PHARMACY MANUAL

MK-2870-027

(Sacituzumab Tirumotecan (sac-TMT))

TROFUSE-027

SPONSOR MERCK SHARP & DOHME LLC
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(hereinafter referred to as MSD or Sponsor)

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Contents

1 Glossary

ABS	Acrylonitrile Butadiene Styrene copolymer
AE	Adverse Event
AxMP	Auxiliary Medicinal Product
AoR	Acknowledgement of Receipt
BRC	Batch Release Certificate
CCQM	Country Clinical Quality Manager
CFG BRC	Clinical Finished Good Batch Release Certificate
CDT	Counterfeit, Diversion and Tampering
CID	Component ID
CoI	Blue Coloring
CRA	Clinical Research Associate
CS	Clinical Scientist
CSRF	Clinical Supply Return Form
CSTD	Closed System Transfer Device
CTT	Clinical Trial Team
DEHP	Diethylhexl-Phthalate
DP	Drug Product
DPE	Dosing Past Expiry
eCRF	Electronic Case Report Form
EEA	European Economic Area
EVA	Ethyl vinyl Acetate
eTMF	electronic Trial Master File
FDA	US Food and Drug Administration
Fsi	Fluro silicone
HB	Hydrophobic barrier
ICH GCP	International Conference on Harmonisation Good Clinical Practice
GMP	Good Manufacturing 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
PO	Polyolefin
PP	Polypropylene
PTFE	Polytetrafluoroethylene
PU	Polyurethane

PVC	Polyvinyl Chloride
RED	Re-Evaluation Date
RT	Room Temperature
SDR	Source Document Review
SDV	Source Document Verification
Si	Silcone
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 CRA is your primary Point of Contact for study-related questions.

The Role	The Name	Contact details	The questions
Clinical Scientist (CS)	Malissa Diehl	E-mail: malissa.diehl@merck.com	Questions regarding the details outlined within this Pharmacy Manual.
IRT Coordinator	Carlos Lee	Phone: +1 (215) 993-0130 E-mail: juan.lee@merck.com	IRT issues

3 Study Interventions

Table 1. 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
Part 1	Experimental	sac-TMT	Biological/ Vaccine	Powder, For Solution	200mg/vial	300 mg 500 mg 750 mg 1000 mg	Intravesical	QW for 6 weeks	Test Product	IMP	Central
Part 1	Experimental	Antihistamine	Drug	Unassigned	Per Approved Product Label	Per Approved Product Label	Per Approved Product Label	Before sac-TMT IVES instillation	Rescue Medication	NIMP/ AxMP	Local
Part 1	Experimental	H2 receptor antagonist	Drug	Unassigned	Per Approved Product Label	Per Approved Product Label	Per Approved Product Label	Before sac-TMT IVES instillation	Rescue Medication	NIMP/ AxMP	Local
Part 1	Experimental	Acetaminophen (or equivalent)	Drug	Unassigned	Per Approved Product Label	Per Approved Product Label	Per Approved Product Label	Before sac-TMT IVES instillation	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
Part 1	Experimental	Dexamethasone (or equivalent)	Drug	Unassigned	Per Approved Product Label	8 to 10 mg (or equivalent)	Per Approved Product Label	Before sac-TMT IVES instillation	Rescue Medication	NIMP/ AxMP	Local

EEA=European Economic Area; IMP=investigational medicinal product; NIMP/AxMP=non-investigational/auxiliary medicinal product.

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.

4 Blinding

Sac-TMT will be sourced, prepared, and administered as an open label product. The Sponsor, investigator, and participant will know the study intervention administered.

5 Clinical Supply 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 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 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, a **Clinical Supply Complaint** should be initiated. See Section 7 for more information on Clinical Supply Complaint Reporting.

File the Acknowledgement of Receipt (signed Shipment records) and documented Alarm status and/or temperature report at site.

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

6 Storage and Temperature Monitoring

Table 2. Storage Requirements

Product	Storage Temperature	Other storage requirements
sac-TMT	2-8°C (36-46°F)	Protect from light

The clinical supplies must be stored under the clinical label storage conditions immediately after proper verification has been performed. Clinical supplies must be stored in a temperature controlled, secure location with limited access.

