Investigational Product Manual

Protocol Number C5731002/RC48G001

IND: 145674

EU CT Number: 2022-500030-28

A Phase 2 Multi-Cohort, Open-Label, Multi-Center Clinical Study Evaluating the Efficacy and Safety of Disitamab Vedotin (RC48-ADC) Alone or in Combination with Pembrolizumab in Subjects with Locally Advanced Unresectable or Metastatic Urothelial Carcinoma That Expresses HER2

Pfizer labels will include Kit/Container numbers but the 4G IRT system will NOT use them for Investigational Product assignment. The 4G IRT system will be used in the same manner as it has been, assigning ONLY the quantity of vials to select (without regard to kit/container numbers).

Seagen, a wholly owned subsidiary of Pfizer, Inc.

Worldwide Research & Development

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Revision HistoryVersion	Version Date	Summary of changes
3.0	**19MAR2025**	**Minor Update** **Footer:** Updated the order of the Protocol numbers to match the protocol **Section 6.1: Storage and Temp Monitoring of IP at a Clinical Site:** • Corrected F temp equivalent to 2°C from 32°F to 36°F
2.0	**06MAR2025**	**This version was not sent to sites.** **Title Page:** • Update the order of the protocol numbers to match the protocol; • Remove EudrCT; • Add disclaimer about the Pfizer labels containing a Kit number but 4G will not use that number **Approvals:** • Updated SCL to Michael Fitzpatrick **Source Documents:** • Update Protocol to V10 **Sect 3: Study Overview:** • Update subjects to participants • Increase the cohort number to 6 • Add Cohort G **Sect 3.1: Pfizer Supplied Investigational Products:** • Add disclaimer about the Pfizer labels containing a Kit number but 4G will not use it **Section 6.1: Storage and Temp Monitoring of IP at a Clinical Site:** • Update the Disitamab vedotin temp excursion reporting range to be 2-25°C from 0-25°C **Section 7: Dosage and administration Instructions:** • Added note to refer back to section 3 for dosing details • Added a max dose by dose level table for clarity **Section 7.4.1: Prep and Admin of Disitamab vedotin:** • Added Cytotoxic prep reminder • Added maximum dose per dose level table • Added reminder to dispose of used vials and prep material per site standard practices **Section 7.4.2: Prep and Admin of Pembrolizumab:** • Added reminder to dispose of used vials and prep material per site standard practices **Appendix 4: Prep Record for Disitamab vedotin:** • Added Cytotoxic prep reminder • Added maximum dose per dose level table • Added reminder to dispose of used vials and prep material per site standard practices **Appendix 5: Prep Record for Pembrolizumab:** • Added reminder to dispose of used vials and prep material per site standard practices

1.0	**17NOV2024**	First version in the Pfizer process.

Source Documents

This section will only be updated if updates to the source documents impact the information included in this IP Manual. Subsequent amendments or updates that do not impact this IP Manual will not be included as a reference and will not require an update to this section.

1. RC48G001 Protocol Amendment 10, 18DEC2024

2. Dosage and Administration Instructions For PF-08046051 (SGN-DV) Powder for Solution for Infusion, 45 mg-vial for Intravenous Infusion: C573-INX100620312-V1.0-22-AUG-2024

3. Pembrolizumab (MK-3475) Pharmacy Manual for Investigational Studies: Study Version V3.0-28-JUN-2023

Pfizer

Table of Contents

1. Acronyms/Terms/Definitions

Acronym / Term	Definition
HER2/IHC	Human Epidermal Growth Factor Receptor 2 / Immunohistochemistry
LA/mUC	Locally Advanced unresectable or metastatic urothelial carcinoma
IP/IMP/Study Intervention	This includes Investigational Product (IP), Investigational Medicinal Product (IMP) (may also be referred to as Study Intervention in the protocol) in either a non-commercial presentation or commercial presentation with over labeling; comparative agents; concomitant medications; background therapies; or commercial products that are supplied by Pfizer Global Clinical Supply or by approved vendors.
IRT	Interactive Response Technology encompassing an IWRS (Interactive Web Response System)
ISH	In Situ Hybridization
SDS	Safety Data Sheet

2. Study Contacts

Contact your primary point of contact with any questions. Refer to the Investigator Site File (ISF) for study contact information.

3. Study Overview

This is a phase 2, multi-cohort, open-label, multi-center clinical study evaluating the antitumor activity, safety, pharmacokinetics (PK), and immunogenicity of Disitamab vedotin monotherapy or Disitamab vedotin in combination with pembrolizumab in adult participants with locally advanced unresectable or metastatic urothelial carcinoma (LA/mUC) that expresses human epidermal growth factor receptor 2 (HER2) [immunohistochemistry (IHC) 1+ and greater].

The study will have **6 cohorts** as presented below:

Cohorts A and B

Disitamab vedotin 1.5 mg/kg (max dose = 150 mg) intravenous (IV) infusion over 60 minutes (30-90 minutes) on Day 1 of each 14-day cycle

Cohort C

- Cohort C will be composed of 2 sequential parts: **a single-arm part and a randomized part.**
  - **Single-Arm Part:** Participants will receive Disitamab vedotin combined with Pembrolizumab.
  - **Randomized Part:** Participants will be randomized in a 1:1 ratio by HER2 status to either Disitamab vedotin combined with Pembrolizumab or Disitamab vedotin monotherapy.

Disitamab vedotin 1.5 mg/kg (max dose = 150 mg) IV 60 minutes (30-90 minutes) on Days 1, 15, and 29 of each 42-day cycle (6-week)
Pembrolizumab 400 mg IV over 30 minutes (-5/+10 min) on Day 1 of each 42-day cycle (6-week) ***if applicable***

Cohort D (Japan)

Disitamab vedotin 1.5 mg/kg (max dose = 150 mg) IV over 60 minutes (30-90 minutes) on Day 1 of each 14-day cycle

Cohort E (Japan)

Disitamab vedotin 1.5 mg/kg (max dose = 150 mg) IV over 60 minutes (30-90 minutes) on Days 1, 15, and 29 of each 42-day cycle

Pembrolizumab 400 mg IV over 30 minutes (-5/+10 min) on Day 1 of each 42-day cycle

Cohort G (Selected Countries*):

- Participants must have received 1 or 2 prior lines of systemic therapy for LA/mUC, including enfortumab vedotin alone or in combination with pembrolizumab and have experienced disease progression during or after the most recent therapy.
- A minimum of 90 days between final dose of enfortumab vedotin and start of disitamab vedotin administration is required.
- Intervening therapies are allowed between the last final dose of enfortumab vedotin and the start of disitamab vedotin.
    - Prior platinum-containing regimens are allowed.
    - Prior therapy with PD-(L)1 inhibitors as (neo)adjuvant therapy, first-line maintenance therapy, or second-line treatment is allowed.
    - Neoadjuvant or adjuvant systemic therapy, with progression within 12 months of completing the final dose of therapy, is considered as one line of prior therapy.

Disitamab vedotin 1.5 mg/kg (max dose = 150 mg) IV over 60 minutes (30-90 minutes) on Day 1 of each 14-day cycle

*Operationalized in US, Cananda and UK Only

Refer to the protocol for more information on the study design.

3.1. Pfizer Supplied Investigational Products

The table below lists the Investigational Products (IP) that will be provided for this trial by Pfizer.

Product Name	Mechanism of Action	Product Physical Description	Representative Picture of IP
Disitamab vedotin 45 mg/vial powder for concentrate for solution for infusion	Disitamab vedotin (also known as PF-08046051 or SGN-DV) is a novel HER2-directed antibody-drug conjugate (ADC) being developed for solid malignancies that express HER2. Its structure includes a humanized anti-HER2 immunoglobulin G1 (also known as Disitamab vedotin nude antibody, RC48), valine-citrulline linker, and microtubule inhibitor monomethyl auristatin E (MMAE).	Supplied as sterile, preservative-free, white to off-white lyophilized cake or powder, supplied in single-dose glass vials.	
Pembrolizumab 25 mg/mL concentrate for solution for infusion (100 mg/4 mL)	Pembrolizumab is a potent humanized immunoglobulin G4 monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with PD-(L)1 and programmed cell death ligand 2 (PD-L2).	Supplied as a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution in single-use Type I glass vial containing 100 mg/4 mL of pembrolizumab.	TBA

Packaging and Labeling

The IPs for this study is packaged into vials within a carton and are labeled in a way that is consistent with the study design and with the regulatory requirements for each country in which the study is to be performed.

