CELL THERAPY MANUAL
(FOR USE WITH AT-CLOSED® CRYOVIALS)

PROTOCOL NUMBER: **P-105-202**

DATE: **18 FEBRUARY 2022**

VERSION: **3.0**

COUNTRY SPECIFIC: **US**

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Confidentiality Statement

Version History

Date	Version Number	Summary of Changes

18 February 2022	3.0	• Implementation of updated cryovials (AT Closed Vials®) and AT-Adapt™ single-use needleless connection device
		• Updated labeling section with new US labels
		• Appendices updated:
		  ○ Chain of Custody Form: remove cryoshipper label, add secondary label
		  ○ Dose Worksheet: remove secondary label, remove lot number, add back signature lines for "verified by" on Dose Worksheet
		  ○ Moved shipping, handling, and packaging instructions to Appendix

20 July 2021	2.0	• Implementation of the JUDI system for submission of HLA reports • Removal of needleless connectors (eg, Clave™) • Designation of transport of the investigational product at room temperature • Priming of syringe filters at cell therapy lab or bedside • Change in extension tubing for use with peripheral intravenous catheters • Transition to new template and additional edits for clarity
16 November 2020	1.0	• Original

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1 CONTACTS

The parties involved in the processes outlined in this manual, and their corresponding roles, are listed in the table below.

Party Involved	**Role**
AlloVir	Sponsor
ICON	Contract Research Organization (CRO) CRO managing and operating CytoMatch
Brooks (Azenta)	GMP Storage Facility
Cryoport	Cold Chain Logistics (IP shipment from regional storage facility to site)
Cognate BioServices	Drug Product CDMO

For issues which may arise during the conduct of this study, the appropriate contact is listed below.

Issue	**Contact**
General Issues	Primary: Issue Reporting Form emailed to ICON Clinical Research Associate (CRA)
Dose preparation or dosing issues that require **immediate** attention	Primary: Dr. Elizabeth Stoner (AlloVir Medical Monitor) Alternates: ICON CRA, AlloVir RSL
FlexAdvantage Interactive Response Technology (IRT) System technical issues	ICON Helpdesk Email: icophone@iconplc.com Phone: 1-888-426-8801

Direct contact information for study team members is listed below. Please note that study contacts may change. Contact information for the study team can be found in the Site Regulatory Binder. For all communications regarding cellular product, please include the ICON study email study-icr-4690-0006@iconplc.com.

AlloVir Study Team	ICON Study Team
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2 ABBREVIATIONS, TERMS, AND DEFINITIONS

Abbreviation	Definition
AABB	Formerly known as American Association of Blood Banks
AT	Aseptic Technologies
CAR	Chimeric antigen receptor
CDMO	Contract development and manufacturing organization
CRA	Clinical Research Associate
CRO	Contract research organization
CRS	Cytokine Release Syndrome
CTM	Clinical Trial Manager
DMSO	Dimethyl sulfoxide
eCRF	Electronic case report form
FACT	Foundation for the Accreditation of Cellular Therapy
GMP	Good Manufacturing Practice
GVHD	Graft versus host disease
HCT	Hematopoietic cell transplant
HLA	Human leukocyte antigen
IP	Investigational product
IRT	Interactive response technology
ISF	Investigator Site File
IV	Intravenous, -ly
JACIE	The Joint Accreditation Committee International Society for Cellular Therapy - Europe & the European Society for Blood and Marrow Transplantation
LN2	Liquid nitrogen
ML/MM	Medical Lead/Medical Monitor
PM	Project Manager
RSL	Regional Site Liaison
SDS	Safety data sheet
SOP	Standard Operating Procedures
v/v	Volume per volume
VST	Virus-specific T cells

Term	Definition
Chain of Custody	A process that captures drug product handoff across various entities to ensure proper handling, including storage, and temperature conditions
Chain of Identity	A process used to link a specific drug product to a specific patient from enrollment to treatment
Chain of Identity Number	A unique number, used in concert with patient identifiers, to link a specific treatment to a specific patient throughout the process
Shipper / Dewar	A specialized vacuum flask used to hold liquids below ambient temperature. For this study, a shipper / dewar may be used to store/transport cryogens, whose boiling points are much lower than room temperature. The dewar is the liquid nitrogen containment compartment inside of the LN2 Shipper.
Expiry Date	The date before which the drug product and/or placebo must be administered to patients
JUDI	AGMednet's "JUDI Adjudication" is a cloud-based platform that will be used to submit HLA reports and document/track the CytoMatch HLA data verification process.
Manufacturing Lot Number (MFG. #)	A unique identification number assigned to drug product and/or placebo for a single manufacturing run
Patient ID	A unique identification number that is linked to a patient for all study visits/treatments

3 ICON LEGEND

Throughout this manual, the following icons are used to highlight specific aspects of the cell tracking process and/or important steps:

Distinct identifiers used for patient specific cell product

Information entered into IRT

Documentation to send

Form for site to complete

Email notifications

Important Step

4 SYSTEMS USED

The systems referred to throughout this manual are summarized below.

System	Owner	Users	System Used	Process for Obtaining Access	References
FlexAdvantage	ICON	Clinical Site ICON	IRT will be used to screen and randomize patients, acknowledge IP and complete each dosing visit for vial assignment.	CRA will request site access once all start-up activities completed. Access email will be sent from flexadvantage@iconplc.com	FlexAdvantage Site User Reference Guide
Cryoport Logistics for US	Cryoport	Clinical Site ICON Brooks (Azenta) AlloVir	Cold chain logistics system used to track/manage shipments of IP	Access provided via shipment notification email. See Section 9 of this manual for additional details.	N/A
JUDI	ICON	Clinical Site ICON	Submit and verify HLA transcription	JUDI Manual	JUDI Manual

5 INTRODUCTION AND STUDY OVERVIEW

5.1 Introduction

This Cell Therapy Manual is a reference manual for the Investigator and investigative site staff, including the cell therapy laboratory staff, or pharmacist and pharmacy personnel involved in the use of this investigational product (IP). The following is a guidance of minimum acceptable procedures and does not replace an understanding of, or adherence to, the requirements contained in the approved protocol, applicable regulations, guidelines, good clinical practices, aseptic preparation techniques, or Standard Operating Procedures (SOPs) governing this study. Furthermore, this document does not replace cell therapy standards established by accreditation agencies such as Foundation for the Accreditation of Cellular Therapy (FACT), the AABB (formerly known as American Association of Blood Banks), or the Joint Accreditation Committee of the International Society for Cellular Therapy and the European Society for Blood and Marrow Transplantation (JACIE).

The purpose of this Cell Therapy Manual is to provide guidance by outlining minimally acceptable standards for the request, receipt, storage, preparation, dispensation, administration, return/destruction, and IP accountability.

The Cell Therapy Manual will be updated and revised as needed. The most recent approved version will take precedence over any previous version(s).

5.2 Study Information

P-105-202 is a phase 2/3 study to evaluate the efficacy and safety of Viralym-M for the prevention of clinically significant adenovirus (AdV), BK virus (BKV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpesvirus 6 (HHV-6) and JC virus (JCV) infections and/or disease in patients at high risk for these viruses following allogeneic hematopoietic cell transplant (HCT).

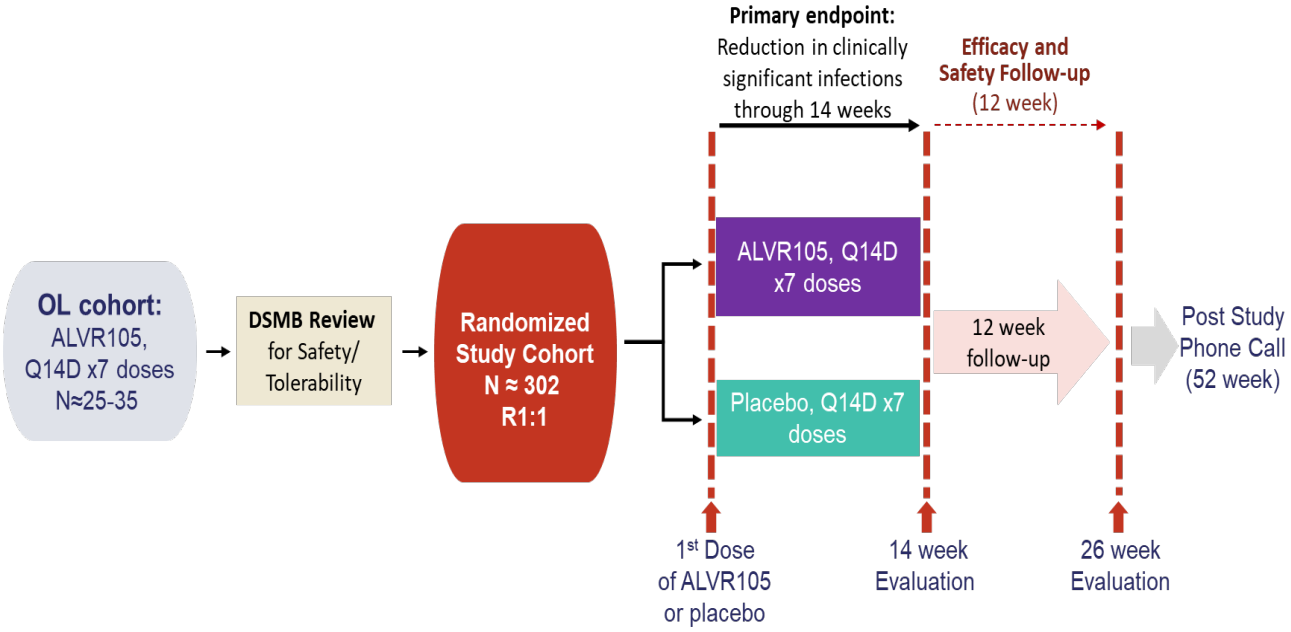
Patients will receive the same volume for injection for all study treatment infusions (Q14 days dosing for 14 weeks).

For Cohort Open Label (OL): Patients greater than 40 kg will receive 4 x 10^7 ALVR105 cells. Patients less than 40 kg will receive 2 x 10^7 ALVR105 cells. All infusions will be administered IV (via peripheral or central line) over approximately 5 minutes as a slow push.

For Phase 3 Cohort: Patients greater than 40 kg will receive 4 x 10^7 ALVR105 cells (or placebo). Patients less than 40 kg will receive 2 x 10^7 ALVR105 cells (or placebo). Cryopreservation media (without cells) will serve as the placebo and will be identical in volume and appearance upon administration. All infusions will be administered IV (via peripheral or central line) over approximately 5 minutes as a slow push.

A study schematic is displayed in Figure 1 below:

Figure 1: Study Flow Chart



6 INVESTIGATIONAL PRODUCT DESCRIPTION

6.1 Composition

Investigational product refers to ALVR105 or placebo. AVLR105 is a biological product consisting of ALVR105 cells (third-party multivirus-specific T cells with specificity for BK virus [BKV], cytomegalovirus [CMV], human herpes virus 6 [HHV-6], Epstein-Barr virus [EBV], and adenovirus [AdV]) in cryopreservation media.

ALVR105 will be supplied in 6.0 mL capacity AT-Closed Vials® (Aseptic Technologies) (formerly referred to as a cryovial) at a concentration of 1×10^7 virus-specific T cells (VSTs)/mL in a volume of approximately 2.5 mL. ALVR105 will be frozen in a cryopreservation media containing 50% volume per volume (v/v) of 25% human serum albumin, 40% (v/v) Hanks balanced salt solution, and 10% (v/v) dimethyl sulfoxide.