TMD should meet the following requirements:

- Min/Max TMD that monitors temperature continuously on a 24-hour basis.
- Calibration records or records of maintenance available and valid (not expired).
- Alarm and thermal buffer (glycol-encased probe) are recommended.

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

Min/Max temperature and/or alarm status must be **checked every business day** to ensure reporting of Temperature Excursion (TE) within 1 business day.

Temperature monitoring records must include dates, time, Min/Max temperatures, TMD and storage location clearly identified (serial numbers of the fridge and TMD). Site personnel should transcribe temperature readings onto a Temperature log every business day. If site uses a Min/Max TMD with data logging capabilities AND has a documented process to check Min/Max temperature and/or alarm status every business day, the temperature data when there is no TE can be transcribed onto temperature log or report printed less frequently but at least monthly.

Receipt and process documentation should be filed in the Pharmacy Binder. The CRA should be contacted with any questions concerning study drug where special or protective handling is indicated.

In the eventuality that the study drug is stored in a different location from the site Pharmacy and/or the solution for instillation (sac-TMT) is prepared in a different location from the site Pharmacy, the study drug will be transferred to/from the site using their local intra-site transfer SOPs in a temperature-controlled manner. A clinical supply transfer log will be completed to ensure the traceability of the study drug and to document the transfer conditions. The patient will be treated at the site location.

Temperature monitoring records must contain temperature recordings as per device (not rounded). To determine whether to report a TE, the temperature values should be **rounded** to whole numbers and compared to the required temperature range before reporting:

- Decimal values from 0.1 to 0.4 round down to the nearest whole number (e.g., 8.3 = 8)
- Decimal values from 0.5 to 0.9 round up to the nearest whole number (e.g., 8.7 = 9)

Temperature monitoring is not required for clinical supplies that will no longer be used (used, expired, site or trial is closed, etc.). Make sure clinical supplies that will no longer be used and clinical supplies that are not temperature monitored are segregated from the clinical supplies available for dispensing to participant so that no mix-up can occur.

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

7 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.

For simplicity, in this manual both Clinical Supply Complaints and Site Temperature Excursions will be referred to as 'Clinical Supply Complaints'.

Clinical Supply Complaint should be reported to clinical.complaints.intake@msd.com mailbox using the **Clinical Supply Complaint Form** and submitted electronically in Excel within **1 business day** of first becoming aware of the incident:

- **Product Quality Complaints.** Examples include defective, missing, or broken supplies/labels/devices, broken tablets, inhaler counter issues, change in physical appearance, malfunctioning device, etc.
- **Distribution Complaints** during shipment from MSD / depots to 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).
    - Shipment received in a damaged condition (damaged shipper).
- **Site Temperature Excursions (TE):**
    - Any TE which when rounded falls outside of the clinical label storage conditions at clinical site or during site-to-site / intra-site transfer, after rounding.
    - No reliable temperature data at clinical site - supplies have not been monitored or temperature monitoring device / records do not meet Sponsor requirements (TMD is broken, turned off, calibration expired, clinical supplies transferred without TMD, etc.).

      NOTE: The interruption of continuous temperature monitoring for less than 15 minutes (for example, TMD must be replaced or disconnected to download temperature data) are not reportable, if supplies remain in the required storage conditions.

      If the calibration of the TMD has expired, have it calibrated by a qualified vendor or calibration specialist. Obtain written confirmation that it has been operating in a calibrated state without requiring any adjustments during calibration. This ensures that the temperature data can be considered reliable.

Make sure CRA is copied on the email to the Clinical Complaint Intake Mailbox. Provide **additional documentation** as required on the Form. In case of issues with Excel Macros, ask your CRA to provide the Form without Macros.

Impacted supplies must be **segregated maintaining required storage conditions**, quarantined in IRT and **should not be used or discarded** while the complaint is being investigated.

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.