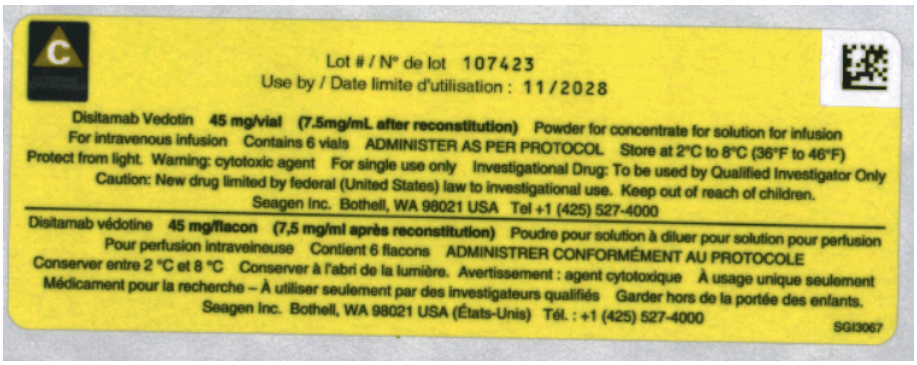
NOTE: Pfizer labels will include Kit/Container numbers but the 4G IRT system will NOT use them for Investigational Product assignment. The 4G IRT system will be used in the same manner as it has been, assigning ONLY the quantity of vials to select (without regard to kit/container numbers).

The IPs will be received in the following presentations (note dispensing of the IPs will be discussed in Section 7.1):

Representative Photos

- Disitamab vedotin 45 mg/vial powder for concentrate for solution for infusion, packaged in a carton containing 6 vials

Legacy Seagen vial Label:



Pfizer Carton Label:

Protocol No.: C5731002 (RC48G001)

Container No.: V1
Contents: 6 single use vial(s)

Disitamab vedotin 45 mg/vial powder for concentrate for solution for infusion

Expiry Date: V3

Prepare and administer as directed in the Protocol / Investigational Product Manual
For Intravenous Infusion Only
Store 2-8 °C

Seagen Inc., Bothell, WA 98021, USA, Tel.: +1 (425) 527-4000

Packaged Lot V2

Pfizer Vial Label:

Protocol No.: C5731002 (RC48G001)
Subject No: _____
Container No.: V1

Disitamab vedotin 45 mg/vial powder for concentrate for solution for infusion

Prepare and administer as directed in the Protocol / Investigational Product Manual
For Intravenous Infusion Only

Seagen Inc., Bothell, WA 98021, USA, Tel.: +1 (425) 527-4000

Packaged Lot V2

- Pembrolizumab 25 mg/mL concentrate for solution for infusion (100 mg/4 mL), packaged in a carton containing 2 vials

Legacy Seagen Label:

Pfizer Carton Label:

Protocol No.: C5731002 (RC48G001)

Container No.: V1

Contents: 2 vials

Pembrolizumab 25 mg/mL concentrate for solution for infusion (100 mg/4 mL)

Expiry Date: V3

Prepare and administer as directed in the Protocol / Investigational Product Manual
For Intravenous Use Only

Store 2 - 8 °C, do not freeze, protect from light
Do not shake vigorously

Seagen Inc., Bothell, WA 98021, USA, Tel.: +1 (425) 527-4000

Packaged Lot V2

Pfizer Vial Label:

Protocol No.: C5731002 (RC48G001)
Subject No: _____
Container No.: V1

Pembrolizumab 25 mg/mL concentrate for solution for infusion (100 mg/4 mL)

Prepare and administer as directed in the Protocol / Investigational Product Manual

For Intravenous Use Only

Seagen Inc., Bothell, WA 98021, USA, Tel.: +1 (425) 527-4000

Packaged Lot V2

4. Interactive Response Technology

The 4G Interactive Response Technology System is used for shipment receipt acknowledgement, drug assignment, and inventory management. The IRT system will also manage the expiry of the supplies with regards to drug assignment. The system will not allow for assignment of materials that could potentially be used past the labeled expiry of the materials.

System: https://seagen.4gclinical.com
Support: https://support.4gclinical.com/

A 4G Guide is also provided for this protocol. These guides can be accessed via a link on the IRT system or provided by your primary point of contact.

5. Product Ordering, Receipt, and Inventory Management

5.1. Product Ordering

Initial Shipment

IP Provided by Sponsor

The initial shipment of IP to the clinical site will be automatically triggered upon site activation or first participant screened.

Re-Supply or Subsequent Shipments

IP supplied by Sponsor

The IRT system will ensure appropriate levels of IP are present at the site based upon enrollment and the protocol visit schedule. If a site is expecting a significant increase in enrollment rate, primary point of contact must be alerted.

Shipping Timelines

From the time a shipment order is generated, it will take approximately 3 to 5 business days to deliver these supplies to the investigator site. Orders from the distribution warehouses will only be shipped Monday through Wednesday, therefore, the clinical site must plan accordingly. These timelines may be extended in countries that require import licenses or proforma invoices for import.

5.2. Product Receipt

Upon receipt of IP shipments, the pharmacist or designee must inspect and inventory the shipment contents as described below to ensure contents match the accompanying shipping documentation (shipping invoice) and are acceptable for dispensing.

The IPs are shipped at 2 to 8 °C (36 to 46 °F) with allowable limits programmed into the temperature monitoring device:

- Disitamab vedotin 45 mg/vial powder for concentration for solution for infusion
- Pembrolizumab 25 mg/mL concentrate for solution for infusion (100 mg/4 mL)

Shipments of IPs will include temperature monitoring devices. Follow the temperature monitoring device instructions included in the shipment upon receipt at the clinical site. It is recommended to record the temperature monitoring device number on the shipping invoice report to support reconciliation.

In certain regions, investigational products for this study may be shipped in a recyclable shipper. These shippers will contain prepaid return paperwork. Please follow the instructions provided with the shipment to allow for reuse.

A GPS Tracking Device may be affixed to shippers to allow for tracking of IP shipments. These may be disposed of unless otherwise instructed. If instructed to return, please use the mailing envelope and label included with the shipment.

NOTE: The temperature monitoring device included in the shipment will only alarm if a temperature excursion occurred during the shipment process.

Upon arrival of a shipment, immediately follow the Temperature Monitoring Instruction Sheet included in the shipment. See Appendix 1 for an example.

A Temperature Monitoring Device will be included in the shipment (see Appendix 1 for instructions). Sites must always print and file or file electronically the shipping temperature data report from USB devices whether alarmed or not. Follow the Temperature Monitoring Instructions sheet included in the shipment.

For All Shipments:
Upon arrival of a shipment, sites must immediately:

- Stop the temperature monitoring device immediately upon receipt so it does not record any false high temperatures as it is taken out of the box.
- If the shipment consists of more than one shipper each shipper will have its own temperature monitor, so please take note of which monitoring device ID/Logger ID is associated with which shipper.
- Inspect the IP to ensure they were received in good condition (e.g., undamaged, with tamper seals intact, etc.). See Section 5.3: Lost, Damaged or Incomplete Shipments.
- Check the amount and condition of the IP against the packing slip or other accompanying document(s).
- Verify the labels to ensure that they match the protocol number and container numbers (Kit IDs) stated on the shipping invoice.
- The shipping invoice will be located in the first shipper ONLY for shipments that consist of multiple shippers. Each box will have the box number designated (e.g., 1 of 2, 2 of 2, etc.)
- Place the IP in the appropriate labeled storage conditions as quickly as possible.
- Acknowledge the received shipment as per the instruction on the shipping invoice and file in the investigator site file.

- Once the IP arrives, log in to the IRT system website to acknowledge the shipment per the 4G Guide.
- Once the shipment is acknowledged via the IRT system, the site must file and maintain a copy of the IRT system generated shipment confirmation within the local site files.
- 4G (IRT) is able to accept both a missing or damaged temperature monitor entry. In these cases, the kits are automatically quarantined in the system until it can be determined if an excursion has taken place.
- If a shipment arrives with a temperature excursion, enter the excursion data into 4G. It will be automatically put into quarantine in the system and the site does not have to take additional action within the IRT system. Refer to Appendix 2 on how to report the Temperature Excursion.
- Appendix 2: Example Site Temperature Excursion Report Form is only needed in the case of SITE STORAGE excursion ONLY.
- **NOTE:** Failure to complete receipt/acknowledgement in the IRT system in a timely manner will impact the ability to assign IP to participants and impact resupply shipment triggers.

