PHARMACY MANUAL

NEMTABRUTINIB (MK-1026-010)

BELLWAVE-010

Part 1

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

Contents

1. Glossary

AxMP	Auxiliary Medicinal Product
AoR	Acknowledgement of Receipt
BID	Twice a day
CCQM	Country Clinical Quality Manager
CDT	Counterfeit, Diversion and Tampering
CID	Component ID
CLL	Chronic Lymphocytic Leukemia
CRA	Clinical Research Associate
CSRF	Clinical Supply Return Form
CTT	Clinical Trial Team
EEA	European Economic Area
eTMF	electronic Trial Master File
GMP	Good Manufacturing Practice
ICH GCP	International Council for Harmonisation Good Clinical Practice
IMP	Investigational Medicinal Product
IP	Investigational Product
IRT	Interactive Response Technology
NIMP	Non-Investigational Medicinal Product
SDR	Source Document Review
SDV	Source Document Verification
SOP	Standard Operating Procedure
SSITFB	Study-Specific Investigator Trial File Binder
TE	Temperature Excursion
TMD	Temperature Monitoring Device

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)	Victoria Fox	Phone: +1 (617) 851-3701 E-mail: victoria.fox@merck.com	Questions regarding the details outlined within this Pharmacy Manual.
IRT Coordinator	Tracey Rothrock	Phone: +1 (215) 6524657 +1 (215) 993-4269 E-mail: tracey.rothrock@merck.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
Experimental group	Experimental	Nemtabrutinib	Drug	Tablet	5 mg and 20 mg	45 mg and 65 mg	Oral	Daily, until disease progression, unacceptable toxicity, discontinuation criteria met or up to 2 years	Test Product	IMP	Central
Comparator group	Active Comparator	Venetoclax	Drug	Tablet	10 mg, 50 mg and 100 mg	20 mg to 400 mg	Oral	Daily, until disease progression, unacceptable toxicity, discontinuation criteria met or up to 2 years	Comparator	IMP	Central or local

- 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.
- For commercially available venetoclax, the unit dose strength and formulation may vary depending on market availability.
- Dosage levels represent intended assignments. Comorbidities, polypharmacy, or adverse event management may necessitate dosage levels other than those specified above. Reference the 'Dose Modification' section of the protocol for additional detail. Central and local sourcing may not be universally available in all countries. Reference the contact list above for assistance with questions relating to sourcing.

4. Blinding

MK-1026-010 is an open label trial. The Sponsor, investigator, and participant will know the study intervention administered.

5. Clinical Supply Receipt at Site

Section 5 is only applicable to centrally sourced Nemtabrutinib and Comparator(s). For locally sourced comparator(s), follow local regulatory guidelines or institutional SOP(s).

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 Data Logger shows ALARM, 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 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 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 of Drug Product

Product	Storage Temperature	Other storage requirements
MK-1026	2-30°C (36-86°F)	Store in the original package in order to protect from moisture. Do not Freeze
Venetoclax	Store in compliance with locally approved product label	Not Applicable

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 documentation 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.

Minimum/Maximum temperature and/or alarm status must be **checked every business day** to ensure reporting of Temperature Excursion within 1 business day. The principal investigator or designee is responsible for ensuring that the temperature is monitored throughout the total duration of the trial and that records are maintained.

Temperature monitoring records must include dates, time, Min/Max temperatures, TMD and storage location clearly identified (serial numbers of the 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 Minimum/Maximum temperature and/or alarm status every business day, the temperature data when there is no temperature excursion can be transcribed onto temperature log or report printed less frequently but at least monthly.

Temperature monitoring records must contain temperature recordings as per device (not rounded). To determine whether to report a temperature excursion, 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)
- Then compare the rounded values to the required temperature range to determine if there is an excursion.

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.

7. Clinical Supply Complaint Reporting

Section 7 is only applicable to centrally sourced Nemtabrutinib and Comparator (s). For **locally sourced product,** report to local sourcing vendor, pharmacy or manufacturer directly as per local regulatory guidelines or institutional SOP (s) if applicable

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 or any temperature excursions outside of the label storage conditions at clinical site or during the transfer, which puts product disposition (i.e., usability) in question.