Cryopreservation media (without cells) will serve as the placebo. Placebo will be provided in the same 6.0 mL capacity AT-Closed Vials as ALVR105 and will be identical to ALVR105 in volume and appearance.

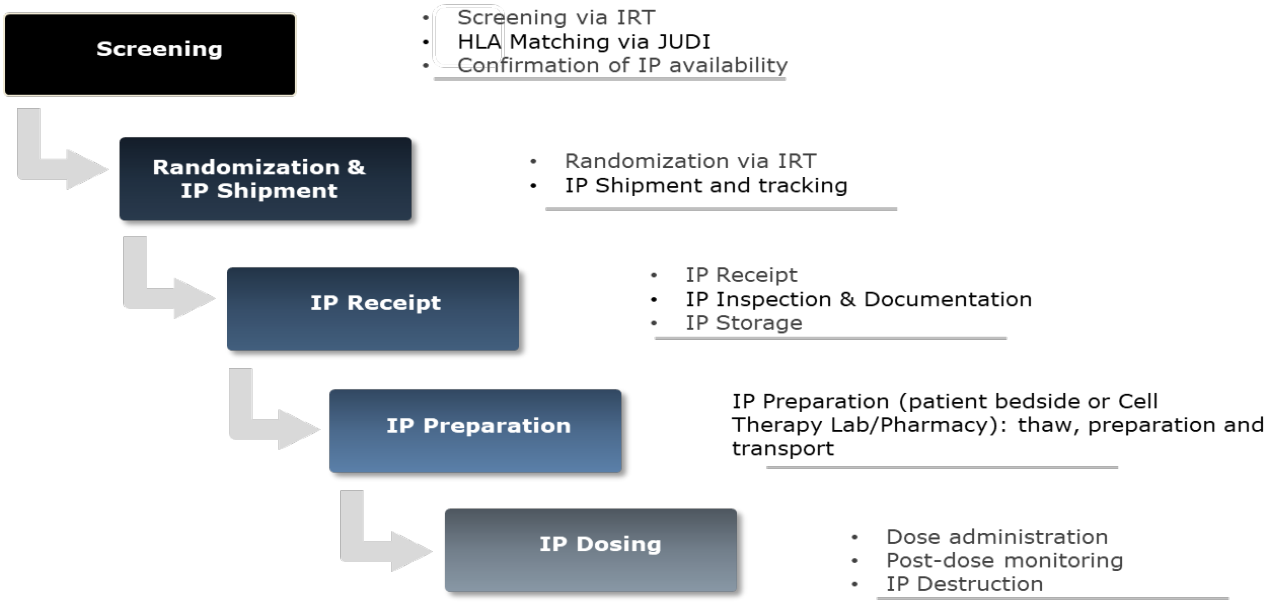
6.2 Human Leukocyte Antigen (HLA) Matching

CytoMatch™ (AlloVir, Inc.), a validated computer algorithm, will be used to select the optimal ALVR105 cell line for an individual patient based on the overall level of HLA match between (a) the cell lines within the bank and the patient and (b) the cell lines within the bank and the hematopoietic cell transplant (HCT) donor.

6.3 Overview of IP Process

A high-level overview of the steps the clinical site will perform to receive IP, prepare the IP, and administer the IP to a study participant is displayed in Figure 2.

Figure 2: IP Process



7 PACKAGING AND LABELING

The packaging and labeling of the IP is outlined in the following sections.

ALVR105 drug product and/or placebo is supplied to sites in AT-Closed Vials packed in a cryobox shipped in an LN2 shipper.

7.1 Packaging

<table>
<tr>
<td>AT-Closed Vials® (Aseptic Technologies) (formerly referred to as a cryovial)
IP will be supplied in 6 mL AT-Closed Vials at a concentration of 1×10^7 cells/mL in a volume of approximately 2.5 mL.

The vials are cryogenic, self-standing and capped with a snap-fit cap that protects septum.</td>
<td> 
<table>
<tr><td>AT-Closed Vial</td><td>6.0 mL</td></tr>
<tr><td>Height</td><td>40.3 mm including the cap, (-1 mm with cap removed)</td></tr>
<tr><td>External vial diameter</td><td>25.0 mm</td></tr>
</table></td>
</tr>
<tr>
<td>Cryobox
Dimensions: L 133 × W 133 × H 57 mm
Maximum Capacity: 25 vials
Note: The AT-Cryobox (5x5) 6mL can be used to store IP at the site; return to Depot is not required.</td>
<td> 
</td>
</tr>
<tr>
<td>LN2 Shipper
High Volume LN2 shipper will have a rack and may hold multiple cryoboxes. Each cryobox contains the Investigational Product for only one patient. If a site is expected to receive multiple patients' IP in a single day, the LN2 shipper may contain multiple cryoboxes (shipments) for multiple patients. Carefully check the Brooks (Azenta) BioInventory. The Cryoport LN2 shipper pictured here is representative of the LN2 shipper that will be used by Brooks.</td>
<td> 
</td>
</tr>
</table>

Alternative Storage Cryobox.

For sites that cannot store the IP in the AT-CryoBox (5x5), 6mL vial, an alternative size box can be supplied.

All shipments of IP to sites will still come in the AT-CryoBox (5x5), 6mL vial. Upon receipt of an IP shipment sites may transfer the IP shipment to the alternative Cryobox. When transferring the IP from the LN2 Shipper to the LN2 storage tanks, please follow all transfer requirement per Appendix I of this manual. The vials should be stored in the upright position in the storage tank.

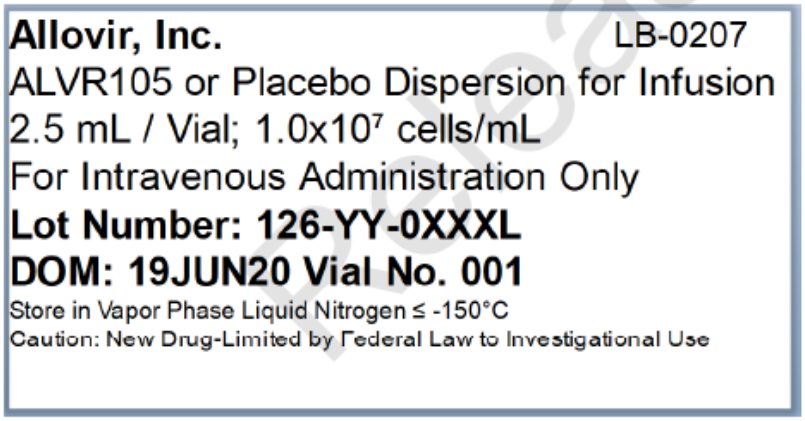
Sites may also use the alternative Cryobox in their LN2 transport shippers for the transport between site locations on the day of the IP preparation. The vials must remain in an upright position during transport.

Upon receipt of the alternative Cryobox sites need to reconfigure the subdivider configuration per the image provided below.

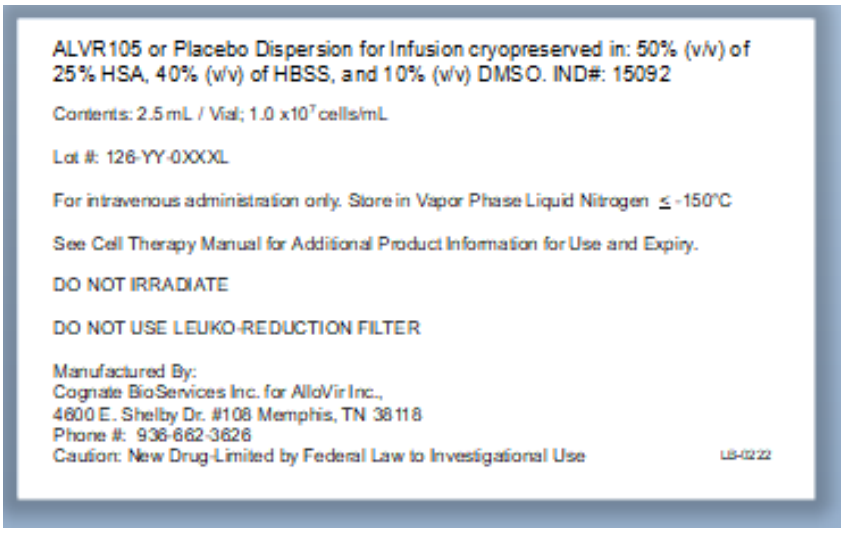
Alternative Cryobox **Dimensions:** L 75 × W 75 × H 51 mm **Maximum Capacity:** 4 vials **Note:** The Cryobox can be used to store IP at the site; return to Depot is not required. **Product reference:** VWR SKU: 89128-202	VWR PolarSafe™, Argos Technologies  Box subdivider reconfiguration 

7.2 Labeling

Sample IP label is shown below.



The secondary label will be provided with the shipment of the IP. A secondary label will be provided for each vial included in the shipment.



The expiration date of each vial will be listed on the IRT Shipment Request Form (shown in Appendix F) which will be included in the IP shipment documentation sent to the site.

8 SHIPMENT AND HANDLING PROCEDURES

Prior to site activation, the site will provide the shipping address, contact information, and times site staff are available to receive IP from the courier. If there are any changes in this information, please contact your CRA. The site will receive 2 shipments per patient as follows.

1. The first shipment will occur approximately 48-96 hours after randomization and will include ALVR105 (best matching cell line available) **or** placebo depending on what patient was randomized to receive. In the Open Label portion of the study all patients will receive ALVR105. Initiation of the first shipment **requires action by the site** as detailed in Section 8.1 below.

2. The second shipment will occur after the site completes registration of dose 3 in IRT and will include ALVR105 (best matching cell lines available) **or** placebo depending on what patient was randomized to receive. Initiation of the second shipment **requires action by the site** as detailed in Section 8.2 below.

The receipt and handling procedures for Shipment 1 and 2 are identical.

Shipment Breakdown

- Table 1 and Table 2 lists the number of ALVR105/placebo vials to be received for Dose 1 dependent upon randomization and patient weight reported at screening.

Table 1: Shipment 1: IP Shipment for Doses 1 through 3 (Patient <40 kg)

Number of Vials	ALVR105/PLACEBO
Three (3)	ALVR105 (best matching cell line available) or placebo depending on what patient was randomized to receive. In OL portion of the study all patients will receive ALVR105.
Total: Three Vials	

Table 2: Shipment 1: IP Shipment for Doses 1 through 3 (Patient ≥40 kg)

Number of Vials	ALVR105/PLACEBO
Six (6)	ALVR105 (best matching cell line available) or placebo depending on what patient was randomized to receive. In OL portion of the study all patients will receive ALVR105.
Total: Six Vials	

- Table 3 and Table 4 lists the number of ALVR105 and placebo, if applicable vials to be received for Dose 2, dependent upon registration of dose 3 in IRT and patient weight reported at screening.

Table 3: Shipment 2: IP Shipment for Doses 4 through 7 (Patient <40 kg)

Number of Vials	ALVR105/Placebo
Four (4)	ALVR105 (best matching cell line available) or placebo depending on what patient was randomized to receive. In OL portion of the study all patients will receive ALVR105.
Total: Four Vials	

Table 4: Shipment 2: IP Shipment for Doses 4 through 7 (Patient ≥40 kg)

Number of Vials	ALVR105/Placebo
Eight (8)	ALVR105 (best matching cell line available) or placebo depending on what patient was randomized to receive. In OL portion of the study all patients will receive ALVR105.
Total: Eight Vials	

8.1 IP Shipment One for Doses 1 through 3

 During patient Screening, the clinical site completes “Screen a Patient” action in IRT and will upload the annotated, redacted HLA source documents (ie, HLA report) for the patient and the patient's HCT donor(s) to the JUDI database. JUDI will notify the site when the transcription of the HLA information from the HLA source documents is available for the site to verify. The site will login to JUDI and verify the HLA transcription within JUDI.

