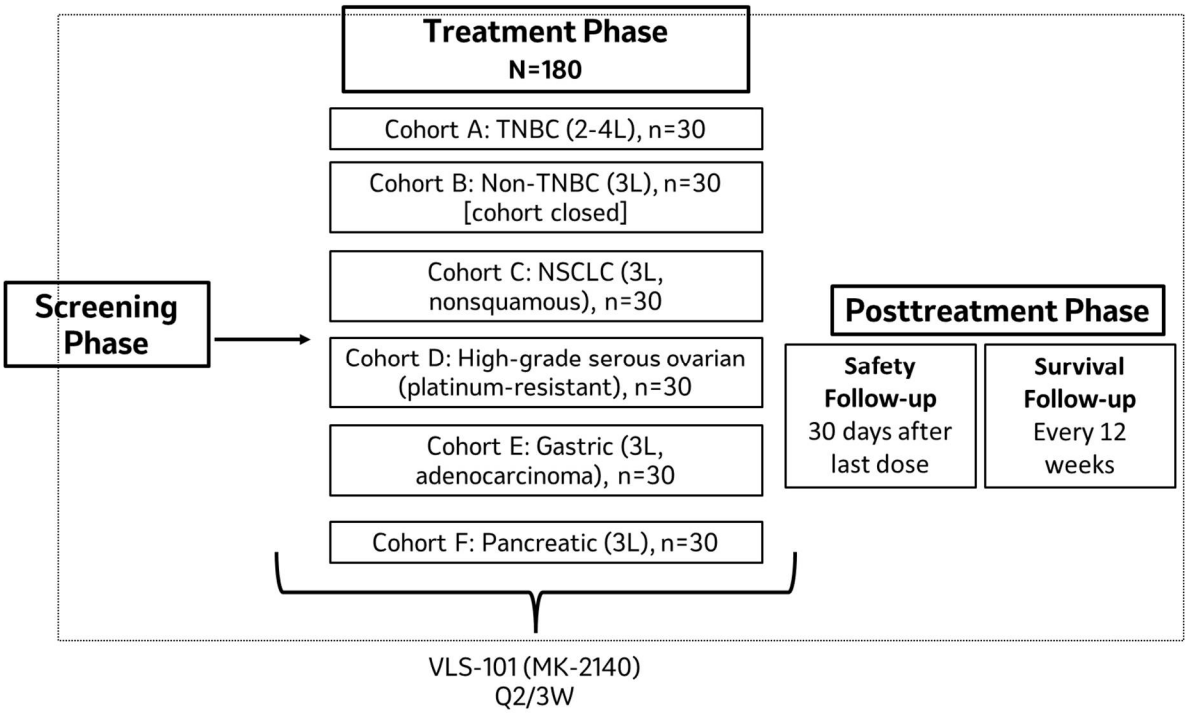
Study Accepts Healthy Volunteers: No

A list of abbreviations is in Appendix 9.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Design



2L=second-line; 2-4L=second to fourth-line; 3L=third-line; N/n=number; NSCLC=non–small cell lung cancer; Q2/3W=every 2/3 weeks; TNBC=triple-negative breast cancer.

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1.3 Schedule of Activities

Table 1 summarizes the schedule of activities for this study.

Table 1 Study Schedule of Activities

Study Period:	**Screening Phase**	**Treatment Phase (3-Week Cycles)**											**EOT/ DC**	**Posttreatment Phase**			**Notes**
Treatment Cycle/Title:	**Visit 1**	**1**			**2**			**3**			**≥4**			**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	
Treatment Day per Cycle:	**-28 to -1[a]**	**1[b]**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**		**30 days from last dose**	**Every 12 Weeks**	**Every 12 Weeks**	
Window (days):			**±1**	**±2**	**±3**	**±1**	**±2**	**±3**	**±1**	**±2**	**±3**	**±1**	**±21**	**+7**	**±7**	**±7**	
Administrative Procedures																	
Informed Consent	X																
Informed Consent for Future Biomedical Research	X																This is optional for the participant.
Inclusion/ Exclusion Criteria	X																
Demographic and Medical History	X																
ECOG (Performance status)	X																
Oxygen saturation	X																
Height	X																
Weight[c]	X				X			X					X				
AE Assessment	X	X	X	X	X			X			X		X	X			
Prior/ Concomitant Medication Review	X	X	X	X	X			X			X		X	X			
12-lead ECG	X																

Study Period:	**Screening Phase**	**Treatment Phase (3-Week Cycles)**											**EOT/ DC**	**Posttreatment Phase**			**Notes**
Treatment Cycle/Title:	**Visit 1**	**1**			**2**			**3**			**≥4**			**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	
Treatment Day per Cycle:	**-28 to -1[a]**	**1[b]**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**		**30 days from last dose**	**Every 12 Weeks**	**Every 12 Weeks**	
Window (days):			**±1**	**±2**	**±3**	**±1**	**±2**	**±3**	**±1**	**±2**	**±3**	**±1**	**±21**	**+7**	**±7**	**±7**	
Study Drug Administration																	
Infusion premedication (if needed)		X	X		X	X		X	X		X						
VLS-101 Administration		X	X		X	X		X	X		X						IV Infusion
Laboratory Assessments																	
Urinalysis	X																
Serum virology (HIV, HBV, and HCV)	X																
Coagulation INR/aPTT	X																
Serum pregnancy test	X	X			X			X			X		X				
Serum chemistry	X	X	X	X	X	X	X	X	X		X	X	X				C2D15 serum chemistry may be collected at a non-study center laboratory.
Hematology	X	X	X	X	X	X	X	X	X		X	X	X				C2D15 hematology may be collected at a non-study center laboratory.
Plasma for VLS-101 pharmacokinetics[d]		X	X	X	X	X		X	X	X	X	X	X				
Serum for ADA[e]		X			X			X			X		X				
Disease-Related Assessments																	
Plasma for ctDNA[f]		X			X			X			X		X				
Tumor for ROR1/other profiling	X																

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Study Period:	**Screening Phase**	**Treatment Phase (3-Week Cycles)**											**EOT/ DC**	**Posttreatment Phase**			**Notes**
Treatment Cycle/Title:	**Visit 1**	**1**			**2**			**3**			**≥4**			**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	
Treatment Day per Cycle:	**-28 to -1[a]**	**1[b]**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**		**30 days from last dose**	**Every 12 Weeks**	**Every 12 Weeks**	
Window (days):			**±1**	**±2**	**±3**	**±1**	**±2**	**±3**	**±1**	**±2**	**±3**	**±1**	**±21**	**+7**	**±7**	**±7**	
Radiological examination[g]	X										X		X		X		First on-study scan: 9 weeks, ±7days. See Section 8.10.4.2 for Efficacy FU requirements.
Vital status		◄															Survival information (vital status) may be requested at any time during the study.
Posttherapy follow-up																	
Posttherapy safety assessment														X			See Section 8.10.4.1.
Survival follow-up															X		See Section 8.10.4.3.

Abbreviations: ADA=antidrug antibodies; AE=adverse event; aPTT=activated partial thromboplastin time; C=cycle; ctDNA=circulating tumor deoxyribonucleic acid; D=Day; DC=discontinuation; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOI=end of infusion; EOT=end of treatment; FU=follow-up; HBV=hepatitis B; HCV=hepatitis C virus; HIV=human immunodeficiency virus; INR=international normalized ratio, IV=intravenous; PD=progressive disease; ROR1=receptor tyrosine kinase-like orphan receptor-1.

[a] Screening procedures may be performed over as many days as necessary provided that screening activities are completed within 28 days before C1D1 of the study.

[b] If obtained within 3 days prior to the start of therapy, serum pregnancy, serum chemistry, and hematology studies collected during screening need not be repeated on C1D1.

[c] The C1 weight measurement may be obtained up to 72 hours before C1D1. If ≥5% change in body weight occurs, weight-based dosing should be readjusted.

[d] Plasma for VLS-101 pharmacokinetics will be collected on C1D1 and C1D8 (predose and EOI), C1D15, C2D1 and C2D8 (predose and EOI),C≥3D1 and C≥3D8 (predose and EOI), C3D15, and at EOT. The acceptable margins relative to EOI is +5 minutes.

[e] Serum for VLS-101-reactive antibodies will be collected once on C1D1 (predose), C2D1 (predose), C≥3D1 (predose), and EOT.

[f] Plasma for ctDNA will be collected once on C1D1 (predose), C2D1 (predose), C≥3D1 (predose), and EOT.

[g] The baseline evaluation should occur within 28 days before C1D1. Scan timing should follow calendar days and should not be adjusted for delays in cycle starts. An EOT radiology assessment should be performed unless the participant already has radiographic confirmation of PD ≤4 weeks before permanent study drug discontinuation.

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2 INTRODUCTION

According to the NCI SEER program, ~40% of American men and women will develop cancer during their lifetimes [National Cancer Institute 2017]. In 2020, an estimated 1,806,590 people in the United States will be diagnosed with a new cancer and >15,000,000 are living with cancer. Despite advances in cancer prevention, diagnosis, and treatment, ~606,520 patients died of this disease in 2020. Thus, cancer remains a continuing public health concern of major proportions.

Among those patients who develop a fatal cancer, most will have a solid tumor malignancy derived from epithelial or mesenchymal tissues that has metastasized, resulting in life-threatening organ dysfunction. While metastatic disease is largely incurable, patients can be offered systemic hormonal, chemotherapeutic, or immunotherapeutic agents to delay tumor progression, manage disease-related complications, and extend life. Patients typically receive sequential therapies in an attempt to control disease manifestations. However, due to the acquisition of drug resistance, progressively less activity is observed; the disease course is characterized by a continuous decrease in the quality and the duration of tumor response with each subsequent treatment. Novel mechanisms of action are needed to safely offer new treatment options for patients with metastatic cancers that have become resistant to existing therapies.

VLS-101/MK-2140 is an antibody-drug conjugate that is an antagonist of ROR1-positive tumors. VLS-101/MK-2140 is under study for the treatment of metastatic solid tumors as monotherapy. This is a Phase 2, nonrandomized, single-arm, multisite, open-label, study evaluating the efficacy, safety, PK, immunogenicity, and pharmacodynamics of VLS-101/MK-2140 in participants with metastatic solid tumors that are likely to express ROR1.

Refer to the MK-2140 IB for further information.

2.1 Study Rationale

The purpose of this study is to provide critical efficacy, safety, PK, immunogenicity, and pharmacodynamic data in support of continued clinical development of VLS-101 and is typical for Phase 2 studies intended to evaluate efficacy of an investigational therapy in patients with cancer.

2.2 Background

2.2.1 Receptor Tyrosine Kinase-like Orphan Receptor 1

ROR1 is a type 1 transmembrane protein that shares homology with other receptor tyrosine kinases and shows high evolutionary conservation [Masiakowski, P. 1992] [Forrester, W. C., et al 1999] [Yoda, A., et al 2003]. The extracellular portion contains immunoglobulin-like sequences, a cysteine-rich domain homologous to frizzled receptors for various Wnt ligands, and a Kringle domain. The cytoplasmic portion contains a tyrosine kinase-like domain followed by serine/threonine- and proline-rich motifs.

Based on studies in rodents, ROR1 is an embryonic factor that is physiologically expressed during early embryogenesis and plays a critical role in neural, skeletal, and vascular organogenesis [Oishi, I., et al 1999] [Al-Shawi, R., et al 2011] [Matsuda, T., et al 2001] [Lyashenko, N., et al 2010]. Functional studies in primary embryonic cells suggest that binding of the secreted glycoprotein ligand, Wnt5a, results in heterodimerization of ROR1 with ROR2 (the other member of the ROR family) and can stimulate neuronal synapse formation [Paganoni, S., et al 2010]. During fetal development, the expression of ROR1 decreases [Masiakowski, P. 1992] [Al-Shawi, R., et al 2011] [Paganoni, S., et al 2010]. Normal adult tissues lack surface expression of the ROR1 protein [Fukuda, T., et al 2008] [Hudecek, M., et al 2010] [Zhang, S., et al 2012] [Liu, Y., et al 2015] except for rare B-lymphocyte precursors known as hematogones (thenon-neoplastic counterpart to precursor-B ALL) [Broome, H. E., et al 2011].

However, consistent with a role as an onco-embryonic factor, high levels of ROR1 protein expression have been found in multiple cancers, including both solid tumors [Zhang, S., et al 2012] [Balakrishnan, A., et al 2017] and hematological malignancies [Daneshmanesh, A. H., et al 2013] ROR1 expression and activation appear to be correlated with features of tumor aggressiveness in models of breast cancer, lung cancer, gastric cancer, melanoma, and CLL [Li, P., et al 2010] [Gentile, A., et al 2011] [Zhang, S., et al 2012] [Yamaguchi, T., et al 2012] [Daneshmanesh, A. H., et al 2013] [Hojjat-Farsangi, M., et al 2013] [Hojjat-Farsangi, M., et al 2013] [O'Connell, M. P., et al 2013] [Hamilton, G., et al 2015] [Ida, L., et al 2016] [Janovska, P., et al 2016]. ROR1 expression is also associated with markers for CSCs, which appear relatively resistant to conventional therapy and repopulate tumors following standard treatment [Zhang, S., et al 2014] [Jung, E. H., et al 2016] [Hamilton, G., et al 2015] [Katoh, M. 2017] [Cao, J., et al 2018]. It is also expressed on cells that have developed greater invasiveness and metastatic potential because theyhave undergone EMT [Cui, B., et al 2013] [Hamilton, G., et al 2015] [Jung, E. H., et al 2016] [Cao, J., et al 2018]. In multiple cancers, ROR1 expression has been associated with poor clinical outcomes [Zhang, H., et al 2014] [Zhang, S., et al 2014] [Cui, B., et al 2016] [Zhou, J. K., et al 2017].

2.2.2 ROR1 in Solid Tumors

Consistent with a role as an onco-embryonic factor, high levels of ROR1 gene and protein expression have been found in multiple solid tumors [Balakrishnan, A., et al 2017] [Zhang, S., et al 2012]. Breast, lung, ovarian, pancreatic and gastric carcinomas have some of the highest expression of ROR1.

A tissue microarray study of tumor specimens from 112 patients with breast cancer found that 72% expressed ROR1, including 40% with high ROR1 staining and 32% with moderate or low ROR1 staining [Zhang, S., et al 2012]. ROR1 expression appears to be more common in aggressive subtypes such as TNBC and basal-like breast cancer [Klemm, F., et al 2011] [Zhang, S., et al 2012] [Cui, B., et al 2013] [Bleckmann, A., et al 2016] [Chang, H., et al 2015] [Balakrishnan, A., et al 2017] [Li, C., et al 2017] [Fultang, N., et al 2019] [Pandey, G., et al 2019] but appears to increase in expression in TNBC, ER/progesterone receptor–positive, and/or HER2-positive breast cancers following treatment with chemotherapy, the antibody-drug conjugate trastuzumab emtansine, or corticosteroids (as are commonly

administered in support of chemotherapy) [Islam, S. S., et al 2019] [Fultang, N., et al 2020] [Obradovic, M. M. S., et al 2019] [Zhang, S., et al 2019] ROR1 expression has been repeatedly demonstrated to be associated with shorter disease-free survival, metastasis-free survival, and OS in patients with breast cancer [Cui, B., et al 2013] [Chien, H. P., et al 2016] [Cao, J., et al 2018] [Islam, S. S., et al 2019] [Obradovic, M. M. S., et al 2019] [Pandey, G., et al 2019].

