# PHARMACY MANUAL

## SACITUZUMAB TIRUMOTECAN

## (sac-TMT, MK-2870)

## AND

## Pembrolizumab (MK-3475)

MK-2870-033 /GOG-3119/ENGOT-en29/ TroFuse-033

SPONSOR MERCK SHARP & DOHME LLC
126 East Lincoln Ave.
P.O Box 2000
Rahway, NJ 07065
(hereinafter referred to as MSD or Sponsor)

# Contents

# 1 Glossary

| | |
|---|---|
| ABS | Acrylonitrile Butadiene Styrene copolymer |
| AE | Adverse Event |
| AxMP | Auxiliary Medicinal Product |
| BRC | Batch Release Certificate |
| C1D1 | Cycle 1, Day 1 |
| CDT | Counterfeit, Diversion and Tampering |
| CID | Component ID |
| CoI | Blue Coloring |
| CRA | Clinical Research Associate |
| CS | Clinical Scientist |
| CSRF | Clinical Supply Return Form |
| CSTAM | Clinical Supply Transfer Approval Memo |
| CSTD | Closed System Transfer Device |
| DEHP | Diethylhexl-Phthalate |
| DP | Drug Product |
| DPE | Dosing Past Expiry |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| EEA | European Economic Area |
| EVA | Ethyl vinyl Acetate |
| eTMF | electronic Trial Master File |
| Fsi | Flurosilicone |
| GMP | Good Manufacturing Practice |
| HB | Hydrophobic barrier |
| ICH GCP | International Council for Harmonisation Good Clinical Practice |
| IMP | Investigational Medicinal Product |
| IP | Investigational Product |
| IRT | Interactive Response Technology |
| ISF | Investigator Site File |
| IV | Intravenous |
| NIMP | Non-Investigational Medicinal Product |
| PC | Polycarbonate |
| PE | Polyethylene |
| PES | Polyether sulfone |
| PI | Polyisoprene |
| PICC | Peripherally inserted central catheter(s) |
| PO | Polyolefin |
| PP | Polypropylene |
| PQC | Product Quality Complaint |
| PS | Polysulfone |
| PTFE | Polytetrafluoroethylene |
| PU | Polyurethane |
| PVC | Polyvinyl Chloride |
| RED | Re-Evaluation Date |

| | |
|---|---|
| RT | Room Temperature |
| Sac-TMT | Sacituzumab Tirumotecan |
| SCID | Scan ID |
| SDR | Source Document Review |
| SDV | Source Document Verification |
| Si | Silicone |
| SOP | Standard Operating Procedure |
| SS | Stainless Steel |
| SWFI | Sterile Water for Injection |
| TE | Temperature Excursion |
| TMD | Temperature Monitoring Device |
| TOTM | Trioctyl Trimellitate |
| TPE | Thermoplastic Elastomer |
| USP | United States Pharmacopeia |

# 2 Contact List

The Clinical Research Associate (CRA) is your primary Point of Contact for study-related questions.

| The Role | The Name | Contact details | The questions |
|---|---|---|---|
| Clinical Scientist (CS) | Francisco Vicente Hinestrosa Hurtado | Phone: +57-1-592-0773<br><br>E-mail: francisco.vicente.hinestrosa.hurtado@merck.com | Questions regarding the details outlined within this Pharmacy Manual. |
| | Stephanie Shapiro | Phone: +1-843-991-2201<br><br>E-mail: stephanie.shapiro@merck.com | |
| Interactive Response Technology (IRT Coordinator) | Visalakshi Mandavilli | Phone: +1-215-652-0329<br><br>E-mail: visalakshi.mandavilli@merck.com<br><br>E-mail: IRT.Helpdesk@signanthealth.com | IRT issues |

# 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/ Vaccination Regimen | Use | IMP or NIMP / AxMP | Sourcing |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Induction | Experimental | Pembrolizumab (MK-3475) | Biological/ Vaccine | Solution | 25 mg/mL | 200 mg | IV Infusion | Day 1 of Each 3week Cycle for 6 Cycles | Test Product | IMP | Central |
| Induction | Experimental | Carboplatin | Drug | Solution | Per Approved Product Label | AUC 5 (mg/mL/ min) | IV Infusion | Day 1 of Each 3-week Cycle for 6 Cycles | Background Treatment | NIMP / AxMP | Local or Central |
| Induction | Experimental | Paclitaxel | Drug | Solution | Per Approved Product Label | 175 mg/m$^2$ | IV Infusion | Day 1 of Each 3-week Cycle for 6 Cycles | Background Treatment | NIMP / AxMP | Local or Central |
| Induction | Experimental | Docetaxel (in place of paclitaxel, only after Sponsor consultation) | Drug | Solution | Per Approved Product Label | 75 mg/m$^2$ | IV Infusion | Day 1 of Each 3-week Cycle for 6 Cycles | Background Treatment | NIMP / AxMP | Local or Central |

| Arm Name | Arm Type | Intervention Name | Intervention Type | Dose Formulation | Unit Dose Strength (s) | Dosage Level(s) | Route of Administration | Regimen/ Treatment Period/ Vaccination Regimen | Use | IMP or NIMP / AxMP | Sourcing |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Maintenance Arm A | Experimental | sac-TMT (MK-2870) | Biological/ Vaccine | Injection, Powder, Lyophilized , For Solution | 200 mg per vial | 4 mg/kg | IV Infusion | Days 1, 15, and 29 of Each 6-week Cycle for up to 14 Cycles (Equaling 42 Doses) | Test Product | IMP | Central |
| Maintenance Arm A | Experimental | Pembrolizumab (MK-3475) | Biological/ Vaccine | Solution | 25 mg/mL | 400 mg | IV Infusion | Day 1 of Each 6-week Cycle for 14 Cycles; Participants May Be Eligible for Second Course (9 additional cycles) | Test Product | IMP | Central |
| Maintenance Arm A Subsequent Treatment Arm A Subsequent Treatment Arm B | Experimental | H1 Receptor Antagonist | Drug | Unassigned | Per Approved Product Label | Per Approved Product Label | Per Approved Product Label | Before sac-TMT Infusion | Rescue Medication | NIMP / AxMP | Local |
| Maintenance Arm A Subsequent Treatment Arm A Subsequent Treatment Arm B | Experimental | H2 Receptor Antagonist | Drug | Unassigned | Per Approved Product Label | Per Approved Product Label | Per Approved Product Label | Before sac-TMT Infusion | Rescue Medication | NIMP / AxMP | Local |

| Arm Name | Arm Type | Intervention Name | Intervention Type | Dose Formulation | Unit Dose Strength(s) | Dosage Level(s) | Route of Administration | Regimen/ Treatment Period/ Vaccination Regimen | Use | IMP or NIMP / AxMP | Sourcing |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Maintenance Arm A Subsequent Treatment Arm A Subsequent Treatment Arm B | Experimental | Acetaminophen (or Equivalent) | Drug | Unassigned | Per Approved Product Label | Per Approved Product Label | Per Approved Product Label | Before sac-TMT Infusion | Rescue Medication | NIMP / AxMP | Local |
| Maintenance Arm A Subsequent Treatment Arm A Subsequent Treatment Arm B | Experimental | Dexamethasone (or Equivalent) | Drug | Unassigned | Per Approved Product Label | 8 mg to 10 mg (or equivalent) | Per Approved Product Label | Before sac-TMT Infusion | Rescue Medication | NIMP / AxMP | Local |
| Maintenance Arm A Subsequent Treatment Arm A Subsequent Treatment Arm B | Experimental | Steroid Mouthwash (Dexamethasone or Equivalent) | Drug | Solution | Per Approved Product Label | 2 mL to 5 mL | Oral | 4 Times Daily | Rescue Medication | NIMP / AxMP | Local or Central |

| Arm Name | Arm Type | Intervention Name | Intervention Type | Dose Formulation | Unit Dose Strength (s) | Dosage Level(s) | Route of Administration | Regimen/ Treatment Period/ Vaccination Regimen | Use | IMP or NIMP / AxMP | Sourcing |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Maintenance Arm B | Experimental | Pembrolizumab (MK-3475) | Biological/ Vaccine | Solution | 25 mg/mL | 400 mg | IV Infusion | Day 1 of Each 6-week Cycle for 14 Cycles; Participants May Be Eligible for Second Course (9 additional cycles) | Comparator | IMP | Central |
| Subsequent Treatment Arm A | Experimental | sac-TMT (MK-2870) | Biological/ Vaccine | Injection, Powder, Lyophilized, For Solution | 200 mg per vial | 4 mg/kg | IV Infusion | Days 1, 15, and 29 of Each 6-week Cycle Until Criterion for Discontinuation is Met | Test Product | IMP | Central |
| Subsequent Treatment Arm A | Experimental | Pembrolizumab (MK-3475) | Biological/ Vaccine | Solution | 25 mg/mL | 400 mg | IV Infusion | Day 1 of Each 6-week Cycle for 14 Cycles | Test Product | IMP | Central |
| Subsequent Treatment Arm B<br><br>*see footnote below | Experimental | sac-TMT (MK-2870) | Biological/ Vaccine | Injection, Powder, Lyophilized, For Solution | 200 mg per vial | 4 mg/kg | IV Infusion | Days 1, 15, and 29 of Each 6-week Cycle Until Criterion for Discontinuation is Met | Test Product | IMP | Central |

AUC=area under the curve; EEA=European Economic Area; IMP=investigational medicinal product; IV=intravenous; NIMP/AxMP=noninvestigational/auxiliary medicinal product; sac-TMT=sacituzumab tirumotecan and MK-2870.