Please refer to the JUDI Manual for detailed instructions.

Shipment of the IP to the investigative site's cell therapy laboratory will occur after randomization.

The procedure for reporting HLA type, shipping and receiving IP, and communication and documentation requirements are listed below:

 Upon screening a potential patient, the clinical site reports the following information through IRT using the action "Screen a Patient":

- Gender
- Year of patient's birth
- Visit date

The ICON and AlloVir study team are notified when the site completes this action. IRT assigns the patient ID.

The site will print the transaction confirmation from IRT and file it in the subject documentation.

↓

The site uploads the annotated, redacted electronic copy of the HLA source document for the patient and patient's HCT donor(s) to the JUDI system. The HLA report must be submitted in JUDI as soon as possible after screening. Please reference the JUDI Manual for additional instructions.

↓

Site receives an email notification from the IRT of ALVR105 match availability. If an ALVR105 match is not identified in the bank, the site will receive an email notification from the IRT indicating that this patient is not eligible for participation in the study. The clinical site should screen fail the subject in IRT if the patient is not eligible.

↓

After match availability is confirmed, the site is able to randomize patient and will receive notification of an upcoming shipment of IP. Upon randomization and initiation of IP shipment the site will receive an email notification from Cryoport which will include the following information:

- **US:** Cryoport Shipment Order Number and Live View link for shipment tracking. The Cryoport link can be used to view the shipper's location and temperature

If there are delays in the shipment of IP, the site will receive an email notification from Cryoport. In the unlikely event a shipment delay prohibits the site from receiving the delivery, follow the Issue Reporting Instructions found in Section 10 of this manual.

8.2 IP Shipment Two for Doses 4 through 7

The Second shipment of IP is automatically initiated after the clinical site registers dose 3 in the IRT.

9 RECEIPT, HANDLING, UNPACKING PROCEDURES

IP receipt, handling and unpacking procedures are included in Appendix I.

10 ISSUE REPORTING

Investigative product must be stored in vapor phase LN2 temperature conditions (≤ -150°C) prior to thaw for dosing. Temperature excursions that occur at the site will be evaluated on a case-by-case basis by AlloVir. When a temperature excursion (ie, temperature > -150°C) occurs, the site will follow the Issue Reporting instructions below.

Urgent issues during dose preparation or dosing that require immediate attention will be reported by the site to the AlloVir Medical Lead by phone. The RSL should also be contacted. See Section 1 for more details.

Throughout the study, the site will report issues that arise by completing the Issue Reporting Form (Appendix G) and submitting form via email to the CRA.

Issues reported on the form will include, but not be limited to, the following:

- Issues with IP
- Reconciliation/destruction
- Temperature excursions (on site or in transit)

As noted above, the site is to report urgent issues by phone immediately and submit the Issue Reporting Form after resolution of the urgency.

Completed Issue Reporting Forms should be filed in the Investigator Site File (ISF).

11 RANDOMIZATION AND IP ASSIGNMENT

Trained site personnel access IRT initially to screen a patient. Treatment assignments for patients are determined as described in the protocol. Patients are randomized or assigned IP (in OL portion) via the IRT according to the protocol. The IRT reserves IP vials after randomization. The IRT vial assignment confirmation must be printed and filed.

Once a patient is screened in the IRT by the site, a patient ID is assigned. ICON operates CytoMatch and then IRT so that specific vials of IP are reserved for the patient and shipped to the site by the depot, Brooks (Azenta).

11.1 Randomizing a Patient and Assigning IP Vial(s)

Sites should make every effort to administer the first dose of IP within 1-2 days of receipt.

At the time of randomization, trained site personnel access the IRT to randomize the patient. The IRT randomization transaction confirmation is to be printed out and filed in the ISF.

Following randomization in IRT, IP will be shipped to the site. Upon receipt of IP at the site the site staff will complete the "Shipment Assessment" transaction in the IRT to acknowledge shipment receipt and vial status. Once vials are acknowledged in IRT and available for use, the site staff can assign vials for dosing in IRT. The IRT vial assignment transaction documentation is to be printed out in duplicate, for filing and reference during IP preparation.

The site staff will refer to the vial assignment transaction to remove the appropriate IP vial(s) from storage.

Randomizing a Patient (Refer to IRT User Manual for detailed instructions)

Site selects Patient ID in IRT and "Randomization" tab and enters required information which includes:

- Visit Date
- Patient Weight
- Letermovir status, Donor Type, and Campath/ATG treatment

Completing this action will randomize the patient in the IRT and will enable the site staff to assign the IP vial(s) for the first dose.

Assigning Vials for Doses 1 through 7 (Refer to IRT User Manual for detailed instructions)

Site staff selects Patient ID and "Dispensation" tab in IRT and selects the correct visit number, then clicks "Dispense Vials and vial assignment will be provided.

The transaction confirmation will list the expiration dates of the vials assigned.

At the conclusion of the action, sites will print the transaction confirmation from IRT in duplicate, for filing and for reference during IP preparation.

The ICON and AlloVir study team are notified when the site completes this action.

The site will receive 1 or 2 vials of IP (depending on patient weight) for each study patient for each dose; it is imperative to select only the specific vials allocated by the IRT for each specific patient to ensure the appropriate vials are prepared.

Registration of dose 3 in the IRT will automatically generate shipment of IP for doses 4 to 7 to the clinical site.

12 DOSE CALCULATION AND EQUIPMENT

Preparation of the IP should be performed per the instructions in the Cell Therapy Manual and in alignment with the site's SOPs.

12.1 Dose Calculations

Patients who weigh <40 kg will receive 2 x 10^7 ALVR105 cells or placebo, while patients who weigh ≥40 kg will receive 4 × 10^7 cells or placebo for each infusion. Patients will receive the same dose for all infusions of study treatment. Body weight at screening will be used to determine cell (or placebo) dose.

The volume and quantity of IP required will be determined based on the patient's weight (at screening) according to Table 5 below:

Table 5: ALVR105 Dosing Schematic

Patient Weight	Dose (Cells)	Volume Drawn into Syringe(s)	IP Vials Required
<40 kg	2×10^7	2 mL	1
≥40 kg	4×10^7	4 mL	2

12.2 Equipment and Supplies

The supplies listed will be utilized to support dosing:

Equipment provided by ICON/AlloVir:

- 5 mL Luer lock syringes
- AT-Adapt™ (single-use needleless connection device)
- Hemo-Nate® syringe filter (referred to as "Hemo-Nate filter" below)
- Syringe caps
- 3-way stopcock
- Syringe labels (please see Syringe Label Template Appendix D)

Equipment provided by site:

- LN2 Freezer (able to hold vials in liquid phase of liquid nitrogen in an upright position)
- Infusion tubing for IV injection
- Dry-Block heater or water bath
- Bag of sterile normal saline (eg, 50 or 100 mL, but any volume is acceptable) for priming of IV line and flushing of line and syringe
- 5 or 10 mL normal saline flush for priming the Hemo-Nate filter

12.3 Prohibited Equipment/Supplies

The only filter that should be used for the infusion is the Hemo-Nate filter provided by the Sponsor. **No in-line leuko-reduction filters should be placed between the syringe containing IP and the patient.**

13 CHECKPOINT – PRIOR TO INITIATING THAW – OVERVIEW OF PROCESS

Prior to initiating thaw, it is important to coordinate the timing of IP thaw and infusion with the patient's nurse/study coordinator. Study treatment must be infused within 30 minutes of completion of thawing. The person designated to thaw the cells should contact and receive confirmation from the clinical team that the patient is cleared and ready to receive treatment and the patient is randomized and IP has been assigned in the IRT.

Critical Checks
• Patient is in the infusion location and ready to receive the infusion
• Peripheral or central IV access is in place
• Hemo-Nate filter has been primed (if being done in a biological safety cabinet) or ready to be primed (if being done at bedside)
• IV lines have been primed

The infusion of IP must be completed within 30 minutes following completion of the thawing of the designated vial(s) of IP. To ensure this timeframe, all documentation and labels should be prepared prior to removal of IP from vapor phase LN2 storage. If the Hemo-Nate filter is to be primed in a biological safety cabinet, this should also be done prior to thawing IP. Investigative product should be thawed at a satellite location close to the infusion location when feasible.

13.1 Preparation Instructions for each dosing visit

1. Upon receiving confirmation from the clinical team at the clinical site, retrieve the Dose Worksheet (Appendix H) and the IRT Site User Manual.
   a. Upon randomization, the IRT will assign the IP vial(s) to be administered and these will be listed on the IRT Shipment Request document with the expiration date of the vial. Vials for Dose 1 through 3 will be shipped after randomization. Note that the number of vials assigned will be based on the patient's weight at screening.
2. Retrieve the appropriate secondary IP labels.
3. Review the IRT transaction confirmation and ensure the assigned vials are not expired. (If a vial is expired, do not proceed with the thaw and infusion, and follow the Issue Reporting instructions in Section 10 of this manual.)
4. Transcribe the patient ID and vial number from the IRT transaction confirmation onto the printed syringe label.

5. Remove the designated IP vial(s) from vapor phase LN2 storage with protective equipment as indicated by the site SOP. Record the time of removal from vapor phase LN2 freezer on the Dose Worksheet (Appendix H).
6. Proceed with the thawing IP immediately as detailed in Section 14.

13.2 Emergency Recovery Procedure

If the IP vial is observed to be cracked when removed from storage, or if cracks or leaks occur during thawing or preparation, **immediately notify the Investigator or Sub-Investigator and follow the directions in Section 1 of this manual for "urgent issues during dose preparation or dosing that require immediate attention."** The Investigator/Sub-Investigator and Sponsor will determine whether to use or discard the IP.

