LIBERATE

Pharmacy Manual

Midodrine for the early liberation from vasopressor support in the ICU

Version 2.0

Date: January 2, 2024

Clinical Trials.gov NCT05058612

Contents

Glossary of Terms

CC	Coordinating Center
DIN	Drug Identification Number
DMCC	Data Management and Coordination Centre
ICU	Intensive Care Unit
IP	Investigational Product
IV	Intravenous
QI	Qualified Investigator
SP	Strathcona Pharmacy
TDL	Task Delegation Log

Section 1: Study Summary

Title	Midodrine for the early liberation from vasopressor support in the ICU
Short Title	LIBERATE
Coordinating Centre	Department of Critical Care Medicine, University of Alberta
Background	Resuscitation and hemodynamic support with intravenous (IV) vasopressors is a prime indication of treatment in intensive care unit (ICU) settings. Oral vasopressors, such as midodrine, have been historically used for hemodynamic support in non-critically ill patients, but their study in patients as a potential IV vasopressor sparing therapy has been limited. Previous studies evaluating the use of midodrine have been small in scale and limited to septic patients. The LIBERATE study will evaluate the expanded role of midodrine for any vasoplegic patient supported in ICU settings.
Primary Outcome	• ICU length of stay
Secondary Outcomes	• All-cause mortality at 90 days • Hospital length of stay • Length of IV vasopressor support • Re-initiation of IV vasopressors • Rates of ICU readmission
Tertiary Outcomes	• ICU costs • Hospital costs • Total healthcare costs • Cost-effectiveness
Safety Outcomes	• Adverse Events • Severe Adverse Drug Reactions • Suspected Unexpected Serious Adverse Reactions
Study Design	Parallel group blinded randomized controlled trial
Inclusion Criteria	• Age > 18 years • Receipt of any IV vasopressor support for > 24 hours • Decreasing vasopressor requirements
Exclusion Criteria	• Vasopressor peak requirements > 24 hours • Contraindication to midodrine or enteral medications • Previous receipt of midodrine in last 7 days • Expected death or anticipated withdrawal of life-sustaining therapies • Pregnancy
Study Intervention	Experimental arm: midodrine 10mg PO every 8 hours. Control arm: placebo
Randomization	Eligible patients will be randomized in a 1:1 ratio to midodrine or placebo. We will use permuted blocks of undisclosed and variable size. We will stratify by randomization by site.
Sample Size	We will enroll a total of 1,000 patients. Site enrollment targets are 1-4 subjects per month.
Follow-up	Daily during ICU stay for up to 30 days and at 90-days after study eligibility.

Section 2: Coordinating Centre Contact Information

Study Chair

Name and Institution	Address, Phone, Email
Oleksa Rewa, MD MSc FRCPC Department of Critical Care Medicine Faculty of Medicine and Dentistry University of Alberta	2-124E Clinical Sciences Building, 8440-112 ST NW, Edmonton, T6G 2B7 CANADA T: 780.263.3280 F: 780.492.1500 E: rewa@ualberta.ca

Data Management and Coordination Centre (DMCC)

The University of Alberta Critical Care Research Office will serve as the Data Management and Coordination Centre for the LIBERATE study. The study database will be housed on secure servers at the University of Alberta in Edmonton, Alberta.

For questions about study operations please contact:
Dawn Opgenorth, Project Manager
Department of Critical Care Medicine
University of Alberta
2-124 Clinical Sciences Building
8440 112 Street
Edmonton, AB T6G 2B7
dawno@ualberta.ca

Section 3: Site Initiation

3.1 Training

All site research personnel that have been delegated tasks associated with LIBERATE should be qualified by education, training, and experience to assume responsibility for the proper conduct of a randomized controlled trial in accordance with Good Clinical Practice and Health Canada Division 5 regulations. All site research personnel must complete the *Personal Training Documentation for Study Staff* document (Appendix 1). The completed document must be filed in the site regulatory binder and made available upon request.