For commercially available supplies, the unit dose strength or formulation may vary, depending on market availability.

* Information about treatment for non-evaluable /unknown TROP2 treatment group can be found on protocol section 6.1.3

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.

In this protocol, premedication is required for sac-TMT. Refer to Section 6.6.2. H2 receptor antagonists administered, if available, per approved product label or institutional standards.

If participants require more time to recover after induction treatment than the protocol-specified time period (4 weeks ±7 days) between Induction C6D1 and the Prerandomization Visit, up to 2 additional cycles of 200 mg pembrolizumab (Induction C7D1 and C8D1) may be administered **before** randomization to Maintenance. Sponsor consultation is required before C7D1.

# 4 Blinding

Sac-TMT (MK-2870) and/or pembrolizumab will be sourced, prepared, and administered as an open label product. The Sponsor, investigator, and participant will know the study intervention administered.

# 5 Accountability and Reconciliation

According to the International Council for Harmonisation Good Clinical Practice (ICH-GCP) guidelines, the responsibility for clinical supply management, including accountability, handling, dispensing, administration and return, rests with the investigator/institution. It is necessary to maintain the following Clinical Supply **Accountability Records.**

- ✓ delivery to the site documented on the **Shipping Records** (see Section 6),
- ✓ the use by each participant documented on the **Participant Clinical Supply Accountability Log** (see Section 11), including documenting that the participants were provided the doses specified by the protocol,
- ✓ inventory at site tracked in IRT (see Section 10),
- ✓ the **Return to Sponsor** (CSRF) or **alternative Disposition Records** (see Section 16),
- ✓ the **Destruction Records** (see Section 16).

These records should include dates, quantities, the component IDs (CIDs), Label Batch/Lot numbers, and expiration dates (if applicable) assigned to the product(s) and participant(s) to ensure full traceability. If the association between CID, Batch/Lot numbers, and expiration dates is documented at investigator site within other site records, such as shipping records, Batch Release Certificates (BRC), or in IRT, only CID numbers need to be recorded in the Accountability records. In such instances, Batch/Lot numbers and expiration dates can be omitted.

**All** clinical supplies received from the Sponsor shall be **reconciled** with the clinical supplies destroyed or returned to the Sponsor, to ensure that all kits/CIDs are accounted for. All discrepancies must be investigated and explained by the investigator site/pharmacy personnel on the Accountability Records.

Clinical Supply Accountability Records (or equivalent) must be readily available for review/inspection at any time by the CRA, Sponsor and/or regulatory authorities. A copy of Clinical Supply Accountability Records should be provided to Sponsor for filing in Sponsor electronic trial master file (eTMF).

Subject to country regulations, the clinical label will not display the Protocol ID number for certain centrally sourced products, but the product will be assigned to only ONE clinical trial before shipping to investigator sites.

- Confirm the receipt of the shipment in the IRT system of the clinical trial, as indicated on the Packing List.
- Upon receipt at the site, **store products from each clinical trial separately** to facilitate easier retrieval of the kits assigned to participants.
- The allocation of pooled kits to trial participants will be carried out using a unique **CID number** across the trials, thereby eliminating the need to verify the Protocol ID.

- Investigator sites will have the option to use **MSD Scan ID (SCID) barcode scanning app** to verify Protocol ID in case the Packing List is lost, or the kit is misplaced. Refer to the SCID App Instructions for more information

Consult your CRA if you want to use your Clinical Supply Accountability Record templates or the system to ensure that it contains all the information from the Sponsor template and meets data privacy requirements.

# 6 Receipt at Site

Immediately upon receipt of clinical supplies, locate the **Temperature Data Logger** and **Data Logger Site Instructions**. Stop Logger temperature tracking, check and document **Alarm Status**.

If there is NO ALARM, clinical supplies are acceptable for use. STORE the supplies under the labeled storage conditions immediately after proper verification has been performed, confirm receipt of shipment in IRT, and document the Alarm Status or file temperature report.

If Data Logger shows ALARM, the supplies cannot be used at this time. Download and file the temperature report. Impacted supplies must be segregated maintaining required storage conditions, a **Clinical Supply Complaint** should be initiated, and receipt of product should be confirmed in IRT with Temperature Excursion (TE).

NOTE: During clinical supply transit from MSD/depot to clinical sites, the Data Loggers may be preprogrammed with different temperature range requirements, based on product stability. Therefore, it's important that TEs are reported only in case of alarm.

Check the received clinical supply inventory and compare it to the accompanying Shipment records. Acknowledge the receipt of supplies by signing the shipment records and confirming the receipt of shipment in IRT. In case of Shipping errors or Product Quality Complaints (PQCs), a **Clinical Supply Complaint** should be initiated. See Section 8 for more information on Clinical Supply Complaint Reporting.

File the **Shipping Records** (Packing List or Drug Order Form or Shipping Request) signed and dated or with IRT confirmation attached.

Follow the **Data Logger Site Instructions** included in the shipment on how to handle the Data Logger and the Shipper.

# 7 Storage and Temperature Monitoring

| Product | Storage Temperature | Other storage requirements |
|---|---|---|
| Sac-TMT (MK-2870) | 2-8°C (36-46°F) | Protect from light |
| Pembrolizumab (MK-3475) | 2-8°C (36-46°F) | Store in original packaging to protect from light |

DO NOT FREEZE

The clinical supplies must be stored or transferred under the **clinical label storage conditions** in accordance with the requirements of the Sponsor and applicable local regulations, immediately after verification of the received or transferred supplies has been performed.

Temperature control at the investigator site is required from the time the clinical supply is received until the preparation or equilibration to room temperature before preparation begins or until the clinical supply is no longer needed for use (e.g., used, deemed unacceptable for use, expired, after the last participant completed the trial treatment, or when the site or trial is closed, etc.). To prevent administration of clinical supplies that are no longer temperature-monitored, they shall be physically segregated, the country and/or site must be canceled in IRT, or the clinical supply must be marked as quarantined or damaged in IRT. Refer to the section(s) 12.1.5 (In-use stability) for the temperature monitoring requirements during the preparation, transfer of the prepared product, or administration to the participant.

Clinical supplies must be stored in a temperature-controlled, secure area (such as controlled temperature storage units, rooms, or refrigerators) with access limited to the Investigator and authorized staff.

**Temperature Monitoring Device** (TMD) should meet the following requirements for the temperature data to be considered reliable:

- Function **continuously** 24 hours a day, 7 days a week. Continuous temperature monitoring can be interrupted for approximately up to 15 minutes to replace TMD, download data or move supplies in a stable environment where the temperature is unlikely to change rapidly. For example, refrigerated supplies remain in the working refrigerator or are transferred in a proper shipper or room temperature supplies are transferred indoors.
- **Calibration** records or records of maintenance available and valid (not expired).
- **Min/Max TMD** that can log data and generate **electronic reports** is preferred. If TMD does not generate a report, a Min/Max TMD should be used.
- **An alarm**, a **backup TMD**, and a probe with a thermal buffer (glycol-encased probe) are recommended.

If site TMD does not meet Sponsor requirements, Sponsor can provide the TMD upon request.

The temperatures of the primary TMD must be verified by the pharmacist or a delegate **on a daily basis**. In the event that site personnel are not present during a weekend or holidays, the temperature check for that weekend or those holidays should occur on the following business day. Clear temperature data before the first use of the TMD at site and with each download/data transcription to make sure Min/Max temperature records cover the period since the last download/transcription.

**Temperature monitoring records** should be documented using one of the following options:

a) If the TMD generates a report and

   i. the site has a documented process for reviewing temperatures daily or has arrangements for notifying personnel of alarms**:** The temperature report, when there is no reportable TE, can be filed less frequently but at least monthly, or before the CRA visit, whichever occurs earlier.

   ii. the site does not have a documented process for reviewing temperatures daily or arrangements for notifying personnel of alarms: The site personnel should document the daily verification by filing and signing the temperature report every business day.

b) If the TMD does not generate a report, site personnel should transcribe the Min/Max temperatures onto the temperature log every business day.

If the report cannot be downloaded and filed, an alternative, though less preferable method is transcribing the Min/Max temperatures onto the temperature log.

In the event of **reportable TE**, detailed temperature monitoring data pertaining to the TE should be downloaded and reported to the Sponsor **as soon as possible, preferably within one business day**.

**Temperature monitoring records** should contain TMD and storage location clearly identified (serial numbers of the fridge and TMD), temperature records, including Min/Max temperatures (if available), dates and time of record, initials or signature of staff recording the information on the log or reviewing it on the report.

If TMD does not record Min/Max temperatures, the logging interval on the report should be 15 minutes or shorter. Set the short logging interval to preferably 5 minutes or less for a more accurate calculation of the duration of TE

Use Sponsor provided **TEMPLATE Temperature Monitoring Log** or other site temperature monitoring records. These documents can be found in the Investigator Site File (ISF).