High levels of ROR1 gene or protein expression have been found in lung cancers [Gentile, A., et al 2011] [Zhang, S., et al 2012] [Karachaliou, N., et al 2014] [Liu, Y., et al 2015] [Zheng, Y. Z., et al 2016] [Liu-Kreyche, P., et al 2019] [Balakrishnan, A., et al 2017]. A tissue microarray study of tumor specimens from 64 patients with lung cancers found that 77% expressed ROR1, with a high level of ROR1 staining evident in most ROR1-positive samples [Zhang, S., et al 2012]. In an IHC analysis in 232 patients with lung adenocarcinoma, tumors from 218 (94%) patients showed evidence of ROR1 expression characterized as weak (21%), moderate (41%), or strong (31%) [Zheng, Y. Z., et al 2016]. Among the types of NSCLC, ROR1 expression has appeared to be more common in lung adenocarcinomas than in squamous cell lung carcinomas [Zhang, S., et al 2012] [Liu, Y., et al 2015] [Balakrishnan, A., et al 2017]. Higher ROR1 expression has been significantly associated with advanced-stage disease and lymph node metastasis in patients with lung cancers [Zheng, Y. Z., et al 2016]. The association between ROR1 expression and adverse OS is particularly strong in lung cancers [Zheng, Y. Z., et al 2016] [Saleh, R. R., et al 2019].

High levels of ROR1 expression have been reported in ovarian cancer [Zhang, H., et al 2014] [Zhang, S., et al 2014] [Zhang, S., et al 2012] [Balakrishnan, A., et al 2017]. High expression of ROR1 was also associated with poor clinical outcome as measured by disease-free and OS [Zhang, H., et al 2014]. Expression was also positively correlated with stage, grade, and lymph node involvement. High expression of ROR1 was associated with worse DFS (HR: 2.9, 95% CI: 1.6-5.1) and OS (HR: 3.5, 95% CI: 2.0-6.3).

High levels of ROR1 expression have been reported in gastric cancer [Chang, H., et al 2015]. Compared with other solid tumors, gastric cancers have some of the greatest gene expression according to data from TCGA available in the public domain (cbioportal.org). Expression of ROR1 in gastric cancer was positively correlated with expression of pAKT, pCREB, and proliferation as measured by Ki-67 labeling index. ROR1 expression was also positively associated with tumor stage and the presence of perineural invasion.

High levels of ROR1 expression have also been reported in pancreatic cancer [Zhang, S., et al 2012] [Xu, G. L., et al 2018]. However, one study found a more modest expression of ROR1 in pancreatic cancers [Balakrishnan, A., et al 2017]. Compared with other solid tumors, pancreatic cancers have very high gene expression according to data from TCGA available in the public domain (cbioportal.org).

2.2.3 Summary

The accumulating data regarding its role in cancer and lack of expression in normal tissues indicate that ROR1 represents an attractive therapeutic target for cancer intervention. For

patients with breast cancer, the data indicate that ROR1 expression may be particularly frequent among those with TNBC or basal-like breast cancer or among those whose cancer has progressed following prior cytotoxic therapy. For patients with NSCLC, it appears that ROR1 expression is most evident in those with metastatic lung adenocarcinoma, especially among thosewith therapy-resistant disease. For ovarian, gastric, and pancreatic cancers, ROR1 is highly expressed and associated with poor prognostic features. Collectively, the data support the potential for therapeutic benefit in these groups of patients with a ROR1-targeted treatment.

Refer to the IB/approved labeling for detailed background information on MK-2140.

2.2.4 Chemistry

2.2.4.1 MK-2140 (VLS-101)

MK-2140 (VLS-101) is an ADC comprising:

- The humanized IgG1 monoclonal antibody, UC-961 (previously also known as cirmtuzumab) that recognizes an epitope on the extracellular domain of ROR1
- A proteolytically cleavable mc-vc-PAB linker, and
- The antimicrotubule agent, MMAE.

MK-2140 (VLS-101) has a target mean drug-to-antibody ratio of 4.0 ± 0.5 (distribution: 0 to 8). The combination of mc-vc-PAB and MMAE, was selected for conjugation to UC 961 given the well characterized pharmacology, toxicology, clinical efficacy, and clinical safety of this linker-toxin combination, as exemplified by the FDA- and EMA-approved anti-CD30 ADC, brentuximab vedotin (Adcetris™) [U.S. Prescribing Information 2019]; the anti-CD79b ADC, PV (Polivy™) [U.S. Prescribing Information 2020]; and the anti-nectin-4 ADC, enfortumab vedotin-ejfv (Padcev™) [U.S. Prescribing Information 2021]. A schematic of MK-2140 (VLS-101) is provided in Figure 2.

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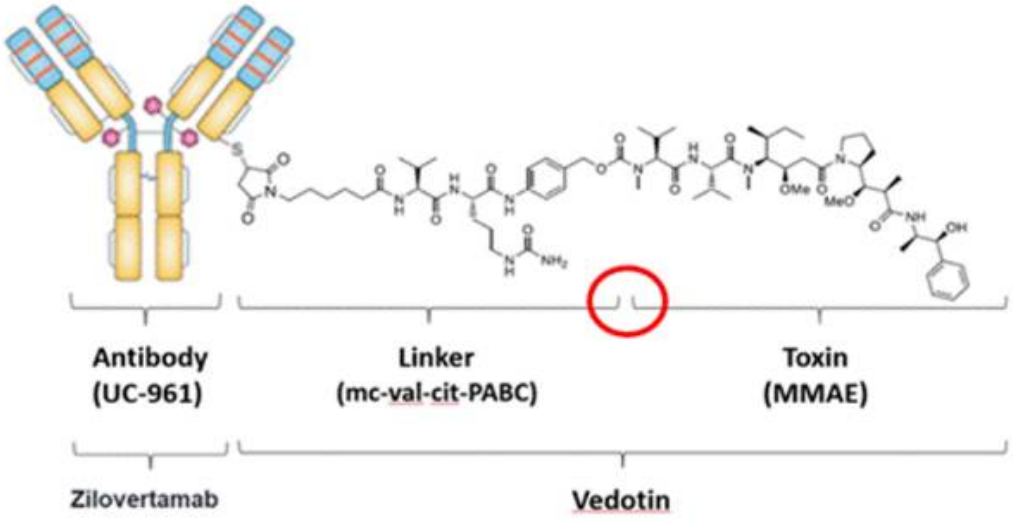
Figure 2 Schematic view of MK-2140 (VLS-101) Antibody, Linker, and Toxin Components



Abbreviations: mc-val-cit-PABC=maleimidocaproyl-valine-citrulline-para-aminobenzoate; MMAE=monomethyl auristatin E.

2.2.4.2 Mechanism of Action

MK-2140 (VLS-101) is a ROR1 targeting ADC as described above, comprising UC-961 conjugated to vedotin (the combination of mc-vc-PAB and MMAE). The anticancer activity of MK-2140 (VLS-101) is due to the binding of the ADC to ROR1-expressing cells, internalization of the ADC-ROR1 complex with trafficking to tumor cell lysosomes, and release of MMAE via lysosomal proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the tumor cell, subsequently inducing cell-cycle arrest and apoptotic tumor cell death.

The cell surface protein, ROR1, mediates signals from its ligand, the secreted glycoprotein, Wnt5a. Consistent with its role in influencing the fate of stem cells during embryogenesis, ROR1 expression is observed on invasive malignancies that revert to an embryonic transcriptional program. Expression of ROR1 is frequently expressed on the malignant cells of patients with hematological cancers but is not on normal adult tissues; thus, ROR1 has a favorable selectivity profile as a therapeutic target.

2.2.4.3 Pharmacology

ROR1 is a type 1 transmembrane protein that shares homology to other receptor tyrosine kinases and shows high evolutionary conservation [Masiakowski, P. 1992] [Forrester, W. C., et al 1999] [Yoda, A., et al 2003] [Katoh, M. 2017]. The extracellular portion contains immunoglobulin-like sequences, a cysteine-rich domain homologous to frizzled receptors for various Wnt ligands, and a Kringle domain. The cytoplasmic portion contains a tyrosine kinase-like domain followed by serine/threonine- and proline-rich motifs.

Based on studies in rodents, ROR1 is an embryonic factor that is physiologically expressed during early embryogenesis and plays a critical role in neural, auditory, skeletal, and vascular organogenesis [Matsuda, T., et al 2001] [Al-Shawi, R., et al 2011] [Lyashenko, N., et al 2010]. Functional studies in primary embryonic cells suggest that binding of the secreted glycoprotein ligand, Wnt5a, results in heterodimerization of ROR1 with ROR2 (the other member of the ROR family) and can stimulate neuronal synapse formation [Paganoni, S., et al 2010]. During fetal development, the expression of ROR1 decreases [Al-Shawi, R., et al 2011] [Paganoni, S., et al 2010]. Normal adult tissues lack surface expression of the ROR1 protein [Hudecek, M., et al 2010] [Zhang, S., et al 2012] [Liu, Y., et al 2015] except for rare B-lymphocyte precursors known as hematogones, the non-neoplastic counterpart to precursor-B ALL [Broome, H. E., et al 2011].

However, consistent with a role as an onco-embryonic factor, high levels of ROR1 protein expression have been found in multiple cancers, including both hematological malignancies [Daneshmanesh, A. H., et al 2013] and solid tumors [Zhang, S., et al 2012] [Zhang, S., et al 2012] [Liu, Y., et al 2015]. Among hematological cancers, these studies indicate near universal expression of ROR1 expression in CLL/SLL and MCL and document evidence of ROR1 expression in many patients with MZL, FL, DLBCL, ALL, T-cell cancers, and AML [Barna, G., et al 2011] [Shabani, M., et al 2011] [Bicocca, V. T., et al 2012] [Daneshmanesh, A. H., et al 2013] [Hogfeldt, T., et al 2013] [Karvonen, H., et al 2017] [Yu, J., et al 2018] [Diamanti, P., et al 2019] [Karvonen, H., et al 2019].

The accumulating data regarding its role in cancer and lack of expression in normal tissues indicate that ROR1 represents an attractive, tumor-specific therapeutic target for cancer intervention. Collectively, these data support the potential for therapeutic benefit from a ROR1 targeted treatment in patients with relapsed refractory DLBCL.

2.2.4.3.1 MMAE Pharmacology and Toxicology

The IC_{50} for MMAE in the hERG tail current assay has been estimated to be >100 μM. These data suggest a low risk of QT prolongation with MMAE as predicted by the hERG assay, because this in vitro concentration is several orders of magnitude higher than the expected mean plasma C_{max} of MMAE in patients who are treated with a clinical dose of MK-2140 (VLS-101). Such expectations are supported by lack of QT prolongation in participants receiving brentuximab vedotin.

In cell-free systems evaluating its effects on tubulin, MMAE was shown to inhibit microtubule polymerization, disrupting the intracellular microtubule network. Such effects result in cell-cycle arrest leading to apoptosis, especially in rapidly dividing tissues.

Binding of MMAE to plasma proteins is low to moderate, suggesting that variation in the binding capacity of plasma proteins does not have a major impact on the concentration of free drug in the plasma. MMAE rapidly distributes to erythrocytes, resulting in a blood-to-plasma ratio of 2.

Refer to the IB for more information on MMAE pharmacology and toxicology for MK-2140.

2.2.5 Preclinical and Clinical Studies

In studies evaluating its binding kinetics [Choi, M. Y., et al 2018], UC-961 showed high-affinity binding against the ROR1 epitope with an equilibrium dissociation constant (Kd) of 2 nM. Cellular binding to ROR1 in ROR1-positive JeKo-1 MCL cells showed highly reproducible binding in the linear range of the assay with a EC_{50} of ~9.5 ng/mL [Choi, M. Y., et al 2018].

In vitro incubation of Wnt5a-treated CLL cells with UC-961 was shown to disrupt the ROR1/ROR2 heterooligomer [Yu J, Chen L, Cui B, Widhopf GF 2nd, Shen Z, Wu R 2016]. UC-961 also inhibited the capacity of Wnt5a to recruit GEFs to either ROR1 or ROR2, thus blocking downstream activation of the oncogenic GTPases, Rac1 and RhoA, and inhibiting phosphorylation of HS1 [Hasan, M. K., et al 2017].

Similarly, in primary lymphoma cells from patients with MCL, UC-961 could inhibit the capacity of Wnt5a to induce Rac1 activation and could impair cycling of the malignant cells [Yu, J., et al 2018].

In vivo, UC-961 significantly inhibited the growth of human CLL-derived MEC1-ROR1 cells in mice and attenuated tumor expression of ROR1 (consistent with internalization of the receptor in the presence of the antibody) [Yu J, Chen L, Cui B, Widhopf GF 2nd, Shen Z, Wu R 2016]. In the ROR1 × TCL1 immune-competent human transgenic mouse model that had been used to evaluate the precursor antibody, D10 [Widhopf, G. F. 2nd, et al 2014], UC-961 treatment caused reductions in leukemic B cells in the spleens of the animals [Yu J, Chen L, Cui B, Widhopf GF 2nd, Shen Z, Wu R 2016].

In support of clinical testing of UC-961, University of California San Diego, performed a GLP safety pharmacology, toxicology, and toxicokinetic study of UC-961 in Wistar rats [Choi, M. Y., et al 2018] [Choi MY, Widhopf GF, Wu, CCN, Cui B, Lao, F, Sadarangani A 2015]. The study evaluated UC-961 at doses of 40, 120, and 400 mg/kg given weekly for 5 doses over 28 days with a 28-day recovery. In all dosing cohorts, UC-961 was well tolerated and showed no adverse clinical signs, clinical pathology findings, or histopathological effects. Toxicokinetic data indicated that UC-961 accumulated in the serum with successive weekly administrations of the drug, reaching trough concentrations by Day 28 of ~800, ~3100, and 4700 µg/mL at doses of 40, 120, and 400 mg/kg, respectively. Based on the results of this study, UC-961 showed no drug-related adverse effects despite the achievement of substantial drug exposures; accordingly, the NOAEL in rats was the highest dose tested (400 mg/kg).

University of California San Diego also performed a single-dose safety and PK study of UC-961 in 3 cynomolgus monkeys at a dose of 40 mg/kg [Choi, M. Y., et al 2018] [Choi MY, Widhopf GF, Wu, CCN, Cui B, Lao, F, Sadarangani A 2015]. The results indicated no adverse clinical, hematology, clinical chemistry, or circulating immunocyte perturbations despite achieving a mean C_{max} of 2,023 µg/L and a mean $t_{1/2}$ of 14.8 days. Clinical evaluation of UC-961 has comprised a Phase 1a, sequential, 3+3 dose-escalation study that enrolled 26 adult men and women with relapsed or refractory CLL/SLL [Choi MY, Widhopf GF 2nd, Ghia EM, Kidwell RL, Hasan MK, Yu J, et al. 2018]. Study participants received a total of 4

IV infusions of UC-961 monotherapy given over infusion times of 1.5 to 4 hours at dose levels ranging from 0.15 to 20 mg/kg (the highest planned dose).

UC-961 was very well tolerated. AEs were primarily Grade 1 or 2 in intensity and comprised events that were most commonly related to the underlying CLL/SLL, intercurrent illness, comorbidity, or concomitant medications. There was no evidence of dose-dependent increases in the incidence or severity of AEs. No DLTs were observed, no Grade ≥4 events were reported, no drug-related SAEs occurred, and no MTD was established within the tested dose range. Infusion reactions were not evident. TLS was not seen.

UC-961 PK parameters of C_{max} and AUC increased in a generally dose-proportional manner with mean C_{max} values ranging from ~20 µg/mL to >360 µg/mL. Following the last (fourth) dose in participants across the dose range of 1 to 20 mg/kg, mean $t_{1/2}$ values for the UC-961 antibody ranged from 22.9 to 32.7 days.

Pharmacodynamic assessments showed dose- and exposure-dependent reductions in ROR1 expression on CLL/SLL cells across the range of UC-961 doses. UC-961 also decreased downstream markers of ROR1 signaling in circulating CLL cells.