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 Temperature Excursions.
    - Temperature Data Logger-related issues (malfunctions, temperature device not started or not included in the shipment).
    - Shipping errors (partial shipments, extra, missing, or incorrect CIDs, wrong product shipped, product shipped to incorrect site, documentation errors).
    - Shipment received in a damaged condition (damaged shipper).
- **Site Temperature Excursions (TE):**
    - Any temperature excursions 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 (temperature monitoring device is broken, turned off, calibration expired, clinical supplies transferred without temperature monitoring device, etc.).

Make sure CRA is copied on the email to 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 to inventory in IRT.
- Supplies deemed **Not Acceptable** for use should be removed from the inventory by the site, reconciled and returned / sent for destruction. Sponsor will damage supplies in IRT to trigger a resupply.

Clinical Supply Complaint Form and supporting documentation should be filed at site.

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

- Temperature excursions in the Temperature Data Logger report with NO ALARM - supplies are acceptable for use.
- Inability to download Temperature Data from Data Logger (centrally sourced clinical supply shipments only) - contact MRL Logistics by sending an email to gcspolicy@msd.com;
- Missing shipment paperwork/documentation in the package - contact your CRA
- Temperature Excursions on reconstituted supplies - follow in-use stability requirements in Pharmacy Manual or contact your CRA.
- 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.

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

8. Clinical Supply Accountability and Reconciliation

Section 8 is only applicable to centrally sourced Nemtabrutinib and Comparator (s). For locally sourced comparator (s), follow local regulatory guidelines or institutional SOP (s)

The Clinical Supply **Accountability Records** should allow full traceability at CID level 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 Disposition Records (disposition documented on the Accountability Log and/or 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/destroyed CIDs.

These records should include dates, quantities, and the CIDs assigned to the product(s) and participant(s) to ensure full traceability at CID level. CIDs can be traced to the Batch numbers and expiry dates on the shipping records in IRT. IRT will 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 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 (see Section 13 for more information on destruction).

9. Interactive Response Technology (IRT)

IRT for clinical supply management is only applicable to centrally sourced Nemtabrutinib and Comparator (s). For locally sourced comparator (s), follow local regulatory guidelines or institutional SOP (s).

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 supply temperature excursions.
- 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 designated 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 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/ Study-Specific Investigator Trial File Binder 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**.

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

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

11. IP Preparation and Administration

11.1. MK-1026 (Nemtabrutinib)

11.1.1. Drug Product

- Nemtabrutinib is a tablet for oral administration and does not require preparation.
- Both **5mg and 20mg** tablets will be used to meet the dose levels for this trial. Thirty-three (33) tablets will be available in a bottle.
- Nemtabrutinib will be labeled in accordance with text that is in regulatory compliance with each participating country and is translated into the required language(s) for each country. Nemtabrutinib tablets are packaged in white/opaque high-density polyethylene (HDPE) bottles with white/opaque polypropylene caps.
- Until dispensed to the subjects, Nemtabrutinib should be stored in a secure locked area, accessible to authorized personnel only.
- A Safety Data Sheet (SDS) will be provided upon request.
- The participant should be aware of the side effects of Nemtabrutinib documented in the Informed Consent Form.

11.1.2. Dispensing and Administration

- Nemtabrutinib is for oral use. The tablets should be swallowed whole with water under fasting conditions (either one hour prior to a meal or 2 hours after the meal).
- Nemtabrutinib should be taken at approximately the same time each day. However, on scheduled, study visit days, participants will be instructed not to take their dose of

Nemtabrutinib prior to their clinic visit and until after their assessments have been performed.

- In all cycles, if a Nemtabrutinib dose is missed or delayed beyond 6 hours of when it was scheduled, the participant should skip that dose and take the next dose at the usual time of administration.
- If the participant vomits the first dose of Nemtabrutinib, the participant may be rechallenged at the discretion of the investigator.
- The participant will be dispensed enough drug for one (1) cycle on Day 1 of each cycle.

