bb2121 PRODUCT HANDLING MANUAL (North America & Europe)

V6.0 (11Aug2022) – V7.0 (22JUN2023)

Summary of Changes

Section	Content
All Sections	- Used ***QMS-TMP-31104H-1, v01 Modified 11 May 2023*** Template which includes approved verbiage and formatting throughout the document. Please refer to the ***QMS-TMP-31104H-1, v01 Modified 11 May 2023 Summary of Changes*** for details on all template level updates that were made. - Changed 'IDP cryobag(s)' to 'cryobag(s)' - Added references to the applicable section numbers in the bb2121 Product Handling Form
Cover Page	- Updated version from 6.0 to 7.0 - Updated version date from 11AUG2022 to 22JUN2023
Table of Contents	- Table of Contents updated to align with sections - Formatting/capitalization corrected
Table of Abbreviations	- **Removed**: SCLT Scheduling and Cell Logistics Team (since it is spelled out throughout document)
COI Check 1 (EU only)	- Wording below added *Delivery Note bb2121 FDP EU* **(when applicable)**
COI Checks 2, 3, 4 and 5 (EU only)	- Wording below added **'For countries that provide subject's first name, subject's last name and DOB on the following documents, those identifiers (including correct spelling) must also be verified:'**

Section 4- Chain of Identity Verification (EU only)	- The following text was updated: ▪ Site staff receiving the shipment of the IDP ▪ Site staff transferring the product to on-site storage (if applicable) ▪ The staff who prepare the product (thaw and dose preparation) ▪ The administration staff at the time of bb2121 administration changed to ▪ **The** site staff receiving the shipment of the IMP ▪ **The** site staff transferring the product to on-site storage (if applicable) ▪ The **site** staff who prepare the product (thaw and dose preparation) ▪ **The site staff who are administering the bb2121 product**
Section 5.3.2- Inside the Shipper (EU only)	- Wording below added *Delivery Note bb2121 Final Drug Product (FDP)* ***when applicable***
Section 7 – Sample Product Labeling	- Due to the addition of an inner cassette label in some studies and/or regions, the following language was updated: 'There are three labels for each IDP cryobag pictured below: **cassette label, tag label** and **bag label**.' changed to 'There are four possible label types for IMP pictured below: **cassette label, inner cassette label, tag label** and **bag label**.' - Sample Inner Cassette Label section and image added
Section 9.1 Supplies	- 'Water bath or other approved thaw instrument (37ºC)' changed to 'Water bath or other approved thaw instrument set to 37ºC'

Bristol Myers Squibb™

Ide-cel (bb2121) Product Handling Manual North America

For Use With
Ide-cel (bb2121)
Clinical Studies

Version 7.0
22 JUN 2023

TABLE OF CONTENTS

TABLE OF ABBREVIATIONS

Anti IL-6	Anti-Interleukin 6
BCMA	B-Cell Maturation Antigen
CAR	Chimeric Antigen Receptor
cGMP	Current Good Manufacturing Practice
COA	Certificate of Analysis
COI	Chain of Identity
DMSO	Dimethyl Sulfoxide
DOB	Date of Birth
EDC	Electronic Data Capture
GMO	Genetically Modified Organisms
IATA	International Air Transport Association
ID	Identification
IMP	Investigational Medicinal Product
IRT	Interactive Response Technology
ISF	Investigator Site File
IV	Intravenous
LD	Lymphodepleting
LN_2	Liquid Nitrogen
LVV	Lentiviral Vector
MNC	Mononuclear Cell
(0.9%) NaCl	Normal Saline
PBMC	Peripheral Blood Mononuclear Cell
POCF	Product Order Confirmation Form
PPE	Personal Protective Equipment

1 CONTACTS

CLINICAL STUDY TEAM

Contact Medical Monitor:

- All medical issues regarding subjects treated with Investigational Medicinal Product (IMP)

Consult the study protocol for Medical Monitor contact information.