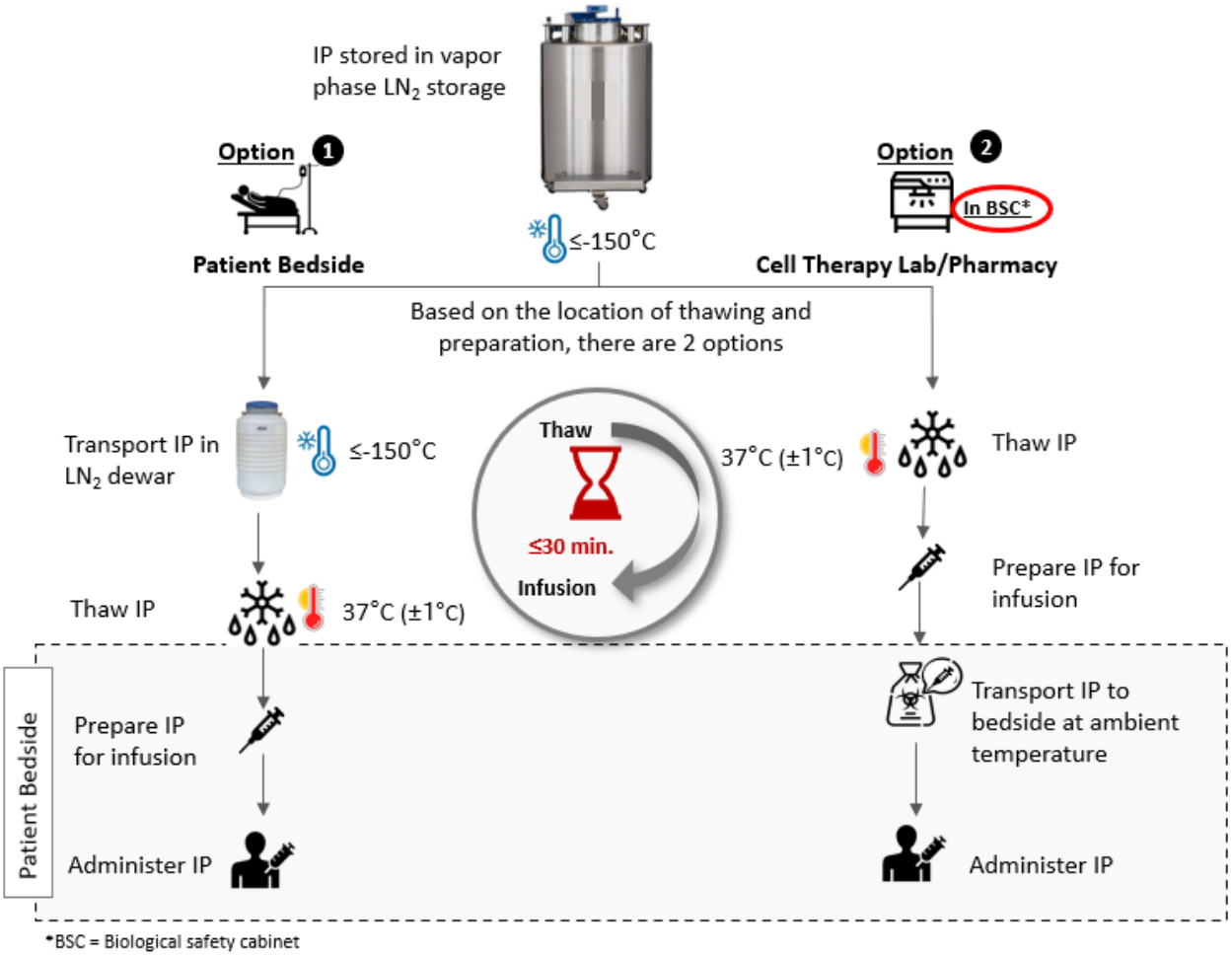
13.3 Thawing Procedure for Dosing

There are **two options** for the location of thawing and preparing IP:

- Option 1: Thaw IP at the patient's bedside or in a nearby area
- Option 2: Thaw IP in the Cell Therapy Laboratory or Pharmacy or a similar location

These options are summarized in Figure 3 below and discussed in greater detail below.

Figure 3: Storage to Infusion Flowchart



There are also **two options** for the location for priming the Hemo-Nate filter:

- Option 1: Thaw at bedside (which is covered in the section on Administration below)
- Option 2: Thaw in a biological safety cabinet or similar equipment in the Cell Therapy Laboratory, Pharmacy, or a similar location. When the priming step is done in a biological safety cabinet, it should occur **prior** to thawing the IP.

For sites that prefer to prime the Hemo-Nate filter in a biological safety cabinet, follow the instructions immediately below:

1. Remove the Hemo-Nate filter from its packaging under aseptic conditions (eg, in a biological safety cabinet; see Section 15 on Preparation of syringe below for additional details on acceptable equipment) and attach a syringe containing sterile normal saline. Prime the Hemo-Nate filter by injecting a minimum of 1 mL of normal saline through the filter, allowing the excess to spill into a container. It is acceptable to prime with a larger volume if using a prefilled syringe (eg, 5 or 10 mL).
2. Follow the steps for thawing the IP and transfer it to a 5 mL syringe (See Section 15 on Preparation of syringe below for the next steps.

14 THAWING OF IP

There are **two options** for the location of thawing and preparing IP (Figure 3). The site should select an option that will ensure that the 30-minute time limit between the end of thawing of IP and the end of the infusion of IP will be met.

The infusion of IP must be completed within 30 minutes following completion of the thawing of the designated vial(s) of IP. This does not include the flushes after administration of the IP.

Option 1: Thaw IP at the patient's bedside or in a nearby area

Place frozen vials in an LN2 dewar for transport to ensure that they are held at the correct specified temperature

Take all necessary measures to avoid prolonged exposure of the cryopreserved vials to conditions outside of the LN2 shipper and/or vapor phase freezer. It is critical to minimize the time the IP is handled outside the LN2 shipper and/or vapor phase LN2 freezer to no more than one (1) minute.

Transport the IP to the patient bedside location or preparation room on the patient ward or in the clinic or infusion center.

Proceed to the thaw and preparation steps as described below.

Option 2: Thaw IP in a biological safety cabinet in the Cell Therapy Laboratory or Pharmacy (or a similar location).

Proceed to the thaw and preparation steps as described below. Then transport the IP to the patient's bedside.

Place the syringe in a biohazard bag or equivalent, then place the bag into a suitable transport container at ambient temperature per site SOPs. Transport the container to the infusion site.

If thawing multiple IP vials (for the same patient), thaw all vials at the same time in the same manner.

1. Immediately thaw designated vial(s) in a Dry-Block Heater at 37°C (±1°C) per site SOPs. It is also acceptable to thaw vials in a pre-heated 37°C (±1°C) water bath within a sealed bag consistent with clinical site's SOPs. **Do not shake vials in water bath.**

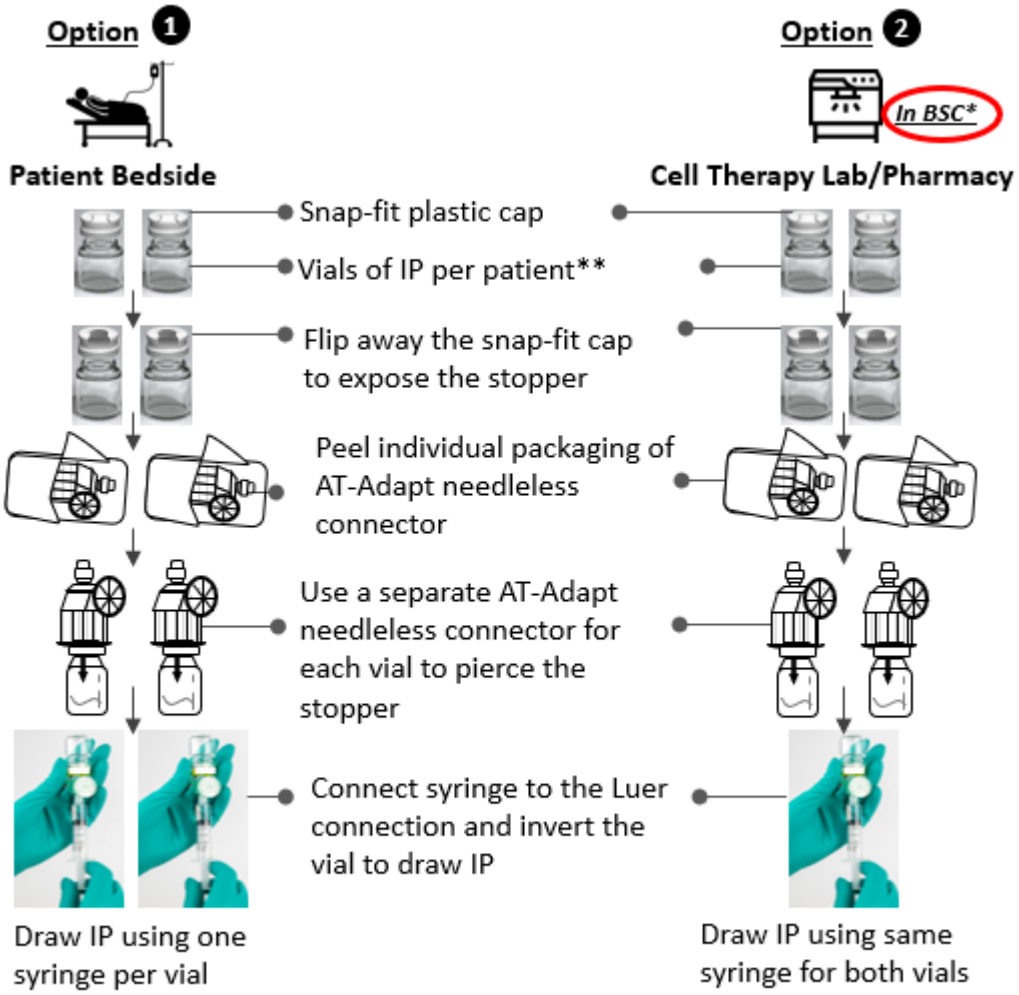
2. Observe the designated vial(s) of IP carefully as the thaw time may vary.

3. The IP can be considered fully thawed when there are no more ice crystals visible inside the vial. At this time, the vial(s) should be removed from the thawing device and thoroughly wiped with an alcohol swab.

4. Record the time of thaw completion for the designated vial(s) on the Dose Worksheet (Appendix H).

15 PREPARATION OF SYRINGE

Figure 4: Preparation of IP



*BSC = Biological safety cabinet

Note: **patients weighing ≥40 kg will receive 2 vials of IP. Patients weighing <40 kg will receive one vial of IP

Option 1: Preparation of IP at the patient's bedside or in a nearby area

To ensure sterile conditions, use one syringe per IP vial. If there are multiple vials required to complete the full dose, draw the volume indicated for each vial into a separate syringe.

1. Use the AT-Adapt™ needleless collection device to draw the prescribed dose into each labeled 5 mL Luer lock syringe. Use a new AT-Adapt™ needleless collection device for each individual syringe.

Option 2: Preparation in a biological safety cabinet in **the Cell Therapy Laboratory or Pharmacy**

1. Use the AT-Adapt™ needleless collection device for AT-Closed Vials to draw the appropriate dose into a labeled 5 mL Luer lock syringe. Use a new AT-Adapt™ needleless collection device for each individual vial.

2. Aseptically withdraw IP under sterile conditions from each vial in a class II biological safety cabinet or class II (or ISO class 5) laminar flow hood or more stringent equipment (eg, class III biological safety cabinet or aseptic isolator). See Table 5 above for the number of IP vials and volume to be drawn, which depends on the patient's weight at screening.

    - Each IP vial will contain approximately 2.5 mL of IP. After withdrawing the specified 2 mL from each vial, there should be residual volume left. If two IP vials are indicated, draw 2 mL from each vial into a single 5 mL syringe (rather than into two separate syringes). Dispose of used vials as biohazard waste in accordance with local governing regulations and clinical site SOPs.

3. **If your site plans to prime the Hemo-Nate filter in the biological safety cabinet** attach the primed Hemo-Nate filter to the syringe containing the IP and place the sterile syringe cap on the exposed end of the filter. Make sure that all three components are securely attached.

4. **If your site plans to prime the Hemo-Nate filter at the bedside**, cap the syringe with a sterile cap.