3.2 Delegation of Responsibilities

The site research team must provide the Coordinating Centre with a completed Task Delegation Log (TDL). The purpose of this log is to outline the key delegated tasks assigned to appropriately qualified individuals. All pharmacy personnel performing activities on the Responsibility List must be included on the Study Site Task Delegation Log.
The Delegation Log should:
1. Identify each individual involved in the conduct of LIBERATE and to whom the Qualified Investigator has delegated key tasks
2. Include the effective start date of their designated activities for each individual assigned to the study
3. Be kept up-to-date over the course of the study

Section 4: Investigational Product Information

4.1 Investigational Product (IP) Specifications

Group 1: Each capsule will consist of 2 crushed tablets of 5mg MAR-Midodrine HCl (10mg total) along with Microcystalline cellulose.

Product Name	Manufacturer	DIN	Product Description
Midodrine Hydrochloride	**Marcan Pharmaceuticals Inc.**	**02473992**	**5mg Tablet**

Product Name	Manufacturer	Product Description
Cellulose, NF/EP (microcrystalline)	**Medisca**	Microcrystalline cellulose is a purified, partially depolymerised cellulose prepared by treating alpha-cellulose, obtained as a pulp from strains of fibrous plant material, with mineral acids. It has no specific adverse reaction profile.

Group 2: Each matching placebo capsule contains only microcrystalline cellulose.

Prior to IP shipment to sites, a random batch of capsules containing 10mg midodrine HCl will be analyzed by Keystone Labs Inc. for drug dosage testing verification as per Health Canada requirements. Once the analysis is completed and the dosage in each capsule is confirmed, the IP will be shipped to the sites for study usage.

The expiry date for the IP is 6 months from the date of compounding.

4.2 Storage and Allowable Temperature Excursions

For the purpose of the study, the IP must be stored at room temperature (15-30°C). Temperature excursions are allowed between -20°C± 5°C and +50°C± 2°C for a maximum of 7 days.

4.3 Temperature Monitoring

The following temperature monitoring guidelines have been developed in accordance with Health Canada's *Guidelines for environmental control of drugs during storage and transportation* (GUI-0069_V3)

On-site Storage
Sites must maintain a temperature log and record daily minimum and maximum temperatures to ensure the IP has been stored at the specified temperature ranges until dispensing. These logs should be available upon request.

During Shipment
Temperatures during IP shipment will be monitored in one of two ways:

1. A temperature monitoring device will be shipped with the package
2. If temperature data during shipment is not available, temperature exposures will be mapped during transit (temperature conditions through chain of custody)

Unacceptable temperature excursions (see section 4.2) should be reported to the Coordinating Centre and the study IP should be sequestered until further instructions from the Coordinating Centre.

4.4 Receipt of Study IP

Upon receipt of the IP from the compounding pharmacy, the study team member designated to receive the study IP will examine the condition of the IP containers for damage and will review the data from the temperature monitoring device for study excursions before completing the site specific questions on the Investigational Product Delivery Form (Appendix 4).

The Study Site should contact the Coordinating Centre immediately if the IP is not in good condition or if unacceptable temperature excursions have been observed and should sequester the IP until further instructions are received.

Section 5 – Dispensing and Randomization

The IP will be prepared by either a dedicated research pharmacy if available at the site, or will be pre-dispensed and labelled by the compounding pharmacy in Edmonton.

5.1 Scenario 1 - Dedicated Research Pharmacy at site:

- The Research Pharmacy is responsible for randomization of study participants. The Coordinating Centre will provide the Research Pharmacy with a site-specific randomization table and corresponding Randomization ID#s.
- The Research Pharmacy will order their IP supply by emailing an order form (Appendix 2) to the compounding pharmacy, Strathcona Pharmacy (SP). The order form will include the number of capsules of midodrine, and placebo being ordered. The amount ordered is at the Research Pharmacy's discretion and should be based on the number of anticipated enrollments within 6 months (the IP expiry period)
- The Research Pharmacy will receive bulk supplies of midodrine and placebo IP.
- When a patient is enrolled into the study the Research Pharmacy will assign the next sequential treatment according to the table, prepare the container of IP and label the IP with the corresponding Randomization ID # (i.e., ABC-001).