SCHEDULING AND CELL LOGISTICS TEAM

Please contact the **Scheduling and Cell Logistics Team** for urgent and non-urgent questions related to:

- Apheresis appointment allocation
- Treatment scheduling: mononuclear cell (MNC) collection procedure and IMP shipment
- IMP delivery, cancellation, date change, or time change
- Scheduling the return of IMP
- *Cell Therapy 360 Clinical Trial Scheduling Portal* questions
- Urgent non-medical issues related to product receipt, preparation, and administration
- Lost or damaged IMP / Product complaints

The *Cell Therapy 360 Clinical Trial Scheduling Portal* (www.CT360.com) is available to provide quick and secure access to schedule subject's apheresis and IMP delivery in a simple online scheduling platform. The *Cell Therapy 360 Clinical Trial Scheduling Operations Manual* provides all the information regarding notifications, scheduling of apheresis and IMP delivery.

Scheduling and Cell Logistics Team:
scheduling@celltherapy360.com

Telephone Numbers:

Australia +61 800879571	Greece +30 80044141519	Romania +40 800400667
Austria +43 800010026	Germany +49 8000008900	South Korea +82 800228774
Belgium +32 80011805	Italy +39 800147638	Spain +34 900876136
Canada +1 8559990170	Israel +1809349385	Sweden +46 200753421
Czech Republic +420 800050013	Japan +81 0531320069	Switzerland +41 800892047
Denmark +45 80810719	Netherlands +31 8003155500	U.K. +44 8000318188
Finland +358 800145816	Norway +47 80011601	U.S.+1-888-805-4555
France +33 805118685	Poland +48 800012960	

2 TRAINING: HANDLING AND ADMINISTRATION

Training on the processes and procedures detailed within this *IMP Product Administration/Handling Manual* is required for site staff responsible for receipt, transfer, storage, preparation, administration, and disposal of IMP. Documentation of this training is required and should be maintained in the Investigator Site File (ISF).

3 OVERVIEW

Ide-cel (bb2121) is defined as an autologous T lymphocyte-enriched product that contains cells transduced with an anti-B-cell maturation antigen (BCMA) chimeric antigen receptor (CAR) lentiviral vector (LVV) (anti-BCMA02 CAR LVV) encoding a CAR targeting human BCMA.

The ide-cel (bb2121) IMP will be supplied in a cryobag inside a metal cassette and shipped in a metal rack within an International Air Transport Association (IATA) approved dry vapor shipper (a Dewar encased in a protective outer shipping container). The ide-cel (bb2121) IMP is formulated in the final infusible cryopreservation solution containing 50% Plasma-Lyte A (V/V) and 50% CryoStor CS10 (V/V), resulting in a final dimethyl sulfoxide (DMSO) concentration of 5%, in a cryobag (the final container intended for clinical use).

3.1 MANUFACTURING PROCESS

The IMP is manufactured in accordance with current Good Manufacturing Practice (cGMP) from autologous peripheral blood mononuclear cells (PBMC) that are isolated from a leukapheresis unit obtained from a subject via apheresis collection procedure detailed in the *Adult MNC Collection Procedure*.

4 CHAIN OF IDENTITY VERIFICATION

Chain of Identity (COI) is the ability to link a subject's autologous cellular material from the time of MNC collection through product administration. Specific controls and linkage elements are implemented at every process step to mitigate the risk of subject material mix-up and maintain COI.

Two unique identifiers will be used alongside the subject's first name, last name, and date of birth (DOB) to maintain the COI throughout.

Unique Identifier	Description	Source
Subject's First Name, Last Name, DOB	Subject's key identifiers	Subject's Medical Record
Subject Identification (ID) Number	Subject's ID number used on all study documentation	Interactive Response Technology (IRT) System or Electronic Data Capture (EDC) System
JOIN	A unique product specific identifier, the JOIN is associated to the subject's autologous blood product from the time of the MNC collection through IMP administration	Product Order Confirmation Form (POCF)

5 IMP AVAILABILITY, SHIPMENT AND RECEIPT

5.1 AVAILABILITY FOR ADMINISTRATION

Please refer to the *Cell Therapy 360 Clinical Trial Scheduling Operations Manual* for all guidelines related to apheresis appointment allocation, scheduling of MNC collection procedure, product shipment, earliest availability date and earliest delivery date.

5.2 SHIPMENT TO SITE OF CARE

Cryopreserved IMP will be shipped in a liquid nitrogen (LN_2) dry vapor shipper to the site of care's designated address/department on the date and time specified on the *POCF*.

5.3 CONTENTS OF LN_2 DRY VAPOR SHIPPER

NOTE: Do not open the inner chamber of the LN_2 dry vapor shipper until the time of product preparation on the day of administration unless your site is approved for on-site storage.