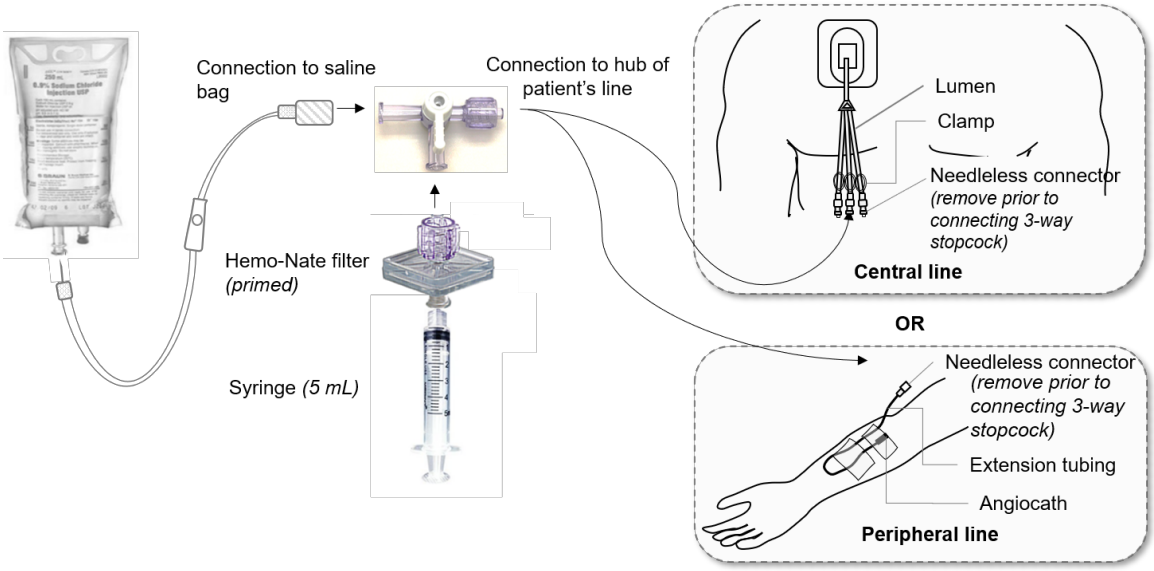
5. Affix the prepared label to the 5 mL Luer lock syringe.

6. Place the syringe (with the primed Hemo-Nate filter attached if priming was done in the biological safety cabinet) in a biohazard bag or equivalent, then place the bag into a suitable transport container per site SOPs.

7. Transport the container at ambient temperature to the infusion site.

16 ADMINISTRATION OF IP

Figure 5: Set-Up for IP Administration



The investigative site personnel will administer the IP as outlined below and per institutional guidelines. Patient safety monitoring during the administration should follow institutional guidelines.

16.1 Premedication

Premedication is not required, except for patients with a prior history of reaction to blood products who will receive premedication with diphenhydramine 0.25 to 0.5 mg/kg IV or orally (maximum dose 25 mg) or a different antihistamine preferred by the study site and/or acetaminophen (paracetamol) 5 to 10 mg/kg IV or orally (maximum dose 1000 mg) prior to study treatment administration. **Premedication with corticosteroids is prohibited**. Any premedication required by a patient will be provided by the site. Any premedication administered to the patient should be recorded in the patient's concomitant medication log.

16.2 Administration Instructions

The IP infusion must be completed within 30 minutes following completion of the thawing of the designated vial(s) of IP. This does not include the flushes after administration of the IP.

Site personnel complete the Dose Worksheet (Appendix H) during preparation and dosing of the IP. Complete the Dose Worksheet for each dose prepared and administered to the patient.

Site personnel to update the Chain of Custody form (Appendix C) after administration of IP.

1. Stop all other infusions prior to the administration of IP.

2. Obtain baseline vital signs prior to the infusion.

3. A bag of normal saline (eg, 50 or 100 mL, but any volume is acceptable) should be attached to the patient's IV tubing for use prior to and after IP administration.

4. Remove the needleless connector (eg, Clave) from the central line lumen or peripheral IV that will be used for the infusion.

5. Connect the 3-way stopcock directly to the patient's IV line.

6. **If your site plans to prime the Hemo-Nate filter at the bedside**, remove the Hemo-Nate filter from its packaging and attach a syringe containing sterile normal saline to it. It is acceptable to use whatever volume of normal saline is available (eg, 5 or 10 mL). Prime the Hemo-Nate filter by injecting a minimum of 1 mL of normal saline through the filter (allowing the excess to spill into a sink or container). Leave normal saline flush syringe attached to filter

7. Connect the primed Hemo-Nate filter to the 3-way stopcock.

8. **Only use the Hemo-Nate filter provided. Do not use a leuko-reduction filter**.

9. Take the Luer-locking syringe containing IP and review the information on the syringe label(s). Confirm that the patient ID listed on the syringe label(s) matches the ID of the patient intended to receive the infusion.

10. If the IP is contained in multiple syringes, check the labels from each syringe and verify the total volume.

11. Remove the normal saline flush syringe from the 3-way stopcock, remove the syringe cap from the first syringe containing the IP, and attach the syringe containing the IP to the filter that has been attached to the 3-way stopcock. **However, if your site plans to prime the Hemo-Nate filter in the biological safety cabinet**, it will arrive at the bedside already attached to the syringe containing IP. In this scenario, remove the syringe cap from the Hemo-Nate filter (which will have the IP-containing syringe still attached to the other side) and attach the exposed end of the filter to the 3-way stopcock.

12. Administer IP as a slow IV push. The total time for the IV push should be approximately 5 minutes, even if multiple syringes are administered.

13. Following the IP infusion with each syringe, turn the 3-way stopcock and aspirate 5 mL of normal saline from the IV bag into the syringe used to administer the IP and flush it into the patient **as a slow IV push**. If only one syringe is used for the IP infusion, perform this procedure twice. If two syringes are used for the IP infusion, flush with 5 mL of saline once after IP is administered from the first syringe and twice after it is administered from the second syringe. The Hemo-Nate filter and the syringe used to administer IP must remain attached during the saline flushes. Do not use separate (new)

syringes for the saline flushes as these flushes are intended to collect residual IP from the syringe that was used to administer the IP. IV extension tubing should be avoided whenever possible. If extension tubing is necessary for use with a peripheral IV, increase the flush volume as needed to ensure that the entire dose of IP is administered.

14. If the IP was provided in two syringes, administer the IP with the next syringe following the same steps as for the first syringe (ie, repeat steps 12 and 13).

15. Document the start and stop time that the IP infusion was completed (the time *before* the final saline flushes were administered).

16. Once the IP infusion is complete, dispose of the syringe as biohazard waste in accordance with local governing regulations and clinical site SOPs.

17. Remove the 3-way stopcock and place a new needleless connector, if applicable, on the end of the central line lumen or peripheral IV.

In the event that the entire dose is not administered, the reason(s) for not administering the entire dose as well as the volume administered must be documented in the patient's source documentation.

17 POST-ADMINISTRATION

Patients will be monitored according to institutional standards for the administration of cellular therapy and, at a minimum, according to the following requirements:

- Patients in an outpatient setting must remain in the clinic for ≥1 hour after the end of the infusion.
- Patients must remain on continuous pulse oximetry for ≥30 minutes after the end of the infusion.
- Vital signs will be monitored after the final flush has been administered (or within 5 minutes thereof), and at 15, 30, 45, and 60 minutes (±5 minutes of each of these time points) after the final flush.

These monitoring criteria establish the minimum required duration of monitoring for patients in an outpatient setting. The patient may be monitored in the clinic for a longer duration if the institutional standards for the administration of blood products require a longer monitoring period, or if the Investigator chooses to extend the monitoring period based on their clinical judgment.

All post infusion measurements must be recorded in the electronic case report form (eCRF), including any post-dose reactions reported by or observed in the patient. Patients will receive supportive care for acute or chronic toxicity, including blood components, antibiotics, or other interventions as appropriate per local treatment guidelines. See study protocol for additional information.

If a patient experiences a reaction post-infusion, then diphenhydramine 0.25 to 0.5 mg/kg IV or orally (maximum dose 25 mg) or a different antihistamine preferred by the study site may be administered as treatment (even if received as premedication). Acetaminophen 5 to 10 mg/kg IV or orally (maximum dose 1000 mg) may also be given if it was not given as premedication or if at least 6 hours has elapsed since the prior dose. If optimal control of the infusion reaction is not achieved, prednisone or an equivalent medication may be considered at a dose of ≤0.5 mg/kg/day prednisone equivalents. If administered, document accordingly.

17.1 Monitoring for and Management of Cytokine Release Syndrome

The following recommendations have been adapted from recommendations for patients receiving chimeric antigen receptor (CAR)-T cells who develop cytokine release syndrome (CRS).[1] Cytokine release syndrome is common following CAR-T cell therapy, but remains a theoretical concern following infusion of VSTs. No cases of CRS were observed in 58 patients in the Phase 2 CHARMS study of VSTs for viral infections following allogeneic HCT.[2] Nevertheless, investigators should remain vigilant for the signs and symptoms of CRS, particularly during the first four weeks following VST infusion, and should be prepared to treat patients immediately for CRS should it develop. Investigators should also counsel patients to seek immediate medical attention if they develop concerning clinical findings. At the first sign of CRS, immediately evaluate the patient for hospitalization and institute treatment as outlined below or according to treatment protocols in use at the study site. Cytokine release syndrome typically begins within 1 to 14 days (median 2 to 3 days) after CAR-T cell therapy.[3] Suspected adverse events should be reported according to recommendations outlined in the study protocol.

It is also important to note that the common symptoms of CRS are not unique to CRS and clinicians must be cautious and exclude other causes of fever, hypotension, hemodynamic instability, and/or respiratory distress, such as an overwhelming infection.[4]

Table 6: Treatment of Cytokine Release Syndrome

CRS Grade	CRS Severity	Management
1	Prodromal syndrome: Low-grade fever, fatigue, anorexia	Observe in person; exclude infection; administer antibiotics per local guidelines if neutropenic; provide symptomatic support.
2	CRS requiring mild intervention (≥1 of the following): • High fever • Hypoxia • Mild hypotension	Administer antipyretics, oxygen, intravenous fluids and/or low-dose vasopressors as needed.
3 to 4	CRS requiring moderate to aggressive intervention (≥1 of the following): • Hemodynamic instability despite IV fluids and vasopressor support • Worsening respiratory distress, including pulmonary infiltrates increasing oxygen requirement including high-flow oxygen and/or need for mechanical ventilation • Rapid clinical deterioration	Administer high-dose and/or multiple vasopressors, oxygen, mechanical ventilation and/or other supportive care as needed. Administer tocilizumab: • Patient weight <30 kg: 12 mg/kg IV over 1 hour • Patient weight ≥30 kg: 8 mg/kg IV over 1 hour (maximum dose 800 mg) If there is no clinical improvement, repeat tocilizumab after a minimum interval of 8 hours. If there is no response to a second dose of tocilizumab, consider a third dose of tocilizumab or pursue alternative measures for treatment of CRS. Limit to a maximum total of 4 doses of tocilizumab. If there is no clinical improvement within 12 to 18 hours of the first tocilizumab dose, or if there is worsening at any time, administer methylprednisolone 2 mg/kg IV as an initial dose, then 2 mg/kg IV per day until vasopressors and high-flow oxygen are no longer needed, then taper.

Abbreviations: CRS = cytokine release syndrome; IV = intravenous.

References

1. KYMRIAH® (tisagenlecleucel) suspension for intravenous infusion, prescribing information. https://www.novartis.us/sites/www.novartis.us/files/kymriah.pdf. Accessed on 09 May 2021.
2. Tzannou I, Papadopoulou A, Naik S, et al. Off-the-shelf virus-specific T cells to treat BK virus, human herpesvirus 6, cytomegalovirus, Epstein-Barr virus, and adenovirus infections after allogeneic hematopoietic stem-cell transplantation. J Clin Oncol. 2017;35(31):3547-3557.
3. Porter DL and Maloney DG. Cytokine release syndrome (CRS). Post TW, ed. UpToDate. Waltham, MA. Updated 06 Apr 2020. https://www.uptodate.com/contents/cytokine-release-syndrome-crs. Accessed on 09 May 2021.
4. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019;25(4):625-638.

18 INVESTIGATIONAL PRODUCT ACCOUNTABILITY

18.1 General Accountability

The Investigator is responsible for IP accountability, reconciliation, and record maintenance during the study, including documentation of the receipt of the IP and administration to the patient. Records will be maintained indicating the receipt and dispensation of all study IP shipments. The CRA will review accountability records at regular intervals as part of the clinical site monitoring visit. The responsible cell therapy laboratory personnel or designated staff at the investigational site must keep accurate records and inventory of study IP shipments received, the IP administered per patient, the IP stored, and the IP destroyed. This information must be recorded on the Chain of Custody form (Appendix C).

