CBER DMPQ CMC/Facility BLA Review Memorandum

BLA STN 125738/0

Product Name: omidubicel

Reviewer: Rabia Ballica, PhD, Biologist, MRB1/DMPQ

1. BLA#: STN 125738/0

2. APPPLICANT NAME AND LICENSE NUMBER
Gamida Cell Ltd.; 2223

3. PRODUCT NAME/PRODUCT TYPE
Non-Proprietary/Proper/USAN: omidubicel
Proprietary Name: OMISIRGE

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

a. Pharmacological category: Refer to the Office of Therapeutic Products (OTP) Chemistry, Manufacturing, and Controls (CMC) review memo.
b. Dosage form: Suspension for infusion
c. Strength/Potency: $\geq 8.0\times10^8$ total viable cells with a minimum of 8.7% CD34+ cells (9.2×10^7 CD34+ cells), and $\geq 4.0\times10^8$ total viable cells with a minimum of 2.4×10^7 CD3+ cells
d. Route of administration: Intravenous
e. Indication(s): (b) (4)

5. MAJOR MILESTONES

- Original application (Rolling BLA): February 02, 2022
- Filing meeting: July 13, 2022
- Internal mid-cycle meeting: September 19, 2022
- Mid-cycle applicant teleconference: October 3, 2022
- Pre-license inspection (PLI) of manufacturing site in Israel (Kiryat Gat Israel): October 18 – 25, 2022
- Major amendment: November 18, 2022
- Late-cycle meeting: February 23, 2023
- Action due date: May 01, 2023

6. DMPQ CMC/FACILITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Rabia Ballica, OCBQ/DMPQ/MRB1	Drug substance
Rabia Ballica, OCBQ/DMPQ/MRB1	Drug product
Rabia Ballica, OCBQ/DMPQ/MRB1	Facilities and equipment

7. INTER-CENTER CONSULTS REQUESTED
None for DMPQ review and evaluation

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
June 01, 2022	STN 125738/0.2 Seq# 0003	Module 3 submission; Review clock starts

Date Received	Submission	Comments/ Status
June 09, 2022	Amendment STN 125738/0.3 Seq# 0004 (DMPQ information request (IR) #1)	Cover letter for foreign inspection history for Kiryat Gat Israel (KGI)
June 29, 2022	Amendment STN 125738/0.7 Seq# 0008 (DMPQ IR#2	Foreign inspection history (certificate) for KGI
July 25, 2022	Amendment STN 125738/0.12 Seq# 0013 (OTP IR)	3.2.S.2 Control of Materials: -Information on sterility of cord blood unit (CBU) as a starting material, shipping conditions, and visual inspection for damages/leaks - Information on microbial content controls for raw materials
August 17, 2022	Amendment STN 125738/0.16 Seq# 0017 (DMPQ IR#3)	Validation report for aseptic process simulation (APS) and foreign inspection history for testing facilities (b) (4) (b) (4)
September 02, 2022	Amendment STN 125738/0.19 Seq# 0020 (OTP IR)	Available data for stability and container closure integrity testing (VP402-R)
September 08, 2022	Amendment STN 125738/0.21 Seq# 0022 (OTP IR)	Information on manufacturing capacity and raw material controls (e.g., sterility, endotoxin)
October 07, 2022	Amendment STN 125738/0.29 Seq# 0030 (DMPQ IR#4)	Additional information on facilities and equipment, APS initial validation and re-qualification reports and their associated protocols, validation of container closure integrity testing (CCIT) method and associated deviations, and shipper and shipping validation
November 08, 2022	Amendment STN 125738/0.34 Seq# 0035 (OTP IR)	Information on new APS protocol and runs

Date Received	Submission	Comments/ Status
November 10, 2022	Amendment STN 125738/0.35 Seq# 0036 (OTP IR)	Complete data (including sterility and endotoxin data) for Cultured Fraction (CF), Non-cultured Fraction (NF), and Infusion Solution (IS) stability
November 30, 2022	Amendment STN 125738/0.39 Seq# 0040 (OTP IR)	Additional information on new APS runs and associated protocol (interim report)
January 06, 2023	Amendment STN 125738/0.44 Seq# 0045 (DMPQ IR#5)	Final report for the new APS runs and additional information on the associated protocol
January 20, 2023	Amendment STN 125738/0.47 Seq# 0048 (OTP IR)	An update on endotoxin release limit to specify it in EU/mL (instead of patient body weight)
January 31, 2023	Amendment STN 125738/0.49 Seq# 0040 (OTP IR)	Updates on: -Batch analysis for the new process performance qualification (PPQ) lots – manufactured to reduce the residual impurity levels -Stability studies

9. Referenced REGULATORY SUBMISSIONS (e.g., IND, BLA, 510K, Master File, etc.)

The following were cross-referenced on Form FDA 356h: IND 014459, (b) (4) Cross-reference letters along with related referenced information were not included in STN 125738/0.2 (Module 3 submission).