# 8 Clinical Supply Complaint and Site TE Reporting

**Clinical Supply Complaint** - any communication concerning manufacturing, packaging, labeling or distribution of a clinical supply that describes a potential defect related to its identity, strength, quality, or purity after it is released and has left the control of an MSD-approved packaging facility for distribution which puts product disposition (i.e., usability) in question.

The Clinical Supply Incidents listed below should be reported by completing the Online Clinical Supply Incident Form **as soon as possible, preferably within one business day** of first becoming aware of the incident:

**www.csincident.msd.com**

In the event of system downtime or technical issues, email the completed backup **Clinical Supply Complaint and Site Temperature Excursion Form** in Excel along with any additional supporting records (as applicable), to clinical.comppjarlaints.intake@msd.com mailbox.

- **Product Quality Complaints (PQC)** specific to manufacturing, packaging, and labeling of a product. Examples include defective, missing, or broken supplies/labels, change in physical appearance, malfunctioning device, etc., particulates or discoloration observed etc.
- **Distribution Complaints** specific to distribution issues during shipment from MSD depots to investigator sites:
    - Shipping TEs.
    - Temperature Data Logger-related issues (malfunctions, temperature device not started or not included in the shipment).

- Shipping errors (partial shipments, extra, missing, or incorrect kits, wrong product shipped, product shipped to incorrect site, documentation errors).
- Damaged Shipment (damaged shipper).

- **Site Temperature Excursions (TE):**
  - TE outside of the clinical label storage conditions at investigator site, including site-to-site, intra-site or site to participant transfer.

- Use the table below to determine if you have a **Reportable Site TE**:

| **Label Storage Condition** | **Reportable Site Temperature Excursion** after applying standard rounding rules* below 0°C do not round | | | **Non-reportable Site Temperature Excursion** after applying standard rounding rules* below 0°C do not round | |
|---|---|---|---|---|---|
| **Room temperature** | Report if <2 °C or >40 °C for **any period of time** | Report if outside of label storage conditions for **>15 minutes** | Report if supplies are **not monitored** for **>15 minutes** or for **any period of time** where the temperature is likely to change rapidly** | Do NOT report if ≥2°C to ≤40 °C for **≤15 minutes** | Do NOT report if supplies are not monitored for **≤15 minutes** where the temperature is unlikely to change rapidly** |
| **Refrigerated** | Report if <0 °C or >25 °C for **any period of time** | Report if outside of label storage conditions for >15 minutes | Report if supplies are **not monitored** for **>15 minutes** or for **any period of time** where the temperature is likely to change rapidly** | Do NOT report if ≥0°C to ≤25 °C for **≤15 minutes** | Do NOT report if supplies are not monitored for **≤15 minutes** where the temperature is unlikely to change rapidly** |

** Use standard rounding rules: If the decimal portion of excursion is 0.5°C and above, round up (for example, 1.5°C would be rounded up to 2°C). If the decimal portion of excursion is 0.4°C and below, round down (for example, 8.4°C would be rounded down to 8°C).*
*** Examples of environments where the temperature is likely to change rapidly include but are not limited to transferring refrigerated or frozen products at room temperature or transferring any products outdoors, outside of controlled hospital settings.*

- Planned and short exposures (recommended to be less than 5 minutes) of refrigerated or frozen products at room temperature—such as handling for label checks or transferring between the shipper and the refrigerator or freezer—are not considered a Reportable Site TE.

  - **No reliable temperature data at investigator site** – clinical supplies have not been monitored for >15 minutes or for any period of time in the environment where the temperature is likely to change rapidly. Examples include, but are not limited to the TMD being broken, turned off, removed from the refrigerator, not included in the shipper during transfer, the time period after the expiry of TMD calibration, temperature not being monitored continuously, or TMD/records not meeting MSD requirements.

    Continuous temperature monitoring can be interrupted for approximately up to 15 minutes in a stable environment where the temperature is unlikely to change rapidly to replace the TMD, download data or move supplies.

If the **calibration of the TMD has expired**, and no backup TMD is available, arrange for recalibration by a qualified service provider or calibration specialist. If no adjustments to the TMD are required, as confirmed on the calibration certificate or other written record, the previous temperature data recorded by the expired TMD can be considered reliable.

Make sure CRA is notified of the incident.

Submit **additional information:**

- For **Shipping TE** submit the **Packing List** and **Temperature Report** from the ALARMED Data Logger.
- For **Distribution Complaints** submit the **Packing List**. When clinical supply is shipped to the incorrect site, submit **a photo of the outer shipper labels**.
- For **Reportable Site TE** submit the temperature data.

Impacted supplies must be physically **segregated maintaining required storage conditions**, **quarantined in IRT** to prevent them from being assigned to a participant, and **should not be used or discarded** while the incident is being investigated, unless otherwise instructed by the Sponsor.

Should sample return be required to facilitate the investigation, the instructions and necessary documentation will be provided by the Sponsor.

Sponsor will send you the **Disposition Report**:

- Supplies deemed **Acceptable** for use should be returned to inventory at site. Sponsor will return these to inventory in IRT.
- Supplies deemed **Not Acceptable** for use should be reconciled and segregated for return or destruction. Sponsor will mark the supplies as damaged in IRT to trigger a resupply.

Clinical Supply Complaint Form, temperature records and all other supporting documentation should be filed at site.

The following incidents should NOT be reported on the Clinical Supply Complaint and Site TE Form:

- **Locally sourced medicinal product incidents** (e.g., sourced by local service provider or pharmacies): Report to local sourcing service provider, pharmacy, or manufacturer directly, if applicable, for a usage statement on product suitability. Inform your <CRA> as soon as possible.
- **Shipping TEs with NO ALARM** (centrally sourced clinical supply shipments from MSD / depot to investigator sites only): Not reportable, supplies are acceptable for use.
- **Issues with Temperature Data Download from Shipment Data Logger** (centrally sourced clinical supply shipments from MSD / depot to investigator sites only) - contact MSD Logistics at gcspolicy@msd.com;
- **Missing Shipment Records:** Contact MSD Logistics at gcspolicy@msd.com or contact your CRA.
- **Shipping to the Incorrect location of the Correct Site:** Perform an Intra-site Transfer and notify your CRA for investigation of the root cause.

- **Clinical supplies damaged at site** (e.g., broken, wet, mold) which puts product usability in question: Impacted supplies are deemed unusable, shall be physically segregated for return/destruction and marked as quarantined in IRT. If only secondary packaging is damaged, but the primary packaging/tamper seal is intact, site pharmacist can determine if the product can be used. If there are any doubts about product usability, do not use the product. Inform your CRA as soon as possible.
- **Site TE that, when rounded, do not meet the criteria for a Reportable Site TE:** Not reportable, no impact on clinical supplies.
- **TE During Product Preparation or Administration:** Follow the in-use stability requirements in section(s) 12.2.5 or contact your CRA to consult the Clinical Trial Team.
- **Issues Related to Improper Product Preparation for Dosing:** Consult your CRA.
- **Site Dispensing Errors** that do not affect product usability (e.g., trial participant receiving incorrect study therapy or dose): Inform your CRA.
- **Adverse storage of clinical supplies that are no longer needed for use** (used, expired, site or trial is closed, etc.): Not reportable.
- **Alleged Counterfeit, Diversion and Tampering (CDT)** (e.g., Clinical Supplies suspected to be stolen, opened, or altered by an unknown party): Inform your CRA.
- .

Follow the instructions on the **Clinical Supply Complaint Form**.

# 9 Transfer

- Sac-TMT (MK-2870) vial and Pembrolizumab (MK-3475) vial (prior to piercing) and/or admixture transfers shall be performed according to site procedures in compliance with the applicable Sponsor and local requirements as verified and approved by CRA. Temperature control and full traceability must be ensured.
- **Intra-site transfer** of sac-TMT (MK-2870) and Pembrolizumab (MK-3475) is a transfer between two locations of the same clinical site or Satellite site overseen by the same Principal Investigator (PI).
    - The decision to use shippers, temperature monitoring devices, and transfer records should be assessed using a risk-based approach, taking into consideration the storage conditions of the product (refrigerated or RT), expected transfer duration (less or more than 15 minutes), transfer conditions (indoors or outdoors), and other relevant factors.
    - To mitigate the risk of temperature excursion, it is recommended to utilize shippers and/or temperature monitoring devices during transfers that have a higher likelihood of temperature fluctuations. The examples of such transfers include those longer than 15 minutes or those conducted outdoors.