The study IP **CAN NOT** be used for any purposes other than those outlined in the study protocol. Under no circumstances should the Investigator, cell therapy laboratory personnel, or other site personnel use the IP or supplies provided for any purpose other than as directed by the protocol, without prior authorization from AlloVir.

18.2 Destruction of the Investigational Product

Sites should dispose of used vials as biohazard waste in accordance with local governing regulations and clinical site SOPs/written procedures. For unused vials, approval is required to destroy at site.

Prior to IP destruction, the SOP or written procedure for destruction must be reviewed and approved by the sponsor and/or CRO. Email approval will be filed at the site. Approval is expected if the following criteria are met:

- Site must have a documented procedure for destroying IP
- Procedure must state that destruction will follow applicable laws and regulations
- Procedure must state that the destruction will be documented, including what was destroyed, how it was destroyed, and when it was destroyed

If the site is FACT- or JACIE-accredited, approval of the IP destruction process will still need to be provided by the CRA.

Once approval of the site's IP destruction process has been received the site can proceed with the destruction of specific vials of IP as per their SOP/written procedure.

Destruction of unused IP must be documented on the Chain of Custody form (Appendix C).

IP vials (used or unused) and all infusion materials (syringes, infusion tubes, etc.) containing IP should be treated and disposed of as biohazard waste in accordance with local governing regulations and clinical site SOPs/written procedure.

19 BLINDING AND UNBLINDING PROCEDURES

19.1 Maintaining the Blind

The integrity of the study blind and randomization procedures must be maintained over the course of the study. Shipment of vials containing IP will be triggered by the IRT following the randomization of a potential patient. Upon arrival of IP at the site, the site staff will follow the procedures laid out in this Cell Therapy Manual and in alignment with their site's SOPs.

Upon randomization of a patient, the IRT assigns specific vials to be administered for the first dose which are documented on a report generated by the IRT

The IRT will assign specific vial(s) for the subsequent dose(s) as applicable per the Protocol.

19.2 Blinded Site Staff Responsibilities

The investigators, research staff, and patients are to remain blinded to treatment assignment.

19.3 Unblinded Site Staff Responsibilities

In Open Label Phase, unblinded cell therapy lab staff must ensure the appropriate procedures are in place to keep blinded individuals (ie, investigators, research staff, and patients) blinded to treatment assignment. In Phase 3, all personnel will be blinded.

19.4 Emergency Unblinding Procedure

The blind is anticipated to be broken only in extreme situations. Before any potential unblinding, the reasons and rationale for the unblinding should be discussed with AlloVir, and the medical lead or designee. The Investigator and designated study site staff are the only personnel at the study site who are authorized to decide to unblind a patient's treatment assignment group in an emergency situation.

In the case of an emergency, the Investigator (and/or a delegated sub-investigator if the Investigator is unavailable) has the sole responsibility for determining if unblinding of a participant's study treatment assignment is warranted. Participant safety must always be the first consideration in making such as determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the medical lead prior to unblinding a participant's IP assignment unless this could delay emergency treatment of the participant. Please consult the IRT User Manual for instructions.

If a participant's treatment assignment is unblinded, the Sponsor or medical lead must be notified within 24 hours of breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and electronic CRF, as applicable.

Unblinding at the clinical site for any reasons other than a medical emergency will be considered a protocol deviation.

20 LIST OF APPENDICES

Appendix A: FlexAdvantage IRT Guide

Appendix B: Cryoport Temperature Stability Report

Appendix C: Chain of Custody Form

Appendix D: Syringe Label

Appendix E: Brooks (Azenta) Pack Out Slip

Appendix F: FlexAdvantage IRT Shipment Request Form

Appendix G: Issue Reporting Form

Appendix H: Dose Worksheet

Appendix I: Receipt, Handling, Unpacking Procedures

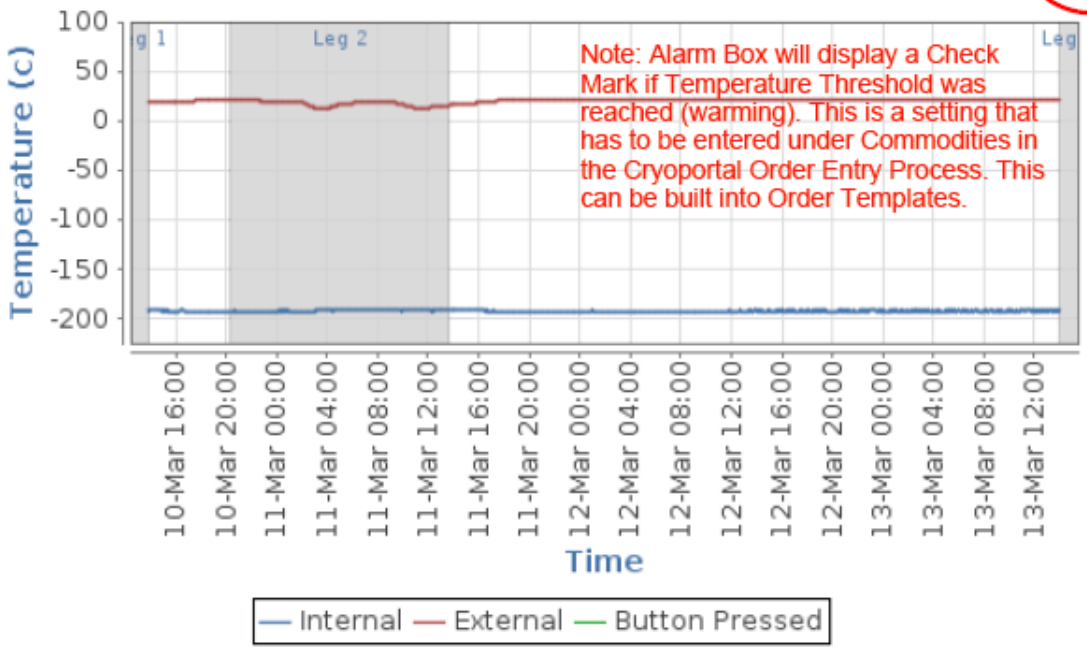
20.1 Appendix A: FlexAdvantage IRT Guide (provided separately)

20.2 Appendix B: Cryoport Temperature Stability Report

Temperature Stability Report - Order #
Package #1 Logger #
Lot/Serial Number:

cryoport

ALARM



Alarm Zones	Allowed Time	Total Time	No. of violations	Status
No band defined				

Internal Temperature Stats Summary is displayed under Logging Results

Logging Results

Internal High/Low/Average/Std Dev:	-191.9/-194.6/-192.6/0.3 °C	Transit Start at:	03/09/2020
External High/Low/Average/Std Dev:	21.2/11.3/19.5/2.1 °C	Arrived at:	03/16/2020
		Alarm at:	
		File created:	03/16/2020

Condition Monitoring System

Part Number:	ACC-9123	Description:	SmartPak II Data Logger (PT300D)
Serial Number:		Battery Voltage:	4.13 V - 3.88 V
Calibration Certificate #:	Not Required	Calibration Due Date:	Not Required
Part Number:		Description:	Thermocouple SmartPak II
Serial Number:			
Calibration Certificate #:		Calibration Due Date:	10/07/2020
Recorded By:		Date:	03/09/2020

CONFIDENTIAL
FOR INFORMATIONAL USE ONLY

20.3 Appendix C: Chain of Custody Form

Appendix C - AlloVir Chain of Custody Form V3.0
P-105-202

PATIENT AND INFORMATION			
Site Number:		Investigator Name:	
Patient ID:			

SHIPMENT INFORMATION: DOSES 1 THROUGH 3			
Order ID: *Listed on FlexAdvantage Shipment Request*			
Check Documentation Received:	☐ Brooks (Azenta) Pack-Out Slip ☐ *FlexAdvantage* Shipment Request ☐ Certificate(s) of Conformance ☐ Shipper return labels ☐ Safety Data Sheet (SDS) ☐ Secondary label booklets (1 per vial)	Was there intact zip ties present on the cryoshipper upon delivery?	☐ Y ☐ N
		Were all contents listed on the *FlexAdvantage* Shipment Request received?	☐ Y ☐ N
Date and Time Vials removed from shipper:	___ / _____ / _____ _____ DD MMM YYYY HH:MM	Did the cryoshipper Temperature Stability Report note any temperature alarms occurring during transit?	☐ Y ☐ N
If the contents were missing from the shipment or if a temperature alarm occurred during shipment, please follow the issue reporting instructions in the Cell Therapy Manual.			

PATIENT AND INFORMATION			
Site Number:		Investigator Name:	
Patient ID:			

SHIPMENT INFORMATION: DOSES 4 THROUGH 7

Order ID: *Listed on FlexAdvantage Shipment Request*			
Check Documentation Received:	☐ Brooks (Azenta) Pack-Out Slip ☐ *FlexAdvantage* Shipment Request ☐ Certificate(s) of Conformance ☐ Shipper return labels ☐ Safety Data Sheet (SDS) ☐ Secondary label booklets (1 per vial)	Was there an intact zip tie present on the cryoshipper upon delivery?	☐ Y ☐ N
		Were all contents listed on the *FlexAdvantage* Shipment Request received?	☐ Y ☐ N
Date and Time Vials removed from shipper:	___ / _____ / _____ _____ DD MMM YYYY HH:MM	Did the cryoshipper Temperature Stability Report note any temperature alarms occurring during transit?	☐ Y ☐ N
If the contents were missing from the shipment or if a temperature alarm occurred during shipment, please follow the issue reporting instructions in the Cell Therapy Manual.			

PATIENT AND INFORMATION			
Site Number:		Investigator Name:	
Patient ID:			

DOSE 1 (SECONDARY LABEL)
Attach secondary label below (ONE FOR EACH VIAL THAT YOU PREPARE FOR INFUSION)

PATIENT AND INFORMATION			
Site Number:		Investigator Name:	
Patient ID:			

DOSE 2 (SECONDARY LABEL)
Attach secondary label below (ONE FOR EACH VIAL THAT YOU PREPARE FOR INFUSION)

PATIENT AND INFORMATION			
Site Number:		Investigator Name:	
Patient ID:			

DOSE 3 (SECONDARY LABEL)
Attach secondary label below (ONE FOR EACH VIAL THAT YOU PREPARE FOR INFUSION)

PATIENT AND INFORMATION			
Site Number:		Investigator Name:	
Patient ID:			

DOSE 4 (SECONDARY LABEL)
Attach secondary label below (ONE FOR EACH VIAL THAT YOU PREPARE FOR INFUSION)

PATIENT AND INFORMATION			
Site Number:		Investigator Name:	
Patient ID:			

DOSE 5 (SECONDARY LABEL)
Attach secondary label below (ONE FOR EACH VIAL THAT YOU PREPARE FOR INFUSION)

PATIENT AND INFORMATION			
Site Number:		Investigator Name:	
Patient ID:			

DOSE 6 (SECONDARY LABEL)
Attach secondary label below (ONE FOR EACH VIAL THAT YOU PREPARE FOR INFUSION)

PATIENT AND INFORMATION			
Site Number:		Investigator Name:	
Patient ID:			

DOSE 7 (SECONDARY LABEL)
Attach secondary label below (ONE FOR EACH VIAL THAT YOU PREPARE FOR INFUSION)

PATIENT AND INFORMATION			
Site Number:		Investigator Name:	
Patient ID:			

PATIENT AND INFORMATION			
Site Number:		Investigator Name:	
Patient ID:			