5.2 Scenario 2 - No Research Pharmacy at site/ICU Pharmacist part of blinded study team:

- Individual Study Sites email an order form (Appendix 3) to the compounding pharmacy (Strathcona Pharmacy) for IP for X number of patients (likely 12 - 15 at a time depending on the site's rate of recruitment)
- The compounding pharmacy prepares and provides the IP to the Study Site in individual pre-dispensed containers. Containers will be identified only with a Kit# (which will be the randomization # when assigned to a study subject), lot# and expiry date.
- Study Site will receive and store IP.
- When a patient is enrolled into the study, the Research Coordinator or treating ICU pharmacist will select the next sequentially numbered IP container and assign the patient the Kit# listed on the IP label. The Kit# will be the subject's randomization #.

5.3 Unused Randomization Numbers

All randomization/kit#s must be assigned to a participating subject to maintain the integrity of the study randomization process. If a randomization number is not used (i.e., the pre-dispensed IP expires before being used in **Scenario 2**), the Study Site should notify the Coordinating Centre.

5.4 Investigational Product Labeling

The site pharmacy or qualified member of the study team will generate an appropriate study product label. The contents of the label will be in accordance with all applicable regulatory requirements (local and Health Canada). The IP label will include the following information:

Site Pharmacy information/ Informations de la pharmacie du site …

Investigator/Chercheur principal: Study Coordinator/Coordonnateur de l'étude:

LIBERATE STUDY/ Étude LIBERATE

Patient Name/ Nom du patient: _____ **Randomization No/No de randomisation**: _____

Patient ID#/Dossier: _____ DOB/DDN: _____Unit/unité: _____

Midodrine 10mg or matching placebo capsule/ Capsule de Midodrine 10mg ou de placebo

Take ONE capsule every 8 hours from time of study inclusion to 24 hours post IV vasopressor termination/
Prendre UNE capsule toutes les 8 heures à partir du moment de l'inclusion de l'étude jusqu'à 24 heures après l'arrêt du vasopresseur IV

Date Dispensed/Date distribué: ____/____/_____ Expiry/date d'expiration: ____/____/_____ Lot#: _____

Store at Room Temperature/ Entreposer à température _____ **capsules**

Investigational product to be used by qualified investigators only/Produit expérimental à utiliser uniquement par des chercheur qualifiés

Sponsor/ Commanditaire: The Governors of the University of Alberta/ Les gouverneurs de l'Université de l'Alberta, South Academic Building, University of Alberta, Edmonton, AB T6G 2B7

5.5 Destruction of Investigational Product

If a prepared dose of IP was not administered to the participant, the unused IP must be returned to the Study Site's pharmacy for proper accountability and destruction according to national guidelines and provincial requirements. Discarding if the IP must be documented on the Master Drug Accountability Log (Appendix 5).

Section 6: Documentation

Regardless of how the IP is dispensed the Study Site will be responsible for:

- maintaining documentation on IP received, dispensed and discarded in the Master Drug Accountability Log (Appendix 5)
- ordering additional IP as required
- Temperature logs where IP is being stored on site (see section 4.3)

Section 7: Blinding

Intensivists, research personnel, ICU personnel, participants, members of the Executive and Steering Committees, and the data analysts will be blinded to the treatment allocations. Only the pharmacist of each participating research pharmacy who will dispense the IP (midodrine or placebo) will be unblinded. Pharmacists working at the ICU must be kept blinded and should not be responsible for preparing the IP.