  - As a general rule, a TMD and a Shipper are required when the expected duration of the transfer is longer than 15 minutes. If the expected duration of the transfer is shorter than 15 minutes, the shipper is usually required for all products transferred outdoors, outside of controlled hospital settings and for frozen products transferred indoors and outdoors. Use transfer records when sac-TMT (MK-2870) and Pembrolizumab (MK-3475) stock is relocated due to site or site pharmacy relocation, or when intra-site transfers require transportation.
  - Due to the sensitivity of sac-TMT (MK-2870), sites must ensure temperature control within internal pathways such that temperatures do not exceed 25°C. If this criterion cannot be confirmed, then validated temperature monitoring devices must be used to ensure stability of sac-TMT (MK-2870).
  - Once the site process is approved by CRA, **routine** intra-site transfers do not need individual approvals. **Ad-hoc** intra-site transfers, such as **site or pharmacy relocation**, should be approved by CRA on a case-by-case basis.
- Sac-TMT (MK-2870) and Pembrolizumab (MK-3475) **from one clinical site to another** and transfer/return of clinical supply **from a clinical site to a primary or secondary depot** should remain the exception in accordance with GMP requirements. Each transfer must be approved by the Sponsor on the **Clinical Supply Transfer Approval Memo (CSTAM)** and documented on the **Clinical Supply Transfer Checklist**, provided by the Sponsor.

# 10 Interactive Response Technology (IRT)

This study will utilize IRT for the handling of clinical supplies at all investigator sites. Intervention allocation/randomization will occur centrally using an IRT system.

IRT will be used by the site personnel for the following clinical supply management functions:

- The initial clinical supply shipment will be triggered automatically by IRT upon site activation in the system. Re-supply shipments will also be triggered automatically when supply quantities at the site fall below a pre-specified threshold.
- Confirm receipt of all clinical supply shipments
- Obtain CID numbers assigned to participant.
- Quarantine clinical supplies in case of TE.
- Obtain replacement CIDs for damaged or otherwise unusable study drug.
- Generate IRT Clinical Supply Return Form to return clinical supplies to Sponsor or to document alternative disposition of the product.
- Track clinical supply inventory at site.
- The primary investigator or sub-investigator will have privileges to perform emergency unblinding of participants for safety reasons.

The unblinded site personnel, blinded study personnel, and the primary investigator will be granted access to IRT. Site personnel will have privileges to perform IRT procedures required for their role.

Confirmation of allocation/randomization will be sent via e-mail to site personnel who performed the transaction.

The IRT confirmation is to be filed in the Pharmacy Binder/ISF as applicable.

Should there be any concerns/issues with the process noted above, the site personnel will contact the CRA for guidance as to how to proceed.

Refer to **IRT Manuals** for more information.

# 11 Participant Clinical Supply Accountability Records

As required by ICH GCP, the DISPENSING Log of the **Participant Clinical Supply Accountability Log** provides a record of the dispensation of investigational product(s) according to the protocol. It ensures traceability and accountability of investigational product(s) along with records of receipt at the investigator site, the inventory and the return to the Sponsor or alternative disposition of unused product(s) in the Investigator Site File. After trial completion or termination, a copy of the completed DISPENSING log or equivalent record, shall be provided to Sponsor for filing in eTMF.

The Log should be completed for all centrally sourced clinical supplies and locally sourced IMP. Use of Sponsor log is highly recommended as our template contains all required information to be collected per ICH GCP and the protocol, and it is well prepared to meet data privacy requirements. The alternate format of this log (example.g., Site Drug Accountability System records, Site Inventory Log, if used) should be validated by the CRA to make sure it contains **all information from the Sponsor template** and meets **data privacy requirements**. If it does, the Sponsor Log does not need to be used by the site.

**All** fields indicated on a trial-specific Sponsor Participant Clinical Supply Accountability Log are required to be collected for this study **at investigator site** on this log or other source records identified on the source document identification log. If the alternate site records cannot be filed in the Sponsor eTMF (e.g., if information is scattered across multiple site records or if data privacy requirements are not met and cannot be redacted) then the minimum information marked with asterisk (*) must be transcribed by the site onto one record (either the sponsor log or an alternate site log) to be uploaded to the Sponsor eTMF. This will need to be signed and dated by the individual completing the transcription to verify that the information matches the original source record. The CRA must be given direct access to the original source or a certified copy of transcribed information for SDV Source Record Review. Transcribing data from site records to the Sponsor Log is discouraged. Instead, the investigator site should work with the CRA to choose templates that meet Sponsor requirements during site initiation.

The PREPARATION and ADMINISTRATION Logs are used as source records to record the use of the product by each participant, including the documentation that the participants were provided with the doses specified by the protocol. If these logs are maintained from the DISPENSING Log, their copies do not need to be filed in Sponsor eTMF.

ADMINISTRATION Log shall be kept separately from the DISPENSING and PREPARATION Log and some preparation information like Date, Time and Volume prepared may need to be copied to the administration log to align with the site practice.

Follow the instructions on the **Participant Clinical Supplies Accountability Log**.

# 12 Clinical Supply Preparation

For preparation of infusions/instillations, choose suitable ancillary equipment (Infusion Pumps, Infusion sets, Instillation Components) that are registered for use in accordance with their marketing authorizations. The ancillary equipment should be used in accordance with the manufacturer's instructions.

## 12.1 Drug Product sac-TMT (MK-2870)

**Sac-TMT (MK-2870) Solution for Infusion 200mg/vial**

Sac-TMT (MK-2870) drug product is a white or off-white lyophilized powder supplied in single-use Type I glass vial sealed with an elastomeric stopper and capped with an aluminum flip-off seal, containing 20 mg/mL of sac-TMT (MK-2870) once reconstituted.

### 12.1.1 Dose Calculation

- The preparation of infusion solutions should be based on the participant's actual body weight in kilograms (kg).

Calculate the required dose amount based on dose level and participant's weight. For all study interventions in the Induction Phase that are administered based on weight, the participant's weight at screening or at Cycle 1, Day 1 (C1D1) Induction should be used to calculate the initial dose. For all study interventions in the Maintenance Phase that are administered based on weight, the participant's weight at the pre-randomization visit should be used to calculate the initial dose. The participant's weight will be determined before each dose of sac-TMT (MK-2870). If, at any time throughout the course of treatment, the participant's weight changes by ≥10% from baseline, the dose will be recalculated using this new weight and will be considered the new baseline for all subsequent dosing calculations. The dose(s) of study intervention(s) should be recalculated as needed throughout the study. Dose adjustments for changes in body weight <10% are permitted per institutional standards.

- Required **dose** amount (mg) = dose level (mg/kg) * participant weight (kg).

- Calculate the **volume of Drug Product (DP) (mL)** to be used for admixture preparation by dividing the calculated dose by 20mg/mL (final concentration of reconstituted product) and rounding to the next 0.1mL.
    - For any variations from rounding guidance consult Sponsor for review

- Calculate the required number of sac-TMT (MK-2870) **vials** by dividing the required dose amount (mg) by 200 mg (per vial) and rounding to the next whole number.

**Example 1 (4 mg/kg dose)**
Dose level = 4 mg/kg, participant weight = 68.2 kg
Required dose amount (mg) = 4 mg/kg * 68.2 kg = 272.8 mg

Volume of DP to be used for admixture preparation: 272.8 mg / 20 mg/mL = 13.64 mL
Rounded to next 0.1 mL = 13.6 mL of DP

Required number of sac-TMT (MK-2870) vials = 272.8/200 = 1.364
Rounded to next whole number = 2 vials

### 12.1.2 Method of Preparation

The preferred method of dose preparation is the volumetric method.

Aseptic technique must be strictly observed throughout the preparation procedure. Sac-TMT (MK-2870) should be handled as hazardous drug. Follow applicable special handling and disposal procedures per local SOP and/or regulations. Use of a biosafety cabinet is preferred; however, it is not mandatory unless specified by site SOP.

If use of gravimetric preparation is mandatory due to local site procedures, the following requirements must be satisfied and documented: For gravimetric preparation method using density of sac-TMT (MK-2870) solution, a value of 1.038 g/mL should be used.

**Reconstitution**

Prior to the vial being pierced, the vial should be brought to room temperature (RT) prior to mixing. Sac-TMT (MK-2870) drug product vials must be reconstituted with 10 mL of sterile water for injection (SWFI) prior to dilution. Gently add the SWFI down the side of the vial. After all SWFI has been added, gently swirl the vial to promote dissolution of the lyophilized powder. Ensure all powder has gone into solution and that there are no visible particles. After all powder has gone into solution, gently swirl one more time before using for admixture preparation to ensure homogeneity of the reconstituted solution.

DO NOT SHAKE OR FREEZE THE RECONSTITUTED SOLUTION.

### 12.1.3 Diluent

Sac-TMT (MK-2870) infusion solutions should be prepared in 0.9% Sodium Chloride Injection, USP (normal saline) or regional equivalent or 5% Dextrose Injection, USP (5% dextrose) or regional equivalent.

The final concentration of sac-TMT (MK-2870) in the infusion solution should be between **0.5 mg/mL and 5.0 mg/mL.**

Local guidelines should be followed for collection of diluent information such as manufacturer, lot, and expiry. When the diluent is provided by MSD, the Participant Clinical Supply Accountability Log (or equivalent) should be used for collection of diluent information.

### 12.1.4 Infusion Device Components (IDC)

IDCs contain the Closed System Transfer Device (CSTD) and other infusion components in the fluid path (e.g., syringe, needle, IV bags, infusion set materials like in-line filters, tubing, connectors, etc.) for intravenous (IV) and injectable (syringes and needles) investigational product delivery.

Ensure that only the approved IDCs listed in sections 12.1.4.1 CSTD (Closed System Transfer Devices) and 12.1.4.2 Other Infusion Components are used. Contact the Sponsor via the CRA to check for compatibility of the IDCs used, and do not use until approved. If there is any change in the IDC, please notify the Sponsor through the CRA/uCRA.