In summary, UC-961 therapy showed no overt drug-related adverse effects despite attaining high sustained systemic drug exposures and inhibition of ROR1-mediated signaling in CLL cells, thus documenting the safety and specificity of ROR1 targeting. However, the naked UC-961 antibody lacked clinical antitumor activity, suggesting that inhibition of ROR1 signaling might not be sufficient for clinical efficacy and supporting the development of a UC-961-based ADC, specifically VLS-101.

There are no completed clinical studies of VLS-101/MK-2140.

2.2.6 Ongoing Clinical Studies

Zilovertamab vedotin in various hematological malignancies is being evaluated in Study MK-2140-001. Zilovertamab vedotin has been administered IV Q3W, Q2/3W, or Q3/4W, with doses ranging from 0.5 mg/kg to 2.5 mg/kg.

The preliminary results from MK-2140-001 suggest that zilovertamab vedotin has a predictable PK profile consistent with those observed with other MMAE-containing ADCs approved for other indications, ie, brentuximab vedotin (Adcetris™) [U.S. Prescribing Information 2019]; PV (Polivy™) [U.S. Prescribing Information 2020]; and the anti-nectin-4 ADC, enfortumab vedotin-ejfv (Padcev™) [U.S. Prescribing Information 2021]. For zilovertamab vedotin, the ADC, and MMAE, have a terminal $t_{1/2}$ of approximately 4 days. Maximum MMAE concentrations are reached 4 days after dosing, reflecting the time scale of systemic release of MMAE.

Available safety data (27-NOV-2020) suggest the safety profile of zilovertamab vedotin at the doses tested is tolerable and manageable. There were no DLTs observed among 7 participants who received the lower doses of zilovertamab vedotin at 1.5 mg/kg (n=3), 1 mg/kg (n=3), and 0.5 mg/kg (n=1) out of the 32 participants administered zilovertamab

vedotin at Q3W of the dose-escalation portion of the study. At 2.25 mg/kg, a DLT was observed in 1 of 10 (10%) participants who completed Cycle 1, comprising asymptomatic neutropenia (Grade 4); the event was managed successfully by dose reduction and pegfilgrastim support. At 2.5 mg/kg, DLTs were observed in 3 of 14 (21.4%) participants, comprising asymptomatic neutropenia (Grade 4), febrile neutropenia (Grade 3), and diarrhea (Grade 3); these events were managed by dose reduction and supportive care. TLS has not been observed in any of the patients as of the 27-NOV-2020 safety data cutoff date.

Preliminary efficacy results from participants with DLBCL in Study MK-2140-001 (data extract February 2021) resulted in an ORR of 42.9% (6 of 14) for participants treated with zilovertamab vedotin Q3W compared with 33.3% (3 of 9) for participants treated with zilovertamab vedotin Q2/3W or Q3/4W; thus, there was no evident difference in ORR between dosing schedules. These efficacy results provide clinical proof of concept for targeting ROR1 with zilovertamab vedotin and show durable objective responses in patients with advanced heavily pretreated cancers.

Refer to the respective IB for ongoing clinical study data for MK-2140.

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

The design and conduct of this Phase 2 study of VLS-101 considers patient medical need, the importance of the drug target in the planned treatment setting, nonclinical efficacy and safety information, and clinical findings with VLS-101 and related drugs. The collective data supportthe following conclusions:

- Metastatic cancers are serious, disabling, and life-threatening disorders. Existing therapies can induce prolonged regressions but typically lose effectiveness over time. New therapies with new mechanisms of action are needed to overcome disease resistance and improve outcomes.

- ROR1 expression offers a cancer-specific marker in several cancers. Through selective targeting of ROR1-positive tumor cells, VLS-101 may safely improve clinical outcomes for patients with previously treated cancers.

- The potential for beneficial clinical efficacy of VLS-101 against ROR1-positive cancers is well founded on evaluation of its therapeutic effects in relevant in vitro and in vivo efficacy models.

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- The safety of advancing the development of VLS-101 in this study is well supported by nonclinical evaluations of UC-961 and VLS-101 pharmacology, PK, and toxicology; by Phase 1 clinical assessment of the safety, PK, and pharmacodynamics of UC-961; and by Phase 1 clinical assessment of the safety, PK, pharmacodynamics, immunogenicity, and efficacy of VLS-101. These data are supplemented by nonclinical information regarding MMAE, and prior clinical experience with the commercially available ADCs brentuximab vedotin (anti-CD30), polatuzumab vedotin (anti-CD79b), and enfortumab vedotin (anti-nectin-4).

- This collective information provides a basis for participant enrollment criteria; dose selection; administration of appropriate dosing regimens and supportive care; and safety, PK, and efficacy monitoring within this study.

- Given the seriousness of previously treated, progressive cancers and the aggregate potential benefits considered in the context of potential risks, clinical development of VLS-101 in patients with relapsed or refractory solid tumors is justified.

The rationale for specific design features of the study is provided in relevant sections of the protocol, including Section 2.1 (Study Rationale), Section 3 (Hypotheses, Objectives, and Endpoints), Section 4 (Study Design), Section 5 (Study Population), and Section 6 (Study intervention)

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

In male and female participants with advanced/metastatic solid tumors:

Objectives	Endpoints
Primary	
• To document the proportion of study participants who achieve an objective tumor response per RECIST 1.1 as assessed by blinded independent central review (BICR)	• ORR, defined as the proportion of participants who achieve a confirmed CR or PR per RECIST 1.1 as assessed by BICR

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Objectives	Endpoints
Secondary	
• To document the proportion of study participants who achieve an objective tumor response per RECIST 1.1 as assessed by investigator • To characterize the duration of antitumor efficacy and to assess survival in participants receiving VLS-101 • To document the safety of VLS-101 • To evaluate the pharmacokinetic profile of VLS-101	• ORR, defined as the proportion of participants who achieve a confirmed CR or PR per RECIST 1.1 as assessed by investigator • Time to response (TTR), defined as the interval from the start of study therapy to the first documentation of objective tumor response • Duration of response (DOR), defined as the interval from the first documentation of objective tumor response to the earlier of the first documentation of disease progression or death from any cause • Progression-free survival (PFS), defined as the interval from the start of study therapy to the earlier of the first documentation of disease progression or death from any cause • Time to treatment failure (TTF), defined as the interval from the start of study therapy to the earliest of the first documentation of disease progression, the permanent cessation of study drug due to an AE, or death from any cause • Overall survival (OS), defined as the interval from the start of study therapy to death from any cause

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Objectives	Endpoints
	• Type, frequency, severity, timing of onset, duration, and relationship to study drug of any treatment-emergent adverse events (TEAEs); laboratory abnormalities; serious adverse events (SAEs); or adverse events (AEs) leading to interruption, modification, or discontinuation of study treatment (referencing the NCI Common Terminology Criteria for Adverse Events [CTCAE], Version 5.0, for grading of the severity of AEs and laboratory abnormalities) • Derived total VLS-101, total antibody, and MMAE pharmacokinetic parameters (including, as appropriate for the analyte: C_{max} and AUC, as determined using noncompartmental methods)
Tertiary/Exploratory	
• To explore the effects of VLS-101 on pharmacodynamic markers relating to disease manifestations • To correlate baseline tumor characteristics with outcomes in participants administered VLS-101 • To document the supportive care profiles of VLS-101 • To assess the immunogenicity of VLS-101	• Percent change in tumor dimensions, defined as the percent change from baseline in the sum of the longest diameters of non-nodal target lesions and the shortest diameters of nodal target lesions • Type, frequency, and timing of use of supportive care and other concomitant medications • Changes in concentrations of circulating tumor-associated protein and DNA markers (as measured using appropriate immunoassay and sequencing methods) • Baseline tumor protein expression of ROR1 and markers relating to tumor proliferation, apoptosis, and immunosurveillance (as assessed by IHC and/or fluorescent-activated cell sorter [FACS])

Objectives	Endpoints
	• Baseline tumor mutation, gene expression, and protein expression status (as assessed by appropriate techniques) • The incidence of ADA will be summarized by regimen

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 2, nonrandomized, single-arm, multisite open-label study evaluating the efficacy, safety, PK, immunogenicity, and pharmacodynamics of VLS-101/MK-2140 in patients with metastatic solid tumors that are likely to express ROR1. Evaluation of VLS-101 in participants with specific tumor types will be determined by the Sponsor considering available data on the frequency of ROR1 expression, VLS-101 activity in relevant animal models, and medical need. Accrual of the following cohorts is planned:

- Cohort A: Participants with previously treated TNBC (ie, with disease that is ER-negative, progesterone receptor-negative, and HER2-negative)
- Cohort B: Participants with previously treated non-TNBC (ie, with disease that is ER-positive and/or progesterone receptor–positive, and HER2-negative)
- Cohort C: Participants with previously treated nonsquamous NSCLC
- Cohort D: Participants with platinum-resistant ovarian cancer
- Cohort E: Participants with previously treated gastric cancer
- Cohort F: Participants with previously treated pancreatic cancer

Because a validated ROR1 expression assay is not yet available and because it is still necessary to explore whether the extent and magnitude of ROR1 expression determine response to VLS-101, study participants will not be preselected for ROR1 expression, but archival or fresh tumor tissue will be collected for post hoc correlation with clinical outcomes.

VLS-101 will be administered IV using the RDR as derived from a previous Phase 1 evaluation. Drug administration can continue until the occurrence of any of the events noted in Section 7.1 below.

Enrollment of each cohort will be performed using a 2-stage Simon design, in which the enrollment of further participants with that tumor type to the second stage will be decided based on the tumor response rate in the first stage and the totality of data.

Specific procedures to be performed during the study, including prescribed times and associated visit windows, are outlined in Section 1.3 of the SoA. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

The study has been designed to provide critical efficacy, safety, PK, immunogenicity, pharmacodynamic, and biomarker data in support of continued clinical development of VLS-101 and is typical for Phase 2 studies intended to evaluate efficacy of an investigational therapy in patients with cancer.

Centralized conduct of the study using experienced sites, investigators, laboratories, and CROs is intended to provide a consistent approach to assessments of VLS-101 efficacy, safety, and pharmacology. A central IRC review offer systematic expert interpretations of efficacy findings.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The proposed endpoints are relevant to the pathophysiology and clinical manifestations of solid tumors, the biology of ROR1, the known pharmacology of VLS-101, and the goals of the study in providing information regarding drug efficacy. These types of endpoints have been employed in prior studies evaluating other ADCs and anticancer agents and can be evaluated with acceptable accuracy and reliability.

Determinations of the magnitude and duration of changes in tumor size will be based on well-established response and progression criteria as applied to radiographic or laboratory measurements. Beyond assessing the ability of the study drug to control tumor growth, tumor assessments will also be considered in defining the proper duration of treatment for each study participant. The specific endpoints of overall tumor control evaluated in this trial are customarily assessed and reported in studies of new therapies in patients with cancer. ORRs provide integrated assessments of the magnitude and extent of changes in tumor dimension that conveniently categorize and describe treatment effects. PFS offers a well-established outcome measure that directly measures treatment effect, conveys important longitudinal information regarding tumor control, can be characterized in all participants using intention-to-treat principles, and is readily analyzed using statistical methods such as Kaplan-Meier techniques.

TTR and DOR are important in characterizing the rapidity of achieving tumor shrinkage and the duration of tumor control. TTF offers a further characterization of participant outcome that incorporates the added dimension of drug tolerability; the degree of correspondence between PFS and TTF provides an assessment of how commonly chronic or cumulative

adverse effects are compromising the ability to maintain therapy. The 9- to 12-week cadence of tumor assessments is consistent with the expected natural history of response and progression in relapsed/refractory solid tumors, current clinical practice, and the goals of the trial in documenting meaningful VLS-101-mediated tumor regression.

Evaluation of plasma VLS-101 and MMAE concentrations will be performed using bioanalytical methods that have been validated for use in animal toxicology studies and in this clinical study. Plasma samples will be retained for any necessary follow-up assays.

An exploration of VLS-101 immunogenicity is critical to determining the utility of the drug when administered chronically. Correlations between the presence/absence of positivity for ADAs, PK and pharmacodynamic markers, activity, and safety of VLS-101 may be explored.

4.2.1.2 Safety Endpoints

Type, frequency, severity, timing of onset, duration, and relationship to study drug of any TEAEs; laboratory abnormalities; SAEs; or AEs leading to interruption, modification, or discontinuation of study treatment (referencing the NCI CTCAE, Version 5.0, for grading of the severity of AEs and laboratory abnormalities).

In defining the therapeutic ratio of a new drug, it is imperative that its safety profile be fully characterized. Proper description of each AE or laboratory abnormality requires an understanding of the type, incidence, timing, severity, and relatedness to study drug. In this study, particular focus will be placed on monitoring for toxicities that were encountered in the nonclinical studies of VLS-101 and prior clinical studies with VLS-101 and other MMAE-containing ADCs [U.S. Prescribing Information 2019] [U.S. Prescribing Information 2020] [U.S. Prescribing Information 2021] [Saber H, Leighton JK. 2015]. For consistency of interpretation, AEs will be coded using the standard MedDRA. The severity of AEs and laboratory abnormalities will be graded using the CTCAE, Version 5.0 [National Cancer Institute 2017]. Standard definitions for seriousness will be applied (see Appendix 3.3). In the evaluation of safety, particular scrutiny will be applied to Grade ≥3 AEs, SAEs, and AEs causing interruption, dose modification, or discontinuation of study drug.

4.2.1.3 Pharmacokinetic Endpoints

Derived total VLS-101, total antibody, and MMAE PK parameters (including, as appropriate for the analyte: C_{max} and AUC, as determined using noncompartmental methods).

PK blood sampling will characterize VLS-101 exposure and disposition. These data may be used to evaluate PK parameters by weight, age, sex, race, hepatic impairment (evaluating participants with no, mild, or moderate hepatic impairment as categorized by the NCI ODWG criteria), and renal impairment (evaluating participants with no [eClCR ≥90 mL/minute], mild [eClCR ≥60 to <90 mL/minute], or moderate [eClCR ≥30 to <60 mL/minute] renal impairment). Sampling during Cycle 1 will generate VLS-101 plasma concentration-time curves; sampling predose and postdose during subsequent cycles will provide steady-state VLS-101 exposure data while minimizing inconvenience for study participants and study center staff (see Section 8.6).

4.2.1.4 Pharmacodynamic Endpoints

Evaluations of circulating tumor markers may offer insights into tumor status during VLS-101 therapy that may supplement radiographic data in evaluating participant benefit.

Baseline evaluations of tumor ROR1 expression, and tumor mutational, gene expression, and protein expression status are intended to generate participant selection hypotheses for future studies.

4.2.1.5 Antidrug Antibodies

Formation of ADA can potentially confound drug exposures at therapeutic doses and prime for subsequent infusion-related toxicity. ADA response at the beginning of each cycle will be determined to understand drug metabolism, exposure, and safety. The incidence of ADA and neutralizing ADA will be evaluated and summarized over time by dose. Correlations between the presence/absence of positivity for ADAs and PK and pharmacodynamic markers, activity, and safety of VLS-101 will be explored.

4.2.1.6 Planned Exploratory Biomarker Research

The mechanism of action of many antitumor agents is not completely understood and much remains to be learned regarding how best to leverage new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer treatments administered, as well as determinants of AEs in the course of our clinical studies. These efforts may identify novel predictive/pharmacodynamic biomarkers and generate information that may better guide single-agent and combination therapy with antineoplastic drugs. To identify novel biomarkers, biospecimens (ie, blood components, tumor material) will be collected to support analyses of cellular components (eg, protein, DNA, RNA, metabolites) and other circulating molecules. Investigations may include, but are not limited to:

Germline (blood) genetic analyses (eg, SNP analyses, whole exome sequencing, whole genome sequencing)

This research may evaluate whether genetic variation within a clinical study population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in the patient population. Furthermore, it is important to evaluate germline DNA variation across the genome to interpret tumor-specific DNA mutations. Finally, MSI may be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer).