5.3. Lost, Damaged or Incomplete Shipments

If a shipment is lost, incomplete or does not arrive in a satisfactory condition, contact the assigned primary point of contact. Damaged materials must be physically quarantined in a way that prevents inadvertent dispensing. Do not use/dispense/discard until disposition instructions are provided.

Once specific instructions are received acknowledgement can occur in the IRT system as instructed by the Sponsor. If the assigned primary point of contact cannot be reached, reach out to the 4G Support.(See Section 4: Interactive Response Technology).

5.4. Inventory Management

Based on the design of this study, the site should expect to have approximately 8 to 12 in inventory at any one time, depending on the site's enrollment. Ensure that the IP storage location can accommodate this amount of material. See Section 8 for additional information on investigational product accountability.

6. Storage, Handling, and Temperature Monitoring of IP at the Clinical Site

6.1. Storage and Temperature Monitoring of Investigational Product at a Clinical Site

Refer to section 7.3 for information on the prepared product

Temperature spikes outside of the labeled storage conditions as noted in the table below are considered reportable temperature excursions based on the Temperature Excursion Reporting Requirements.

NOTE: Shipping temperature range may differ from site storage requirements. Refer to the table below for site storage requirements prior to initial dose preparation. For shipping storage conditions, refer to Section 5.2, Product Receipt.

Product	Storage Condition	Storage Requirement	Temperature Excursion Reporting Requirements	Comments
Disitamab vedotin 45 mg/vial powder for concentrate for solution for infusion	Refrigerator	2 to 8° C (36 to 46 °F)	Report excursions if recorded temperature is: • Below 2° C (36 °F) or above 25° C (77 °F) for any time period • Between 2° C (36 °F) and 25° C (77 °F) and ≥ 30 minutes outside of labeled conditions	IP vials must be protected from light until time of use.

Product	Storage Condition	Storage Requirement	Temperature Excursion Reporting Requirements	Comments
Pembrolizumab 25 mg/mL concentrate for solution for infusion (100 mg/4 mL)	Refrigerator	2 to 8° C (36 to 46 °F)	Report excursions if recorded temperature is: • Below 0° C (32 °F) or above 25° C (77 °F) for any time period • Between 0° C (32 °F) and 25° C (77 °F) and ≥ 30 minutes outside of labeled conditions	Protect from Light. Do not shake. Do not freeze.

The temperature of all locations where IP is stored at a clinical site must be monitored continuously and verified as appropriate per the site processes, using a temperature monitoring device that measures minimum and maximum temperatures daily. The site may utilize temperature devices with minimum and maximum memory capabilities to monitor temperatures when a site is not operational (e.g., weekends and holidays) however the site must be able to verify and document the minimum and maximum temperatures occurring over the entire non-operational periods once normal operations are resumed. Sites may apply their own policies and procedures if the Sponsor requirements are met.

NOTE: Numeric temperature values may be rounded to the nearest whole number to establish if an excursion has occurred (e.g., Values at or above 0.5 are rounded up. Values at or below 0.49 are rounded down).

6.2. Temperature Excursions at Clinical Site

If any of the following occur, the site must **immediately** quarantine the IP supply in the appropriate storage conditions as indicated on the product label. Report all temperature excursions, as defined in section 6.1, including suspected temperature excursions. Be prepared to complete the Investigator Site Temperature Excursion Report Form (See Appendix 2 as an example) along with site temperature data. E-mail documentation to the Clinical Supply Temperature Excursion Support mailbox GCSTempExcursionSupport@pfizer.com, copying the primary point of contact. Ensure you are utilizing the most current Temperature Excursion Reporting form. This form can also be provided upon request via email to GCSTempExcursionSupport@pfizer.com. In rare cases, primary point of contact can work with sponsor to authorize an equivalent form from the site.

- A temperature excursion occurs while any Sponsor supplied product is at the site
- The temperature is not monitored continuously (for example, a temperature monitoring device malfunctions)
- Advice is needed on whether or not a temperature deviation is considered a temperature excursion
- The documented temperatures and/or duration of an excursion are not available for any reason
- Ensure the temperature excursion form is filled out completely

The site must not use the quarantined supplies until specific instructions are received from the Sponsor. If it is determined that the materials are to be designated "unacceptable for use", the materials must be physically quarantined in a way that prevents inadvertent dispensing and the Sponsor will initiate a replacement shipment to the site.

6.3. Special Handling of IP

Recommendations in the Safety Data Sheet (SDS) must be followed. The SDS will be provided upon request.

The IP in this study has special handling requirements. The IP used in this study is a Cytotoxic/Hazardous.

- Disitamab vedotin

CYTOTOXIC and/or HAZARDOUS HANDLING INFORMATION

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment shall undertake the preparation, handling, and safe disposal of chemotherapeutic and/or hazardous agents.

OTHER HANDLING INFORMATION

For clinical sites that have an off-site location for storage, preparation or administration of IP, an IP transport procedure must be provided to the clinical study team for review. At minimum the procedure must identify the designated operators of the dose preparation and transportation steps, a description of the transport container and process to maintain and record temperature during the transit time, and a method to log departure and arrival times.

6.4. Expired IP Handling

If your site has IP that has expired, the materials must be physically quarantined in a way that prevents inadvertent dispensing and the Sponsor will initiate a replacement shipment to the site. Do not destroy the quarantined supply until instructed to do so by your primary point of contact.

7. Dosage and Administration Instructions

Weight-based dosing for Disitamab vedotin is based on the subject's actual body weight at baseline. Doses must be adjusted for patients who experience a +/-10% or greater change from baseline weight during the study.

Note: For participants weighing greater than 100 kg; the Disitamab vedotin dose will be 150 mg per infusion.

Disitamab vedotin duration of the IV drip infusion is recommended to be approximately 60 min (30–90 min, no shorter than 30 min).

Pembrolizumab should be administered approximately 30 minutes as an IV infusion about 30 minutes after completion of Disitamab vedotin.

See Section 3.0 for Dosing Details

Dose Modifications (see Section 5.3.3 of Protocol Amendment 10)

- **Disitamab vedotin**

Initial Dose	1st Dose Reduction	2nd Dose Reduction	3rd Dose Reduction
1.5 mg/kg	1.25 mg/kg	1 mg/kg	0.75 mg/kg

Note:

*Dose reductions to below 0.75 mg/kg are not allowed. Participants who would require a dose reduction to below 0.75 mg/kg should discontinue Disitamab vedotin. Once reduced, the dose of Disitamab vedotin should not be re-escalated.

***In the event of a dose reduction, the weight used to calculate the total dose will be 100 kg for patients weighing more than 100 kg.**

Dose Level	Maximum Dose
1.5 mg/kg	**150 mg**
1.25 mg/kg	**125 mg**
1 mg/kg	**100 mg**
0.75 mg/kg	**75 mg**

7.1. Drug Dispensing Per Visit

The table below describes the product to dispense at each dispensing visit. Refer to the 4G Guide for additional dispensing instructions in the IRT.

Cohorts A, B, and D (Japan) 1 cycle = 2 weeks, Day 1 of each 2-week cycle
Cohorts C and E (Japan) 1 cycle = 6 weeks, Day 1, Day 15, and Day 29 of each 6-week cycle

Disitamab vedotin dose	Containers Dispensed at this Visit
1.5 mg/kg	**Required number of vials** based on participant's weight (kg) ***Note: Maximum weight used to calculate any dose is 100 kg***
1.25 mg/kg	
1 mg/kg	
0.75 mg/kg	

Cohorts C* and E (Japan) 1 cycle = 6 weeks, Day 1 of each 6-week cycle

Pembrolizumab Dose	Containers Dispensed at this Visit
400 mg	**FOUR** x Vials of Pembrolizumab 25 mg/mL concentrate for solution for infusion

* Participants enrolled in Cohort C will be randomized to if they will receive Pembrolizumab or not.

7.2. General Preparation Guidelines

Only clinical site personnel who are appropriately trained on the procedures detailed in this document may perform the preparation and administration steps specified in this IP Manual. Clinical site personnel involved in these procedures must comply with all applicable regulations and standards. The preparation and administration of all sterile products must be performed using aseptic technique. Utilize local site procedures as appropriate.