### 12.1.4.1 CSTD (Closed System Transfer Devices)

CSTD is a drug transfer device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of the hazardous drug or vapor concentrations outside the system.

Use of spikes or other CSTDs and other infusion components are permitted as long as the pharmacist is aware of the void volume (volume of fluid that is left in the device) and that the materials of construction in the fluid path are compatible.

The CSTDs and other infusion components that have been tested for contact material compatibility and dose accuracy are listed in the table below:

| Supplier | CSTD Parts | Void volume for CSTD set (measured) (mL) |
|---|---|---|
| EquaShield | Polypropylene (PP), silicone (Si), hydrophobic barrier (HB), stainless steel (SS), polyisoprene (PI), polyvinyl chloride (PVC) | 0.20 |
| BD Texium | PP, Si, PVC, polytetrafluoroethylene (PTFE), thermoplastic elastomer (TPE), polycarbonate (PC), acrylic, acrylonitrile butadiene styrene copolymer (ABS), nylon, polyurethane (PU) | 0.21 |
| ICU Medical ChemoClave | Si, PVC, PC, acrylic, ABS, nylon, polyethylene (PE), flurosilicone (Fsi) | 0.42 |
| ICU Medical ChemoLock | Si, SS, PC, ABS, PE, Fsi | 0.64 |
| B Braun TEVADAPTOR | ABS, PI, silicone oil, PVC, PC, SS | 0.25 |

| Supplier | CSTD Parts | Void volume for CSTD set (measured) (mL) |
|---|---|---|
| BD PhaSeal | PTFE, TPE, PP, SS, ABS, Si | 0.17 |

CSTDs are not required to be used with sac-TMT (MK-2870) but can be used if required per local practice.

CSTD is a drug transfer device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of the hazardous drug or vapor concentrations outside the system.

Use of spikes or other CSTDs and other infusion components are permitted as long as the pharmacist is aware of the void volume (volume of fluid that is left in the device) and that the materials of construction in the fluid path are compatible.

The CSTDs and other infusion components that have been tested for contact material compatibility and dose accuracy are listed in the table below

| Supplier | CSTD Parts | Void volume for CSTD set (measured) (mL) |
|---|---|---|
| EquaShield | Polypropylene (PP), silicone (Si), hydrophobic barrier (HB), stainless steel (SS), polyisoprene (PI), polyvinyl chloride (PVC) | 0.20 |
| BD Texium | PP, Si, PVC, polytetrafluoroethylene (PTFE), thermoplastic elastomer (TPE), polycarbonate (PC), acrylic, acrylonitrile butadiene styrene copolymer (ABS), nylon, polyurethane (PU) | 0.21 |
| ICU Medical ChemoClave | Si, PVC, PC, acrylic, ABS, nylon, polyethylene (PE), flurosilicone (Fsi), | 0.42 |

| Supplier | CSTD Parts | Void volume for CSTD set (measured) (mL) |
|---|---|---|
| ICU Medical ChemoLock | Si, SS, PC, ABS, PE, Fsi, | 0.64 |
| B Braun TEVADAPTOR | ABS, PI, silicone oil, PVC, PC, SS | 0.25 |
| BD PhaSeal | PTFE, TPE, PP, SS, ABS, Si | 0.17 |

CSTDs are not required to be used with sac-TMT (MK-2870) but can be used if required per local practice.

### 12.1.4.2 Other Infusion Components

Other infusion components for intravenous (IV) investigational product delivery include, but are not limited to, syringes, needles, IV bags, infusion set materials (e.g., in-line filters, tubing, connectors, etc.).

Use of in-dwelling ports [including ones containing titanium (Ti), polyether ether ketone (PEEK), and polyoxymethylene (POM), Polysulfone (PS) and Silicone] are considered acceptable for sac-TMT (MK-2870).

Peripherally inserted central catheters (PICC) are considered approved for sac-TMT (MK-2870) if the body of the catheter is made from an already approved material (e.g. PU).

Use of colored infusion components (e.g., tubing) is acceptable as long as the material itself is compatible, and the colorant is confirmed as non-fluid contacting (not in fluid path).

Choose a suitable infusion bag material. The bag may be empty, or it may contain diluent. The following materials are compatible with sac-TMT (MK-2870) and acceptable for use.

When assessing a material for compatibility, only those materials of construction in the fluid path that have the largest contact (longest time/surface area) with the drug product will be assessed for given

component type (i.e., for a line only the material of the line and the filter, not the luer locks, injection ports, etc.).

The table below is only applicable for **IV administration**.

| | **Syringe** | **Needle** | **IV Bag** | **Infusion Line** | **0.2 µm Filter membrane[a]** | **Catheter (for IV use)** |
|---|---|---|---|---|---|---|
| *Solution in Fluid Path* | *Drug Product or Admixture* | *Drug Product or Admixture* | *Admixture* | *Admixture* | *Admixture* | *Admixture* |
| PP | ☑ | | ☑ | ☑ | | |
| SS[b] | | ☑ | | | | |
| | | | | | | |
| PVC + Diethylhexl-Phthalate (DEHP)[c] | | | ☑ | ☑ | | ☑ |
| | | | | | | |
| Polyolefin (PO)[d] | | | ☑ | ☑ | | |
| Ethylvinyl Acetate (EVA) | | | ☑ | ☑ | | |
| PU | | | | ☑ | | ☑ |
| PE[e] | | | ☑ | ☑ | | ☑ |
| BD Vialon [same as PU] | | | | ☑ | | ☑ |
| Polybutadiene (PBD) | | | | ☑ | | |
| FEP[f] | | | | | | ☑ |

| | | | | | | |
|---|---|---|---|---|---|---|
| Polyethersulfone (PES) | | | | | ☑ | |
| Polysulfone (PS) | | | | | ☑ | |
| Polyamide (Nylon) | | | | | ☑ | |
| Si | ☑ | | | | | |

[a] required (refer to section 13.1)

[b] Stainless Steel is an alloy that can be composed of different metals (ex. Chromium, Nickel, etc.)

[c] All forms of PVC with or without plasticizer (e.g., DEHP), are considered compatible

[d] Polyolefin (PO) is a mixture of PP (Polypropylene) and PE (Polyethylene), if PO is selected from the table PP and PE are also considered compatible.

[e] Polyethylene can also be referred to as LDPE (Low Density Polyethylene) or HDPE (High Density Polyethylene)

[f] Medical grade fluoropolymers ( Tetrafluoroetheylene /TFE, Polytetrafluoroethylene/PTFE (teflon), Ethylene tetrafluoroethylene/ETFE, Fluorinated ethylene propylene/FEP) can be considered as a class. If one is found compatible, the others are also acceptable for use. For MK-2870 FEP is considered approved based on acceptable data for PTFE in CSTD.

*For preparation of infusions, choose suitable ancillary equipment (Infusion Pumps, Infusion sets) that are registered for use in accordance with their marketing authorizations. The ancillary equipment should be used in accordance with the manufacturer's instructions.*

### 12.1.5 In-use stability

Prior to the vial being pierced, the vial should be kept at refrigeration, protected from light and then brought to RT prior to mixing. Microbiological in-use stability time starts when the first vial is pierced.

**Sac-TMT (MK-2870) reconstituted drug product** is recommended to be used immediately after preparation. If not used immediately, the reconstituted drug product can be stored in its original container at refrigerated conditions for up to 24 hours or ambient conditions for up to 12 hours prior to preparation of admixture solution. Sac-TMT (MK-2870) reconstituted drug product should be refrigerated ONLY if it cannot be used to prepare the admixture solution in less than 12 hours after reconstitution.

**Sac-TMT (MK-2870) admixture solution** for IV administration can be stored at RT for up to 8 hours including infusion time. Sac-TMT (MK-2870) admixture solution can be refrigerated at 2-8°C (36-46°F) as long as the total cumulative storage time at RT and refrigerated time does not exceed 16 hours, including infusion time. Sac-TMT (MK-2870) admixture solution should be refrigerated ONLY if it cannot administered in less than 8 hours.

Temperature monitoring records are required when sac-TMT (MK-2870) reconstituted drug product or admixture solution is refrigerated or when the intra-site transfer of sac-TMT (MK-2870) solution is performed leaving the controlled hospital/clinic setting (transport outside) per Section 9. The solution can only be accounted for as refrigerated when stored with a Temperature Monitoring Device and reported temperature between 2-8°C. Time when temperature was above 8°C should be deducted from the 8-hour RT time bucket.

DO NOT SHAKE OR FREEZE THE VIAL(S) or sac-TMT (MK-2870) INFUSION SOLUTION.

DO NOT USE sac-TMT (MK-2870) INFUSION SOLUTION IF DISCOLORATION OR VISIBLE PARTICLES ARE OBSERVED.

TEs on reconstituted supplies should NOT be reported to Clinical Complaint Intake mailbox.