Do NOT report the following incidents to the Clinical Complaint Intake Mailbox:

- TEs in the Temperature Data Logger report with NO ALARM - supplies are acceptable for use. If it has been documented at site that there was NO ALARM in the received Temperature Data Logger, the absence of a temperature report from the Data Logger is not deemed a reportable event.
- Inability to download Temperature Data from Data Logger (centrally sourced clinical supply shipments only) - contact Sponsor Logistics by sending an email to gcspolicy@msd.com;
- Missing shipment paperwork/documentation in the package - contact your CRA
- Shipping to the incorrect location of the site - perform Intra-Site Transfer of Clinical Supplies and contact your CRA to investigate and address the root cause which may be due to incorrect drug shipping address details in Sponsor systems.
- TE during product preparation or administration - follow in-use stability requirements in Pharmacy Manual or contact your CRA. Product equilibration to room temperature before preparation is also considered a part of preparation.
- Issues clearly related to improper pharmacy preparation for dosing (Examples include improper reconstitution, Pharmacy Manual instructions not followed) - contact your CRA.
- Site dispensing errors which do not put product disposition in question (trial participant who received incorrect study therapy or an incorrect dose, etc.) - contact your CRA.
- Confirmed trial participant errors - trial participant misplacing supplies, adverse storage of supplies by trial participant (e.g., supplies left in hot/cold car, trial participant's refrigerator loses power) and failure to follow instructions for use (e.g., prepared injector out of sequence). Contact your CRA.
- Temperature "excursions" which when rounded fall within the required storage conditions - supplies are acceptable for use. Refer to rounding rules.

- Clinical supplies damaged at site (e.g., got broken, wet, mold) which puts product disposition (i.e., usability) in question - contact your CRA. Supplies are automatically deemed unusable, they should be segregated for return/destruction and quarantined in IRT. If only secondary packaging is damaged, but the primary packaging/tamper seal is intact, site pharmacist can decide if product can be used. If there are any doubts about product usability, do not use the product.
- Dosing Past Expiry (DPE): contact your CRA and/or notify the GCP investigation mailbox (gcp.cs.inv@msd.com).
- Adverse storage of Clinical supplies that will no longer be used (used, expired, site or trial is closed, etc.).
- Alleged Counterfeit, Diversion and Tampering (CDT) - contact your CRA.
- Locally sourced product Complaints - report to local sourcing supplier, pharmacy or manufacturer directly if applicable.

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

8 Clinical Supply Accountability and Reconciliation

The Clinical Supply Accountability **Records** should allow full traceability at CID level of all kits (used and unused), received by clinical site, and should include:

- ✓ delivery to the Site: Acknowledgement of Receipt (AoR) (signed and dated shipping records such as drug order form or packing list or shipping request),
- ✓ the use by each participant (Participant Clinical Supply Accountability Log),
- ✓ the Return to Sponsor (CSRF) or alternative Disposition Records (locally destroyed kits and discrepancies (lost kits) documented on the Participant Clinical Supply Accountability Log CSRF or equivalent document),
- ✓ the Destruction Records (Destruction certificate or AoR from the destruction facility) of unused clinical supplies destroyed locally at site/site subcontracted destruction facility with traceability to CSRF/ equivalent document or destroyed kits.

These records should include dates, quantities, and the CIDs assigned to the product(s) and participant(s) to ensure full traceability. CIDs can be traced to the Batch numbers and expiry dates on the shipping records, BRC and/or in IRT. IRT can be used to check available clinical supply inventory at site at any given moment and as a supporting tool to perform clinical supply reconciliation. Clinical Supply Accountability Records 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 eTMF.

Reconciliation of clinical supplies received from the Sponsor and maintenance of Clinical Supply Accountability Records is the responsibility of clinical site/pharmacy personnel to ensure that all kits/CIDs are accounted for. All discrepancies must be investigated and explained by the clinical site/pharmacy personnel on the Accountability Records. Destruction of **unused** clinical supplies should be carried out only after reconciliation by the clinical site staff and CRA as confirmed by their signatures on the CSRF or equivalent (see Section 15 for more information on destruction).

9 Interactive Response Technology (IRT)

This study will utilize IRT for the handling of clinical supplies at all investigator sites. Intervention allocation 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 site personnel, 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.

10 Participant IP Accountability

As required by Good Clinical Practice Guidelines, the **Participant Clinical Supply Accountability Log** provides documentation that the investigational products have been used according to the protocol and documents the final accounting of investigational products dispensed. The Log should be completed for

all centrally sourced clinical supplies and locally sourced IMPs. After completion or termination of the trial, this documentation should be located in the files of the investigator/ institution and sponsor. 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 (for example 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**.