For Disitamab vedotin
It is strongly advised that all handling and preparation of sterile and cytotoxic or hazardous products be carried out in Class II of types A2, B1, and B2 and Class III Biological Safety Cabinet (BSC). **Class I, laminar air flow (LAF) and Class II type A1 must NOT be used.**

For Pembrolizumab
It is recommended that all preparations be carried out in a laminar flow hood/cabinet using aseptic technique for sterile products. If a laminar air flow hood is not available, a Class II – III biosafety cabinet should be used. Class I biosafety cabinets should not be used. Only the necessary materials should be present in the working area during each preparation step.

7.3. In-Use Shelf Life and Storage Requirements of IP

If the prepared IP is left at temperatures beyond the recommended storage requirements, contact the primary point of contact.

Product	Storage Conditions	Storage Requirement	Comments
Disitamab vedotin 45 mg/vial powder for concentrate for solution for infusion	Post-reconstitution	Opened and reconstituted vials should be used immediately. If not used immediately, reconstituted drug product must be stored under refrigeration at 2 to 8°C (36 to 46 °F) and product must be used within 24 hours after reconstitution.	It is recommended that Disitamab vedotin vials and solutions be protected from direct sunlight until the time of use.
	Prepared (in- use stability)	The prepared dosing solution should be used immediately. The total duration of room temperature exposure may not exceed 4 hours from vial opening to start of administration. If not used immediately, solutions must be stored under refrigeration at 2 to 8°C (36 to 46 °F) for 24 hours.	Protect the prepared dosing solution from direct sunlight until time of use.

Product	Storage Conditions	Storage Requirement	Comments
Pembrolizumab 25 mg/mL concentrate for solution for infusion (100 mg/4 mL)	Prepared (in- use stability)	Vials of pembrolizumab should be allowed to reach room temperature prior to dose preparation. Pembrolizumab solutions may be stored at room temperature for a cumulative time of up to 6 hours. This includes room temperature storage of admixture solutions in the IV bags and the duration of infusion. IV bags may be stored under refrigeration at 2 °C to 8 °C (36 °F to 46 °F), total cumulative storage time at room temperature and refrigeration should not exceed 24 hours.	Protect from light by storing in the original carton until time of use. **DO NOT** shake or freeze the pembrolizumab solution for infusion. **DO NOT** use Pembrolizumab if discoloration is present.

7.4. Preparation and Administration

7.4.1. Preparation and Administration of Disitamab vedotin 45 mg/vial powder for solution for infusion

Key points to note:

- Dose preparation must be performed using sterile handling techniques in compliance with local, state, and national laws/regulations.
- **Do not prepare a single dose of Disitamab vedotin using vials from different lots. Use vials from the same lot number for a given dose.**
- THE VIAL MUST NOT BE SHAKEN OR VIGOROUSLY SWIRLED.
- Total infusion volume should be adjusted to maintain a final concentration of ≥ 0.19 and ≤ 1.9 mg/mL
- **Disitamab vedotin MUST NOT BE ADMINISTERED as an IV Push or bolus.**
- Each vial is for single use only. Each vial is for use in a single participant, for a single dose.
- Document all steps performed as indicated in the Preparation Record (Appendix 4). The Preparation Record form is required. The use of alternative preparation records must be approved by the Sponsor's Clinical Research Pharmacist.

Study Supplies Required for Preparation and Administration of IP

SUPPLIES
Check that the labelling details on the outer containers of the supplies correspond with these instructions and the clinical protocol. If the supplies available at the site do not correspond with the list below, contact the primary point of contact.
Supplies Provided by Pfizer
Drug product (Active): Disitamab vedotin 45 mg/vial powder for concentrate for solution for infusion. These are for single use only. They are for single use in a single participant for a single dose.
Supplies Provided by the Clinical Site
Sterile Water for Injection (for vial reconstitution)
Diluent: Diluents should meet regional/local compendia requirements and be an authorized product in the local country • 0.9% Sodium Chloride Injection (Normal Saline) 100 or 250 mL
Syringes: Appropriately sized luer-lock latex-free polypropylene (PP) syringes
Needles: Stainless steel needles, appropriately sized
Infusion Bags: • Empty IV bags composed of one of the materials listed below that can hold a volume of 100 mL or 250 mL • 100 mL or 250 mL pre-filled 0.9% Sodium Chloride IV bags composed of one of the materials listed below **The following infusion bag materials are compatible with Disitamab vedotin:** • **Polyvinyl chloride (PVC)** • **Ethylene-vinyl acetate (EVA)** • **Polyethylene (PE)** • **Polyolefin (PO)** • **Polypropylene (PP)**
IV lines/extension sets: PVC IV administration lines with 0.2 or 0.22 micron polyethersulfone (PES) in-line filter, to be used with infusion pump. For infusion lines without an in-line filter, an extension set containing the aforementioned type of filter may be used in series.
Closed System Transfer Devices (CSTDs): Disitamab vedotin compatibility with CSTDs is unknown. CSTDs can be used if available and acceptable based on-site policy.

Preparation and Administration Instructions:

<table>
<tr><th colspan="2">DISITAMAB VEDOTIN DOSE PREPARATION</th></tr>
<tr><td colspan="2">USE APPROPRIATE SITE AND LOCAL PROCESSES AND PROCEDURES FOR THE HANDLING, PREPARATION AND ADMINISTRATION OF HAZARDOUS/CYTOTOXIC AGENTS</td></tr>
<tr><td colspan="2">Calculation of Dose Volume</td></tr>
<tr><td>1</td><td>Determine the total dose of Disitamab vedotin required for each participant based on the dose calculated in the equation below.
$Total\ Dose\ of\ Disitamab\ vedotin\ (mg)\ =\ patient\ weight\ (kg) * dose\ level$

Weight used to calculate the total dose will be 100 kg for patients weighing more than 100 kg.

<table><tr><th>Dose Level</th><th>Maximum Dose</th></tr><tr><td>1.5 mg/kg</td><td>150 mg</td></tr><tr><td>1.25 mg/kg</td><td>125 mg</td></tr><tr><td>1 mg/kg</td><td>100 mg</td></tr><tr><td>0.75 mg/kg</td><td>75 mg</td></tr></table></td></tr>
<tr><td>2</td><td>Determine the volume of Disitamab vedotin required for each participant based on the dose calculated in the step above and the equation below.
$Volume\ of\ Disitamab\ vedotin\ required\ (mL)\ =\ \frac{Total\ Dose\ (mg)}{7.5\ mg/mL}$</td></tr>
<tr><td>3</td><td>Determine number of vials of Disitamab vedotin needed:
$Number\ of\ vials\ Disitamab\ vedotin\ =\frac{Total\ Dose\ (mg)}{45\ mg/vial}$
Round up to the nearest whole vial.</td></tr>
<tr><td colspan="2">Reconstitution of Drug Product</td></tr>
<tr><td>4</td><td>Obtain the number of vials calculated in Step 3 and all necessary supplies prior to preparation.

Use vials from the same lot number for a given dose.</td></tr>
<tr><td>5</td><td>Reconstitute lyophilized Disitamab vedotin by adding 6 mL sterile water for injection to each vial.

The concentration of reconstituted Disitamab vedotin is 7.5 mg/mL with an extractable volume of 6 mL.</td></tr>
<tr><td>6</td><td>Gently swirl the vial until contents are completely dissolved (5-10 minutes). THE VIAL MUST NOT BE SHAKEN OR VIGOROUSLY SWIRLED. Slight “bubbling” of the solution upon reconstitution may be observed.

Allow the reconstituted vial to settle for a minute to allow bubbles to dissipate.</td></tr>
<tr><td>7</td><td>The reconstituted solution should not contain any visible particulate matter or discoloration.
The reconstituted product should be a clear to light yellow solution. If particulate matter or discoloration is found, do not use.</td></tr>
</table>

Preparation of Infusion	
8	Further dilute with 0.9% Sodium Chloride (Normal Saline) solution for injection in an IV infusion bag to achieve a final concentration of ≥ **0.19 and ≤ 1.9 mg/mL.** **If using a PREFILLED 0.9% Sodium Chloride infusion bag:** • Withdraw and discard a volume of 0.9% Sodium Chloride equal to the volume of IP (see Step 2) from the infusion bag. • Withdraw and inject the volume of IP (mL) (see Step 2) into the infusion bag. **If using EMPTY infusion bag:** • Add the required volume of 0.9% Sodium Chloride to the infusion bag: $$\textbf{\textit{Required Volume of 0.9\% Sodium Chloride = Total Volume − IP Dose Volume}}$$ • Withdraw and inject the volume of IP (mL) (see Step 2) into the infusion bag. **NOTE:** All prefilled infusion bags have an overage compared to their label, so the final dose volume will be slightly higher than the labeled volume.
9	Gently invert the prepared IV bag to mix. DO NOT SHAKE to avoid creating foam in the bag. Dispose of used vials and preparation materials per site standard procedures
10	Attach an appropriate label to the prepared IV bag per local regulations.