## 12.2 Drug Product Pembrolizumab (MK-3475) for IV Infusion

**Pembrolizumab (MK-3475) Solution for Infusion, 100 mg/ 4 mL vial**

Pembrolizumab (MK-3475) Solution for Infusion is a sterile, non-pyrogenic aqueous solution supplied in single-use Type I glass vial containing 100 mg/4 mL of pembrolizumab (MK-3475). The product is preservative-free, latex free solution which is essentially free of extraneous particulates.

- Pembrolizumab (MK-3475) Solution for Infusion vials are filled to a target of 4.25mL (106.25mg) to ensure recovery of 4.0mL (100mg).

### 12.2.1 Dose Calculation

**200 mg Fixed Dose**

- **2 vials (100 mg/4 mL)**
- **8 mL total**

**400 mg Fixed Dose**

- **4 vials (100mg/4 mL)**
- **16 mL Total**

### 12.2.2 Method of Preparation

The preferred method of dose preparation is the volumetric method.

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 4.0 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 (MK-3475) solution, a value of 1.03 g/mL should be used.

Aseptic technique must be strictly observed throughout the preparation procedure. Use of a biosafety cabinet is preferred since no anti-microbial preservative is present in the product; however, it is not mandatory unless specified by site standard operating procedure.

If particles seen in the unpierced vials, these will need to be reported as Clinical Supply Complaints.

### 12.2.3 Diluent

Pembrolizumab (MK-3475) infusion solutions should be prepared in 0.9% Sodium Chloride Injection, USP (normal saline) or regional equivalent or 5% Dextrose Injection, USP (5% dextrose) or regional equivalent.

The final concentration of pembrolizumab (MK-3475) in the infusion solution should be between **1 mg/mL and 10 mg/mL.**

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.

Calculate the volume of pembrolizumab (MK-3475) and normal saline required to prepare the infusion (admixture) bag

Volume of pembrolizumab (MK-3475) (mL) = required dose amount (mg) / 25 (mg/mL)

Volume of normal saline = total infusion volume – volume of pembrolizumab (MK-3475) from above

If a bag pre-filled with normal saline is being used, remove the excess volume of normal saline using a sterile syringe (Polypropylene, latex-free) attached to a suitable needle. Keep in consideration the excess bag fill volume as well as the volume of pembrolizumab (MK-3475) to be added to the bag to prepare the infusion solution. 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. If the site would like to proceed without removing excess saline they must ensure that the concentration of MK-3475 would still fall within acceptable range.

If an empty bag is being used, withdraw the necessary volume of normal saline from another appropriate bag and inject into the empty bag. Keep in consideration the volume of pembrolizumab (MK-3475) to be added to the bag to prepare the infusion solution.

Withdraw the required volume of pembrolizumab (MK-3475) from the vial(s) (up to 4 mL from each vial) using a sterile syringe attached to a suitable needle. The vial(s) may need to be inverted to remove solution.

Volume of pembrolizumab (MK-3475) (mL) = required dose amount (mg) / 25 (mg/mL)

**Note:** If it is necessary to use several vials, it is advisable to withdraw from several vials into a suitable size single use syringe using a new needle for each vial.

Add the required pembrolizumab (MK-3475) into the infusion IV bag containing normal saline and gently invert the bag 10-15 times to mix the solution.

Discard any unused portion left in the vial as the product contains no preservative

The infusion bags with pembrolizumab (MK-3475) and bags with placebo must be labeled the same way in accordance with clinical practice to maintain the blind.

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. Please contact CRA/uCRA if particulates are noticed for further instructions. Be prepared to provide the following information:

- IV bag manufacture, lot and expiry
- Target volume of admixture solution in the IV bag (e.g. 100 mL, 200 mL etc.)
- Amount of drug product (mL or mg) added to the bag
- Drug product lot
- Brief description of the nature of visible particles (color, shape, size, numbers etc.).

Prevention of particulates:

- Minimize agitation (Please note there is particulate formation when there is over agitation of the product and when concentrations are less than 1 mg/mL)
- Ensure dilution of admixture solution is 1mg/mL to 10 mg/mL
- Minimization of headspace (empty space over the liquid) in syringes and admixture bags
- Avoid siliconized products during preparation

If particles are seen in the admixture solution, these need to be reported to the CRA/uCRA. These should not be reported directly as Clinical Supply Complaints.

Local guidelines should be followed for collection of diluent information such as manufacturer, lot, and expiry. When the diluent is provided by MSD, the Participant clinical supply accountability log should be used for collection of diluent informationInfusion

### 12.2.4 Device Components (IDC)

IDCs contain the Closed System Transfer Device (CSTD) and other infusion components in the fluid path (e.g., syringe, needle, IV bags, infusion set materials like in-line filters, tubing, connectors, etc.) for intravenous (IV) and injectable (syringes and needles) investigational product delivery.

Ensure that only the approved IDCs listed in sections 12.1.4.1 CSTD (Closed System Transfer Devices) and 12.1.4.2 Other Infusion Components are used. Contact the Sponsor via the CRA to check for compatibility of the IDCs used, and do not use until approved. If there is any change in the IDC, please notify the Sponsor through the CRA.

#### 12.2.4.1 CSTD (Closed System Transfer Devices)

CSTD is a drug transfer device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of the hazardous drug or vapor concentrations outside the system.

CSTDs are not required to be used with pembrolizumab (MK-3475) but can be used if required per local practice.

Use of spikes or other CSTDs and other infusion components are permitted if the pharmacist is aware of the void volume (volume of fluid that is left in the device) and that the materials of construction in the fluid path are compatible. Please consider the void volume while preparing and administering the product and flush if appropriate

The CSTD's and other infusion components that have been tested for contact material compatibility and dose accuracy include:

| Supplier Name (or equivalent)* | Void Volume for CSTD set (measured) (mL) | Materials tested for CSTD |
|---|---|---|
| EquaShield | 0.20 | Polypropylene(PP)<br>Silicone (Si), Silicone Oil<br>Stainless steel (SS)<br>Polyisoprene (PI)<br>Polyvinyl chloride (PVC)<br>Polytetrafluoroethylene (PTFE)<br>Thermoplastic elastomer (TPE)<br>Polycarbonate (PC)<br>Acrylic (Nylon)<br>Acrylonitrile butadiene styrene copolymer (ABS)<br>Polyurethane (PU)<br>Flurosilicone (Fsi) |
| BD Texium | 0.21 | |
| ICU Medical ChemoClave | 0.42 | |
| ICU Medical ChemoLock | 0.64 | |
| B Braun<br>TEVADAPTOR | 0.25 | |
| BD<br>PhaSeal | 0.17 | |

### 12.2.4.2 Other Infusion Components

Infusion Components for intravenous (IV) and injectable (syringes and needles) for investigational product delivery include, but are not limited to, syringes, needles, IV bags, infusion set materials (e.g., in-line filters, tubing, connectors, etc.).

When assessing a material for compatibility, only those materials of construction that have the largest contact (longest time/surface area) with the drug product will be assessed for given component type (i.e., for a line only the material of the line and the filter, not the luer locks, injection ports, etc.).

Use of in-dwelling ports (including ones containing titanium (Ti) , polyether ether ketone (PEEK), and polyoxymethylene (POM), Polysulfone (PUS) and Silicone) are considered acceptable.

Peripherally inserted central catheters (PICC) are considered approved for MK3475 if the body of the catheter is made from an already approved material (e.g. PU).

Use of colored infusion components (i.e., tubing) is acceptable as long as the material itself is compatible, and the colorant is confirmed as non-fluid contacting (not in fluid path).

**Silicone rubber and Silicone oil :** The use of silicone oil as a lubricant is not preferred; however, its presence does not pose a significant issue. In contrast, silicone tubing, which is composed of silicone rubber, is deemed acceptable for use. Choose a suitable infusion bag material. The bag may be empty, or it may contain diluent. The following materials are compatible with pembrolizumab (MK-3475) and acceptable for use,

| | Syringe | Needle | IV Bag | Infusion Line | In-line Filter membrane | 0.2 µm Filter[a] membrane | IV Catheter |
|---|---|---|---|---|---|---|---|
| *Solution in Fluid Path* | *Drug Product or Admixture* | *Drug Product or Admixture* | *Admixture* | *Admixture* | *Admixture* | *Admixture* | *Admixture* |
| Polypropylene (PP) | ☑ | | ☑ | ☑ | | | ☑ |
| Stainless Steel** | | ☑ | | | | | |
| Polyvinyl chloride (PVC) + DEHP[2] | | | ☑ | ☑ | | | ☑ |
| Polyolefin (PO)* | | | ☑ | ☑ | | | |
| Ethylvinyl Acetate (EVA) | | | ☑ | ☑ | | | |
| PE | | | ☑ | ☑ | | | ☑ |
| Glass | | | ☑ | | | | |
| PU | | | | ☑ | | | ☑ |
| FEP[3] | | | | | | | ☑ |
| Polybutadiene (PBD | | | | ☑ | | | ☑ |
| Polyamide (Nylon) | | | | | ☑ | ☑ | |
| Polysulfone | | | | | ☑ | ☑ | |
| polyvinylidene fluoride (PVDF) | | | | | ☑ | ☑ | |
| Acrylic co polymer (Versapor) | | | | | ☑ | ☑ | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| mixed cellulose ester (MCE or MEC) | | | | | ☑ | ☑ | |
| Surfactant Free Cellulose Acetate (SFCA) | | | | | ☑ | ☑ | |
| Regenerated Cellulose (RC) | | | | | ☑ | ☑ | |
| Polyether_sulfone (PES) | | | | | ☑ | ☑ | |
| Polycarbonate | ☑ | | | | | | |

[a] required

*Polyolefin (PO) is a mixture of PP (Polypropylene) and PE (Polyethylene), if PO is selected from the table PP and PE are also considered compatible.