All fields indicated on a trial-specific Sponsor Participant Clinical Supply Accountability Log are required to be collected for this study **at clinical site** on this log or other source documents identified on the source document identification log. Clinical sites or CRA should not remove any information from the study specific logs without consulting Clinical Trial Team (CTT) or CCQM to make sure ICH GCP, study specific and data privacy requirements are met. Information marked with asterisk (*) is the minimum information required to be copied to **Sponsor eTMF** per ICH GCP. If the alternate site log cannot be copied to the Sponsor eTMF (e.g., includes multiple site documents or data privacy requirements are not met) then the minimum information marked with asterisk (*) must be transcribed by the site onto one document (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 document. The CRA must be given direct access to the original source or a certified copy of transcribed information for SDR/SDV.

Disposition of **used sponsor provided clinical supplies** should be documented at the clinical site and a completed copy should be filed in the Sponsor eTMF. If disposition of used clinical supplies is documented on a **Clinical Supply Return Form (CSRF)** or equivalent document, DISCARD section on this log is **optional**.

It is preferred that hazardous waste (e.g., **used** vials, syringes, oncology products) is destroyed locally at clinical site according to site procedures that meet Sponsor requirements as verified and approved by CRA.

The original log is retained at the site and a completed copy of Participant Clinical Supply Accountability Log (DISPENSING/PREPARATION and DISCARD sections if used) is filed in the Sponsor eTMF.

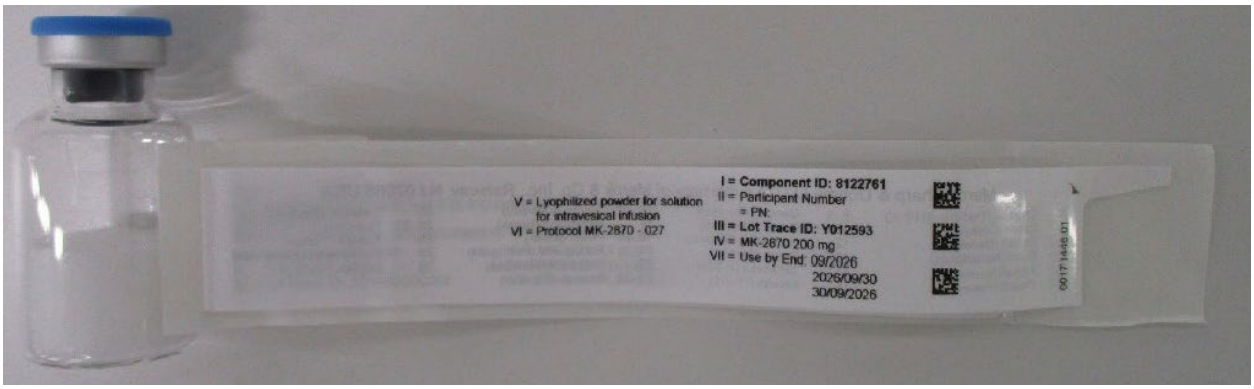
Follow the instructions on the **Participant Clinical Supplies Accountability Log**.

11 IP Preparation

11.1 Drug Product sac-TMT (MK-2870)

Sac-TMT powder for intravesical instillation is a sterile, non-pyrogenic lyophilized powder supplied in single-use Type I glass vial containing **200 mg/vial** (20 mg/ml) of sac-TMT. The lyophilized drug product must be reconstituted with 10 mL of sterile water for injection (SWFI) prior to use. The reconstituted product is a preservative-free solution which is essentially free of extraneous particulates. Sac-TMT

Drug Product (DP) vials are filled with excess to ensure recovery of 10 mL (200 mg) after reconstitution. An example of the sac-TMT vial is shown below.



11.2 Dose Calculation

The preparation of intravesical solution should be based on Table 3 below.