Dose	Suggested Total Volume
Up to 150 mg	100 mL

DISITAMAB VEDOTIN ADMINISTRATION	
1	Prior to dosing the participant, adhere to normal standard of care and aseptic techniques. Prepared solutions that are refrigerated should be allowed to reach room temperature prior to administration. Make sure the prepared dosing solution is not cold to the touch.
2	Attach the infusion line to the appropriate port of the dosing solution bag. Administer through a low-protein-binding 0.22 or 0.2 micron in-line filter. Prime the infusion line according to site policies and procedures.
3	Parenteral drug products should not contain any visible particulate matter or discoloration prior to administration, whenever solution or container permit.
4	Administer via infusion pump as a **60-minutes (30-90 minutes) IV infusion**. The rate of infusion should be per institutional standard, but should not exceed 500 mL/hr. **NOTE:** Do not administer as an IV push or bolus.
5	Recommended to immediately conduct a normal saline flush, per site standard operation procedures, at the same rate to clear the infusion set of residual drug.
6	Record administration details in the Case Report Form (CRF).

7.4.2. Preparation and Administration of Pembrolizumab 25 mg/mL concentrate for solution for infusion (100 mg/4 mL)

Key points to note:

- Dose preparation must be performed using sterile handling techniques in compliance with local, state, and national laws/regulations.
- **Prevention of particulates:**
  - Minimize agitation
  - Ensure dilution of admixture solution is 1 mg/mL to 10 mg/mL
  - Minimization of headspace (empty space over the liquid) in syringes and admixture bags
  - Avoid siliconized product during preparation (Please note there is particulate formation when there is over agitation of the product and when concentrations are less than 1 mg/mL)If the infusion bag is excessively handled or shaken, particulates may form. If this occurs discard the bag and create a new bag taking care not to shake.
- Do not shake/agitate or freeze the vial(s).
- **DO NOT SHAKE OR FREEZE THE PEMBROLIZUMAB INFUSION SOLUTION.**
- **DO NOT USE PEMBROLIZUMAB IF DISCOLORATION IS OBSERVED.**
- The final concentration of Pembrolizumab in the infusion solutions should be between **1 mg/mL and 10 mg/mL.**
- **DO NOT ADMINISTER THE IP AS AN IV PUSH OR BOLUS.**
- **DO NOT COMBINE, DILUTE OR ADMINISTER AS AN INFUSION WITH OTHER MEDICINAL PRODUCTS.**
- On days when administered with Disitamab vedotin, pembrolizumab should be administered approximately 30 minutes after completion of Disitamab vedotin. A delay of 15 minutes may be used for subsequent infusions if the previous infusion was well tolerated.
- Each vial is for single use only. Each vial is for use in a single participant, for a single dose.
- Document all steps performed as indicated in the Preparation Record (Appendix 5). The Preparation Record form is required. The use of alternative preparation records must be approved by the Sponsor's Clinical Research Pharmacist.

SUPPLIES
Check that the labelling details on the outer containers of the supplies correspond with these instructions and the clinical protocol. If the supplies available at the site do not correspond with the list below, contact the primary point of contact.
Supplies Provided by Pfizer
Drug product (Active): Pembrolizumab 25 mg/mL concentrate for solution for infusion (100 mg/4 mL). These are for single use only. They are for single use in a single participant for a single dose.
Supplies Provided by the Clinical Site
Diluent: Diluents should meet regional/local compendia requirements and be an authorized product in the local country • 0.9% Sodium Chloride Injection (Normal Saline) OR • 5% Dextrose Injection (D5W)
Syringe: Appropriately sized luer-lock latex-free polypropylene (PP) syringes
Needles: Stainless steel needles, appropriately sized
Infusion Bags: • Empty IV bags composed of one of the materials listed below that can hold a volume of 50 mL to 250 mL • 50 mL, 100 mL or 250 mL pre-filled 0.9% Sodium Chloride or D5W IV bags composed of one of the materials listed below **The following infusion bag materials are compatible with Pembrolizumab:**

Infusion Lines/Sets: Approved materials:

- PVC plasticized with Di(2-Ethylhexyl)Phthalate (DEHP)
- PVC, DEHP free
    - Since it is still a PVC set, DEHP must be replaced with another plasticizer. If the alternate plasticizer is Dioctyl Terephthalate (DEHT) or Tris (2-Ethylhexyl) Trimellitate (TOTM) then it is okay.
- Non-PVC (polyolefin)
- EVA
- PE lined polyolefin
- PP
- Low density polyethylene (LDPE)
- Clear PUR (PVC Free, DEHP Free)
- Acrylic
- Polymethylmethacrylate (PMMA)
- Silicone rubber with Fluorosilicone
    - The manual instructs to avoid silicon-based products during preparation. This section talks about neat silicone oil like silicionized syringes etc. Silicone tubing is different and can be used. In other words, solid is good like in silicone tube and liquid is not good like sprayed silicone oil in siliconized syringes. If the site uses an in-line filter, they can use the syringe with the silicon-based lubricant, but it is not preferred.
- Polyethylene terephthalate (PET)
- Stainless steel
- Polybutadiene
- Polycarbonate (PC)
- Isoprene rubber
- PVC
- Polyethersulfone (PES) (membrane pore size 0.2-micrometer) non-PVC multilayer co-extrusion infusion bag: three layers co-extrusion infusion bag; PP/ PP/ PP
- Acrylonitrile butadiene styrene (ABS)
- Polytetrafluoroethylene (PTFE)
- Dioctyl terephthalate (DOTP)

It is required to use an in-line, add-on, or extension set containing a sterile, non-pyrogenic, low-protein binding 0.2 to 5 micron filter made of PES during administration

Pumps: Infusion pump that is compatible with the IV lines

Closed System Transfer Devices (CSTDs): Use of spikes or other CSTDs are permitted as long as the pharmacist is aware of the hold-up volume (volume of fluid that is left in the device), and the contact time is less than or equal to 30 minutes. Sponsor approval is only needed for spikes/CSTDs with contact time greater than 30 minutes to ensure compatibility of the device. The 30-minute contact time doesn't include infusion time.

- The CSTD's (all include a vial adapter, syringe adapter and the IV bag spike) found to be compatible with pembrolizumab include:
    - BD SmartSite™/Texium™
    - B Braun Tevadaptor®
    - ICU Medical ChemoClave®
    - ICU Medical ChemoLock™
    - BD PhaSeal™

Preparation and Administration:

PEMBROLIZUMAB DOSE PREPARATION	
Preparation of Pembrolizumab	
1	Obtain 4 vials of pembrolizumab 100 mg solution for IV infusion. Prior to dose preparation, allow the vials to reach room temperature, then gently invert or swirl the vials to mix thoroughly. **Do not shake and avoid foaming.** If particles or discoloration are observed, do not use the vial(s) and notify the primary point of contact.
2	Follow the preparation steps below according to the type of IV infusion bag used for dose preparation. Choose a suitable infusion bag size so that the following conditions are met: **1.** The infusion volume to bag capacity ratio should not be less than 0.3. In other words, the bag must be filled to at least 30% of its capacity. **2. The final concentration of the diluted solution should be between 1 mg/mL to 10 mg/mL.** **If an Empty IV Infusion Bag is being used:** 1. Add the necessary volume of normal saline or dextrose solution into the empty bag. 2. Keep in consideration the volume of pembrolizumab to be added to the bag to prepare the infusion solution. **If a bag pre-filled with Normal Saline IV Infusion bag is being used:** 1. Remove the excess volume of normal saline or dextrose using a sterile syringe attached to a suitable needle. 2. Keep in consideration the excess bag fill volume as well as the volume of pembrolizumab to be added to the bag to prepare the infusion solution. 3. This helps ensure that the concentration in the bag can be accurately calculated and falls within the acceptable range of 1 mg/mL to 10 mg/mL. 4. If the site would like to proceed without removing excess saline, they must ensure that the concentration of pembrolizumab would still fall within acceptable range. Sponsor recommends reconstitution and administration of pembrolizumab that follows the parameters in this document, however if use of gravimetric preparation is mandatory due to local site procedures, the following requirements must be satisfied and documented: • Draw the required volume up to 4 mL (100 mg) of pembrolizumab from each vial • Limit the number of punctures of each vial to one For gravimetric preparation method using density of pembrolizumab solution, a value of 1.03 g/mL should be used
3	Withdraw the required volume of pembrolizumab from the vials (up to 4 mL from each vial) using a sterile syringe attached to a suitable needle. **400 mg = 16 mL** **Note:** It will be necessary to use FOUR vials, it is advisable to withdraw from each vial into a suitable size single use syringe using a **new needle** for each vial.
4	• Add the required pembrolizumab dose volume into the infusion bag containing the NS or D5W. • Mix diluted solution by gentle inversions. • Dispose of used vials and preparation materials per site standard procedures • Label according to local, standard practice.