Genetic (DNA) analyses from tumor

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (ie, mutations, methylation status, microsatellite instability). Key molecular changes of interest to oncology drug development include the mutational burden of tumors and the clonality of T-cells in the

tumor microenvironment. Increased mutational burden (sometimes called a 'hyper-mutated' state) may generate neoantigen presentation in the tumor microenvironment. To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Thus, genome-wide approaches may be used for this effort. Note that to understand tumor-specific mutations, it is necessary to compare the tumor genome with the germline genome. Microsatellite instability may also be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer). Circulating tumor DNA and/or RNA may also be evaluated from blood samples.

Tumor and/or blood RNA analyses

Both genome-wide and targeted mRNA expression profiling and sequencing in tumor tissue and/or in blood may be performed to define gene signatures that correlate to clinical response to treatment with antitumor therapies. Specific gene sets (ie, those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes may also be evaluated (eg, IL-10). MicroRNA profiling may also be pursued as well as exosomal profiling.

Proteomics and IHC using blood and/or tumor

Tumor and/or blood samples from this study may undergo proteomic analyses (eg, PD-L1 IHC). Therefore, tumor tissue may be subjected to proteomic analyses using a variety of platforms that could include, but are not limited to, immunoassays and liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for antitumor therapy.

Other blood-derived biomarkers

In addition to expression on the tumor tissue, PD-L1 and other tumor derived proteins can be shed from tumor and released into the blood. Assays such as ELISA measure such proteins in serum. Correlation of expression with response to therapy may identify new approaches for predictive biomarkers in blood, representing a major advance from today's reliance on assessing tumor biomarkers. This research would serve to develop such assays for future clinical use.

Other molecular changes of interest include the subtype of T-cells in the tumor microenvironment. The T-cell repertoire from tumor tissue and blood components may be evaluated.

Biomarker research using the human microbiome

The human microbiome plays a critical role in maintaining tissue homeostasis. Abnormal composition of the microbiome has been observed in several disease states, including digestive cancers and other malignancies. Furthermore, the composition of different bacterial signatures may be predictive of the efficacy of chemotherapeutic agents, and participant response. The microbiome may thus serve as a valuable diagnostic tool for properly assessing and managing disease states.

4.2.1.7 Future Biomedical Research

The Sponsor will conduct FBR on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes, depending on which specimens are consented for FBR.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for FBR is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of FBR research are presented in Appendix 5.

4.3 Justification for Dose

The initial starting dose for the current study was based on the efficacy, PK, and safety data in the Phase 1 FIH study, MK-2140-001 (VLS-101-0001). In this dose-escalation and cohort-expansion study of VLS-101 in participants with hematological malignancies, a VLS-101 starting dose of 2.5 mg/kg was recommended for further evaluation when administering the drug using the Q1/3W schedule since this was the identified MTD.

A dose of 2.5 mg/kg using a Q1/3W schedule was also initially chosen for patients with solid tumors. However, emerging serum PK data in patients with heme malignancies showed that the ADC was eliminated quickly ($t_{1/2}$ ~4 days) relative to the three-week dosing schedule. Limited receptor occupancy data collected in CLL and MCL patients also showed that high levels of occupancy could not be maintained for the duration of the 3-week cycle. Preliminary serum PK data in patients with solid tumors was found to be similar to that in patients with heme malignancies. Intratumoral concentrations within solid tumors are limited by ADC penetration and are likely significantly lower than in serum. To increase intratumoral exposures in solid tumors while maintaining drug tolerability, the dosing schedule is being altered to 2.0 mg/kg Q2/3W. The 2.0 mg/kg Q2/3W schedule has been tolerated in patients with hematologic malignancies and has been determined to be the MTD on this schedule. Since toxicities to VLS-101 are likely to be driven by systemic exposure, and systemic exposure was found to be similar between hematologic and solid tumors, the toxicity profile of this regimen is also expected to be similar to that already established in the ongoing study of hematologic malignancies. The switch to a more frequent schedule is expected to improve the possibility of detecting an efficacy signal in solid tumors.

4.3.1 Starting Dose for This Study

This study will have a single starting dose of VLS-101 for most patients, of 2.0 mg/kg, which was recommended for Phase 2 evaluation in adults when administering VLS-101 Q2/3W. Participants who require coadministration of a strong inducer of CYP3A4 should also initiate therapy at a VLS-101 starting dose of 2.0 mg/kg. Participants requiring coadministration of a

strong inhibitor of CYP3A4 and for whom use of an alternate therapy is not possible should initiate therapy at a VLS-101 starting dose of 1.5 mg/kg. Dose for participants who discontinue a CYP3A4 inhibitor (for example, participants who complete a prescribed antibiotic course) may be increased as per Table 5 guidelines to a maximum dose of 2.0 mg/kg, if warranted by the benefit/risk evaluation for that participant at that time. Doses may be adjusted downward or upward to accommodate individual subject tolerance, as described in Section 6.6. If ≥5% change in body weight occurs, weight-based dosing should be readjusted. Active study participants enrolled prior to protocol amendment 4 will remain on their current dose.

4.3.2 Maximum Dose/Exposure for This Study

Participants may receive VLS-101 until any discontinuation criteria (Section 7.1) are met. The highest dose level reached in a Q2/3W dosing regimen was 2.25 mg/kg, and the MTD was 2.0 mg/kg.

4.3.2.1 Rationale for Dose Interval

In this study, VLS-101/MK-2140 will be administered Q2/3W based on the PK, safety, and efficacy results observed to date.

Preliminary zilovertamab vedotin PK data are available for 18 participants with solid tumors in MK-2140-002. PK was found to be similar in hematological malignancies and solid tumors. Based on PK studies at the dose used in this study, the mean Cycle 1 T_{max} values for VLS-101, total antibody, and MMAE were 0.5, 0.5, and 48 hours, respectively. The mean $t_{1/2}$ values for total antibody and VLS-101 were 5.1 and 3.1 days, respectively.

For detailed information, refer to the IB for PK, safety, and efficacy data for MK-2140.

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory result or at the time of final contact with the last participant, whichever comes last.

For studies conducted in the European Economic Area (EEA), the local start of the study is defined as First Site Ready (FSR) in any Member State.

4.4.1 Clinical Criteria for Early Study Termination

Recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

Early study termination will be the result of the criteria specified below:

Incidence or severity of adverse drug reactions in this or other studies suggest a potential health hazard to participants

Plans to modify or discontinue the development of the study drug

Ample notification will be provided in the event of Sponsor decision to no longer supply MK-2140.

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), our studies include people of varying age, race, ethnicity, and sex. The collection and use of these demographic data is to follow all local laws and guidelines in keeping with the needs for participant confidentiality while supporting the study of the disease, its related factors, and the IMP under investigation.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

A participant is eligible for inclusion in the study if the participant meets all of the following criteria:

Type of Participant and Disease Characteristics

- Performance status of 0 or 1 on the ECOG performance scale assessed within 7 days before the start of study treatment.
- Histologically or cytologically confirmed diagnosis of solid tumor as documented in medical history.
- Presence of metastatic disease that has progressed during or following previous treatment.
- Presence of radiographically measurable disease as determined by investigator (defined as the presence of ≥1 non-osseous tumor lesion that measures ≥10 mm in longest dimension [≥15 mm in shortest dimension for lymph nodes]) and is outside of any prior radiation field).

  Note: Participants with skin only disease are excluded. Participants who have metastatic disease fulfilling the previous criteria in addition to skin disease can be enrolled.
- Availability of pretreatment tumor tissue from at least one of the following sources:
  - Fresh tumor biopsy obtained by a core needle, excisional, or incisional biopsy; or punchbiopsy (for cutaneous disease); or

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- Archival sample from a previous biopsy (if obtained since last prior therapy and within 24 weeks prior to the start of study therapy).

  Note: Bone specimens are not acceptable.

  Details pertaining to tumor tissue submission can be found in the procedures manual.

- Completion of all previous therapy (including surgery, radiotherapy, chemotherapy, immunotherapy, or investigational therapy) for the treatment of cancer ≥2 weeks before the start of study therapy.

Have life expectancy at least 3 months from enrollment.

Meet the following cohort-specific inclusion criteria:

- **Cohort A: TNBC**

  - Have pathologically confirmed TNBC, as defined by the most recent ASCO/CAP guidelines

    Note: Participants initially diagnosed with hormone receptor–positive and/or ER2-positive breast cancer must have confirmation of TNBC in a tumor biopsy obtained from a local recurrence or distant metastasis site.

  - At least 1 and no more than 3 prior lines of cytotoxic therapy for metastatic disease

  - Have completed treatment for Stage I-III breast cancer, if indicated, and ≥6 months elapsed between the completion of treatment with curative intent (eg, date of primary breast tumor surgery or date of last adjuvant chemotherapy administration, whichever occurred last) and first documented local or distant disease recurrence

    Note: Participants presenting with de novo metastatic TNBC are eligible for the study.

    Note: Adjuvant radiation therapy is not considered treatment with curative intent for the purpose of calculating the ≥6-month interval requirement described above.

    Note: First documentation of local or distant disease recurrence must be in the form of a dated biopsy, pathology, or imaging study report. A laboratory report indicating tumor marker elevation cannot be used as documentation of local or distant disease recurrence, unless accompanied by dated biopsy, pathology, or imaging study report.

- **Cohort B: Non-TNBC**

  - No more than 2 prior lines of cytotoxic chemotherapy for metastatic disease

  - HER2-negative disease only and prior treatment with at least hormonal therapy, CDK4/6 inhibitor, and cytotoxic chemotherapy

    Note: HER2+ disease is excluded.

  - Participants with advanced/metastatic, symptomatic visceral spread at risk of rapidly evolving into life-threatening complications, such as lymphangitic lung metastases, bone marrow replacement, carcinomatous meningitis, significant symptomatic liver metastases, shortness of breath requiring supplemental oxygen, symptomatic pleural effusion requiring supplemental oxygen, symptomatic pericardial effusion, symptomatic peritoneal carcinomatosis, or the need to achieve rapid symptom control are excluded.

    Note:

    - Participants with symptomatic pleural effusion who have dyspnea at rest requiring supplemental oxygen, but which is alleviated by drainage of the fluid can be enrolled.

    - Participants with symptomatic ascitic effusion caused by peritoneal carcinomatosis, which is alleviated after drainage of the ascitic fluid can be enrolled.

    - Participants with symptomatic liver metastases include participants with rapidly increasing bilirubin > 1.5 x ULN in the absence of biliary obstruction with involvement of over than 50% of liver parenchyma by the disease.

- **Cohort C: NSCLC**

  - Adenocarcinoma (nonsquamous) histology

  - Progression of disease on no more than 2 prior lines of therapy for metastatic disease

  - Prior treatment with a checkpoint inhibitor and platinum-containing regimen, which may be given as combination therapy or separately, unless previously treated with a tyrosine kinase inhibitor for actionable molecular biomarker

  - At least one prior platinum-containing regimen

    Note: Completion of treatment with a platinum-containing doublet as neoadjuvant or adjuvant therapy or as part of definitive chemoradiation treatment for early-stage disease (Stage I-III) will satisfy the prior platinum treatment requirement

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- Patients whose disease is positive for EGFR-sensitizing-mutation, ALK rearrangement, ROS1 rearrangement, BRAF-V600E mutation, NTRK gene fusion, MET exon 14 skipping mutation, or RET rearrangement must have received at least 1 relevant tyrosine kinase inhibitor.

- **Cohort D: Ovarian Cancer (Including Fallopian Tube Cancer and Primary Peritoneal Cancer)**

  - High-grade serous histology or carcinosarcomas with a high-grade serous component

  - Has radiographic evidence of disease progression within 6 months (180 days) after the last dose of platinum-based chemotherapy for ovarian cancer (ie, platinum-resistant disease)

  - No more than 1 prior line of therapy for platinum-resistant disease

  - No limit on prior platinum-containing regimens for platinum sensitive disease

  - Primary platinum-resistant or refractory patients may be enrolled if they have had at least 1 TFI of at least 6 months after a nonplatinum agent

    Note: Maintenance therapies do not count as prior lines of treatment.

- **Cohort E: Gastric Cancer**

  - Adenocarcinoma histology

  - No more than 2 prior lines of therapy, except for patients whose disease overexpresses HER2 where an additional line of HER2-directed monotherapy is allowed

  - GEJ patients allowed, if adenocarcinoma

  - Patients with peritoneal metastases are excluded

- **Cohort F: Pancreatic Cancer**

  - Has histologically confirmed diagnosis of metastatic or locally advanced PDAC

    Note: Histologies other than adenocarcinoma including mixed histology are not allowed.

  - No more than 2 prior lines of therapy for unresectable or metastatic disease

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Note: Maintenance regimens administered with the purpose of maintaining response after treatment will not be considered as separate lines of therapy. For example, PARP inhibitor maintenance therapy after initial chemotherapy will be counted as 1 line of systemic therapy (such as FOLFIRINOX followed by olaparib for BRCA mutated pancreatic cancer). Participants who have not received PARP maintenance after initial platinum-based chemotherapy for known BRCA mutated pancreatic cancer but initiate PARP therapy alone after first-line chemotherapy after documented disease progression after initial chemotherapy will be eligible.

Note: Adjuvant therapy will be counted as a line of therapy if a participant progressed during therapy or within 6 months of completion of last dose of therapy.

Note: Locoregional therapies will not be counted as a line of therapy.

Adequate organ function (post-nadir following any prior myelosuppressive therapy) as defined in the following (Table 2).

Table 2 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count	>1500/mcL
Platelets	>75,000/mcL
Hemoglobin[a]	>8 g/dL
Renal	
Creatinine OR Measured or calculated[b] CrCl (GFR can also be used in place of CrCl)	≤1.5 x ULN or ≥30 mL/min for participants with creatinine levels >1.5 x ULN
Hepatic	
Total bilirubin	≤1.5 x ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 x ULN
AST (SGOT) and ALT (SGPT)	<3 X ULN or ≤5 × ULN for participants with liver metastases

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

a. Criteria must be met without packed red blood cell (pRBC) transfusion within the prior 2 weeks. Participants can be on stable dose of erythropoietin (≥ approximately 3 months).

b. Creatinine clearance (CrCl) should be calculated per institutional standard.

Demographics

Is male or female, at least 18 years of age, at the time of providing informed consent. Note: Men with breast cancer may participate in this study.

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Male Participants

If male, agrees to the following during the intervention period and for at least 110 days after the last dose of VLS-101/MK-2140:

- Refrains from donating sperm

  PLUS either:

- Abstains from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agrees to remain abstinent

  OR

- Uses contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause, documented from the site personnel's review of the participant's medical records, medical examination, or medical history interview) as detailed below:

  - Uses a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

  - Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Female Participants

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

- Not a WOCBP

  OR

- A WOCBP and:

  - Uses a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 4 during the intervention period and for at least 50 days after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

- Has a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours before the first dose of study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.5.

- Abstains from breastfeeding during the study intervention period and for at least 20 days after study intervention VLS-101/MK-2140.

- Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

The participant (or legally acceptable representative) has provided documented informed consent/assent for the study. The participant may also provide consent/assent for FBR. However, the participant may participate in the study without participating in FBR.

Additional Categories

Willingness and ability of the participant to comply with scheduled visits, drug administration plan, protocol-specified laboratory tests, other study procedures (including all tumor biopsy/aspirations and radiographic studies), and study restrictions.

Negative viral serology or adequate therapy for HIV, HBV, and HCV infection:

- HIV: Absence of serum HIV antibodies; or absence of HIV virus in the blood by quantitative assay; or ongoing antiretroviral therapy for HIV for ≥4 weeks before the start of study therapy and blood HIV viral load <400 copies/mL; and

- HBV: Absence of serum HbsAg and serum HBcAb; or absence of HBV in the blood by quantitative assay; or receiving suppressive anti-HBV therapy before the start of study therapy; and

- HCV: Absence of serum HCV antibody; or absence of HCV in the blood by quantitative assay; or receiving anti-HCV therapy and blood HCV viral load below the limit of quantitation.