5.3.1 Outside the Shipper

- Label with shipper expiration date and time
- Courier waybill

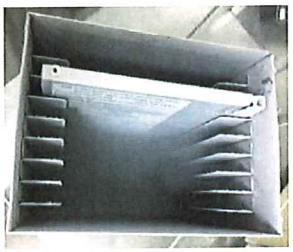
5.3.2 Inside the Shipper

- *bb2121 Product Handling Form*
- Two (2) "spare" zip-ties, (used to secure the outer lid closed prior to returning the empty LN_2 dry vapor shipper)
- Tamper evident seal (tamper tag)
- "Empty" label (for return of the empty LN_2 dry vapor shipper)
- Label with shipper expiration date and time
- Completed courier waybill (for return of the LN_2 dry vapor shipper)
- Temperature monitor

NOTE: Temperature monitor does not display temperature.

5.3.3 Inside the Inner Chamber

- Metal rack
- Metal cassette(s) holding the cryobag(s) which contain the cryopreserved IMP



5.4 RECEIPT OF LN_2 DRY VAPOR SHIPPER AT SITE OF CARE

1. Confirm correct subject, product information and shipping address noted on the external LN_2 dry vapor shipper label matches *POCF*.
2. Sign for the receipt of the LN_2 dry vapor shipper.
3. File a copy of the signed courier waybill in the ISF.
4. Confirm shipper is free of damage and the tamper evident seals (zip ties, securing the shipper dome lid, and/or tamper evident tag, securing the Dewar lid) are intact.
   Contact the Scheduling and Cell Logistics Team if issues are noted.
5. Confirm planned removal of IMP from LN_2 dry vapor shipper is prior to the expiration date and time on the shipping label (example below).

COI CHECK 1: Two site staff must verify the subject's first and last name (including correct spelling), subject's date of birth, subject's ID number and JOIN on the following documents match:

Product Order Confirmation Form (POCF) and Subject's Medical Records	*bb2121 Product Handling Form* ***This becomes source document for COI checks from this step forward***

6. Complete *bb2121 Product Handling Form* (Section 2).

Sample Shipping Label

The shipper expiration time is recorded in the local time zone at the site of care

6 IMP STORAGE

There are two delivery/storage options:

1. **Just in Time Delivery**: IMP will arrive post lymphodepleting (LD) chemotherapy on the business day prior to/or on the day of administration and will remain in the LN_2 dry vapor shipper until the time of preparation for administration.
2. **On-Site Storage *(Prior approval required by the Sponsor)***: IMP will arrive prior to LD chemotherapy and will be transferred to an on-site vapor phase LN_2 storage freezer.

The method of storage for IMP will depend on site capabilities and local regulations.

6.1 STORAGE OF IMP IN LN_2 DRY VAPOR SHIPPER

The LN_2 dry vapor shipper should be stored upright in a limited access, secure, well-ventilated area from the time of arrival on site until the time of preparation for administration of IMP.

6.2 APPROVED ON-SITE VAPOR PHASE LN_2 STORAGE

This section is for sites that have obtained prior Sponsor approval to store IMP on site.

6.2.1 Preparation for Transfer

- The transfer of all IMP from LN_2 dry vapor shipper to an on-site vapor phase LN_2 storage freezer or from on-site vapor phase LN2 storage freezer to site's own transportable LN2 dry vapor container **must be completed within 2 minutes** and performed by two site staff
- A minimum dwell period of 60 minutes in vapor phase LN2 at **-130°C** or below is required between each transfer
- Proper Personal Protective Equipment (PPE) should be worn as per institutional guidelines while handling the LN_2
- Have the *bb2121 Product Handling Form* ready for the COI check

6.2.2 Transfer to On-Site Vapor Phase LN_2 Storage Freezer

The steps below must be completed within 2 minutes

1. Open the inner chamber of the LN_2 dry vapor shipper, remove the metal rack containing the IMP and document the time of removal on the *bb2121 Product Handling Form* (Section 3).
2. Remove the metal cassette and complete the COI check below.
3. Repeat step 2 for each additional metal cassette.
4. Transfer IMP metal cassette(s) to your site's storage rack.