Table 3. Dose Calculation

	Dose level 0*	**Dose level 1**	**Dose level 2**	**Dose level 3**	**Dose level 4**
Dose per protocol	**150 mg***	**300mg**	**500mg**	**750mg**	**1000mg**
	Step 1. Confirm how many vials are needed.				
Total number of vials required	1 vial	2 vials	3 vials	5 vials	6 vials
	Step 2. Reconstitution *Each vial must be reconstituted with 10 mL of sterile water for injection (SWFI) prior to dilution (see Section 11.3.1)*				
	Step 3. Calculate volume of DP from each vial(s) to be added with diluent to make up final volume of 60 ml.				
Volume of DP to be used for admixture preparation	180mg** / 20 mg/mL = 9 mL	360mg** / 20 mg/mL = 18 mL	600mg** / 20 mg/mL = 30 mL	900mg** / 20 mg/mL = 45 mL	1200mg** / 20 mg/mL = 60 mL
	***Note: Amount in calculations accounts for total amount in a 60 mL admixture solution, from which 50 mL will be administered.*				

Admixture preparation from reconstituted vials	1st vial: 9 mL	1st vial: 10 mL 2nd vial: 8 mL	1st vial: 10 mL 2nd vial: 10 mL 3rd vial: 10 mL	1st vial: 10 mL 2nd vial: 10 mL 3rd vial: 10 mL 4th vial: 10 mL 5th vial: 5 mL	1st vial: 10 mL 2nd vial: 10 mL 3rd vial: 10 mL 4th vial: 10 mL 5th vial: 10 mL 6th vial: 10 mL
Volume of diluent to be added	51 mL	42 mL	30 mL	15 mL	0 mL
Final volume of admixture prepared	60 mL	60 mL	60 mL	60 mL	60 mL
Final volume of admixture administered	50 mL (plus hold-up volume)	50 mL (plus hold-up volume)	50 mL (plus hold-up volume)	50 mL (plus hold-up volume)	50 mL (plus hold-up volume)
Final concentration	3.0 mg/mL	6.0 mg/mL	10.0 mg/mL	15.0 mg/mL	20.0 mg/mL

*Participants may de-escalate to 150 mg if unacceptable toxicity is observed at DL1.

11.3 Method of Preparation

The preferred method of dose preparation is the volumetric method.

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 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 solution, a value of 1.038 g/mL should be used.

11.3.1 Reconstitution

Prior to the vial being pierced, the vial should be brought to room temperature prior to mixing. Each sac-TMT drug product vial 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 THE RECONSTITUTED SOLUTION.

11.3.2 Admixture Preparation

Admixtures should be prepared in accordance with Table 3. Please refer to Table 4 and Table 5 for a list of compatible materials.

Dose Levels 0, 1, 2, and 3:

- Choose a drug-compatible empty IV bag size (e.g. 100 mL).
- Using a sterile, drug-compatible, suitable-size, single-use syringe, add the necessary volume of diluent to the empty bag. Keep in consideration the volume of sac-TMT to be added to the bag to prepare the solution for instillation. Refer to Table 3 for the volume of diluent and DP necessary for each dose level.
- Using a new sterile, drug-compatible, suitable-size, single-use syringe attached to a new needle, withdraw the required volume of sac-TMT from the vial(s) (up to 10 mL from each vial). The vial(s) may need to be inverted to remove solution.

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

- Add the required volume of sac-TMT into the IV bag containing diluent and gently invert the bag 10-15 times to mix the solution.
- Discard any unused portion left in the vial(s).

Dose Level 4:

- Choose a drug-compatible empty IV bag size (e.g. 100 mL).
- Using a sterile, drug-compatible, suitable-size, single-use syringe, withdraw the required volume of sac-TMT from the vial(s) (10 mL from each vial). The vial(s) may need to be inverted to remove solution. Refer to Table 3 for the volume of DP necessary.

Note: It is advisable to withdraw from multiple vials into a suitable-size single-use syringe using a new needle for each vial.

- Add the required volume of sac-TMT into the IV bag.
- Discard any unused portion left in the vials.

11.4 Diluent

- sac-TMT intravesical solutions should be prepared in locally sourced 0.9% Sodium Chloride Injection, USP (normal saline) or regional equivalent. Alternatively, locally sourced 5% Dextrose Injection, USP (5% dextrose) or regional equivalent can also be used.

- For instillation of 1000 mg dose, the reconstituted solution should be used without any dilution.
- The final volume of sac-TMT solution for intravesical administration should be 50 mL (plus hold-up volume) for all dose levels, as described in Table 3.

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 information.

11.5 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 components are permitted as long as the pharmacist is aware of the hold-up volume (volume of fluid that is left in the device) and that the materials of construction in the fluid path are compatible.