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5.2 Exclusion Criteria

The participant must be excluded from the study if the participant meets any of the following criteria:

Medical Conditions

Peripheral neuropathy of Grade >1.

- Clinically active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain or meningeal metastases may participate and be eligible for treatment provided they are stable and asymptomatic (without evidence of progression by MRI scan of the brain separated by at least 4 weeks after treatment), have no evidence of new or enlarging brain metastases, are evaluated within 4 weeks before first study intervention administration, and are off immunosuppressive doses of systemic steroids at least 2 weeks before enrollment.

  Note: Screening MRI of the brain is onlyrequired in participants with known or clinically suspected CNS malignancy.

- Presence of another cancer with disease manifestations or therapy that could adversely affectparticipant safety or longevity, create the potential for drug-drug interactions, or compromise theinterpretation of study results. A history of a second malignancy, unless potentially curative treatment has been completed with no evidence of recurrence for at least 2 years.

  Note: The time requirement does not apply to participants who underwent successful definitive resection of basal cell carcinoma of the skin, squamous cell carcinoma of the skin, superficial bladder cancer, or carcinoma in situ (eg, breast carcinoma in situ, cervical cancer in situ).

- Uncontrolled ongoing systemic bacterial, fungal, or viral infection (including upper respiratory tract infection) at the time of start of study therapy or any active infection requiring systemic therapy.

  Note: Participants with localized fungal infections of skin or nails are not excluded. Participants may be receiving prophylactic or therapeutic antibiotics if there is no occurrence of fever within 48 hours before starting study therapy.

- Significant cardiovascular event (eg, myocardial infarction, arterial thromboembolism, cerebrovascular thromboembolism) within 4 weeks before the start of study therapy; unstableangina; symptomatic peripheral vascular disease; Grade ≥2 congestive heart failure; uncontrolled Grade ≥3 hypertension (diastolic BP ≥100 mm Hg or systolic BP ≥160 mm Hg) despite antihypertensive therapy; or significant conduction system ECG abnormalities, including second degree AV block type II, third degree AV block, or Grade ≥2 bradycardia.

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Known diagnosis of liver cirrhosis.

- Pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the Screening Visit through 120 days after the last dose of study intervention.
- Prior treatment with a ROR1-directed therapy.
- Known tumor resistance or participant intolerance to a prior MMAE-containing drug.
- History or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that might confound the results of the study or interfere with the participant's participation for the full duration of the study, such that it is not in the best interest of the participant to participate, in the opinion of the treating investigator.
- Known psychiatric or substance abuse disorders that would interfere with the participant's ability to cooperate with the requirements of the study.
- Pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the Screening Visit through 120 days after the last dose of study intervention.
- Not fully recovered from any effects of major surgery without significant detectable infection. Surgeries that required general anesthesia must be completed at least 2 weeks before first study intervention administration. Surgery requiring regional/epidural anesthesia must be completed at least 72 hours before first study intervention administration and participants should be recovered.

Prior/Concomitant Therapy

- Has received prior systemic anticancer therapy, definitive or palliative radiotherapy, including investigational agents within 2 weeks (2 weeks for palliative radiation) before the start of study treatment.

  Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline.

Prior/Concurrent Clinical Study Experience

- Currently participating and receiving study intervention in a study of an investigational agent or has participated and received study intervention in a study of an investigational agent or has used an investigational device within 28 days of administration of MK-2140.

  Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks since the last dose of the previous investigational agent.

Diagnostic Assessments

This is not applicable to this study.

Other Exclusions

This is not applicable to this study.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

5.3.1.1 Diet Restrictions

Participant should maintain a normal diet unless modifications are required to manage an AE, such as diarrhea, nausea, or vomiting.

5.3.1.2 Fruit Juice Restrictions

Participants should be advised to avoid ingestion of grapefruit, grapefruit juice, Seville oranges, or starfruit (all of which contain CYP3A4 inhibitors).

No other specific dietary restrictions are required.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently entered in the study. A minimal set of screen-failure information is required to ensure transparent reporting of screen-failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

Participants who fail screening may be rescreened for eligibility, as clinically indicated.

A participant who discontinues from study intervention OR withdraws from the study will not be replaced.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies provided by the Sponsor will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

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6.1 Study Intervention(s) Administered

The study intervention to be used in this study is outlined in Table 3.

Table 3 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
VLS-101/ MK-2140	Experimental	zilovertamab vedotin	Biological/ Vaccine	Vial	10 mg/mL	2.0 mg/kg	IV Infusion	Q2/3W	Test Product	IMP	Central
VLS-101/ MK-2140	Experimental	zilovertamab vedotin	Biological/ Vaccine	Lyophilized Powder	60 mg	2.0 mg/kg	IV Infusion	Q2/3W	Test Product	IMP	Central

Abbreviations: EEA=European Economic Area; IMP=investigational medicinal product; IV=intravenous; NIMP/AxMP=noninvestigational/auxiliary medicinal product; Q2/3W=repeated 3-week cycles with a drug infusion on Day 1 and Day 8 of each cycle.

The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

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All supplies indicated in Table 3 will be provided per the "Sourcing" column depending on local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc.).

Refer to Section 8.1.8 for details regarding administration of the study intervention.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

VLS-101/MK-2140 will be prepared for dosing as described in the study pharmacy manual associated with this clinical protocol. Specific calculations or evaluations required to be performed to administer the proper dose to each participant are provided. The rationale for selection of doses to be used in this study is in Section 4.3. See pharmacy/procedures manual for further details.

6.2.2 Dose Administration

Details on administration of VLS-101 are provided in the appropriate pharmacy/procedures manual.

6.2.3 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

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The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Participants in this study will be allocated by nonrandom assignment.

6.3.2 Stratification

No stratification based on age, sex, or other characteristics will be used in this study.

6.3.3 Blinding

This is an open-label study; therefore, the Sponsor, investigator, and participant will know the intervention administered.

6.4 Study Intervention Compliance

If there are interruptions in the study intervention schedule or infusion/injection was stopped, the details of and reason for any interruption or infusion/injection cessation of study intervention will be documented in the participant's medical record.

Interruptions from the protocol-specified require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

When study intervention is administered to the participants, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study-site staff other than the person administering the study intervention.

6.5 Concomitant Therapy

Consistent with participant safety and comfort, administration of any prescription or OTC drug products other than study medication will be minimized during the study period. Participants should be discouraged from use of herbal remedies, self-prescribed drugs, tobacco products, or street drugs during their participation in the clinical study and should be counseled to minimize use of alcohol or nonmedical marijuana.

If considered necessary for the participant's well-being, drugs for concomitant medical conditions or for symptom management may be given at the discretion of the investigator. The investigator's decision to authorize the use of any drug other than study drug will take into account participant safety, the medical need, the potential for drug interactions, the

possibility for masking symptoms of a more significant underlying event, and whether use of the drug will compromise the outcome or integrity of the study.

Participants will be instructed about the importance of the need to inform the clinic staff of the use of any drugs or remedies (whether prescribed, OTC, or illicit) before and during the course of the study.

Recommendations regarding specific types of concomitant therapies, supportive care, diet, and other interventions are provided below. To minimize variations in supportive care, the recommended supportive care agents should be considered unless there is a medical rationale in a specific participant for use of an alternative product.

6.5.1 Antibiotics, Antifungals, Antivirals

Care should be taken to avoid or minimize concomitant administration of prophylactic or therapeutic antibacterial, antifungal, or antiviral agents that are strong CYP3A4 inhibitors or inducers (see Appendix 7). Local practices or guidelines regarding infection prophylaxis may be followed.

Participants developing an intercurrent infection during study drug treatment may receive therapeutic antibacterial, antiviral, or antifungal drugs for intercurrent infections as needed. Continuation of study therapy during treatment for an intercurrent infection is at the discretion of the investigator.

6.5.2 Anticancer Therapies Other than the Study Drug

No systemic anticancer therapies (including chemotherapy, antibody therapy, hormonal therapy, immunotherapy, or other experimental therapies) for the participant's cancer are permitted while the participant is receiving study treatment.

The use of palliative radiotherapy should be minimized given the potential of such treatment to confuse assessments of study drug safety and therapeutic effect. However, administration of limited-fraction radiotherapy is permitted after Cycle 1 to control local tumor-related symptoms if irradiation is unlikely to induce major organ toxicity or affect target lesions being followed for tumor response and progression.

6.5.3 Anticoagulants

Use of local anticoagulation or antithrombotic agents to maintain a venous access catheter is permitted. In addition, participants who have preexisting conditions or develop conditions that require anticoagulant therapy may participate in the study.

6.5.4 Antidiarrheals

Participants experiencing diarrhea (and/or abdominal cramping) should have evaluation for causes related to the underlying malignancy, a comorbid condition, an intercurrent illness (eg, infection), or a concomitant medication.

Participants may take loperamide at the earliest sign of a loose stool, an increase in bowel movements by 1 to 2 episodes compared with baseline, or an increase in stool volume or liquidity. The recommended regimen is 4 mg at the first onset of diarrhea, then 2 mg with each succeeding diarrheal stool until the participant is diarrhea-free for at least 12 hours.

Additional antidiarrheal measures may be implemented at the discretion of the investigator. Participants should also be instructed to maintain oral fluid intake to help sustain fluid and electrolyte balance during episodes of diarrhea. Participants with more severe diarrhea or comorbid medical conditions should receive IV hydration or hospitalization, as appropriate.

6.5.5 Antiemetics

If antiemetics are needed, investigators may prescribe serotonin antagonists (eg, granisetron, ondansetron, dolasetron), dopamine antagonists (eg, prochlorperazine, olanzapine), corticosteroids (eg, dexamethasone), or benzodiazepines (eg, alprazolam, diazepam, lorazepam). Based on currently available information regarding MMAE metabolism, the neurokinin 1 receptor antagonist, rolapitant, can be considered together with other antiemetic agents, but aprepitant or netupitant+palonosetron should be avoided because these drugs may inhibit CYP3A4 activity.

6.5.6 Antihistamine, Anti-inflammatory, and Antipyretic Drugs

Antihistamines (eg, cetirizine, diphenhydramine), and anti-inflammatory/antipyretic drugs (eg, acetaminophen [paracetamol], NSAIDs) may be used during the study, as medically warranted.

6.5.7 Corticosteroids

During study therapy, participants may use systemic, enteric, topical, inhaled, or intraarticular corticosteroids as required (eg, for intercurrent medical conditions or antiemetic prophylaxis).

6.5.8 Drugs Known to Inhibit or Induce Cytochrome P450 (CYP)3A4

In vitro data indicate that MMAE is a substrate of CYP3A4/5 and that MMAE is primarily metabolized by CYP3A4. Coadministration of brentuximab vedotin with ketoconazole, a potent CYP3A4 inhibitor, increased exposure to MMAE by ~34% while coadministration of brentuximab vedotin with rifampin, a potent CYP3A4 inducer, reduced exposure to MMAE by ~46% [U.S. Prescribing Information 2019].

Protocol candidates who require chronic therapy with a strong CYP3A4 inhibitor as listed in Appendix 7 should initiate protocol therapy at a VLS-101 starting dose of 1.5 mg/kg while those who chronically require a strong CYP3A4 inducer should initiate protocol therapy at a VLS-101 starting dose of 2.0 mg/kg (given that use of strong CYP3A4 inducers are likely to reduce toxicity associated with free MMAE). Dose adjustments may be made thereafter as recommended in Section 6.6.

During study participation, coadministration of VLS-101 with any of the strong CYP3A4 inhibitors listed in Appendix 7 should be avoided, if possible. However, a participant who develops a condition that may require use of such a drug is not required to permanently discontinue VLS-101 if the participant is experiencing clinical benefit and other options for treating the participant's cancer are limited. If medically appropriate, investigators may wish to use a therapeutic alternative that would not be expected to inhibit this enzyme. For participants who require temporary use of a drug that does affect this enzyme (eg, treatment with a systemic antifungal agent), VLS-101 therapy can be temporarily interrupted and then resumed after completion of the other drug, if interruption would not delay drug treatment > 4 weeks. For participants who require initiation of chronic therapy with a drug that strongly inhibits CYP3A4, investigators must consult with the medical monitor to consider the best course of action. If participants do receive a CYP3A4 inhibitor concomitantly with VLS-101, they should be monitored closely for signs of VLS-101 toxicity and a VLS-101 dose modification may be warranted.

6.5.9 Drugs Known to Prolong the QT Interval

Available nonclinical and clinical data obtained with VLS-101 or with other MMAE-containing ADCs (e.g., brentuximab vedotin, polatuzumab vedotin, or enfortumab vedotin) do not suggest a high risk of cardiac interval QT prolongation [U.S. Prescribing Information 2019] [U.S. Prescribing Information 2020] [U.S. Prescribing Information 2021]. Accordingly, there is no specific restriction on use of concomitant medications that might prolong the QT interval.

6.5.10 Extravasation Support

VLS-101 is neither a venous irritant nor a vesicant. Extravasation is not expected to induce ulcerative necrosis of dermal tissues. However, extravasation of VLS-101 can cause pain, erythema, cellulitis, and serous bulla formation that may require several days to resolve.

During each infusion, it is recommended that the participant be observed for local irritation, infiltration, or extravasation at the infusion site. If there is evidence of infiltration or extravasation, the infusion should be stopped, and the IV cannula should be removed. The infusion may be restarted at another site if clinically appropriate. If a participant has a central venous access device, VLS-101 may be infused through the device. Local toxicity at the site of the infusion should be recorded according to the injection site extravasation/reaction criteria in the General Disorders and Administration Site Conditions section of the NCI CTCAE, Version 5.0.

Participants may be provided with analgesia, drainage of bulla, debridement of exfoliating epidermis, and occlusive dressings. VLS-101 therapy may continue while the participant is recovering from the extravasation.

6.5.11 Hematopoietic Support

Prophylactic or reactive use of G-CSF (pegylated or non-pegylated forms) is encouraged to avoid neutropenic complications and promote neutrophil recovery in support of on-time

VLS-101 retreatment, as appropriate and consistent with current guidelines [Smith, T. J., et al 2015] [National Comprehensive Cancer Network 2022].

Thrombopoietin receptor antagonists (eg, romiplostim or eltrombopag) may be administered to minimize thrombocytopenic complications. However, given lack of definitive evidence confirming their benefit in the management of chemotherapy-induced thrombocytopenia [Zhang, X., et al 2017], administration of such drugs is not specifically recommended.

Use of erythropoietic agents (eg, erythropoietin or darbepoetin) is not recommended based on current guidelines [Rizzo, J. D., et al 2008] [National Comprehensive Cancer Network 2022].

Platelet or red blood cell transfusions may be administered as medically indicated.

6.5.12 Immunization

For participants who are at risk of an infection (eg, influenza, herpes zoster) that might be prevented by immunization, consideration should be given to providing the vaccine prior to initiation of study therapy.

Whether the study drug would increase the risk of live viral vaccines during study therapy is unknown. Pending the acquisition of additional information, live viral vaccination during study therapy should be avoided.

Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy. Investigational vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.

6.5.13 Infusion Reactions

Infusion reaction prophylaxis should be avoided on C1D1 unless infusion reactions become a safety concern during the study. Premedication administered thereafter may include acetaminophen, an antihistamine, and a corticosteroid (see Section 6.6). Participants who have experienced a prior infusion-related reaction should be premedicated for subsequent infusions and consideration should be given to extending the planned infusion time (eg, to 60 minutes or longer).

The following guidelines for managing infusion reactions are provided in case such reactions occur:

- If a Grade 1 infusion reaction occurs, the infusion rate should be slowed to half of the infusion rate at the time of the reaction. The infusion rate may be increased consistent with participant tolerance to a rate no higher than the initial rate.