	RECEIPT			ADMINISTRATION			DESTRUCTION		
Vials *(Lot Number; Vial Number)*	**Received in Good Condition** *(Mark N/A for vials not received)*	**Date Received** *(dd-MON-yyyy)*	**Received and Unpacked By** *(Initials)*	**Administered to Patient**	**Date Administered** *(dd-MON-yyyy)*	**Dispensed By** *(Initials)*	**Date and Time of Destruction** *(dd-MON-yyyy, HH:MM)*	**Destroyed By** *(Initials)*	**CRA Initials/Date** *(dd-MON-yyyy)*
126 - _ _ - _ _ _ _ _ _; _ _ _	☐ Yes ☐ No			☐ Y ☐ N					
126 - _ _ - _ _ _ _ _ _; _ _ _	☐ Yes ☐ No ☐ N/A			☐ Y ☐ N					
126 - _ _ - _ _ _ _ _ _; _ _ _	☐ Yes ☐ No ☐ N/A			☐ Y ☐ N					
126 - _ _ - _ _ _ _ _ _; _ _ _	☐ Yes ☐ No ☐ N/A			☐ Y ☐ N					
126 - _ _ - _ _ _ _ _ _; _ _ _	☐ Yes ☐ No ☐ N/A			☐ Y ☐ N					
126 - _ _ - _ _ _ _ _ _; _ _ _	☐ Yes ☐ No ☐ N/A			☐ Y ☐ N					
	☐ Yes								

126 - _ _ - _ _ _ _ _ _; _ _ _	☐ No ☐ N/A			☐ Y ☐ N					
126 - _ _ - _ _ _ _ _ _; _ _ _	☐ Yes ☐ No ☐ N/A			☐ Y ☐ N					

PATIENT AND INFORMATION			
Site Number:		Investigator Name:	
Patient ID:			

	RECEIPT			ADMINISTRATION			DESTRUCTION		
Vials *(Lot Number; Vial Number)*	**Received in Good Condition** *(Mark N/A for vials not received)*	**Date Received** *(dd-MON-yyyy)*	**Received and Unpacked By** *(Initials)*	**Administered to Patient**	**Date Administered** *(dd-MON-yyyy)*	**Dispensed By** *(Initials)*	**Date and Time of Destruction** *(dd-MON-yyyy, HH:MM)*	**Destroyed By** *(Initials)*	**CRA Initials/Date** *(dd-MON-yyyy)*
126 - _ _ - _ _ _ _ _ _; _ _ _	☐ Yes ☐ No			☐ Y ☐ N					
126 - _ _ - _ _ _ _ _ _; _ _ _	☐ Yes ☐ No ☐ N/A			☐ Y ☐ N					
126 - _ _ - _ _ _ _ _ _; _ _ _	☐ Yes ☐ No ☐ N/A			☐ Y ☐ N					
126 - _ _ - _ _ _ _ _ _; _ _ _	☐ Yes ☐ No ☐ N/A			☐ Y ☐ N					
126 - _ _ - _ _ _ _ _ _; _ _ _	☐ Yes ☐ No ☐ N/A			☐ Y ☐ N					
126 - _ _ - _ _ _ _ _ _; _ _ _	☐ Yes ☐ No ☐ N/A			☐ Y ☐ N					

It is the responsibility of the site to ensure that the investigational product is stored in vapor phase liquid nitrogen (LN2) at ≤ -150°C upon receipt and removal from the shipper.

20.4 Appendix D: Syringe Label

ALVR105 or Placebo

AlloVir, Inc.

P-105-202

Patient ID:_____

Vial Number(S): _____

For Investigational Use Only

For additional information please refer to Cell Therapy Manual

20.5 Appendix E: Brooks (Azenta) Packing Slip

Example - For Reference Only

Brooks Life Sciences
2910 Fortune Circle West
Suite E
Indianapolis, IN 46241
Tel: 317-390-1866

Ship To: Site Name
Site Address

Contact:
Number:

Shipment No: XXXXXXXX
Req. Delivery Date: DD-MON-YYYY
Carrier: World Courier

Project: P-105-202
Storage Temp(s): -190° C

Group(s):
Sample Type(s):

Pkg Pos	Originating ID	ISISS Registration	
Package XXXXXX	**(# samples in package)**		

20.6 Appendix F: FlexAdvantage IRT Shipment Request Form

Allovir
P-105-202
Unblinded Shipment Request

Shipment ID	S-3-89-1308	Shipment Type	MANUAL
Date Requested	01-Jun-2021	Fill Type	FULL
Supplying Warehouse	Brooks	Site Phone Number	123-123-1234
Destination Site Number	123	Site Shipping Address	ICON 1234 Dairy Ashford Sugar Land, TX, 77479 United States
Site Investigator	Nausheen Siddiqui		
Drug Contact Name	MS. Nausheen ..... Siddiqui		
Drug Contact Email	test@test.com		
Patient Number	123-1122		

Please ship the following:

Lot Number + Vial No	Expiration Date
128-ZZ-23TSTB-113	31-Jan-2025
128-ZZ-23TSTB-114	31-Jan-2025
128-ZZ-23TSTB-115	31-Jan-2025
128-ZZ-23TSTB-116	31-Jan-2025
128-ZZ-23TSTB-117	31-Jan-2025
128-ZZ-23TSTB-118	31-Jan-2025
128-ZZ-23TSTB-119	31-Jan-2025
128-ZZ-23TSTB-120	31-Jan-2025
128-ZZ-23TSTB-121	31-Jan-2025
128-ZZ-23TSTB-122	31-Jan-2025

20.7 Appendix G: Issue Reporting Form

APPENDIX G: IP ISSUE REPORTING FORM

ALLOVIR | P-105-202

DECEMBER-2021 | V 3.0

Site Instructions: In the event of an issue regarding investigational product (IP) for ALVR105/placebo, please follow the reporting instructions in the Cell Therapy Manual and email this form with sections A and B, C, or D completed to your CRA.

Once a decision has been made, ICON will communicate the decision to the site via email and include the completed form. **Please file the completed form.**

SECTION A: SITE AND ISSUE INFORMATION			
Site Name / Number		Institution	
PI Name		Address	
Reported by *Print name and title*		Signature/Date	
Email		Telephone	
Please check appropriate box:	☐ IP temperature excursion *(please complete section B)* ☐ Receipt of IP at site *(please complete section C)* ☐ IP product complaint *(please complete section D)* ☐ Other *(please complete section D)*		
Was this an urgent issue?	☐ Yes *(If yes, please complete the box below)* ☐ No		
Please describe the actions taken at the time the urgent issue was discovered.			

SECTION B: TEMPERATURE EXCURSION INFORMATION			
Product Name *Storage Condition is vapor phase liquid nitrogen (LN2) at ≤ -150°C*	ALVR105 or placebo	Affected Lot + Vial #s:	126 - _ _ - _ _ _ _ _ ; _ _ _ 126 - _ _ - _ _ _ _ _ ; _ _ _ 126 - _ _ - _ _ _ _ _ ; _ _ _ 126 - _ _ - _ _ _ _ _ ; _ _ _
Did the excursion occur during shipment of IP to the site?	☐ Yes *If yes, please attached the Cryoport temperature stability report and submit the signed form. Do not complete the remainder of section B.* ☐ No		
Start Date of Excursion (dd-MMM-yyyy)		Duration of Excursion (HH:MM)	

SECTION B: TEMPERATURE EXCURSION INFORMATION			
Start Time of Excursion (24H HH:MM)			
Date of Discovery (dd-MMM-yyyy)		Maximum temperature reached during excursion	
Description and Cause of Excursion			

SECTION C: RECEIPT OF IP AT SITE			
Shipment Order ID:		Affected Lot + Vial #s:	126 - _ _ - _ _ _ _ _ ; _ _ _ 126 - _ _ - _ _ _ _ _ ; _ _ _ ☐ N/A 126 - _ _ - _ _ _ _ _ ; _ _ _ ☐ N/A 126 - _ _ - _ _ _ _ _ ; _ _ _ ☐ N/A
Please describe the issue(s) identified:			

SECTION D: PRODUCT COMPLAINT OR OTHER ISSUE INFORMATION	
Affected Lot + Vial #s:	126 - _ _ - _ _ _ _ _ ; _ _ _ 126 - _ _ - _ _ _ _ _ ; _ _ _ ☐ N/A 126 - _ _ - _ _ _ _ _ ; _ _ _ ☐ N/A 126 - _ _ - _ _ _ _ _ ; _ _ _ ☐ N/A
Please describe the issue(s) identified:	

Please send a completed form to your CRA and wait for further instructions.

SECTION E: ALLOVIR/ICON USE ONLY			
Assessment	☐ Acceptable for use ☐ NOT acceptable for use. Site to destroy affected vials. ☐ Other - see notes.		
Notes			
Name (Print)	Title	Signature	Date

20.8 Appendix H: Dose Worksheet

APPENDIX H: DOSE WORKSHEET
ALLOVIR | P-105-202
DECEMBER-2021 | V 3.0

DOSE WORKSHEET
Site Instructions: Complete this worksheet for **each dose** of Investigational Product prepared and administered to the patient. Prior to preparation for dosing, the patient must be randomized in IRT for dose 1 by completing the action "Randomize a Patient" OR IRT must assign doses 2 through 7 by completing the action "Vial Assignment." Completing these actions will assign the cryovials for the dose. **If an issue arises, please follow the issue reporting instructions in the Cell Therapy Manual.**

PART A: PATIENT AND VIAL INFORMATION **Part A to be completed by cell lab/pharmacy or responsible party who would pull the IP.**			
Site Number:		Investigator Name:	
Patient ID #:			
Patient Weight (Measured at screening)	_ _ . _ kg		
Visit #:	☐ Day 0 (Dose 1) ☐ Day 14 (Dose 2) ☐ Day 28 (Dose 3) ☐ Day 42 (Dose 4) ☐ Day 56 (Dose 5) ☐ Day 70 (Dose 6) ☐ Day 84 (Dose 7)		
Date of randomization:	___ / _____ / _____ DD MMM YYYY		
IRT assigned Vial 1: Vial #	_ _ _	Vial 1 Expiration Date	___ / _____ / _____ DD MMM YYYY
☐ Mark if ONLY 1 vial required (patient weight <40 kg)			
IRT assigned Vial 2: Vial #	_ _ _	Vial 2 Expiration Date	___ / _____ / _____ DD MMM YYYY
Completed By:	Print Name:	Signature:	___ / _____ / _____ DD MMM YYYY
Verified By:	Print Name:	Signature:	___ / _____ / _____ DD MMM YYYY

PATIENT ID #:	
Visit #:	☐ Day 0 (Dose 1) ☐ Day 14 (Dose 2) ☐ Day 28 (Dose 3) ☐ Day 42 (Dose 4) ☐ Day 56 (Dose 5) ☐ Day 70 (Dose 6) ☐ Day 84 (Dose 7)

PART B: INVESTIGATIONAL PRODUCT THAW AND PREPARATION OF ADMINISTRATION SYRINGE **Part B to be completed by cell lab/pharmacy or responsible party for thawing and preparing the syringe. After completing this section, then hand off the entire form to infusion with the prepared syringe.**			
Administration of Investigational Product is to be completed within 30 minutes of thaw completion. If thawing multiple cryovials, thaw all vials at the same time in the same manner.			
Prior to thaw, were the lot and vial numbers listed on the vials double verified against the IRT assignment?	☐ YES ☐ NO		
Date and Time of Removal of Vials from LN Storage	___ / _____ / _____ _____ DD MMM YYYY HH:MM	Was the vial / Were the vials intact, sealed, and frozen?	☐ Yes ☐ No
Date and Time of Thaw Completion	___ / _____ / _____ _____ DD MMM YYYY HH:MM	Indicate method of thawing and thawing temperature:	☐ Water bath ☐ Dri-Block Temperature: _____ ºC
When IP was drawn into the syringe, were the vial numbers listed on the vials double verified against the vial numbers listed on the syringe label?	☐ YES ☐ NO		
Was the patient ID listed on the syringe label double verified against the IRT assignment?	☐ YES ☐ NO		
Completed By:	Print Name:	Signature:	___ / _____ / _____ DD MMM YYYY
Verified By:	Print Name:	Signature:	___ / _____ / _____ DD MMM YYYY