PEMBROLIZUMAB ADMINISTRATION	
1	Prior to dosing the participant, adhere to normal standard of care and aseptic techniques. Prepared solutions that are refrigerated should be allowed to reach room temperature prior to administration. Make sure the prepared dosing solution is not cold to the touch.
2	• Administer diluted solution IV over 30 minutes -5 minutes and +10 minutes through an IV line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter. • Flushing the infusion line is required to ensure the entire contents of the bag are dosed, all remaining drug solution in the line is administered and standardization of care across all sites in the study. The infusion line for all participants must be flushed with saline or 5% dextrose or regional equivalent which was used as diluent, after administration of pembrolizumab infusion. • Document volume administered according to data entry guidelines. • In case of infusion reactions, infusion rate may differ; refer to protocol for specific instructions. • Maximum rate of infusion should not exceed 6.7 mL/min. through a peripheral line or indwelling catheter. • **UNUSED INFUSION SOLUTION FOR INJECTION SHOULD NOT BE USED FOR ANOTHER INFUSION OF THE SAME PARTICIPANT OR DIFFERENT PARTICIPANT** **CAUTION: Do not co-administer other drugs through the same infusion line**
3	Record administration details in the Case Report Form (CRF).

7.5. Dosing and Dispensing Errors

Any error in the prescribing, dispensing or administration of a medicinal product that may cause or lead to inappropriate medication use or participant harm while in the control of the health care professional, participant or consumer must be reported to the Sponsor and/or primary point of contact immediately. Refer to the study protocol for additional information on how to report a dosing or dispensing error.

7.6. Investigational Product Complaints

Any complaints related to distributed clinical supplies provided by the Sponsor for use in a clinical study that alleges a quality defect of a product, device or its labeling or packaging must immediately be reported. Follow the process below to alert the Sponsor.

Process:

- Upon identification of a product complaint, immediately notify the assigned primary point of contact. Please provide the following information in the notification within one business day of discovery:
  - Protocol Number and Site Number
  - Participant ID
  - IP name (example PF-XXX or product name)
  - Date of discovery
  - Packaged lot number and kit number if applicable
  - How long the participant has been enrolled in the clinical study if applicable

- Status of participant within the study (i.e., completed, dose escalated)
- If there was a missed dose or adverse event due to the complaint
- Brief description of the complaint
- Point of discovery (i.e., during drug accountability, or in participant possession)
- Photo of the sample in question

- Quarantine the IP in the appropriate storage conditions and wait for further instructions.
- The site will be notified if additional information or action is needed by the site. *Do not destroy the product as it may need to be returned to the Sponsor.*
- The site must work with the primary point of contact to complete IP complaint documentation for the Sponsor, and/or if requested to ship the material in question back to the Sponsor. If requested to return the product to the Sponsor, the primary point of contact will support the logistics of this shipment.
- The Sponsor will review the complaint and complete an investigation as needed. Once the review/investigation is complete by the Sponsor, the site will be provided a final response by the primary point of contact.

8. Investigational Product Accountability

IMP accountability is the responsibility of the clinical site. Contact the primary point of contact for any concerns with regards to accountability. Please see Appendix 3 for an example Study Drug Accountability Log

The Study Drug Accountability Log must be used. Any requests from sites to use an alternative accountability log must be approved by the sponsor.

Investigational Product Destruction

- **<u>If product can be destroyed on site:</u>**
  - All destruction must be fully documented at the time of destruction on the Study Drug Accountability Log or equivalent document (See Appendix 3 for an example).
  - For **unused/expired IP**, once reconciliation and accountability has been performed by the primary point of contact, the primary point of contact may authorize the destruction by the appropriate site personnel (e.g., Pharmacist or Study Nurse/Coordinator) following local environmental requirements and institutional policies.
  - For **used/partially used** products, reconciliation may not be possible if local site procedure is to destroy immediately after use (e.g., vials, sharps, cytotoxic products, etc.).

- **<u>If product must be sent out for destruction</u>**:
  - Contact the primary point of contact for return/shipment instructions.
  - NO product should be sent for destruction without prior authorization by primary point of contact.
- If local site destruction SOP differs, please provide a copy to the primary point of contact for Sponsor review and approval.

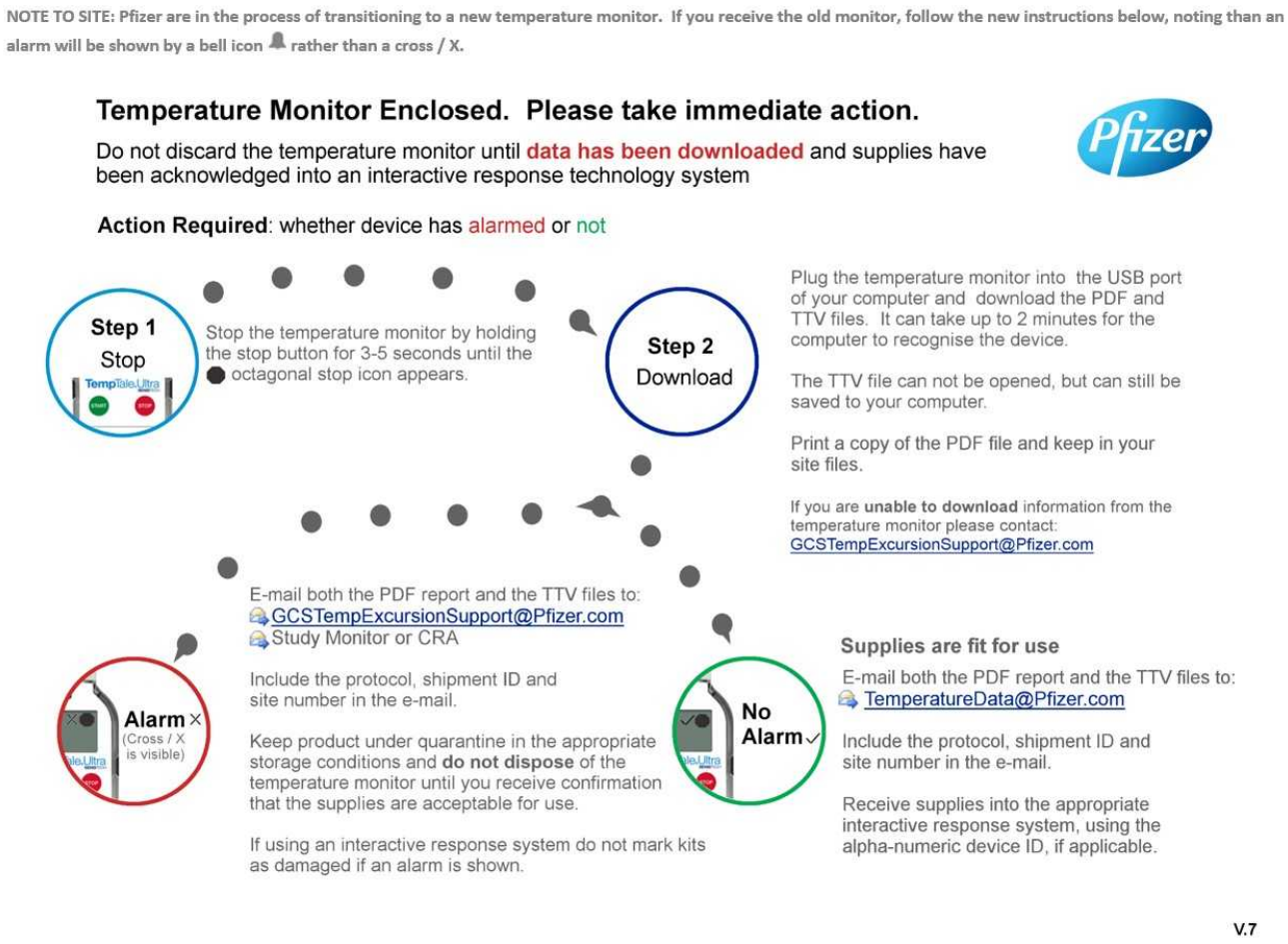
Contact the assigned primary point of contact for any questions related to Investigational Product return or destruction.