- If an infusion reaction Grade ≥2 occurs, the infusion must be interrupted. Medical management (eg, oxygen, epinephrine, bronchodilators) should be instituted, as needed. Use of corticosteroids can be considered if medically necessary. After the severity of the reaction has decreased to Grade ≤1, VLS-101 may be restarted at a rate no higher than half of the infusion rate at the time the infusion was paused. For Grade 4 infusion reactions, VLS-101 should not be resumed.

6.5.14 Procedures/Surgery

Procedures or surgery may be offered to diagnose or treat the participant for intercurrent medical conditions. The extent to which the study drug may affect wound healing is unknown.

Considering ongoing need for control of the underlying cancer and the risk of myelosuppression due to VLS-101, investigators should use clinical discretion in deciding whether to interrupt study therapy before, during, and after surgery or other invasive procedures.

6.6 Dose Modification (Escalation/Titration/Other)

Guidelines for Dose Modification due to Adverse Events for VLS-101

If a participant experiences a TEAE that is suspected to be related to the study drug, appropriate monitoring and supportive care should be instituted consistent with the nature of the event. Inparticular, G-CSF (eg, filgrastim, pegfilgrastim) should be employed to prevent or mitigate drug-induced neutropenia and promote neutrophil recovery in support recovery in support of on-time study drug retreatment.

Table 4 provides recommendations for modifications of VLS-101 dosing considering the worst drug-related AEs or laboratory abnormalities in the current treatment cycle and the implications for drug administration in the next treatment cycle. The dose modification instructions focus on the types of events most often attributed to VLS-101. These recommendations comprise general guidelines; variations from these recommendations may be warranted based on an investigator's individual judgment in considering potential risks, benefits, and therapeutic alternatives available to each participant. Investigators are encouraged to discuss modifications in the dosing regimen with the medical monitor. If ≥5% change in body weight occurs, weight-based dosing should be readjusted.

For participants undergoing a dose reduction, successive adjustments to progressively lower dose levels can be made. If the participant cannot tolerate VLS-101 after a decrease to 1.0 mg/kg, then the participant should be discontinued from study drug therapy. In general, after the VLS-101 dose is reduced, the dose should be maintained at that dose level, even if there is minimal or no toxicity with the reduced dose. However, if the participant tolerates a reduced dose of VLS-101 for ≥3 weeks with no toxicities of Grade ≥2, then the VLS-101 dosing regimen may be reescalated to the next higher dose level, particularly if further evaluation reveals that the AE that led to the dose reduction was primarily related to the underlying malignancy, a comorbid condition, an intercurrent illness, or a concomitant

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medication and a dose escalation is medical warranted (eg, for a participant with stable disease). Successive adjustments to progressively higher dose levels can be made with the caveat that the escalated dose cannot exceed 2.0 mg/kg (in the absence of a strong inhibitor of CYP3A4) or 1.5 mg/kg (for participants who require coadministration of a strong inhibitor of CYP3A4) and should not be attempted in a participant who should be removed from therapy for PD. Dose for participants who discontinue a CYP3A4 inhibitor (for example, participants who complete a prescribed antibiotic course) may be increased as per Table 5 guidelines to a maximum dose of 2.0 mg/kg, if warranted by the benefit/risk evaluation for that participant at that time.

If a participant experiences a TEAE precluding resumption of VLS-101 therapy by the planned Day 1 of the next cycle, the new cycle of treatment may begin when toxicities or laboratory abnormalities have resolved sufficiently and if the participant does not meet criteria for permanent discontinuation of study therapy (as indicated in Table 4). Upon initiation of a new cycle, the current cycle will be considered completed. If toxicity does not resolve to Grade 0 to 1 or to baseline within 28 days, study intervention should be discontinued after consultation with the Sponsor. Only hematologic toxicities are exceptions to this in which they need to resolve to ≤Grade 2. Drug administration may be interrupted or delayed due to any non-AE reason (medical procedure, etc.) for a maximum of 4 weeks without consultation with the Sponsor. If AEs have not resolved in that time frame, the participant should be removed from study. If a participant experiences recurrent Grade 4 nonhematological toxicity, then study intervention should be permanently discontinued, upon consultation with the Sponsor.

If ≥5% change in body weight occurs, weight-based dosing should be readjusted.

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Table 4 Dosing Modification Recommendations

Event(s)	Toxicity Grade (CTCAE v5.0)	Dose Delay or Modification
Neutropenia	≤Grade 1	• Maintain current dose and schedule
	Grade 2	• Maintain current dose and schedule
	Grade 3	• Delay until resolved to ≤Grade 2 (ANC ≥1x10^9/L) • Administer growth factors (eg, G-CSF) as clinically indicated and for all subsequent cycles • Reduce dose by 1 dose level (see Table 5), if clinically indicated
	≥Grade 3 febrile neutropenia or Grade 4	• Delay until resolved to ≤Grade 2 (ANC ≥1x10^9/L) • Administer growth factors (eg, G-CSF) as clinically indicated and for all subsequent cycles • Reduce dose by 1 dose level (see Table 5), if clinically indicated
Thrombocytopenia	Grade 1, 2, or 3	• Maintain current dose and schedule
	≥Grade 3 with hemorrhage or Grade 4	• Delay until resolved to ≤Grade 2 (platelet count ≥50x10^9/L) • Reduce dose by 1 dose level (see Table 5) • Administer transfusion, as appropriate
Diarrhea	Grade 1	• Maintain current dose and schedule • Evaluate for infectious or other causes of diarrhea and treat, as appropriate. Provide antidiarrheal support
	Grade 2 or 3	• Delay until resolved to ≤Grade 1 • Evaluate for infectious or other causes of diarrhea and treat, as appropriate. Provide antidiarrheal support • Reduce dose by 1 dose level (see Table 5)
	Grade 4	• Delay until resolved to ≤Grade 1 • Evaluate for infectious or other causes of diarrhea and treat, as appropriate. Provide antidiarrheal support • Reduce dose by 1 dose level (see Table 5) or permanently discontinue
Neurological Toxicities (including peripheral neuropathy)	Grade 1	• Maintain current dose and schedule
	Grade 2 or 3	• Delay until resolved to ≤Grade 1 • Reduce dose by 1 dose level (see Table 5)
	Grade 4	• Permanently discontinue
Non-hematologic Toxicity Not Otherwise Specified	≤Grade 2	• Maintain current dose and schedule
	Grade 3 or nonrecurrent Grade 4	• Delay until ≤Grade 1 • Reduce dose by 1 dose level (see Table 5)
	Recurrent Grade 4	• Permanently discontinue after consultation with the Sponsor
Abbreviations: ANC=absolute neutrophil count; CTCAE v5.0=Common Terminology Criteria for Adverse Events, Version 5.0; G-CSF=granulocyte colony-stimulating factor.		

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Table 5 VLS-101 Dose Reduction Levels

Dose Level, mg/kg	Dose Level Description	Dosing Schedule
1.0	Dose reduction levels	Q2/3W
1.25		
1.5	Dose reduction level or starting dose in participants who require coadministration of a strong inhibitor of CYP3A4[a]. See Section 4.3.1	
1.75	Dose reduction level	
2.0	Starting dose (in the absence of a strong inhibitor of CYP3A4[a])	

Abbreviations: CYP=cytochrome P450 (enzyme), Q2/3W=repeated 3-week cycles with a drug infusion on Day 1 and Day 8 of each cycle.
[a] A listing of strong inhibitors and inducers of CYP3A4 is provided in Appendix 7.

Dose Modification and Toxicity Management of Infusion-related Reactions Related to Zilovertamab Vedotin

Although zilovertamab vedotin has not been associated with infusion reactions, other monoclonal antibodies have been known to cause severe or life-threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and treatment guidelines on zilovertamab vedotin associated infusion reaction are provided in Table 6.

Table 6 Zilovertamab Vedotin Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade[a]	Treatment[b]	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	• Slow infusion rate to 50% of the infusion rate at the time of the reaction. The infusion rate may be increased consistent with participant tolerance to a rate no higher than the initial rate.	• None
Grade 2 or 3	• Stop infusion • Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics	Administer 30 to 60 minutes prior to infusion: • po or IV antipyretic • (acetaminophen [paracetamol]), 650 to 1000 mg or equivalent • po or IV antihistamine (cetirizine, 10 mg or equivalent) • An NSAID (ibuprofen, 400 to 800 mg orally or equivalent) may be added or substituted for acetaminophen.

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NCI CTCAE Grade[a]	Treatment[b]	Premedication at Subsequent Dosing
	• Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • After the severity of the reaction has decreased to Grade ≤1, zilovertamab vedotin may be restarted at a rate no higher than 50% of the infusion rate at the time the infusion rate was paused.	• A corticosteroid (100 mg of prednisolone or equivalent) as a premedication can be considered.
Grade 4	Stop infusion Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. • Participant is permanently discontinued from further study drug intervention.	• No subsequent dosing

Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events; IV=intravenous; NCI=National Cancer Institute; NSAID=nonsteroidal anti-inflammatory drug; po=orally.

a. For further information, please refer to the Common Terminology Criteria for Adverse Events, Version 5.0 (CTCAE v5.0) at http://ctep.cancer.gov

b. Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.

6.7 Intervention After the End of the Study

There is no study-specified intervention after the end of the study.

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6.8 Clinical Supplies Disclosure

This study is open-label; therefore, the participant, the study-site personnel, the Sponsor, and/or designee are not blinded. Study intervention (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

6.9 Standard Policies

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.1.9, or if available, PCL.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

A participant must be discontinued from study intervention, but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- Any prolonged interruption of study intervention beyond the permitted periods, as noted in Section 6.6. If treatment will not be restarted, the participant will continue to be monitored in the study and the reason for discontinuation of study intervention will be recorded in the medical record.
- The participant has a medical condition or personal circumstance, which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- Radiographic disease progression outlined in Section 8.2.1.4.

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- Any progression or recurrence of malignancy, or any occurrence of another malignancy that requires active treatment.

- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment.

- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 6.6.

For participants who are discontinued from study intervention, but continue to be monitored in the study, all visits and procedures, as outlined in the SoA, should be completed.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from FBR, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

  Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

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8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be used for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each participant over the duration of the study will not exceed the amount specified in the laboratory manual.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study or FBR. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant (or their legally acceptable representative) before participation in the study.

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

Specifics about the study and the study population are to be included in the study informed consent form.

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the FBR consent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study-site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention allocation, site personnel will add the treatment/randomization number to the participant identification card.

The participant ID card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The medical history will collect all active conditions and any condition diagnosed within the prior 10 years that the investigator considers to be clinically important. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

If a medical condition is diagnosed at the time of screening due to the physical examination, laboratory tests, radiologic assessment, other assessment, and/or a combination of these evaluations, the medical condition is to be recorded as a baseline condition along with the participant's other medical history unless due to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in).

Demographic information will be recorded for all participants.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before first dose of study intervention.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study.

All medications related to reportable SAEs and ECIs should be recorded as defined in Section 8.4.3.

All new anticancer therapy initiated after the study start must be recorded in the eCRF. If a participant initiates another anticancer therapy other than the assigned study intervention(s), the study intervention(s) should be discontinued and the participant will move into the Survival Follow-up Phase; if a participant initiates a new anticancer therapy within 30 days after the last dose of the study intervention, the 30-day Safety Follow-up Visit should occur before the first dose of the new therapy.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur before intervention allocation. Each

participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.10.1.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be allocated, by nonrandom assignment, and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation. The assigned screening number will become the participants' treatment number. Once a treatment/randomization number is assigned to a participant, it can never be reassigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number.

8.1.8 Study Intervention Administration

Study intervention(s) will be administered by the investigator and/or study staff according to the specifications within the pharmacy manual. The total volume of study intervention infused will be compared with the total volume prepared to determine compliance with each dose administered.

Refer to Section 6.1 for dose and treatment details.

8.1.8.1 Timing of Dose Administration

Study intervention will follow a 21-day cycle and will begin after all procedures/assessments have been completed as detailed in the SoA (Section 1.3).

Participants will be administered zilovertamab vedotin (VLS-101/MK-2140) administered IV over a planned infusion time of approximately 30 minutes.

8.1.8.2 Timing of Administration for VLS-101

VSL-101 will be administered as an IV infusion on Day 1 and Day 8 of a 21-day cycle. The reason for any variability in administration of VLS-101 outside the protocol-specified window should be documented in the participant's medical chart and recorded on the eCRFs.

All subsequent cycles of study intervention may be administered up to 3 days before or 3 days after the scheduled Day 1 of each cycle due to administrative reasons per the investigator's judgment. All study interventions will begin on Day 1 of each cycle after all predose study procedures and assessments have been completed as detailed in the SoA (Section 1.3).

The pharmacy manual contains specific instructions for (dose calculation, reconstitution, preparation) of VLS-101, and administration.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.10.3.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the final study visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's consent for FBR will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.1.10 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study. The emergency unblinding call center will be available so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.11 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Efficacy Assessments

8.2.1 Tumor Imaging and Assessment of Disease

Throughout this section, the term 'scan' refers to any medical imaging data used to assess tumor burden and may include cross-sectional imaging (such as CT or MRI), medical photography, or other methods as specified in this protocol.

In addition to survival, efficacy will be assessed based on evaluation of scan changes in tumor burden over time, until the participant is discontinued from the study or goes into survival follow-up. The process for scan collection, submission and/or retention can be found in the SIM. Tumor scans by CT are strongly preferred. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated or when mandated by local practice. The same scan technique should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the response assessment based on scans.

Note: For the purposes of assessing tumor scans, the term “investigator” refers to the local investigator at the site and/or the radiological reviewer at the site or at an offsite facility.

If brain scans are performed, MRI is preferred; however, CT imaging will be acceptable, if MRI is medically contraindicated.

Bone scans may be performed to evaluate bone metastases. Any supplemental scans performed to support a positive or negative bone scan, such as plain x-rays acquired for correlation, should also be submitted and/or retained as specified in the SIM.

Other imaging modalities that may be collected, submitted and/or retained, and included in the response assessment include PET scans. Other types of medical imaging (such as ultrasound) should not be submitted and will not be included in response assessment.

8.2.1.1 Initial Tumor Scans

Initial tumor scans at Screening must be performed within 28 days prior to the date of treatment. Any scans obtained after Cycle 1 Day 1 cannot be included in the screening assessment. The site must review screening scans to confirm the participant has measurable disease per RECIST 1.1.

8.2.1.2 Tumor Scans During the Study

The first on-study scan should be performed at 9 weeks (±7 days) from the date of treatment start. Subsequent tumor scans should be performed every 9 weeks (±7 days) or more frequently if clinically indicated. After 36 weeks (±7 days), participants who remain on treatment will have scans performed every 12 weeks (±7 days). Scan timing should follow calendar days and should not be adjusted for delays in cycle starts.

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Scans are to be performed until disease progression is identified by the investigator, or until the start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first.

Objective response should be confirmed by a repeat scan performed at least 4 weeks after the first indication of a response is observed. Participants will then return to the regular scan schedule, starting with the next scheduled time point. Participants who receive additional scans for confirmation do not need to undergo the next scheduled scan if it is fewer than 4 weeks later; scans may resume at the subsequent scheduled time point.

On-study brain or bone scans should be performed if clinically indicated or to confirm CR (if other lesions indicate CR and brain or bone lesions existed at baseline).

8.2.1.3 End-of-Treatment and Follow-up Tumor Scans

If participants discontinue study intervention, tumor scans should be performed at the time of discontinuation (±4 week window) unless previous scans were obtained within 4 weeks of discontinuation. If participants discontinue study intervention due to documented disease progression, this is the final required tumor scan.

If participants discontinue study intervention without documented disease progression, every effort is to be made to monitor disease status by acquiring tumor scans using the same schedule calculated from the date of treatment start, refer to Section 8.2.1.2.