COI CHECK 2: Two site staff must verify the subject's first and last name (including correct spelling), subject's date of birth, subject's ID number and JOIN on the following documents match:

bb2121 Product Handling Form	**IMP cassette label(s)**

5. Complete *bb2121 Product Handling Form* (Section 3).

NOTE: If the IMP transfer is not completed within 2 minutes, contact the Scheduling and Cell Logistics Team immediately.

6.3 TEMPERATURE MONITORING

IMP should be stored in the vapor phase of LN_2 at **-130°C** or below. The Sponsor is responsible for monitoring the LN_2 dry vapor shipper temperature from the time of IMP packaging at the manufacturing facility **until proof of delivery** at the site of care.

The site of care is responsible for monitoring storage temperatures from the point of product receipt at the site of care.

For approved on-site storage LN_2 freezers, sites should ensure continuous monitoring of temperature as agreed during on-site storage qualification and records (e.g., alarm log) must be available for review during monitoring visits.

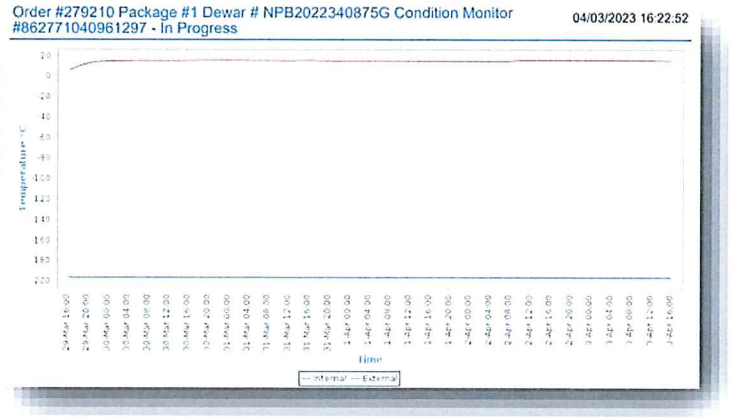
Drug Product Location	Temperature Monitoring Responsible Party	Temperature Data Source
LN_2 dry vapor shipment & receipt	Sponsor	Cryoport Live View Link
LN_2 dry vapor shipper onsite	Site of Care	Cryoport Live View Link-provided to site of care
On-site storage LN_2 freezers	Site of Care	Site of care qualified temperature monitoring alarm system log
Site's own transportable LN2 dry vapor container (when applicable)	Site of Care	Site of care qualified LN2 dry vapor container

6.3.1 Temperature Verification

Once the IMP is scheduled for delivery, the Cryoport Live View Link of the LN_2 Dry Vapor Shipper will be available in the *Cell Therapy 360 Clinical Trial Scheduling Portal*, approximately 1-4 days before the scheduled delivery date and time.

NOTE: If the Cryoport Live View Link is not available in the *Cell Therapy 360 Clinical Trial Scheduling Portal* approximately 1-4 days before the scheduled delivery date, contact the Scheduling and Cell Logistics Team.

- Review the Cryoport Live View Link temperature report to confirm that the LN_2 dry vapor shipper maintained a temperature of **-130 °C or below** from the **point of receipt at the site of care until the removal of the IMP** from the LN_2 dry vapor shipper
- Temperature data gaps are acceptable, if the temperature of the shipper was in an acceptable range before the gap and is within expiry of the shipper
- Prior to removing the IMP from the LN_2 dry vapor shipper, export and print the Cryoport Live View Link report



- Record the LN_2 dry vapor shipper temperature, and verify there have been no temperature excursions prior to removal on the following forms:
  - **At the time of transfer to on-site storage (if applicable):** Record the temperature verification on the *bb2121 Product Handling Form* (Section 3)
  - **At the time of product thaw:** Record the temperature verification on the *bb2121 Product Handling Form* (Section 5)
- Record the subject's JOIN number on the Cryoport Live View Link temperature report and file in the ISF

6.3.2 Temperature Excursions Prior to Receipt of LN_2 Dry Vapor Shipper

In the event of a potential temperature excursion during transport of the IMP, the Scheduling and Cell Logistics Team will immediately inform site staff to NOT proceed until further instructions are provided by the Sponsor. The Scheduling and Cell Logistics Team will reach out to the site of care inquiring if the tamper evident seals (zip ties, securing the shipper dome lid, and/or tamper evident tag, securing the Dewar lid) are intact and not damaged or missing on the LN_2 Dry Vapor Shipper.