11.2. Treatment Group, Venetoclax

11.2.1. Drug Product (Locally sourced)

- Refer to the corresponding prescribing information for details on drug preparation, dispensing and administration.
- Venetoclax is a tablet for oral administration and does not require preparation.
- tablets will be used to meet the dose levels for this trial.
- Venetoclax will be labeled in accordance with text that is in regulatory compliance with each participating country and is translated into the required language(s) for each country.
- The participant should be aware of the side effects of Venetoclax documented in the Informed Consent Form. For any commercially available product that is provided by the trial site, subsidiary or designee, every attempt will be made to source these supplies from a single lot/batch number. Local guidelines or institutional SOP/s should be followed for collection of locally sourced product information such as manufacturer, lot, and expiry, unless otherwise instructed by sponsor. When the product is provided by MSD, the drug accountability log should be used for collection of this information.

11.2.2. Dispensing and Administration

- Venetoclax is for oral use. The tablets should be swallowed whole with water.
- Venetoclax should be taken at approximately the same time each day. However, on scheduled, study visit days, participants will be instructed not to take their dose of Venetoclax prior to their clinic visit and until after their assessments have been performed.
- In all cycles, if a Venetoclax dose is missed or delayed beyond 6 hours of when it was scheduled, the participant should skip that dose and take the next dose at the usual time of administration.

11.3. Dosing Compliance- Nemtabrutinib and Venetoclax

- The participant should return any empty packaging and used product at their next visit. Participants should not throw away any medicines via wastewater or household waste.
- Compliance with investigational product will be evaluated by site staff during each scheduled visits with a study participant. During the scheduled monitoring visits, the CRA will review source documents for accuracy.
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- When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF.
- The dose of study intervention and study participant ID will be confirmed at the time of dosing by a member of the study-site staff other than the person administering the study intervention.
- If there are interruptions in the study intervention schedule, the details of and reason for any interruption should be documented.
- Interruptions from the protocol-specified treatment for ≥21 days require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

12. Electronic Data Capture

The trained site personnel will enter drug administration data of MK-1026-010 in the eCRF in INFORM. The outcome such as intervention start and stop dates, including dates for intervention delays and/or dose reductions will be recorded in the source documents and CRF(s).

13. Clinical Supply Disposition, Return and Destruction

Section 13 is only applicable to centrally sourced clinical supplies. For locally sourced comparator(s), follow local regulatory guidelines or institutional SOP(s)

The FDA and ICH GCP guidelines require that the clinical investigator 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 clinical supplies, 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 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 and prepare the package for return and/or 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, **any unused centrally sourced comparators** that are still not expired or been damaged must be returned to Sponsor. Your CRA will provide further instructions on the return process.

ALL other remaining clinical supplies, including partial and empty containers returned from participants, should either be returned to Sponsor or destroyed locally in accordance with the instruction provided below:

- **Return to the Sponsor**:
  - For US clinical sites, return to the central depot that shipped supplies to the site or local destruction facility that meets MSD requirements:

    Fisher Clinical Services
    Return and Destruction Center
    700B Nestle Way,
    Breinigsville, PA 18031

  - For Ex-US clinical sites, the facility address will be provided by CRA. Make sure supplies are sent for destruction in accordance with all applicable local regulations.
- **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 SSITFB.
  - 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/destroyed CIDs as required per GMP.

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

Any information on the label identifying the participant should be redacted prior to returning the study medication.

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

File Clinical Supply Disposition, Return and Destruction (in case of local destruction of unused clinical supplies) at site and provide a copy to Sponsor eTMF as required by local regulations.

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

14. Summary Of Revisions

Version Number	Revision Date	Revisions to Document
1.0	19-Oct-2022	Initial Version
2.0	15-Dec-2022	Clinical Scientist Contacts Updates
3.0	22-Jun-2013	Updates in accordance with Protocol Amendment 01 for Part 1 only; Clinical Scientist Contacts Updates