<u>Site Sourced Supplies</u>

Manage/destroy locally sourced supplies per local site SOP and/or following local environmental requirements and institutional policies.

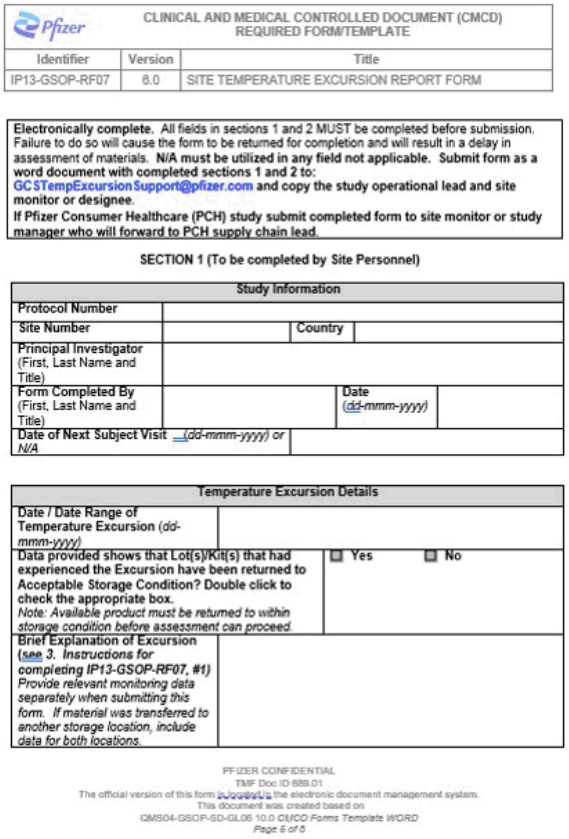
Appendix 1: Example Temperature Monitoring Instruction Sheet

This is an example only. Use the instructions provided in the shipment.



Appendix 2: Example Site Temperature Excursion Report Form

This is an example only. Obtain a copy of the form from the Sponsor.



Pfizer | CLINICAL AND MEDICAL CONTROLLED DOCUMENT (CMCD) REQUIRED FORM/TEMPLATE

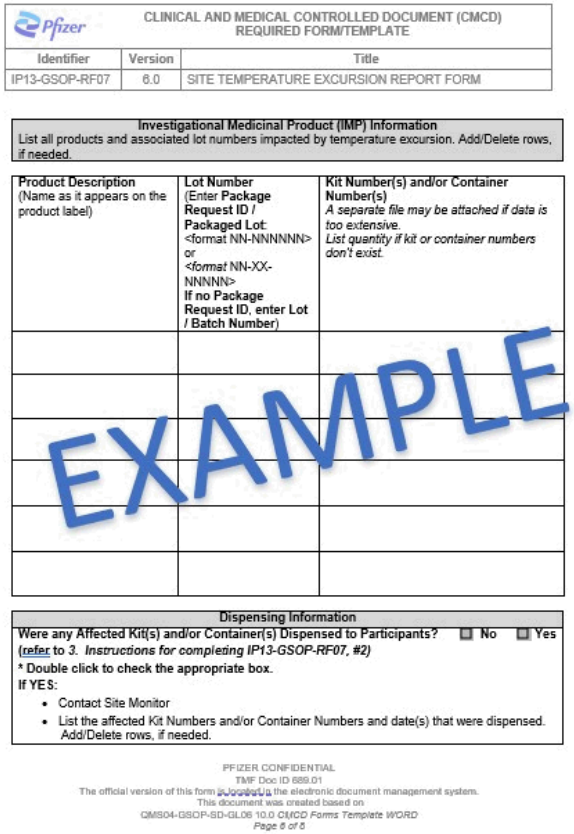
Identifier	Version	Title
IP13-GSOP-RF07	6.0	SITE TEMPERATURE EXCURSION REPORT FORM

Electronically complete. All fields in sections 1 and 2 MUST be completed before submission. Failure to do so will cause the form to be returned for completion and will result in a delay in assessment of materials. **N/A must be utilized in any field not applicable. Submit form as a word document with completed sections 1 and 2 to:** GCSTempExcursionSupport@pfizer.com **and copy the study operational lead and site monitor or designee.**
If Pfizer Consumer Healthcare (PCH) study submit completed form to site monitor or study manager who will forward to PCH supply chain lead.

SECTION 1 (To be completed by Site Personnel)

Study Information			
Protocol Number			
Site Number		Country	
Principal Investigator (First, Last Name and Title)			
Form Completed By (First, Last Name and Title)		Date (dd-mmm-yyyy)	
Date of Next Subject Visit (dd-mmm-yyyy) or N/A			

Temperature Excursion Details	
Date / Date Range of Temperature Excursion (dd-mmm-yyyy)	
Data provided shows that Lot(s)/Kit(s) that had experienced the Excursion have been returned to Acceptable Storage Condition? Double click to check the appropriate box. *Note: Available product must be returned to within storage condition before assessment can proceed.*	☐ Yes ☐ No
Brief Explanation of Excursion (see 3. *Instructions for completing IP13-GSOP-RF07, #1)* *Provide relevant monitoring data separately when submitting this form. If material was transferred to another storage location, include data for both locations.*	



Pfizer | CLINICAL AND MEDICAL CONTROLLED DOCUMENT (CMCD) REQUIRED FORM/TEMPLATE

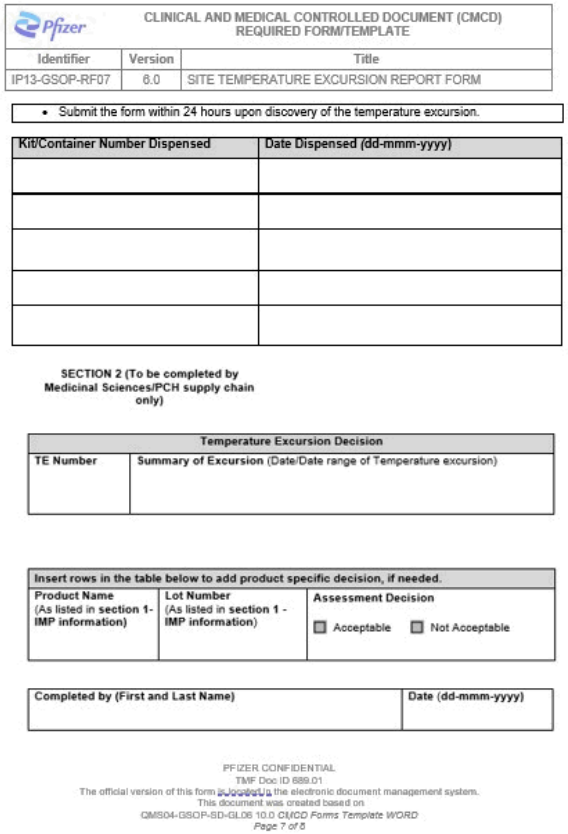
Identifier	Version	Title
IP13-GSOP-RF07	6.0	SITE TEMPERATURE EXCURSION REPORT FORM

Investigational Medicinal Product (IMP) Information
List all products and associated lot numbers impacted by temperature excursion. Add/Delete rows, if needed.

Product Description (Name as it appears on the product label)	Lot Number (Enter Package Request ID / Packaged Lot: <format NN-NNNNNN> or <format NN-XX-NNNNN> If no Package Request ID, enter Lot / Batch Number)	Kit Number(s) and/or Container Number(s) *A separate file may be attached if data is too extensive. List quantity if kit or container numbers don't exist.*

EXAMPLE

Dispensing Information
Were any Affected Kit(s) and/or Container(s) Dispensed to Participants? ☐ No ☐ Yes
(refer to *3. Instructions for completing IP13-GSOP-RF07, #2)*
*** Double click to check the appropriate box.**
If YES:
- Contact Site Monitor
- List the affected Kit Numbers and/or Container Numbers and date(s) that were dispensed. Add/Delete rows, if needed.



Pfizer | CLINICAL AND MEDICAL CONTROLLED DOCUMENT (CMCD) REQUIRED FORM/TEMPLATE

Identifier	Version	Title
IP13-GSOP-RF07	6.0	SITE TEMPERATURE EXCURSION REPORT FORM

- Submit the form within 24 hours upon discovery of the temperature excursion.