If it is determined that the missed parameter(s) are not a temperature excursion and there is no product quality impact, the Scheduling and Cell Logistics Team will instruct the site of care to proceed with drug product receipt. If determined to be a true temperature excursion, the Scheduling and Cell Logistics Team will document the product assessment on the *Cell Therapy Drug Product Temperature Assessment Form*. The completed form will be provided to the site of care with instructions on how to proceed with the drug product. The completed *Cell Therapy Drug Product Temperature Assessment Form* should be filed by the site of care in the ISF.

6.3.3 Temperature Excursions After Receipt of LN_2 Dry Vapor Shipper

- In the event the tamper evident seals (zip ties, securing the shipper dome lid, and/or tamper evident tag, securing the Dewar lid) are not intact, damaged, or missing on the LN_2 Dry vapor shipper, **stop and contact the Scheduling and Cell Logistics Team immediately**
- In the event of a temperature excursion or missed temperature reading after receipt of the LN_2 dry vapor shipper, **stop and contact the Scheduling and Cell Logistics Team immediately**

- In the event of a temperature excursion or temperature alarm while in on-site vapor phase LN_2 storage or while transporting IMP to bedside using site's own transportable LN_2 dry vapor container, **stop and contact the Scheduling and Cell Logistics Team immediately**
- The Scheduling and Cell Logistics Team will immediately inform the site of care to NOT proceed until given further instructions. If it is determined that the event is not a true temperature excursion and there is no product quality impact, the Scheduling and Cell Logistics Team will instruct the site of care to proceed with drug product receipt or preparation

If determined to be a true temperature excursion, the Scheduling and Cell Logistics Team will document the product assessment on the *Cell Therapy Drug Product Temperature Assessment Form*. The completed form will be provided to the site of care with instructions on how to proceed with the drug product. The completed *Cell Therapy Drug Product Temperature Assessment Form* should be filed by the site of care in the ISF.

7 SAMPLE PRODUCT LABELING

There are four possible label types for IMP pictured below: **cassette label, inner cassette label, tag label** and **bag label.**

Due to the manufacturing process of bb2121, the target volumes on the product labels might differ slightly from the actual volumes provided on the *bb2121 Product Handling Form* (Section 1). Sites should always follow the information stipulated on the *bb2121 Product Handling Form*.

7.1 SAMPLE IMP CASSETTE LABEL

First Name: XXXXXXXX

Last Name: XXXXXXXX

DOB: XXXXXXXX

bb2121

IND: 016664
Protocol No.: XXXXXXXX
Subject No.: XXXXXXXX

JOIN: XXXXXXXX
Lot No.: XXXXXXXX
Manufacturing Date: XXXXXXXX
Expiration Date: XXXXXXXX
Bag ID: XXXXXXXX
Target Conc.: 10 x 10^6 cells/mL
Target Volume: XXXXXXXX mL

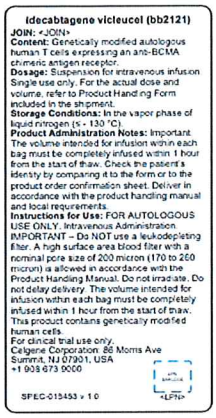
Content
Genetically modified autologous human T cells expressing an anti-BCMA chimeric antigen receptor.

Dosage
Suspension for intravenous infusion. Single use only. For the actual dose and volume, refer to Product Handling Form included in the shipment.

Storage and Transportation
Transport in dry shippers capable of maintaining temperatures ≤ - 130 °C.
Store cryopreservation bags in the vapor phase of liquid nitrogen (≤ -130 °C).

Instructions for Use
FOR AUTOLOGOUS USE ONLY. Intravenous Administration.
IMPORTANT - Do NOT use a leukodepleting filter. A high surface area blood filter with a nominal pore size of 200 micron (160 to 260 micron) is allowed in accordance with the Product Handling Manual.
Only for use in clinical trials.
Do not irradiate. Do not delay delivery.
The volume intended for infusion within each bag must be completely infused within 1 hour from the start of thaw

7.2 SAMPLE IMP INNER CASSETTE LABEL



7.3 SAMPLE IMP TAG LABEL

First Name: XXXXXXXX

Last Name: XXXXXXXX

DOB: XXXXXXXX

bb2121

IND: 016664

Protocol No.: XXXXXXXX

Subject No.: XXXXXXXX

JOIN: XXXXXXXX

Lot No.: XXXXXXXX

Manufacturing Date: XXXXXXXX

Expiration Date: XXXXXXXX

Bag ID: XXXXXXXX

Target Conc.: 10 x 10^6 cells/mL

Target Volume: XXXXXXXX mL

Content

Genetically modified autologous human T cells expressing an anti-BCMA chimeric antigen receptor.