Scans are to be continued until one of the following conditions are met:

- Disease progression as defined by RECIST 1.1
- The start of a new anticancer treatment
- Pregnancy
- Death
- Withdrawal of consent
- The end of the study

8.2.1.4 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study intervention). Imaging scans are to be submitted/retained according to the SIM guidance.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/tissue to be drawn/collected over the course of the study

(from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in the laboratory manual.

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard. Height and weight will also be measured and recorded.

A brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.1.1 Full Physical Examination

The investigator or qualified designee will perform a complete physical examination during the screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exams are described in Section 1.3. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.1.2 Directed Physical Examination

For cycles that do not require a full physical examination as defined in Section 1.3, the investigator or qualified designee will perform a directed physical examination as clinically indicated prior to study intervention administration. New clinically significant abnormal findings should be recorded as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Vital Signs

The investigator or qualified designee will take vital signs at screening, before the administration of each dose of study intervention and during the follow-up period as specified in the SoA. Vital signs include temperature, pulse, respiratory rate, weight, and BP. Height will be measured at Visit 1 only.

Oxygen saturation will also be measured at time points specified in the SoA.

8.3.3 Electrocardiograms

A standard 12-lead ECG will be performed using local standard procedures. The timing of ECGs is specified in the SoA. Clinically significant abnormal findings should be recorded as medical history. Additional ECGs may be performed as clinically necessary.

8.3.4 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.4.1 Laboratory Safety Evaluations (Hematology, Chemistry, and Urinalysis)

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 2.

Laboratory tests for screening should be performed within 3 days before to the first dose of study intervention. An exception is hepatitis and thyroid serologies, which may be performed within 28 days before the first dose. After Cycle 1, predose laboratory safety tests can be conducted up to 72 hours before dosing unless otherwise noted on the flow charts.

Laboratory test results must be reviewed by the investigator or qualified designee and found to be acceptable before administration of each dose of study intervention. Unresolved abnormal laboratory values that are drug-related AEs should be followed until resolution. Laboratory tests do not need to be repeated after the end of treatment if laboratory results are within normal range.

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8.3.5 Pregnancy Testing

- Pregnancy testing: Pregnancy testing requirements for study inclusion are described in Section 5.1. Pregnancy testing (as required by local regulations) should be conducted at monthly intervals during intervention.

  - Pregnancy testing (as required by local regulations) should be conducted for the time required to eliminate systemic exposure after the last dose of each study intervention(s) as noted in Section 5.1. The length of time required to continue pregnancy testing for each study intervention is as follows:

  - MK-2140 (50 days)

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.3.6 Eastern Cooperative Oncology Group Performance Status

The ECOG performance status is standardized criteria to measure how cancer impacts level of functioning (performance status) in terms of ability to care for oneself, daily activity, and physical ability (walking, working, etc.) with Grades 0 to 5.

The investigator or qualified designee will assess ECOG performance status (Appendix 8) at screening, prior to the administration of each dose of study intervention, and during the follow-up period as specified in the SoA.

8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Progression of the cancer under study is not considered an AE as described in Section 8.4.6 and Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators need to document if an AE and/or SAE was associated with a medication error, misuse, or abuse.

Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3. The investigator, who is a qualified physician,

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will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention allocation, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of intervention allocation through 30 days after cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention allocation through 30 days after cessation of study intervention or 30 days after cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of intervention allocation through the time required to eliminate systemic exposure after cessation of study intervention as described in Sections 5.1 and 8.3.5, or 30 days after cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside the time specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 7.

Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.

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Table 7 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period	Reporting Time Period: After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
NSAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/termination ; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential DILI - require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event.

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in treated participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee), including the pregnancy of a male participant's female partner, that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth

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must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 8.4.1.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor will ensure that aggregated efficacy endpoint events and safety data are monitored to safeguard the participants in the study.

8.4.7 Events of Clinical Interest

Selected serious and nonserious AEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

- An overdose of Sponsor's product, as defined in Section 8.5.
- An elevated AST or ALT laboratory value that is greater than or equal to 3X the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2X the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2X the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

  *Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study-site guidance for assessment and follow up of these criteria can be found in the Investigator Study File Binder (or equivalent).

In addition, the following events are considered ECIs for MK-2140/VLS-101 (MK-2140 IB):

- Grade ≥3 infusion reactions
- TLS of any grade
- Grade ≥3 neuropathy

8.5 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose exceeding the prescribed dose for MK-2140 by ≥20% of the indicated dose. No specific information is available on the

treatment of overdose of MK-2140. In the event of overdose, MK-2140 may be discontinued and the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

8.6 Pharmacokinetics

To further evaluate MK-2140 immunogenicity and exposure in these indications, and also to evaluate exposure of the proposed dosing regimen, sample collections for analysis of ADA and PK are currently planned as shown in Section 1.3. Blood samples will be obtained to measure PK of serum MK-2140. The MK-2140 serum C_{max} and minimum concentration (C_{trough}) at planned visits and times will be summarized. Blood samples collected may be stored and further analysis may be performed, if required.

8.6.1 Blood Collection for Plasma MK-2140 (VLS-101)

Sample collection, storage, and shipment instructions for plasma samples will be provided in the laboratory manual.

PK samples should be drawn according to the PK collection schedule for all participants. Every effort should be taken to collect samples at 30 days after end of study intervention.

8.6.2 Blood Collection for Antidrug Antibodies

Sample collection, storage, and shipment instructions for serum samples will be provided in the laboratory manual. Anti-MK-2140 samples should be drawn according to the ADA collection schedule for all participants (Section 1.3). Every effort should be taken to collect samples at 30 days after end of study intervention for ADA. Simultaneous PK sampling is required for interpretation of ADA analysis.

8.7 Pharmacodynamics

Sample collection, storage, and shipment instructions for pharmacodynamic samples will be in the laboratory manual.

8.8 Biomarkers

To identify novel biomarkers, the following biospecimens to support exploratory analyses of cellular components (eg, protein, RNA, DNA, metabolites) and other circulating molecules will be collected from all participants as specified in the SoA:

- Tumor tissue
- Plasma for ctDNA

Sample collection, storage, and shipment instructions for the exploratory biomarker specimens will be in the procedure manual.

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8.9 Future Biomedical Research Sample Collection

If the participant provides documented informed consent for FBR, the following specimens will be obtained as part of FBR:

- Leftover samples listed in Section 8.8.

8.10 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.10.1 Screening

Approximately 28 days before treatment allocation, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Screening procedures may be repeated as clinically indicated.

Documented informed consent must be provided before performing any protocol-specific procedure. Results of a test performed before the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days before the first dose of study intervention.

8.10.2 Treatment Period/Vaccination Visit

Visit requirements are outlined in the SoA (Section 1.3). Specific procedure-related details are provided above in Section 8.

8.10.3 Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study

The Discontinuation Visit should occur at the time study intervention is discontinued for any reason. If the Discontinuation Visit occurs 30 days from the last dose of study intervention, at the time of the mandatory Safety Follow-up Visit, the Discontinuation Visit procedures and any additional Safety Follow-up procedures should be performed. Visit requirements are outlined in the SoA (Section 1.3). Additional details regarding participant withdrawal and discontinuation are presented in Section 7.

8.10.4 Posttreatment Visit

Participants will be required to return to the clinic approximately 14 days after the last dose of study intervention for the poststudy visit. If the poststudy visit occurs less than 14 days after the last dose of study intervention, a subsequent follow-up telephone call should be made at 14 days post the last dose of study intervention to determine if any AEs have occurred since the poststudy clinic visit.

8.10.4.1 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of study intervention or before initiation of a new anticancer treatment, whichever comes first.

All AEs that occur before the Safety Follow-up Visit should be recorded (up to 30 days after the end of treatment).

8.10.4.2 Efficacy Follow-up Visits

Participants who discontinue study intervention for reasons other than verified PD should continue with imaging assessments Q12W as defined in Section 1.3 until: (1) PD is verified or further confirmed by the investigator, (2) initiation of a new anticancer treatment, (3) death, (4) withdrawal of consent, or (5) study conclusion or early termination, whichever occurs first.

8.10.4.3 Survival Follow-up Contacts

Participants who experience confirmed disease progression or start a new anticancer therapy will move into the Survival Follow-up Phase. Participants should be contacted by telephone Q12W beginning from the last point of contact to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

The Sponsor may request survival status be assessed at additional time points during the course of the study. For example, these additional time points may be requested before an efficacy IA, and/or final analysis. All participants who are not known to have died before the request for these additional survival status time points will be contacted at that time.

8.10.5 Vital Status

To ensure current and complete survival information (vital status) is available at the time of database locks, updated vital status may be requested during the study by the Sponsor. For example, updated vital status may be requested before but not limited to, an eDMC review, interim and/or final analysis. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their vital status.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategies and procedures for the primary and secondary analyses of the study. Exploratory and other nonconfirmatory analyses will be outlined in a separate sSAP.

If, after the study has begun, changes are made to primary and/or secondary objectives or the statistical methods related to those objectives, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or other nonconfirmatory analyses made

after the protocol have been finalized but before the conduct of any analyses will be documented in the sSAP as needed and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

Key elements of the SAP are summarized below. The comprehensive plan is provided in Section 9.2 through Section 9.12.

Study Design Overview	A Phase 2, nonrandomized, single-arm, multisite open-label study evaluating the efficacy, safety, PK, immunogenicity, and pharmacodynamics of VLS-101/MK-2140 in patients with metastatic solid tumors that are likely to express ROR1.
Intervention Assignment	Participants will be allocated by nonrandom assignment. This is an open-label study.
Analysis Populations	Efficacy and Safety: (FAS)
Primary Endpoint	ORR per RECIST 1.1 by BICR
Secondary Endpoints	PK parameters including AUC, C_{min}, and C_{max}
Statistical Methods for Efficacy Analyses	The point estimate of ORR will be provided for each tumor type and dosing schedule, together with 95% CI using exact binomial method.
Statistical Methods for Safety Analyses	Summary statistics (eg, counts and percentages) will be provided for the safety endpoints per tumor cohort and dosing schedule.
Interim Analyses	For each disease cohort and dosing schedule, a futility IA is planned for approximately the first 13 participants using Simon's mini-max, 2-stage procedure.
Multiplicity	No multiplicity adjustment is planned.
Sample Size and Power	It is anticipated that up to ~30 participants per disease cohort will be accrued if enrollment proceeds through both stages of the Simon 2-stage enrollment paradigm for that cohort. To allow for the possibility that some participants may not be fully evaluable for efficacy, up to 5 additional participants (~35 total per cohort) may be enrolled. With Simon's mini-max 2-stage design, this study has a power of >0.8 with a significance level of <0.05 when the ORR of a null hypothesis is 5% and the true ORR is 20% for each disease cohort.

9.2 Responsibility for Analyses/In-house Blinding

The statistical analyses of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

The study is open-label (ie, participants, investigators, and Sponsor personnel will be aware of participant intervention assignment after each participant is enrolled and treatment is assigned). Participants will be allocated by nonrandom assignment.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are outlined in Section 3.

9.4 Analysis Endpoints

9.4.1 Efficacy/Immunogenicity/Pharmacokinetics Endpoints

Primary Endpoint

- ORR, defined as the proportion of participants who achieve a confirmed CR or PR per RECIST 1.1 as assessed by BICR

Secondary Endpoints

- ORR, defined as the proportion of participants who achieve a confirmed CR or PR per RECIST 1.1 as assessed by investigator
- TTR, defined as the interval from the start of study therapy to the first documentation of objective tumor response
- DOR, defined as the interval from the first documentation of objective tumor response to the earlier of the first documentation of disease progression or death from any cause
- PFS, defined as the interval from the start of study therapy to the earlier of the first documentation of disease progression or death from any cause
- TTF, defined as the interval from the start of study therapy to the earliest of the first documentation of disease progression, the permanent cessation of study drug due to an AE, or death from any cause
- OS, defined as the interval from the start of study therapy to death from any cause

9.4.2 Safety Endpoints

The primary safety endpoint is the assessment of AEs: type, frequency, severity, timing of onset, duration, and relationship to study drug of any TEAEs; laboratory abnormalities; SAEs; or AEs leading to interruption, modification, or discontinuation of study treatment. The NCI CTCAE, Version 5.0, will be used for grading of the severity of AEs and laboratory abnormalities.

In addition, safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs.

A description of safety measures is provided in Section 8.3.

9.4.3 Pharmacokinetics Endpoints

The PK endpoints will be derived total VLS-101, total antibody, and MMAE PK parameters, including as appropriate for the analyte: C_{max} and AUC, as determined using noncompartmental methods.

Details of the analysis plan for exploratory endpoints will be documented in the sSAP.

9.5 Analysis Populations

9.5.1 Full Analysis Set

The FAS population will be used for the analyses of efficacy and safety data in this study. The FAS includes data from all participants who receive ≥1 dose of study drug and will be used in the analyses of participant characteristics, ORR, CR rate, PR rate, PFS, TTF, OS, study drug administration, and safety.

9.5.2 Responding Analysis Set

The responding analysis set will include data from participants in the FAS who have measurable disease, who can be evaluated for tumor response with both baseline and on-study tumor evaluations, and who achieve an objective response. This analysis set will be used in the analyses of TTR and DOR.

9.5.3 Evaluable Analysis Set

Evaluable analysis sets include participants in the FAS who have the necessary baseline and on-study measurements to provide interpretable results for specific parameters of interest. These analysis sets will be used in the analyses of PK, immunogenicity, pharmacodynamic, and biomarker parameters.

9.6 Statistical Methods

This section describes the statistical methods that address the primary and key secondary objectives. Methods related to exploratory endpoints will be described in the sSAP.

9.6.1 Statistical Methods for Efficacy Analysis

Categorical Endpoints

ORR, CR, and PR rates will be described. In analyses of response rates in the FAS, participants who do not have sufficient baseline and on-study tumor assessments to characterize response (ie, have a best overall response of NE) will be counted as failures. For all analyses, the corresponding 95% CIs will be presented.

Continuous Endpoints

The percent change in tumor dimensions will be described.

Time-to-Event Tumor Control and Survival Endpoints

For time-to-event endpoints, the following definitions and censoring conventions will be applied:

- TTR will be defined as the interval from the start of study therapy to the first documentation of objective tumor response. TTR data will not be censored.

- DOR will be defined as the interval from the first documentation of objective tumor response to the earlier of the first documentation of PD or death from any cause. Data from surviving, non-progressing participants will be censored at the earliest of the time of initiation of antitumor treatment other than the study treatment or the last time that lack of PD was objectively documented. Data from participants who have PD or die after ≥2 consecutive missing tumor assessments will be censored at the last time prior to the missing assessments that lack of PD was objectively documented.

- PFS will be defined as the interval from the start of study therapy to the earlier of the first documentation of PD or death from any cause. Data from surviving, non-progressing participants will be censored at the earliest of the time of initiation of antitumor treatment other than the study treatment or the last time that lack of PD was objectively documented. Data from participants who have PD or die after ≥2 consecutive missing tumor assessments will be censored at the last time prior to the missing assessments that lack of PD was objectively documented.

- TTF will be defined as the interval from start of study therapy to the earliest of the first documentation of PD, the permanent cessation of study drug due to an AE, or death from any cause. Data from surviving participants who do not have treatment failure will be censored at the earliest of the time of initiation of antitumor treatment other than the study treatment or the last on-therapy time that lack of treatment failure was objectively documented. Data from participants who have treatment failure due to PD or die after ≥2 consecutive missing tumor assessments will be censored at the last time prior to the missing assessments that lack of treatment failure was objectively documented.

- OS will be defined as the interval from the start of study therapy to death from any cause. Data from surviving participants will be censored at the last time that the participant was known to be alive.

Time-to-event endpoints will be described in the appropriate analysis sets using Kaplan-Meier methods with appropriate censoring. Medians, ranges, and relevant corresponding CIs will be presented.