Kit/Container Number Dispensed	Date Dispensed (dd-mmm-yyyy)

SECTION 2 (To be completed by Medicinal Sciences/PCH supply chain only)

Temperature Excursion Decision	
TE Number	**Summary of Excursion** (Date/Date range of Temperature excursion)

Insert rows in the table below to add product specific decision, if needed.		
Product Name (As listed in **section 1- IMP information**)	**Lot Number** (As listed in **section 1 - IMP information**)	**Assessment Decision** ☐ Acceptable ☐ Not Acceptable

Completed by (First and Last Name)	Date (dd-mmm-yyyy)

Appendix 3: Example Study Drug Accountability Log

Contact your primary point of contact for a copy of the Study Drug Accountability Log for this study.

Seagen

STUDY DRUG ACCOUNTABILITY LOG

Page __ of __

Protocol #: RC48-G001		Principal Investigator Name:		Site Name:			Site #:	Drug Name:
Date Dispensed (-) or Received (+)	Subject ID Number	Dose <<(mg)>>	Quantity Dispensed (-) or Received (+)	Damaged or Wasted (-)	Balance Forward	Drug <<Lot #>> *(Do not prepare a single dose using vials from different lots.)*	Dispensing Pharmacist Initials	CRA Initials /Date*

EXAMPLE

*NOTE: CRA Initials/Date verify that all information within the row has been source verified and is determined to be accurate.

Appendix 4: Preparation Record for Disitamab vedotin for Intravenous Infusion Administration

For sites initiated in or prior to December 2024 this form is OPTIONAL.
For sites initiated in January 2025 or later this form is **REQUIRED**. The use of alternative preparation records must be approved by the Sponsor's Clinical Research Pharmacist. Prepared by and verified by must be completed by two separate site personnel, one of which is a licensed healthcare provider.

Protocol Number: C5731002 (RC48G-001)		
Participant ID Number (SSID):	**Participant Weight: _____ kg**	**Dose Level: _____ mg/kg**
Date of dose preparation: (DD-MMM-YYYY)**:**	**Dose preparation start time:** (HH:MM)**:** ***(Time needle is inserted into vial during reconstitution)***	**Expiry Date and Time of Prepared Dose:** (DD-MMM-YYYY; HH:MM): ***(Expiry is 4 hours from the time of reconstitution)***
Reconstituted IP: Used immediately. If it cannot be used immediately, the reconstituted IP vials must be stored for no longer than 24 hours at 2 to 8 °C (36 to 46 °F). **Prepared Dosing Solution:** Use immediately. The total duration of room temperature exposure may not exceed 4 hours from vial opening to start of administration. If not used immediately, solutions must be stored under refrigeration at 2 to 8 °C (36 to 46 °F) for 24 hours.		

Equation 1: Disitamab vedotin Dose (mg) = _____ mg/kg X _____ kg = _____ mg (maximum dose = 150 mg)
Dose level **participant weigh**

Dose Level	Maximum Dose
1.5 mg/kg	150 mg
1.25 mg/kg	125 mg
1 mg/kg	100 mg
0.75 mg/kg	75 mg

Equation 2: =

Volume of Disitamab vedotin required (mL) = _____ mg (DV Dose) / 7.5 mg/mL = _____ mL

Equation 3:

Number of vials Disitamab vedotin required = _____ mg (DV Dose) / 45 mg/vial = _____ vials *(round up to next whole vial)*

Equation 4: Required Volume of 0.9% Sodium Chloride = _____ **mL** – _____ **mL** = _____ **mL** *(round to measurable volume)*
Suggested Total Volume — Volume of IP (from Equation 2)

	Printed Name	Signature	Date
Calculated by:			- -
Verified By:			- -

Instructions for Preparation	Data
Use appropriate site and local processes and procedures for the handling, preparation, and administration of Hazardous/Cytotoxic agents. Reconstitute required number of vials(s) from Equation 3 of Disitamab vedotin by adding 6 mL sterile water for injection to each vial. **USE VIALS FROM THE SAME LOT NUMBER FOR ANY GIVEN DOSE.**	Number of vials: _____

Further dilute with 0.9% Sodium Chloride (Normal Saline) solution for injection in an IV infusion bag to achieve a final concentration of ≥ 0.19 and ≤ 1.9 mg/mL. **If using a PREFILLED 0.9% Sodium Chloride infusion bag:** • Withdraw and discard a volume of 0.9% Sodium Chloride equal to the volume of IP (from Equation 2) from the infusion bag. • Withdraw and inject the volume of IP (mL) (from Equation 2) into the infusion bag. **If using EMPTY infusion bag:** • Add the required volume of 0.9% Sodium Chloride (from Equation 4) to the infusion bag. • Withdraw and inject the volume of IP (mL) (from Equation 2) into the infusion bag. **NOTE:** All prefilled infusion bags have an overage compared to their label, so the final dose volume will be slightly higher than the labeled volume.	☐ **PREFILLED IV INFUSION BAG** ☐ 100 mL 0.9% Sodium Chloride IV Infusion Bag ☐ Or other volume: _____ mL 0.9% Sodium Chloride IV Infusion Bag Volume of 0.9% Sodium Chloride **REMOVED** from IV Infusion Bag: _____ mL Volume of investigational product **ADDED** to the IV Infusion Bag: _____ mL Total Volume: _____ mL **OR** ☐ **EMPTY IV INFUSION BAG** Volume of 0.9% Sodium Chloride **ADDED**: _____ mL Volume of investigational product **ADDED**: _____ mL Total Volume: _____ mL
Gently invert the prepared IV bag to mix. DO NOT SHAKE to avoid creating foam in the bag. Attach an appropriate label to the prepared IV bag per local regulations. Dispose of used vials and preparation materials per site standard procedures.	

	Printed Name	Signature	Date
Prepared By:			- -
Verified By:			- -

Contact your primary point of contact immediately to report any dose preparation deviations.

Comments (record any deviations from preparation instructions, storage time and conditions, etc.):

_____

_____

_____

Appendix 5: Preparation Record for Pembrolizumab 25 mg/mL concentrate for solution for infusion

For sites initiated in or prior to December 2024 this form is OPTIONAL.
For sites initiated in January 2025 or later this form is **REQUIRED**. The use of alternative preparation records must be approved by the Sponsor's Clinical Research Pharmacist. Prepared by and verified by must be completed by two separate site personnel, one of which is a licensed healthcare provider.

Protocol Number: C5731002 (RC48G-001)		
Participant ID Number (SSID):	**Participant Dose:** **400 mg**	
Date of dose Preparation (DD-MMM-YYYY)**:**	**Dose preparation start time** (HH:MM)**:** ***(Time needle is inserted into vial)***	**Expiry Date and Time of prepared dose** (DD-MMM-YYYY; HH:MM): ***Expiry is 6 hours from the start of dose preparation***
NOTE: *Pembrolizumab solutions may be stored at room temperature for a cumulative time of up to 6 hours from the start of preparation. This includes storage of drug product solution in vials, dosing solutions in the IV bags and the duration of infusion. Prepared IV bags may be stored in the refrigerator at 2 to 8 °C (36 to 46 °F) for up to 24 hours. If refrigerated, allow IV bags to reach room temperature prior to use.*		

Instructions for Preparation	Data
Obtain **4 vials** of pembrolizumab 100 mg solution for IV infusion. Withdraw 16 mL (4 mL per vial) from the vials of pembrolizumab and transfer into an IV bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Mix diluted solution by gentle inversion. **NOTE:** The final concentration of the diluted solution should be between 1 mg/mL to 10 mg/mL. Dispose of used vials and preparation materials per site standard procedures.	Volume of diluent: _____ mL **Diluent Used:** ☐ 0.9% Sodium Chloride Injection, USP ☐ 5% Dextrose Injection, USP

	Printed Name	Signature	Date
Prepared By:			- -
Verified By:			- -

Contact your primary point of contact immediately to report any dose preparation deviations.
Comments (record any deviations from preparation instructions; storage time and conditions, etc.):

_____

_____

Document Approval Record

Document Name:	IP Manual for C5731002 (RC48G-001)
Document Title:	IP Manual for C5731002 (RC48G-001)

Signed By:	Date(GMT)	Signing Capacity
Fitzpatrick, Michael	19-Mar-2025 15:08:22	Business Line Approver
Hobbs, Michelle Rose	20-Mar-2025 11:52:09	Author Approval