Dosage

Suspension for intravenous infusion. Single use only.
For the actual dose and volume, refer to Product Handling Form included in the shipment.

Product Administration Notes

Important: The volume intended for infusion within each bag must be completely infused within 1 hour from the start of thaw
Check the patient's identity by comparing it to the form or to the product order confirmation sheet.
Deliver in accordance with the product handling manual and local requirements.

Storage Conditions

In the vapor phase of liquid nitrogen (≤ - 130 °C)

Instructions for Use

FOR AUTOLOGOUS USE ONLY. Intravenous Administration.
IMPORTANT - Do NOT use a leukodepleting filter. A high surface area blood filter with a nominal pore size of 200 micron (160 to 260 micron) is allowed in accordance with the Product Handling Manual.
Only for use in clinical trials.
Do not irradiate. Do not delay delivery.
The volume intended for infusion within each bag must be completely infused within 1 hour from the start of thaw

This product contains genetically modified human cells.
FOR AUTOLOGOUS USE ONLY

7.4 SAMPLE IMP CRYOBAG LABEL

bb2121

First Name:XXXXXXXX

Last Name:XXXXXXXX

DOB:XXXXXXXX

Subject No.: XXXXXXXX

JOIN: XXXXXXXX

Lot No.: XXXXXXXX

Bag ID: XXXXXXXX

Target Conc.: 10 x 10^6 cells/mL

Target Volume: XXXXXXXX mL

8 SUBJECT PREPARATION FOR ADMINISTRATION

Do NOT begin the thaw and preparation of IMP until just prior to administration.

8.1 INFUSION SETS

- Infusion sets should allow for all tubing and cryobag(s) to be flushed with normal saline (0.9% NaCl) post administration to ensure all cells are infused.
- A Y-type infusion set is recommended to accommodate the 0.9 % NaCl on the primary line and the cryobag on the secondary line.
- If institutional policy requires the use of filters, a high surface area blood filter with a nominal pore size of 200 micron (170 to 260 micron) is recommended to ensure product quality, product recovery and infusion flow is not impacted.

NOTE: Smaller pore size filters and/or other filters commonly used for blood products should not be used.

8.2 SUBJECT PREPARATION

- Confirm subject has a patent peripheral or central IV
- Prior to the start of IMP thaw, prepare the subject by starting an IV line primed with 0.9 % NaCl
- Concurrent IV fluids and medications must be held during IMP administration
- Monitor vital signs per protocol

8.3 PRE-MEDICATION

- To minimize the risk of infusion reactions, all subjects should be pre-medicated per study protocol

Once the subject is prepared and pre-medicated, site staff responsible for administering IMP should notify the site staff responsible for preparing IMP to begin the thaw process.

9 THAW AND DOSE PREPARATION INSTRUCTIONS

Thaw and preparation of IMP should be performed by staff trained on the handling of LN_2, wearing proper PPE according to institutional guidelines.

9.1 SUPPLIES

Assemble the following supplies **prior to** retrieving IMP from vapor phase LN_2 storage:

- Infusion set (see section 8.1 Infusion Sets)
- PPE per institutional guidelines
- Container for transport of IMP to bedside
  - Qualified transportable LN_2 dry vapor container for transport of cryopreserved IMP in the vapor phase of LN_2 (≤ −130°C) or
  - Container for transport of thawed IMP at room temperature, if applicable
- Water bath or other approved thaw instrument set to 37°C
- Secondary thawing bag
- Dispensing pin(s) (for dose manipulation if required)
- Sterile syringe(s) with Luer-Lock tip (for dose manipulation if required)

9.2 THAW PREPARATION

For each cryobag, the steps from start of thaw (removal from LN_2 storage) to completion of administration should be completed **within 1 hour**. While bb2121 post-thaw stability has been demonstrated for up to 2 hours at room temperature, the **Scheduling and Cell Logistics Team must be contacted immediately** for further guidance, if the 1 hour infusion time frame cannot be met.