Unblinding

Unblinding of the study treatment will only be done when knowledge of the treatment allocation is necessary for the continued safe management of the participant. The treating clinician or Site Investigator should contact the Coordinating Centre if there is need for unblinding and the request will be adjudicated in a timely fashion by the study Principal Investigator or nominated delegate.

Appendix 1: Personal Training Documentation for Study Staff

Full Study Title: Midodrine for the early liberation from vasopressor support in the ICU – The LIBERATE study

A multi center concealed-allocation parallel-group blinded randomized controlled trial to ascertain the effect of midodrine compared to placebo on IV vasopressor duration and ICU length of stay for critically ill patients

Topics:

Update the list as appropriate for the training to be completed.

❑ Study protocol: LIBERATE version _____ dated: _____
❑ Study informed consent form: LIBERATE Consent dated: _____
❑ Study deferred consent form: LIBERATE Deferred Consent dated:_____ ❑NA
❑ Study regained capacity consent form: LIBERATE dated:_____
❑ Mar- Midodrine Product Monograph (Marcan) dated: _____
❑ Part C, Division 5 of the Canadian Food and Drug Regulations
❑ Good Clinical Practice
❑ TCPS2
❑ Transportation of Dangerous Goods (if applicable)
❑ N2 V8 or Local SOPs: List applicable titles:
Investigational Product Management SOP
Adverse Event Reporting SOP
Record Retention SOP (Databse Lock and Archiving)
Informed Consent SOP

Details of Professional Qualification ***(keep copies of each on file at site):***
• **CV signed & dated (yyyy-mmm-dd):_____** • **License/permit expiry date (yyyy-mmm-dd)(*if applicable*)_____** or ❑

mployee/ Research Team Member

By signing this training document, I attest that I have:

- *Read the below listed documents*
- *Understand how to conduct the trial as it relates to the topics above and their delegated responsibilities, and*
- *Had an opportunity to ask questions and receive answers to their satisfaction*

Update the list as appropriate.

- *Read Study protocol: LIBERATE version _____ dated: _____*
- *Read Study informed consent form LIBERATE Consent dated: _____*
- *Read Study deferred consent form: LIBERATE Deferred Consent dated:_____ ❑NA*
- Read Study regained capacity consent form: dated:_____
- *Read Mar-Midodrine Product Monograph (Marcan) dated: _____*

Signature: _____ Date: _____ (yyyy/mmm/dd)

Appendix 2: IP Order Form – Scenario 1 - Sites With Research Pharmacy

LIBERATE STUDY

A Concealed-Allocation parallel-Group Blinded Randomized Controlled Trial to Ascertain the Effect of Midodrine Compared to Placebo on IV Vasopressor Duration and ICU Length of Stay for Critically Ill Patients

Investigational Product Order Sheet

Email your order to:
will@strathconapharmacy.com
erinp@strathconapharmacy.com
dawno@ualberta.ca

Date of order:_____

_____ **(#) capsules of IP** containing 2 crushed tablets of 5 mg MAR-Midodrine HCl along with microcrystalline cellulose

_____ **(#) identical capsules of matching placebo** containing microcrystalline cellulose

(The labeling should have the study name LIBERATE, quantity of capsules, identity of contents (Investigational Product -MAR-Midodrine HCl vs Matching Placebo) as well as the expiration date)

Ship product to:
(SITE ADDRESS and contact information)

For Strathcona Pharmacy use only

(√)	
☐	product prepared (product plus 5 additional capsules of IP for dosage testing)
☐	**5 capsules of IP** (contents of capsules is 2 crushed tablets of 5mg MAR-Midodrine HCl along with microcrystalline cellulose) shipped for dosage testing to: **Keystone Labs,** **ATTN: Rod Szarka** **7225 Roper Road NW, Edmonton, Alberta, T6B 3J4** **Phone: 587-458-8411**
☐	Pass result from Keystone Labs received prior to shipping product to study pharmacy
☐	Order shipped to study pharmacy on date: _____