PATIENT ID #:	
Visit #:	☐ Day 0 (Dose 1) ☐ Day 14 (Dose 2) ☐ Day 28 (Dose 3) ☐ Day 42 (Dose 4) ☐ Day 56 (Dose 5) ☐ Day 70 (Dose 6) ☐ Day 84 (Dose 7)

PART C: ADMINISTRATION OF INVESTIGATIONAL PRODUCT **Part C to be completed by the infusion team.**			
Follow IP administration instructions in Cell Therapy Manual – Administration **Prior to administration, double verify the patient ID against the patient ID listed on the syringe label.**			
Date and Time of Administration Start	___ / _____ / _____ _____ DD MMM YYYY HH:MM	Date and Time of Administration Completion *(not including post-infusion flush)*	___ / _____ / _____ _____ DD MMM YYYY HH:MM
Was administration completed within 30 minutes of thaw completion?	☐ YES ☐ NO		
Confirm that the Hemo-Nate syringe filter was utilized:	☐ YES		
Completed By:	Print Name:	Signature:	___ / _____ / _____ DD MMM YYYY
Verified By:	Print Name:	Signature:	___ / _____ / _____ DD MMM YYYY
The following fields are to be completed only if the dose was interrupted or the entire volume was not administered.			
If the dose was interrupted, reason for dose interruption:			
Date and Time of Administration Pause	___ / _____ / _____ _____ DD MMM YYYY HH:MM	Date and Time of Administration Re-start	___ / _____ / _____ _____ DD MMM YYYY HH:MM
Total volume administered	_____ mL	Estimated remaining volume after administration completion: ***(Complete only if the entire volume was not administered)***	_____ mL

PART D: FLUSH **Part D to be completed by the infusion team.**			
Follow IP administration instructions in Cell Therapy Manual - Administration			
Date and Time of Flush Start	___ / _____ / _____ _____ DD MMM YYYY HH:MM	Date and Time of Flush Completion	___ / _____ / _____ _____ DD MMM YYYY HH:MM
Saline Flush Volume	_____ mL		
Completed By:	Print Name:	Signature:	

			___ / _____ / _____ DD MMM YYYY
Verified By:	Print Name:	Signature:	___ / _____ / _____ DD MMM YYYY

IP vials and all infusion materials (syringes, infusion tubes, etc.) containing IP should be treated and disposed of as biohazard waste in accordance with local governing regulations and clinical site SOPs.

20.9 Appendix I: Receipt, Handling, Unpacking Procedures

20.9.1 Receipt of Product at the Investigative Site

The site will receive an email notification from Cryoport when the IP is delivered. The Temperature Stability Report (Appendix B) will also be emailed to and filed by the site. The Cryoport Live View Link provided in the initial order notification email can be used to view the LN2 shipper's location and temperature.

The site personnel receiving the LN2 shipper will inspect the LN2 shipper and handle AT-Closed Vials as described in Section 20.9.2 below. Prior to unpacking the shipper, the site will transcribe the lot and vial numbers from the IRT shipment request form onto the Chain of Custody form (Appendix C) and file the documentation per site SOPs. The site reviews AT-Closed Vial labels and checks received lot and vial numbers against the IRT shipment request form prior to placing the IP into long-term LN2 freezer on site. It is critical to limit the amount of time that IP is out of cryogenic conditions (≤ -150°C) to ≤ 1 minute.

Upon completion of inspection, unpacking, and storage at the site (see inspection instructions below), the site reports the following information in IRT:

- Shipment Order ID
- Shipment condition at receipt
- Date Received and Date and Time of Removal of Cell Product from the LN2 Shipper
- At the conclusion of the action, site will print the transaction confirmation from IRT and file it.

If you have unacknowledged shipments at your site, you may be blocked from performing certain actions within IRT.

20.9.2 Inspection of Shipment

External Inspection of the LN2 Shipper

- Carefully transport the LN2 shipper to unpacking area for inspection. The shipper must always be maintained in an upright position.
- Inspect the LN2 shipper for any damage or disruption to the seal. Ensure that the zip ties were intact at the time of delivery and document on Chain of Custody form (Appendix C).

Courier Shipment Label

- Inspect the courier shipment label that arrived with the LN2 shipper. Confirm the courier shipment label arriving with the LN2 shipper matches courier shipment label received in the Cryoport email notification.

Temperature

- Review the Cryoport Temperature Stability Report (Appendix B) to confirm there were no temperature excursions during transit. If the report notes a temperature excursion during transit, follow the Issue Reporting instructions in Section 10 of this document.
- The Cryoport Live View Link provided in the initial order notification email can be used to view the shipper's location and temperature.

20.9.3 Handling the LN2 Shipper

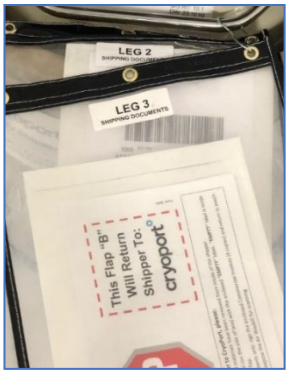
- The LN2 shipper will arrive with black rubber or metal latches zip-tied; use caution when cutting and removing the zip ties.
- Remove the old shipping pouch and discard the Leg 2 (site delivery) Shipping Airway Bill.
- The LN2 shipper will be stored in a safe location.
- The frozen IP should be unloaded same day of the arrival of the LN2 shipper.
- Empty LN2 shipper should be stored in an area with adequate cell signal; avoid areas like basement rooms or refrigerators where data transmission may be blocked.
- The pouch labeled "DOCUMENTS ENCLOSED" with a checklist is adhered to the inner surface of the shipper mushroom lid on the right and will contain four (4) zip ties.
- An unlabeled pouch adhered to the inner surface of the shipper mushroom lid on the left will contain unloading instructions and the "EMPTY" label.

Plastic Pouches adhered to the inner surface of the shipper mushroom enclosure lid.

The clear shipping pouch on the left contains the unloading instructions and EMPTY label.

The shipping pouch labeled "Documents Enclosed" contains commodity shipping labels, shipper certificate, packaging list, four (4) zip ties, and loading instructions.

Three transparent hanging sleeves are attached to the handle of the dewar inside the shipper enclosure. All large sleeves are reusable and should be returned with the shipper to Cryoport **Return shipping instructions are located below under *Returning the Shipper to Cryoport.***



The Leg 2 (site delivery) sleeve contains the Leg 2 airway bill and a new shipping pouch to attach to the shipper for the next shipment. The Leg 3 (return shipment) sleeve contains a sheet warning that the documents contained are intended for shipper return to Cryoport, the Leg 3 airway bill, and a new shipping pouch. An unlabeled sleeve may be included to hold additional Cryoport provided accessories.

20.9.4 Unpacking and Storage of ALVR105 and Placebo

Following delivery and inspection of the IP, the site should transfer the product rapidly from the LN2 shipper to a vapor phase LN2 freezer with continuous temperature monitoring until the day of infusion (please refer to handling instructions below).

- It is the responsibility of the site to ensure Investigational Product (IP), ALVR105 and placebo is stored at ≤ -150°C and to monitor the temperature of the storage conditions.
- Please refer to Figure 6 for a visual representation of the steps required to unpack the LN2 shipper.
-

Take all necessary measures to avoid prolonged exposure of the cryopreserved vials to conditions outside of the LN2 shipper and/or vapor phase freezer. It is critical to minimize the time the IP is handled outside the LN2 shipper to no more than one (1) minute.

- Unlatch the LN2 shipper in one of two ways:
  - If the shipper has Silver Metal Latches, unlock the latches by turning the key to the left. The latch will unhook from the top of the metal hardware.

- If the shipper has Black Rubber Latches, pull the black handle down and away from the shipper.

- Open the lid to expose the dewar.
- Remove the vapor plug to retrieve and remove the Subject-labeled IP packaging from the dewar.
- Replace the vapor plug and allow it to settle down completely.
- Do not tamper with the Smartpak II® Conditioning Monitoring system located at the top of the vapor plug. Cryoport will continue to monitor the GPS location until Leg 3 delivery is completed, and the collected temperature information for Leg 2 will automatically be compiled and sent to all parties once available.

- Visual inspection of the IP should be conducted as close to the LN2 freezer where the IP will be stored as possible.
- The vials must remain upright at all times.
- Carefully remove the vials from the LN2 shipper by taking out the Cryobox from the metal rack and inspecting the Cryobox and vials for damage.
- Review vial labels and check received lot and vial identification (ID) numbers on the Chain of Custody form.
- Place the IP in LN2 freezer at the site as rapidly as possible.
- Complete shipment receipt sections of the Chain of Custody form (Appendix C) and file.

If any issues are found during inspection and handling, follow the Issue Reporting Instructions found in Section 10 of this manual.

Figure 6: Steps outlining unpacking of the LN2 shipper

Step 1 Step 2 Step 3 Step 4 Step 5

20.9.5 Documents

- The following documents will be included:
  - Brooks (Azenta) pack out slip (Appendix E)
  - IRT shipment request (Appendix F)
  - Secondary label(s) (one per vial)
  - Shipper return labels
  - Safety Data Sheet (SDS)
  - Certificates of Conformance (for both ALVR105 and placebo).
- The site will complete and file all documents received with the IP shipment.

20.9.6 Returning the Shipper to Cryoport

- After unloading the IP at the destination site, the LN2 shipper shall be returned to the respective Cryoport facility of origin the day after receipt, as prearranged by ICON and Cryoport on the Cryoportal®.
- Ensure the metal rack has been placed back into the LN2 shipper for return.
- Remove the Leg 2 Airway Bill, clean shipping pouch and "EMPTY" adhesive label from the hanging sleeve labeled "LEG 3" attached to the handle of the dewar inside the enclosure.
- Attach the clean shipping pouch and the Leg 3 Airway Bill to the metal rectangle on the side of the shipper where the original Leg 2 shipping documents were, as described in Section 20.9.3.

- Unpeel/remove any Final Product labels from the side of the shipper as cleanly as possible.
- The adhesive “EMPTY” label should be removed from its backing and fully pasted onto the metal diamond on the side of the shipper.
- Secure the LN2 shipper with four provided zip ties on each of the latches.
  - Silver Metal Latch
    - Insert the zip tie down through the lid catch.
    - Thread the zip tie through the body latch spring loop.
    - Thread the zip tie up through the body latch turn-buckle hole.
    - Bring the zip tie end up to the buckle.
    - Insert zip tie through the lid buckle and tighten.
  - Black Rubber Latch
    - Insert the zip tie through one of the holes on the metal latch hardware.
    - Thread the zip tie horizontally through the hole on the other side of the metal hardware.
    - Insert zip tie through the lid buckle and tighten.
- The empty LN2 shipper may be stored at ambient temperature until ready for pickup.
- Storage location should be in a room-temperature area; the condition monitoring system is sensitive to temperatures refrigerated and lower.

If the site has any issues regarding return of the empty LN2 shipper (including changes to the pickup date, time, or location) the site should contact Cryoport and the CRA or RSL.