Prior to initiation of thaw the following steps should occur:

- Confirm the subject has been pre-medicated
- Obtain the *bb2121 Product Handling Form*
- Confirm that the approved thaw instrument is set to 37°C
- Ensure proper PPE is available for removal of IMP from LN_2 storage

9.3 THAWING PROCEDURE

- When opening the LN_2 shipper or on-site storage tank, confirm the total number of bags in the LN_2 storage is consistent with those listed on *bb2121 Product Handling Form* (Section 1).
- If more than one (1) cryobag is required for a subject, thaw and administer each bag in series.

1. Remove one cassette from vapor-phase LN_2 storage and record the time of removal (Start of thaw) and bag expiration (1 hour later) on the *bb2121 Product Handling Form* (Section 4).
2. Carefully, open the cassette and immediately transfer the cryobag into a secondary plastic thaw bag and seal. Do not unfold the label flap.

COI CHECK 3: Two site staff must verify the subject's first and last name (including correct spelling), subject's date of birth, subject's ID number and JOIN on the following documents match:

bb2121 Product Handling Form	**IMP cassette label(s)** **Cryobag label(s)**

3. Place the cryobag into the sponsor approved thaw instrument without delay.
4. Remove the cryobag from the approved thaw instrument once most of the product has thawed and only a few small ice crystals remain.
5. Remove the cryobag from the plastic thaw bag.
6. Confirm that the cryobag is intact and there are no leaks, cracks, or apparent damage.
7. Complete *bb2121 Product Handling Form* (Section 4).
8. Transfer the *bb2121 Product Handling Form* and the cryobag to the staff performing the dose manipulation (if applicable) and/or the dose administration.

NOTE: Contact the Scheduling and Cell Logistics Team if there is any damage to the cryobag.

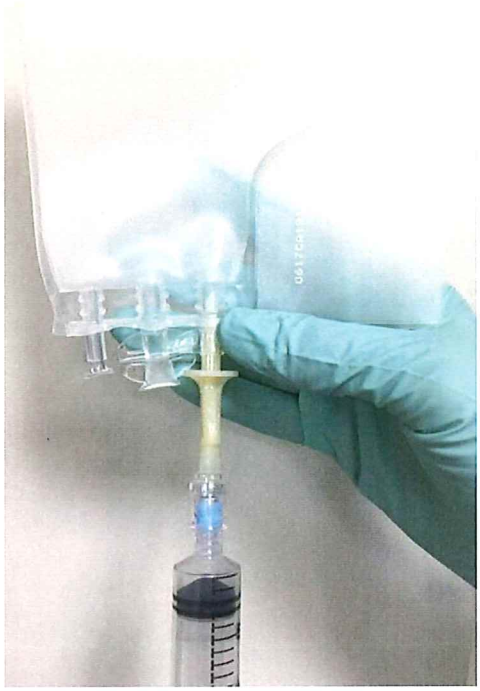
9.4 DOSE PREPARATION

Dose manipulation is the term used to describe the removal of a Sponsor specified volume of CAR+ T cells prior to IMP administration to attain a specific dose.
Note: Dose manipulation will be required in rare circumstances.
If dose manipulation is required, follow the instructions below.

- The volume of IMP that should be removed from each cryobag to achieve dose is communicated on the *bb2121 Product Handling Form* (Section 1).

If dose manipulation of a specific cryobag is required, follow the steps below using aseptic technique for each cryobag:

1. Gently massage the cryobag to ensure a uniform suspension of cells.
2. Remove spike port cap and insert dispensing pin into spike port.
3. Attach Luer-Lok syringe to dispensing pin on spike port.
4. Gently remove volume communicated on the *bb2121 Product Handling Form* (Section 1) with syringe.
5. Verify volume removed (with 2 site staff members) and record on the *bb2121 Product Handling Form* (Section 5).
6. Disconnect syringe and **leave dispensing pin in situ.**
7. Dispose of the syringe and contents and document on the *bb2121 Product Handling Form* (see section 11)
8. Transfer the *bb2121 Product Handling Form* and the cryobag to the staff performing the administration.