If you have any questions please contact: Will Leung (B.Sc. Pharmacy)
Strathcona Pharmacy Centre, 780 432-1409

Dec 6, 2023

Appendix 3: IP Order Form – Scenario 2 - Sites With NO Research Pharmacy

LIBERATE STUDY

A Concealed-Allocation parallel-Group Blinded Randomized Controlled Trial to Ascertain the Effect of Midodrine Compared to Placebo on IV Vasopressor Duration and ICU Length of Stay for Critically Ill Patients

Investigational Product Order Sheet

Email your order to:
will@strathconapharmacy.com
erinp@strathconapharmacy.com
dawno@ualberta.ca

Date of order:_____

Investigational product for _____(#) patients. (42 capsules per patient)

(The labeling should have the study name LIBERATE Study, the randomization#, quantity of capsules, identity of contents (Investigational Product -Midodrine 10mg or Matching Placebo), expiration date and lot#

Ship product to:
(SITE ADDRESS and contact information)

For Strathcona Pharmacy use only

Date completed (dd/mmm/yyyy	**completed by:** (initials)	
		product prepared (product plus 5 additional capsules of IP for dosage testing)
		5 capsules of IP (contents of capsules is 2 crushed tablets of 5mg Midodrine along with microcrystalline cellulose) shipped for dosage testing to: **Keystone Labs,** **ATTN: Rod Szarka** **7225 Roper Road NW, Edmonton, Alberta, T6B 3J4** **Phone: 587-458-8411**
		Pass result from Keystone Labs received prior to shipping product to receiving pharmacy
		Dispense IP as per the LIBERATE study randomization table
		Order shipped to receiving pharmacy

If you have any questions please contact: Will Leung (B.Sc. Pharmacy)
Strathcona Pharmacy Centre, 780 432-1409

Appendix 4: IP Delivery Form

LIBERATE STUDY – Investigational Product (IP) Delivery Form

To:

From:

Strathcona Prescription Centre
8225 105 ST NW Edmonton, AB T6E4H2

Study Site: Order received date: Shipment Date:

Randomization numbers dispensed	# of capsules	Lot #	Expiry Date

Order prepared by:_____

Study site only

- Are there any visible damages to the IP?
  Yes [ ] No [ ]
- Was a temperature tracking device provided during IP transit?
  Yes [ ] No [ ]

If temperature tracking device was provided, were there any temperature excursions during transit? Yes [ ] No [ ] N/A [ ]

Additional notes:
• As per manufacturer guidelines, midodrine remains stable at -20°C± 5°C to 50°C± 2°C for up to 7 days.

Order received by: _____
Date order received:_____

Appendix 5: IP Order Form – Drug Accountability log

MASTER DRUG ACCOUNTABILITY (STOCK BALANCE) LOG

TRIAL SHORT NAME : *LIBERATE*	**SITE NAME :**	**QUALIFIED INVESTIGATOR (QI):**
AGENT NAME: Midodrine 10 mg or placebo	**STORAGE LOCATION:**	

Date drug obtained by study team (DD MMM YYYY)	**Assigned Bottle ID** ***(S2 - same as Kit No)***	**Lot Number**	**Expiry** (DD MMM YYYY)	**Volume** (# capsules)	**Dispensed to:** *(subject randomization ID#)* *(S2 - same as Kit No)*	**Recorder Initials & Date**	**Remaining Balance** (# capsules)	**Volume sent for destruction** (# capsules)	**Date of destruction** (DD MMM YYYY)	**Recorder Initials**	**Comments**

☐ Continued next page. (Add pages as required. Please complete header section on all pages.)

*Investigator to sign and date the Participant Drug Accountability Log at end of study participation

Investigator Signature: _____ Date of Signature: _____

LIBERATE Master Drug Accountability Log 10May2022