9.6.2 Statistical Methods for Safety Analysis

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, vital signs, and ECG measurements.

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All AEs will be listed. AEs will be summarized by counts and frequencies for each dose level. Laboratory tests, vital signs, and other safety endpoints will be summarized as appropriate.

The focus of AE summarization will be on TEAEs, which is defined as an AE that occurs or worsens in the period from the first dose of studydrug administration to 30 days after the final dose of study drug administration. AEs that occur before the first dose of study drug administration or >30 days afterthe final study drug administration will be included in data listings.

AEs will be classified using MedDRA with descriptions by System Organ Class and Preferred Term. The severity of AEs will be graded by the investigator according to the CTCAE, Version 5.0 [National Cancer Institute 2017], whenever possible. If a CTCAE criterion does not exist for a specific type of AE, the grade corresponding to the appropriate adjective will be used by the investigator to describe the maximum intensity of the AE: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal). The relationship of the AE to the study drug will be described based on the categories as outlined in Appendix 3.5. As necessary, attributions of “definitely,” “probably,” or “possibly” related may be aggregated as “related” and attributions of “unlikely” or “unrelated” may be aggregated as “unrelated” to provide a dichotomous description of causal relationships.

Summary tables will be presented to show the number of participants reporting TEAEs by severity grade and corresponding percentages. A participant who reports multiple TEAEs within the same Preferred Term (or System Organ Class) is counted only once for that Preferred Term (or SystemOrgan Class) using the worst severity grade. AE descriptions will be presented in order of decreasing frequency for System Organ Class, and by decreasing frequency in the overall or totalcolumn for a given Preferred Term.

Separate listings and summaries will be prepared for the following types of AEs:

- Study-drug-related AEs
- AEs that are Grade 3, 4, or 5 in severity
- AEs leading to study drug interruption and/or dose modification
- AEs leading to study drug discontinuation
- SAEs (with categorization of the primary outcome that results in the AE being considered serious, eg, life-threatening, requiring hospitalization)

9.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

9.6.3.1 Demographic and Baseline Characteristics

Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be listed and summarized for the FAS.

9.6.3.2 Pharmacokinetic and Pharmacodynamic Modeling Analysis

PK parameters of study interventions will be summarized by planned visit and time for each dose separately.

PK and pharmacodynamics modeling analyses will be documented in the sSAP.

9.7 Interim Analyses

An IA may be conducted to enable future study planning at the Sponsor's discretion, and data will be examined on a continuous basis to allow for dose-finding decisions.

For each disease cohort and dosing schedule, a futility IA is planned using Simon's mini-max, 2-stage procedure. That is, after the first 13 participants (Stage 1) of a given disease cohort under a specific dosing schedule had the opportunity to have their end-of-Cycle 6 radiographic evaluation, if 0 of 13 participants have an objective response based on the investigator assessment, that specific disease cohort and dosing schedule may be stopped for futility. Otherwise, 14 additional participants (Stage 2) will be accrued for a total of 27 participants. The futility bar is not binding, and the totality of the data will be evaluated for decision-making.

The IA constitutes a futility analysis; it will not be used to stop the trial early for positive efficacy. Enrollment may not pause during the IAs. If Stage 1 is considered nonfutile for both breast cancer cohorts, the Sponsor may elect to proceed with Stage 2 independently for each or may combine them in Stage 2.

Final study reporting is expected to occur after all participants have discontinued study treatment or ≥24 weeks after accrual of the final participant (whichever occurs earlier). The exact binomial test will be used in the final analyses because of the practical consideration that accrual cannot be limited to exactly 27 participants and because participants included in the Stage 1 analysis as nonresponding may be included in the final analysis as responding if they experience a late response.

After the final analyses, additional supplemental analyses may be performed to assess long-term PFS and OS and to satisfy regulatory requirements.

9.8 Multiplicity

There will be no multiplicity control in this study.

9.9 Sample Size and Power Calculations

The study will use the Simon 2 stage mini-max approach to test a null hypothesis vs an alternative hypothesis regarding drug activity. For each specific disease cohort and dosing schedule, the study will evaluate a null hypothesis that the ORR is ≤5% against the alternative hypothesis that it is ≥20%. In this instance, 13 participants will be accrued in the first stage. If 0 of 13 participants have an objective tumor response, then enrollment to that cohort may be stopped. Otherwise, 14 additional participants will be accrued for a total of 27 participants. The null hypothesis will be rejected if ≥4 objective responses are observed in the total of 27 participants (15% ORR). This design yields a significance level of <0.05 and a power of >0.80 when the true ORR is 20%. At the end of Stage 1, the probability of erroneously proceeding with the study is 0.49 under the null hypothesis and the probability of erroneously discontinuing the study is 0.05 under the alternative hypothesis.

9.10 Subgroup Analyses

Subgroup analyses of efficacy endpoints will be documented in the sSAP.

9.11 Compliance (Medication Adherence)

Drug accountability data for study intervention will be collected during the study. Any deviation from protocol-directed administration will be reported.

9.12 Extent of Exposure

Descriptive information will be provided regarding the number of VLS-101 infusions prescribed,the number of VLS-101 infusions administered, the VLS-101 body-weight-adjusted and total doses administered, the duration of infusions, the number and timing of prescribed VLS-101 infusion delays or interruptions, dose modifications and therapy interruptions, and the reasons forVLS-101 infusion delays or interruptions, dose modifications, and therapy interruptions.

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10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

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Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for financial disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, frequently known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this

information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked before transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets

regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.1.5 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trials directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.6 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

10.1.7 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the

study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.9 Study and Site Closure

The Sponsor or its designee may stop the study or study-site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 8 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and 5.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 8 Protocol-required Safety Laboratory Assessments

Hematology	Comprehensive Chemistry Panel	Urinalysis	Other
Hematocrit	Albumin	Blood	Pregnancy test (serum or urine)[b]
Hemoglobin	Alkaline phosphatase	Glucose	PT/INR
Platelet count	ALT	Protein	aPTT or PTT
WBC (total and differential)[a]	AST	Specific gravity	Total T3 (or FT3), Total T4 (or FT4), and TSH[c,d]
RBC	Bicarbonate	Microscopic examination, if abnormal results are noted	Anti-HCV
Absolute lymphocyte count[a]	Calcium		HCV viral load[d]
Absolute neutrophil count[a]	Chloride		HCV genotype[d]
	Creatinine		Anti-HBs[d]
	Glucose		HBsAg
	Phosphorus		Anti-HBc (total and IgM)[d]
	Potassium		HBeAg[d]
	Sodium		Anti-HBe[d]
	Total bilirubin		HBV viral load[d]
	Direct bilirubin		Anti-HDV[d]
	Total protein		AFP
	Blood urea nitrogen		CRP
			GGT

Abbreviations: AFP=α fetoprotein; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; CRP=c-reactive protein; FT3=free T3; FT4=free T4; GGT=gamma-glutamyl transpeptidase; HBe=hepatitis B e-antigen; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HDV=hepatitis delta virus; IgM=immunoglobulin M; INR=international normalized ratio; PT=prothrombin time; PTT=partial thromboplastin time; RBC=red blood cell; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; WBC=white blood cell.

a. Report % or absolute results per standard of practice. Report the results in the same manner throughout the study.

b. Perform on women of childbearing potential only 72 hours before Day 1 of Cycle 1. Pregnancy tests must be repeated before every cycle if required or as specified per local regulatory guidance.

c. T3 is preferred; if not available, Free T3 may be tested.

d. If the local laboratory is unable to perform these tests, the site should submit the sample to the central laboratory for testing. Details are provided in the procedure manual.

Investigators must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication Error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product for a perceived psychological or physiological reward or desired non-therapeutic effect.

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
    - Note: 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 study intervention.
    - Note: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol-specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.

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- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

- The term "life-threatening" in the definition of "serious" refers to an event in which the participant 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.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.4 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same time frame as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

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- Is a new cancer (that is not a condition of the study)
- Is associated with an overdose

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.OBJ

Assessment of intensity /toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI CTCAE. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
    - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
    - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
    - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

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- Grade 4: Life threatening consequences; urgent intervention indicated.

- Grade 5: Death related to AE.

Assessment of causality

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medical qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:**

  - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with IMP)?

  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

  - **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

    (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

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- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?
    - ◦ If yes, did the AE recur or worsen?
    - ◦ If yes, this is a positive rechallenge.
    - ◦ If no, this is a negative rechallenge.

    (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study; or (3) Sponsor's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE INIRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
    - Yes, there is a reasonable possibility of Sponsor's product relationship:
        - ◦ There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
    - No, there is not a reasonable possibility of Sponsor's product relationship:
        - ◦ Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

- For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- New or updated information will be recorded in the CRF.

- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.6 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
    - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
    - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
        - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.

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- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

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10.4 Appendix 4: Contraceptive Guidance

10.4.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

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10.4.2 Contraception Requirements

Contraceptives allowed during the study include[a]:

Highly Effective Contraceptive Methods That Have Low User Dependency
Failure rate of <1% per year when used consistently and correctly.

- Progestogen-only subdermal contraceptive implant[b]
- IUS[c]
- Non-hormonal IUD
- Bilateral tubal occlusion
- Azoospermic partner (vasectomized or secondary to medical cause)
  This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days.

  Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Sexual Abstinence

- 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 study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies.

b) If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation.

c) IUS is a progestin releasing IUD.

Note: The following are not acceptable methods of contraception:

- Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM.

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- Male condom with cap, diaphragm, or sponge with spermicide.
- Male and female condom should not be used together (due to risk of failure with friction).

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10.5 Appendix 5: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a) Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b) Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c) Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d) DNA: Deoxyribonucleic acid.

e) RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research[3, 4]

The specimens consented and/or collected in this study as outlined in Section 8.8 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways with which drugs/vaccines may interact
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research[3, 4]

a) Participants for Enrollment

All participants enrolled in the clinical study will be considered for enrollment in future biomedical research.

b) Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c) eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d) Future Biomedical Research Specimen(s)

Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research[3, 4]

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participants' clinical information with future test results. In fact, little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like sex, age, medical history and intervention outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

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5. Biorepository Specimen Usage[3, 4]

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses using the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in future biomedical research protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research[3, 4]

Participants may withdraw their consent for FBR and ask that their biospecimens not be used for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to study use only. If specimens were collected from study participants specifically for FBR, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens[3, 4]

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according

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to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security[3, 4]

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants[3, 4]

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include: lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population[3, 4]

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research[3, 4]

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@MSD.com.

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10.6 Appendix 6: Country-specific Requirements

There are no country-specific requirements.

10.7 Appendix 7: Strong Inhibitors and Inducers of Cytochrome P450 (CYP)3A4

Effect on CYP3A4	Drug
Strong CYP3A4 Inhibitors	boceprevir, clarithromycin, cobicistat, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, idelalisib, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir, paritaprevir and ritonavir (and ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir), telithromycin, troleandomycin,voriconazole
Strong CYP3A4 Inducers	apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin,St. John's wort
Abbreviation: CYP=cytochrome P450 enzyme.	

Source [Food and Drug Administration 2022].

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10.8 Appendix 8: Eastern Cooperative Oncology Group

Grade	Performance Status
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Source [ECOG-ACRIN Cancer Research Group 2016].

10.9 Appendix 9: Abbreviations

Abbreviation	Expanded Term
ADA	antidrug antibodies
ADC	antibody-drug conjugate
ADL	activities of daily living
AE	adverse event
ALK	anaplastic lymphoma kinase
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ASCO/CAP	American Society of Clinical Oncology/College of American Pathologists
AST	aspartate aminotransferase
AUC	area under the curve
AV	atrioventricular
BICR	blinded independent central review
BP	blood pressure
BRCA	breast cancer gene
CD	cluster of differentiation
CI	confidence interval
CLL	chronic lymphocytic leukemia
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CRF	case report form
CRO	contract research organization
CSC	cancer stem cells
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor deoxyribonucleic acid
CTFG	Clinical Trial Facilitation Group
C_{trough}	concentration reached by a drug immediately before the next dose is administered
CYP	cytochrome P450
DFS	disease-free survival
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
EC_{50}	half maximal effective concentration

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Abbreviation	Expanded Term
ECG	electrocardiogram
ECI	event of clinical interest
eClCr	estimated creatinine clearance
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data collection
eDMC	external Data Monitoring Committee
EEA	European Economic Area
EGFR	endothelial growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EMT	epithelial-mesenchymal transition
ER	estrogen receptor
FACS	fluorescent-activated cellsorter
FAS	Full Analysis Set
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FIH	first in human
FL	follicular lymphoma
FOLFIRINOX	folinic acid (leucovorin), fluorouracil (5-FU), irinotecan (Camptosar), oxaliplatin (Eloxatin)
FSR	First Site Ready
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GEF	guanine exchange factors
GEJ	gastroesophageal junction adenocarcinoma
GLP	Good Laboratory Practice
GTP	guanosine triphosphate
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
hERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormone replacement therapy
HS1	hematopoietic-lineage-specific protein 1
IA(s)	interim analysis(ses)
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form

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Abbreviation	Expanded Term
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ID	identification
IEC	Independent Ethics Committee
IgG1	immunoglobulin G1
IHC	immunohistochemistry
IL-10	interleukin-10
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
IRC	Imaging Review Committee
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
kd	equilibrium dissociation constant
Ki-67	proliferation marker for human tumor cells
LAM	lactational amenorrhea method
MCL	mantle cell lymphoma
mc-vc-PAB	maleimidocaproyl-valine-citrulline-para-aminobenzoate
MEC	mouse embryonic epicardial cell line
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	monomethyl auristatin E
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
MTD	maximum tolerated dose
MZL	marginal zone lymphoma
n	number
N/A	not applicable
NCI	National Cancer Institute
NE	not evaluable
NOAEL	no observed adverse effect level
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non–small cell lung cancer
NTRK	neurotrophic tyrosine receptor kinase
ODWG	Organ Dysfunction Working Group
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PAB	para-aminobenzoate
pAKT	phosphorylated AKT (protein kinase B)
PARP	poly-ADP ribose polymerase

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Abbreviation	Expanded Term
PCL	protocol clarification letter
pCREB	phosphorylated cAMP response element binding protein
PD	progressive disease
PDAC	pancreatic ductal adenocarcinoma
PD-L1	programmed cell death ligand 1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PV	Polivy™
Q1/2W	every 1 out of 2 weeks
Q2/3W	Repeated 3-week cycles with a drug infusion on Day 1 and Day 8 of each cycle
Q3W	every 3 weeks
Q3/4W	every 3 out of 4 weeks
Q12W	every 12 weeks
Rac1	Ras-related C3 botulinum toxin substrate 1
RDR	recommended dosing regimen
RECIST 1.1	Response Evaluation Criteria in Solid Tumors 1.1
RhoA	Ras homolog gene family member A
RNA	ribonucleic acid
ROR	receptor tyrosine kinase-like orphan receptor
ROR1	receptor tyrosine kinase-like orphan receptor-1
ROR2	receptor tyrosine kinase-like orphan receptor-2
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SEER	Surveillance, Epidemiology, and End Results
SIM	Site Imaging Manual
SLAB	supplemental laboratory test(s)
SLL	small lymphocytic lymphoma
SNP	single nucleotide polymorphism
SoA	schedule of activities
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	elimination half-life
TCGA	The Cancer Genome Atlas
TCL	T-cell leukemia/lymphoma protein
TEAE	treatment-emergent adverse event
TFI	treatment-free interval
TLS	tumor lysis syndrome
T_{max}	time to maximum plasma concentration
TNBC	triple-negative breast cancer

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Abbreviation	Expanded Term
TTF	time to treatment failure
TTR	time to response
ULN	upper limit of normal
Wnt	secreted glycoproteins important during embryogenesis and tissue homeostasis (orchestrate cell proliferation and polarization)
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of nonchildbearing potential

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