COI CHECK 4: Two site staff must verify the subject's first and last name (including correct spelling), subject's date of birth, subject's ID number and JOIN on the following documents match:

bb2121 Product Handling Form	**Cryobag label(s)**

10 IMP ADMINISTRATION

IMP should only be administered by trained and qualified site staff using standard clinical practice for subjects receiving biological or cellular products. Per protocol, emergency equipment and medications, including Tocilizumab or alternative anti-interleukin 6 (anti-IL-6) pathway agents as allowed per protocol, must be readily available.

If IMP has been outside of vapor phase LN2 storage for longer than 1 hour, do not continue administration. While bb2121 post-thaw stability has been demonstrated for up to 2 hours at room temperature, the **Scheduling and Cell Logistics Team must be contacted immediately** for further guidance, if the 1 hour infusion time frame cannot be met.

10.1 ADMINISTRATION INSTRUCTIONS

If a dose interruption occurs, **contact the Scheduling and Cell Logistics Team** immediately for guidance.

Document the dose volume administered on associated form after completion of infusion.

1. Obtain the *bb2121 Product Handling Form* and the cryobag from the staff that performed the thaw and preparation of bb2121.

COI CHECK 5: Two site staff must verify the subject's first and last name (including correct spelling), subject's date of birth, subject's ID number and JOIN on the following documents match:

bb2121 Product Handling Form	**Cryobag label(s)**
	Certificate of Analysis (COA)

Verify First Name, Last Name, DOB against the subject's medical record and again verbally with the subject prior to infusion.

2. Gently massage the cryobag prior to set up.
3. Confirm dose manipulation has occurred if required (see section 9.4).
4. Attach the cryobag to an infusion set (see section 8.1).
5. Infuse the contents of the cryobag as quickly as tolerated by gravity flow. IMP must be infused **within 1 hour** from the start of thaw.

NOTE: If for any reason, the administration of any individual cryobag is stopped or delayed, contact the Scheduling and Cell Logistics Team and the Medical Monitor immediately for further instruction.

6. After the full volume of the cryobag has been infused, flush both the cryobag and tubing with 30-60 mL of 0.9% NaCl to ensure all cells are infused. Record the infusion end time as end of flush.
7. Monitor subject for infusion reactions during and after administration per the study protocol. If there is no infusion reaction observed proceed to the thaw of the next bag, if applicable.
8. If, for any reason, the entire dose is not administered to the subject, estimate the remaining volume by removing residual IMP with a syringe and a dispensing pin.
9. Complete *bb2121 Product Handling Form* (Section 6).

11 DISPOSAL AND DESTRUCTION

Any unused IMP and materials that have come into contact with the IMP should be disposed of in accordance with the institution's biohazard disposal policy for hazardous clinical material and Genetically Modified Organisms (GMO). Complete *bb2121 Product Handling Form* (Section 7) to verify disposal of unused IMP. Upload the completed form to the *Cell Therapy 360 Clinical Trial Scheduling Portal* per instructions on the form and file in ISF.

12 RETURN OF LN_2 DRY VAPOR SHIPPER

Prepare the empty LN_2 dry vapor shipper for return shipment after administration is complete or after transfer of cryopreserved IMP to on-site vapor phase LN_2 storage freezer. If return of IMP is required for any reason, please contact the Scheduling and Cell Logistics Team for instructions.

12.1 RETURN INSTRUCTIONS

1. Load the rack into the inner chamber of the shipping container and close the inner chamber lid.
2. Remove shipping pouch from the pocket inside the outer shipping container.
3. The shipping pouch contains a courier return label and an **"EMPTY"** label.
4. Remove the **"EMPTY"** label from the shipping pouch and place **"EMPTY"** label on one of the metal plates on the outer shipping container.
5. Place the shipping pouch with the courier return label on one of the metal plates.
6. Close the outer shipping container lid and lock the latch by turning the key to the right.
7. Place LN_2 dry vapor shipper in a courier-scheduled pickup location or contact courier to schedule a pickup.

APPENDIX A: LIST OF RELATED FORMS

Related Form	Source
bb2121 Product Handling Form (PHF)	Arrives with shipment
Product Order Confirmation Form (POCF)	Cell Therapy 360 Clinical Trial Scheduling Portal
Certificate of Analysis (COA)	Cell Therapy 360 Clinical Trial Scheduling Portal
Cell Therapy Drug Product Temperature Assessment Form	Scheduling and Cell Logistics Team