** Stainless Steel is an alloy that can be composed of different metals (eg., Chromium, Nickel, etc.)

Notes regarding Compatibility Table: Unless otherwise specified the following clarifications are applicable and can be taken into consideration when selecting compatible materials from the table above:

1. Polyethylene can also be referred to as LDPE (Low Density Polyethylene) or HDPE (High Density Polyethylene)
2. If polyvinyl chloride (PVC) is listed with the plasticizer DEHP, all forms of PVC (with or without other plasticizers) are also considered compatible.
3. Medical grade fluoropolymers (Tetrafluoroetheylene/TFE, Polytetrafluoroethylene/PTFE (Teflon), Ethylene tetrafluoroethylene/ETFE, Fluorinated ethylene propylene/FEP) can be considered as a class. If one is found compatible, the others are also acceptable for use.

*For preparation of infusions, choose suitable ancillary equipment (Infusion Pumps, Infusion sets) that are registered for use in accordance with their marketing authorizations. The ancillary equipment should be used in accordance with the manufacturer's instructions.*

### 12.2.5 In-use stability

Microbiological in-use stability time starts when the first vial is pierced. From a microbiological point of view, diluted solution should be used as soon as possible after preparation.

Pembrolizumab (MK-3475) admixture solution can be stored at RT for up to 6 hours including infusion time. The 6-hour countdown begins when the vial is pierced and includes room temperature storage of admixture solutions in the IV bags and the duration of infusion. (Please note this 6-hour timeframe is to provide a microbial control strategy. The microbial clock only starts when the product stopper is pierced and not when the vial is removed from the refrigerator.).

Pembrolizumab (MK-3475) admixture solution can be refrigerated at 2-8°C (36-46°F) total cumulative storage time at room temperature and refrigeration should not exceed 24 hours (96 hours is acceptable dependent upon country approved commercial Keytruda label).

Temperature monitoring records, including the time placed in and taken out of refrigerated storage, are required when pembrolizumab (MK-3475) admixture solution is refrigerated or when the intra-site transfer of pembrolizumab (MK-3475) admixture solution is performed leaving the controlled hospital/clinic setting (transport outside). The admixture solution can only be accounted for as refrigerated when stored with a Temperature Monitoring Device and reported temperature between 2-8°C. Time when temperature was above 8°C and below 25°C should be deducted from the 6-hour RT time bucket.

DO NOT SHAKE OR FREEZE THE VIAL(S) or INFUSION SOLUTION.

DO NOT USE PEMBROLIZUMAB (MK-3475) IF DISCOLORATION OR VISIBLE PARTICLES ARE OBSERVED.

TEs on reconstituted supplies should NOT be reported to Online Clinical Supply Incident Form.

# 13 Clinical Supply Administration

## 13.1 Administration guidance for sac-TMT (MK-2870) IV Infusion

Microbiological in-use stability time should include the infusion time.

The duration of the sac-TMT (MK-2870) infusions should be 90 minutes (±15 minutes) using an infusion pump or other medical device validated to control infusion rate. All infusion-related adverse events (AEs) must be monitored. The infusion duration may be adjusted to be longer than 105 minutes at the discretion of investigator, but the infusion of sac-TMT (MK-2870) needs to be completed within 8 hours after the solution is prepared (total of 8 hours at RT). After at least 4 administrations and in the absence of either infusion-related AEs or anaphylactic reactions, the infusion of sac-TMT (MK-2870) may be shortened at the discretion of the investigator but cannot be shorter than 60 minutes.

All participants are to be administered appropriate premedications as outlined in the protocol. Participants are to be closely monitored during and after the infusion as outlined in the protocol for the development of a hypersensitivity reaction and/or infusion reaction. Emergency rescue medications (including epinephrine) and appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.

DO NOT ADMINISTER THE PRODUCT AS AN IV PUSH OR BOLUS.

DO NOT COMBINE, DILUTE OR ADMINISTER THE PRODUCT AS AN INFUSION WITH OTHER MEDICINAL PRODUCTS.

CAUTION: DO NOT SHAKE THE BAGS OTHERWISE THIS MAY RESULT IN FORMATION OF FOAM.

Infuse all contents of the IV bag. Flushing the infusion line is required, and should be performed per local SOP to ensure the entire contents of the bag are administered. The main infusion line for all participants must be flushed with normal saline or 5% dextrose or regional equivalent which was used as diluent, after administration of sac-TMT (MK-2870) infusion.

Refer to the infusion bag and infusion set materials chapter for the compatible materials.

A sterile, non-pyrogenic, low-protein binding 0.2 μm in-line filter must be used during administration to remove any adventitious particles. If the infusion set does not contain 0.2 μm in-line filter, it is recommended to use 0.2 μm add-on filter which may contain an extension line (Note: the materials of the extension line and filter should be compatible to sac-TMT (MK-2870)).

Investigator or authorized site staff will monitor sac-TMT (MK-2870) administration to ensure compliance and proper documentation of the infusion procedure as well as management of infusion reactions should they occur. If there are interruptions in the study intervention schedule or the infusion was stopped, the details of and reason for any interruption or infusion cessation of study intervention will be documented in the participant's medical record.

Ensure that **IV bags/syringes and materials** that are used for preparation and administration are destroyed per investigator site SOP and pursuant to local regulations.

## 13.2 Administration guidance for Pembrolizumab (MK-3475) IV Infusion

Microbiological in-use stability time should include the infusion time.

If refrigerated, allow the IV bags to come to room temperature prior to use. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Pembrolizumab (MK-3475) infusions should be administered in 30 minutes, with a window of -5 and +10 minutes, using an infusion pump. A central catheter is not required for infusion; however, if a subject has a central venous catheter in place, it is recommended that it be used for the infusion.

**Caution**: Do not shake the vials/bags otherwise this may result in formation of foam. If foam is noticed in either vial or bag, the drug product will need to be discarded. A new preparation should be made, taking care not to shake or agitate the product.

A sterile, non-pyrogenic, low-protein binding 0.2 to 5 μm in-line filter made of polyethersulfone (PES) must be used during administration to remove any adventitious particles. If the infusion set does not contain 0.2 to 5 μm in-line filter, it is recommended to use 0.2 to 5 μm add-on filter which may contain an extension line.

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 subjects must be flushed with saline or 5% dextrose or regional equivalent which was used as diluent, after administration of MK-3475 infusion.

Investigator or study staff will monitor pembrolizumab (MK-3475) administration to ensure compliance and proper documentation of the infusion procedure as well as management of infusion reactions should they occur. If there are interruptions in the study intervention schedule or the infusion was stopped, the details of and reason for any interruption or infusion cessation of study intervention will be documented in the participant's medical record.

Refer to the Infusion bag and infusion set materials chapter for the compatible materials.

**Procedure for administration**

- Attach the infusion line to the pump and prime the line, either with normal saline (at least 25 mL) or with infusion solution as per local SOP, before starting the infusion.
- Infuse pembrolizumab (MK-3475) over approximately 30 minutes, with a window of -5 and +10 minutes, through a peripheral line or indwelling catheter.
- 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 subjects 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.
- Whenever possible, the lowest infusion rate should be used that will allow completion of the infusion within the 30 minutes.
- Maximum rate of infusion should not exceed 6.7 mL/min. through a peripheral line or indwelling catheter.
- However, when it is necessary to infuse a larger volume (i.e. 250 mL), the flow rate may go as high as 10 mL/min (maximum) in order to keep the infusion within the window as defined above.

DO NOT ADMINISTER THE PRODUCT AS AN INTRAVENOUS (IV) PUSH OR BOLUS.

DO NOT COMBINE, DILUTE OR ADMINISTER THE PRODUCT AS AN INFUSION WITH OTHER MEDICINAL PRODUCTS.

DO NOT CO-ADMINISTER OTHER DRUGS THROUGH THE SAME INFUSION LINE.

UNUSED INFUSION SOLUTION FOR INJECTION SHOULD NOT BE USED FOR ANOTHER INFUSION OF THE SAME SUBJECT OR DIFFERENT SUBJECT.

Ensure that **used Intravenous Injection (IV) bags/syringes, supplied by clinical site,** and used for preparation and administration are destroyed per site SOP and pursuant to local regulations.

# 14 Electronic Data Capture

Follow the instructions in the **Data Entry Guidelines**.

# 15 Re-Evaluation Date (RED) and Expiry Date Management

The Re-Evaluation Date (RED) and Expiry date, also referred to as the Use By date, represent the time during which the product is expected to remain within established shelf life specifications , if stored under defined conditions, and after which should not be used.

RED will be used throughout this document for simplicity. The RED is available on the clinical label or on BRC or in IRT.