The CSTD's and other components that have been tested for contact material compatibility and dose accuracy are listed in Table 4 below:

Table 4. CSTD Components Compatibility

Supplier	**CSTD Parts**	**Hold-up volume for CSTD set (measured) (mL)**
EquaShield	Polypropylene(PP), Silcone (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

Supplier	CSTD Parts	Hold-up volume for CSTD set (measured) (mL)
ICU Medical ChemoClave	Si, PVC, PC, Acrylic, ABS, Nylon, polyethylene (PE), Flurosilicone (Fsi), Blue Coloring (Col)	0.42
ICU Medical ChemoLock	Si, SS, PC, ABS, PE, Fsi, Col	0.64
B Braun TEVADAPTOR	ABS, PI, silicone oil, PVC, PC, stainless steel	0.25
BD PhaSeal	PTFE, TPE, PP, Stainless steel, ABS, Si	0.17

Contact Sponsor for CSTDs not listed above.

Please consider the hold-up volume while preparing and administering the product.

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

11.6 Syringe, IV bag and instillation materials

Choose a suitable empty IV bag material. The following materials are compatible with sac-TMT and acceptable for use:

Table 5. Compatible Materials

	Syringe	Needle	IV Bag	Catheter
Solution in Fluid Path	*Drug Product or Admixture*	*Drug Product or Admixture*	*Admixture*	*Admixture*
Polypropylene (PP)	☑			
Stainless Steel		☑		
Polyvinyl chloride (PVC) + DEHP			☑	☑
PVC + TOTM			☑	☑
Polyolefin (PO)			☑	
Ethylvinyl Acetate (EVA)			☑	
Polyurethane (PU)				☑
Polyethylene (PE)				☑
BD Vialon				☑
Polyethersulfone (PES)				
Silicone	☑			☑
Latex				☑
PVC				☑

Contact Sponsor for materials not listed above.

11.7 In-use stability

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

sac-TMT reconstituted drug product can be stored in its original container for a cumulative 12 hours at RT or 24 hours under refrigerated conditions. sac-TMT reconstituted drug product should be refrigerated ONLY if it cannot be used to prepare the admixture solution in less than 8 hours after reconstitution.

sac-TMT admixture solution can be stored at RT for up to 8 hours including instillation time. sac-TMT 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 instillation time. Sac-TMT admixture solution should be refrigerated ONLY if it cannot be administered within 8 hours of preparation.

At a 20 mg/mL dosing concentration (1000 mg dose), a cumulative 12 hours at RT or 24 hours under refrigerated conditions are allowable, from reconstitution to administration.

Temperature monitoring records are required when sac-TMT reconstituted drug product or admixture solution is refrigerated or when the intra-site transfer of sac-TMT solution is performed leaving the controlled hospital/clinic setting (transport outside). 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 SOLUTION.

DO NOT USE sac-TMT IF DISCOLORATION OR VISIBLE PARTICLES ARE OBSERVED.

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

12 IP Administration

12.1 IP Administration guidance for sac-TMT

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

Sac-TMT is instilled into the bladder by gentle push instillation using a urinary catheter per local SOP. All instillation-related AEs must be monitored.

All participants are to be administered appropriate premedications as outlined in the protocol. Participants are to be closely monitored during the instillation and post-instillation as outlined in the protocol for the development of a hypersensitivity reaction and/or instillation 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 COMBINE, DILUTE OR ADMINISTER THE PRODUCT WITH OTHER MEDICINAL PRODUCTS.

Caution: Do not shake the reconstituted vials, or prepared syringes/bags, otherwise this may result in formation of foam.

Sac-TMT should be retained in the bladder for 2 hours and then voided. Participants unable to retain the study intervention for 2 hours should be allowed to void sooner, if necessary.

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

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

12.1.1 Syringe/Catheter Method of Administration

1. Perform sterile catheterization with a drug-compatible urinary catheter. Empty bladder completely using a urinary drainage bag.

2. Transfer 50 mL (plus hold-up volume) admixture from the IV bag into a sterile, drug-compatible, suitable-size, single-use syringe.

3. Use an adaptor at the tip of the syringe to prevent spillage or splash during insertion.

4. Instill sac-TMT by gentle push instillation.

6. Remove the syringe. Squeeze the catheter closed and remove the catheter or plug the catheter as indicated, using sterile gauze to help absorb any drops.