Investigator site should monitor dates of the clinical supplies at their location and check RED prior to dispensing / administering clinical supplies to the participant. Unless Investigator site is notified by Sponsor that the RED will be extended, the date should be treated as the final expiry date. Expired supplies should be segregated, reconciled, and returned / sent for destruction. Required storage conditions do not need to be maintained for expired products. Site TEs impacting only expired products are not reportable if participants have not been dosed.

In case of DPE contact your CRA and report the incident by completing the Online Clinical Supply Incident Form:

www.csincident.msd.com

If RED is extended, Sponsor will provide the necessary instructions.

# 16 Return, Alternative Disposition, and Destruction

The ICH GCP guidelines require that the investigator site maintains adequate records of **the return or alternative disposition of** unused product(s) in compliance with the Sponsor and applicable local requirements.

Destruction of **unused** clinical supplies should be carried out only **after reconciliation** by the investigator site staff has been verified and destruction **approved** by CRA as confirmed by their signatures on the CSRF or equivalent document in accordance with Good Manufacturing Practice (GMP) requirements. The IRT CSRF or IRT Report should be used. If an equivalent site return form is used, it should be reconciled with the IRT CSRF /Report to make sure all clinical supply units / CIDs received by the site have been accounted for. If the IRT CSRF cannot be generated, the IRT report containing the clinical supply units / CIDs returned can be attached to the CSRF.

Once the study is terminated or completed, **ALL remaining clinical supplies** must be returned to Sponsor or destroyed locally.

- **Return to the Sponsor**: the facility address will be provided by CRA.
- **Destroy locally at investigator site or at a destruction facility subcontracted by the site** if authorized by CRA and in compliance with Sponsor and applicable local requirements :
    - Clinical supplies are appropriate to be destroyed at investigator site as confirmed by the Sponsor.
    - The investigator site has required facilities and written SOPs in place to undertake destruction.

- The required method of destruction of **all** clinical supplies is **incineration** in accordance with all applicable local regulations. Please contact the CRA for approval to use alternative methods of destruction.
- If **unused** clinical supplies are destroyed locally, the **certificate of destruction or receipt for destruction** with traceability to CIDs / CSRF and the actual quantities destroyed must be provided to the Sponsor in accordance with GMP requirements.

If the local destruction facility process does not meet Sponsor requirements, clinical supplies should be returned to the Sponsor's designated facility.

It is preferred that all **unused** clinical supplies are returned to Sponsor's Designated Facility. Additionally, it is preferred that hazardous waste, such as used vials and syringes, be locally destroyed at the investigator site according to site procedures in compliance with the applicable Sponsor and local requirements as verified and approved by CRA.

Interim returns and/or destruction during the study may also be required. Interim CSRF or equivalent can be used to document interim clinical supply reconciliation by documenting discrepancies identified.

 Follow the instructions on the **Clinical Supply Return Form**.

# 17 Summary Of Revisions

| Version Number | Revision Date | Revisions to Document |
|---|---|---|
| 1.0 | 21-Jan-2025 | Initial Version |
| 2.0 | 09-Apr-2025 | Updated instructional guidance throughout, per GCD SOP 201.29 version 10. |
| 2.0 | 09-Apr-2025 | Section titles and formatting (ie, order of sections) have been updated to align with GCD SOP 201.29 version 10.<br>Please note, only content-related tracked changes have been flagged in this document.<br>• "Clinical Supply Receipt at Site" moved to Section 6 and renamed "Receipt at Site"<br>• "Storage and Temperature Monitoring" moved to Section 7<br>• "Clinical Supply Complaint and Site TE Reporting" moved to Section 8<br>• "Transfer" moved to Section 9<br>• "Interactive Response Technology (IRT)" moved to section 10<br>• "Participant Investigational Product Accountability" renamed to "Participant Clinical Supply Accountability Records" and moved to Section 11<br>• "Investigational Product Preparation" renamed to "Clinical Supply Preparation" and moved to section 12<br>• "Investigational Product Administration" renamed to "Clinical Supply Administration" and moved to Section 13 |

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| | | • "Electronic Data Capture" moved to Section 14<br>• "Clinical Supply Re-Evaluation Date (RED) and Expiry Date Management" renamed to "Re-Evaluation Date (RED) and Expiry Date Management" and moved to Section 15<br>• "Clinical Supply Alternative Disposition, Return, and Destruction" renamed to "Return, Alternative Disposition, and Destruction" and moved to Section 16. |
| 2.0 | 09-Apr-2025 | ICH GCP E6 (R3) updates throughout the document: Changed "patients" and "subjects" to "participants" and source "document" to source "record". |
| 2.0 | 09-Apr-2025 | Changed "clinical" site to "investigator" site throughout, per GCD SOP 201.29 v10 update (for added clarity). |
| 2.0 | 09-Apr-2025 | Section 3: Updated Study Intervention Table in alignment with GCD SOP 201.29. |
| 2.0 | 09-Apr-2025 | Section 5:<br>• Added guidance to include documentation that participants were provided doses specified in the protocol.<br>• Added guidance for the confirmation of receipts of the shipment in IRT, as indicated on the Packing List.<br>• Added guidance regarding the allocation of pooled kits will be carried out using a unique CID number across trials. |
| 2.0 | 09-Apr-2025 | Section 7:<br>• Added guidance that clinical supplies that are stored or transferred must be stored in accordance with requirements of the Sponsor and applicable local regulations.<br>• Added guidance that temperature control at the site is required from the time the clinical supply is received until it is either dispensed or until prepared or until it is no longer needed for use.<br>• Added examples of a temperature controlled, secure area.<br>• Added guidance regarding requirements of temperature monitoring devices – continuous monitoring, electronic reports, backup devices, records/logs, Min/Max temperature, etc.<br>• Added guidance for temperature monitoring records documentation if the site has a process and if the site does not have a process.<br>• Added guidance regarding the timing to reportable temperature excursions (TEs) as soon as possible, preferable within one business day.<br>• Reworded and added clarifying guidance for temperature monitoring records.<br>• Moved and reworded language regarding rounding rules for reportable and non-reportable TEs. |
| 2.0 | 09-Apr-2025 | Section 8:<br>• Updated mailbox for clinical supply complaint to website www.csincident.com. |

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| | | • Added guidance to complete the Clinical Supply Complaint and Site Temperature Excursion Form for system downtime or technical issues.<br>• Removed statement that cosmetic defects are not reportable as PQCs.<br>• Added new table to determine if there is a reportable site temperature excursion that includes the label storage condition, reportable and non-reportable site temperature excursion.<br>• Added guidance if there is no reliable temperature data at clinical site.<br>• Added guidance if the calibration of the temperature monitoring device (TMD) has expired.<br>• Added guidance for incidents should not be reported on the Clinical Supply Complaint and Site TE Form.<br>• Removed statement to that the CRA/uCRA is copied on the email to the Clinical Complaint Intake Mailbox and added that the CRA/uCRA should be notified of the incident.<br>• Added guidance for submitting additional information for a Shipping TE, Distribution Complaints, and a Reportable Site TE.<br>• Added guidance if supply return is required to facilitate investigation, the Sponsor will provide instructions and documentation.<br>• Clarified examples, that are not a reported on the Clinical Supply Complaint and Site TE Form.<br>• Added MSD Logistics mailbox to example for missing shipping records. |
| 2.0 | 09-Apr-2025 | Section 9:<br>• Added clarification regarding requirement) for when a TMD and Shipper are required.<br>• Modified sac-TMT (MK-2870) specific guidance:<br>  ○ "If this criterion cannot be confirmed to …" "… is at risk for being met…" |
| 2.0 | 09-Apr-2025 | Section 10 updated for GCD SOP 201.29 version 10. |
| 2.0 | 09-Apr-2025 | Section 11:<br>• Added clarification and reworded<br>• Added guidance that the completed DISPENSING log should be filed in eTMF.<br>• Added guidance to delete paragraph regarding a separate ADMINSTRATION Log if the trail does not have an unblinded component operational model. |
| 2.0 | 09-Apr-2025 | Section 12:<br>• Reconstitution guidance updated – sac-TMT (MK-2870) drug product vial "must" be reconstituted with SWFI<br>• Removed sentence regarding use of a biosafety cabinet being preferred, as aseptic technique must be followed.<br>• Updated Infusion Device Compatibility guidance |

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| | | • Added guidance that in-dwelling ports made from titanium (Ti), polyether ether ketone (PEEK), polyoxymethylene (POM), polysulfone (PUS), and silicone are approved for use with all MK compounds.<br>• Added guidance that colored infusion components are acceptable if the material is compatible, and the colorant is non-fluid contacting (not in the fluid path).<br>• Added statement that compatibility assessment focuses on materials with the largest contact area and duration with the drug product, excluding components like luer locks and injection ports.<br>• Updated table of compatibility materials by adding Polyolefin, Polyethylene, glass, Fluorinated ethylene propylene, stainless steel and silicone. Included general notes on approvals applicable to all MKs, unless stated otherwise.<br><br>• Added guidance on peripherally inserted central catheters (PICC)<br>• Updated compatible materials in sections 12.1.4.2 and 12.2.4.2 |
| 2.0 | 09-Apr-2025 | Section 15:<br>• Updated guidance for reporting an incident by completing the Online Clinical Supply Incident Form. |