   Note: If the participant has trouble holding the solution, a Foley catheter may be used, and a catheter plug may be inserted onto the end of the catheter after instillation. Depending on the participant's mobility, the catheter may be removed after 2 hours.

7. Instruct the participant to attempt to retain the treatment and not void for 2 hours.

12.2 IP Administration Records

The administration records are required to be retained at site. The Source Data Identification Log needs to identify the source. In case a site does not have a designated form/medical file to capture administration records or prefer to use a sponsor's template, the Administration Log can be utilized by site. It is NOT required to copy the Administration Log for Sponsor eTMF.

In instances where Clinical Supply is reconstituted and administered at the same location or by the same person Clinical Supply Dispensing/Preparation and Administration logs can be combined.

Contact your CRA to discuss clinical supply accountability and administration records.

13 Electronic Data Capture

Trained site personnel will enter study treatment information on the appropriate eCRFs.

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

14 Clinical Supply Re-Evaluation Date (RED) and Expiry Date Management

The RED and Expiry date, also referred to as the Use By date, represent the end of the shelf-life period during which the product is expected to remain stable, if stored in accordance with the instructions provided on the label.

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

Clinical Site should monitor dates of the clinical supplies at their location and check RED prior to dispensing / administering clinical supplies to the participant. Unless Clinical 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 Dosing Past Expiry (DPE) contact your CRA and/or notify the GCP investigation mailbox (gcp.cs.inv@msd.com).

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

15 Clinical Supply Disposition, Return, and Destruction

The FDA and ICH GCP guidelines require that the clinical site maintains adequate records of **the disposition of all clinical supplies received from the Sponsor**, including dates, quantity dispensed to, used by, returned from participants, and returned to the Sponsor. Disposition of all kits, received by clinical site, including supplies destroyed locally or lost, should be documented on:

- **Participant Clinical Supply Accountability log** for used supplies and/or
- **Clinical Supply Return Form (CSRF)** or equivalent documents for used and unused supplies. The IRT CSRF generated in the system should be used. Follow the instructions on the IRT

CSRF. If equivalent site return form is used, it should be reconciled with the IRT CSRF to make sure all kits, received by clinical site have been accounted for.
If supplies are destroyed locally on site or lost, it can be noted on the CSRF as well. As locally appropriate for each site and per local and site regulations, the CRA will determine if site staff or CRA will complete the CSRF or equivalent and prepare the package for return and destruction. Both the trial site representative and the CRA should sign the CSRF (or equivalent) confirming that:

- clinical supply reconciliation performed by site has been verified and accepted by CRA;
- supplies can be returned to Sponsor or supplies can be destroyed locally at site/site subcontracted destruction facility which meets Sponsor's requirements.

Once the study is terminated or completed, **ALL remaining clinical supplies**, including partial and empty containers returned from participants, must be returned to Sponsor or destroyed locally.

- **Return to the Sponsor**: the facility address will be provided by CRA.
- **Destroy locally** by a designated site or site subcontracted destruction facility that meets Sponsor requirements and pursuant to local regulations:
  - The clinical site has required facilities and written SOPs in place to undertake local destruction. Include the clinical site's SOP (or reference made to where it is stored at the site) in the ISF.
  - The method of destruction of both **used and unused** clinical supplies is **incineration** in accordance with all applicable local regulations. Clinical site must contact the Sponsor for approval to use alternative methods of destruction.
  - If **unused** clinical supplies are destroyed locally, the **Destruction Records** must be provided to the Sponsor as required per ICH GCP and GMP. Acceptable Destruction records include a Certificate of destruction and/or Acknowledgement of Receipt (AoR) of clinical supplies from the destruction facility with traceability to CSRF/ equivalent document or destroyed kits as required per GMP. If the clinical site cannot provide the destruction records for locally destroyed unused clinical supplies that meet GMP requirements, the supplies should be returned to the Sponsor.

It is preferred that unused supplies are returned to Sponsor's Designated Facility.

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 locally destroyed kits or any discrepancies (lost kits) identified.

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

16 Summary Of Revisions

Version Number	Revision Date	Revisions to Document
1.0	10-Sep-2024	Original