There were no cross-reference letters needed for the information under DMPQ purview. (b) (4) for (b) (4) was referenced in the BLA.

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

omidubicel is comprised of the cultured fraction (CF) and the non-cultured fraction (NF). Both cell suspensions (CF and NF) are derived from the same umbilical cord blood unit (CBU) and manufactured at the Gamida Cell Ltd.'s manufacturing site located in Kiryat

Gat, Israel (KGI). The KGI manufacturing facility is a (b) (4) (b) (4) currently manufactured. The facility is designed to contain (b) (4) manufacturing (b) (4) (b) (4) Each (b) (4) is designed to include (b) (4) (b) (4) (b) (4) (b) (4) to be built and qualified for the production of CF and NF. (b) (4) (b) (4) The pre-license inspection (PLI) of this facility was conducted by CBER from October 18 – 25, 2022, and no FDA Form 483 was issued (refer to establishment inspection report (EIR) for this PLI). This inspection was classified as No Action Indicated (NAI).

The CF is derived from a single CBU as follows: (b) (4) cells are isolated from CBU through positive selection process using a (b) (4) cell selection equipment on the (b) (4) of manufacturing. (b) (4) At the end of expansion, cells are (b) (4) using (b) (4) processing equipment and then suspended in cryopreservation solution (b) (4) (b) (4) for cryopreservation to obtain CF drug substance (DS). The DS cells are filtered using a (b) (4) filter to remove particles and filled into (b) (4) (b) (4) (FDA 510(k) cleared Class II medical device; (b) (4)). The bag containing the drug product (DP) is then frozen using a qualified controlled rate freezer (CRF).

The (b) (4) cells are derived from the (b) (4) selection step (from (b) (4) selection process). The (b) (4) cells which contain all mature myeloid (such as (b) (4) and (b) (4) and lymphoid (b) (4) cell populations, are suspended in cryopreservation solution (b) (4) for cryopreservation using a controlled rate freezing procedure, within (b) (4) of (b) (4) selection. The cells suspended in (b) (4) are filtered using a (b) (4) filter and filled into (b) (4) freezing bag. The bag containing NF DP is then frozen for cryopreservation using a qualified CRF.

There are no in-process hold steps, because the manufacturing processes for CF and NF are continuous. The frozen CF DP and NF DP are stored in vapor phase of liquid nitrogen until shipment to the transplant site. CF DP and NF DP are thawed and diluted with infusion solution (IS) at a dilution of (b) (4) at the transplant/clinical center prior to intravenous infusion (starting with CF DP). The CF DP and NF DP should be administered within 2 hours of each other.

IS is also manufactured at KGI manufacturing facility by mixing (b) (4) (b) (4) to obtain a final concentration of 8% w/v HSA and 6.8% w/v Dextran 40. IS is filtered into (b) (4) bags using a (b) (4) filter. The sealed IS bags are stored and shipped at 2-8˚C. 250 mL (b) (4) bag for CF dilution is filled with (b) (4) and 50 mL (b) (4) bag is filled with (b) (4) IS for NF dilution.

(b) (4) freezing bags are made of (b) (4) and manufactured by (b) (4) (b) (4)

(b) (4)

per (b) (4) and (b) (4) guidelines. The information on the primary, secondary, and tertiary packaging, which are used in storage and shipment of the cell fractions and IS, appeared acceptable, such as with respect to their materials of construction, shapes, and dimensions.

Quality control (QC) samples, which are taken from CF DP, NF DP, and IS, are tested for release following (b) (4) filtration. The DP and IS samples are tested (b) (4) for sterility and endotoxin. In-process testing for (b) (4) is performed during the manufacture of CF (b) (4) (b) (4) In-process (b) (4) testing is performed at the end of the selection process (b) (4) (b) (4) Endotoxin testing is also performed at the end of the selection process (b) (4) (b) (4)

Process performance qualification (PPQ) batches of CF DP ((b) (4) batches), NF DP (b) (4) batches), and IS ((b) (4) batches) met the release acceptance criteria for sterility ("no growth"; (b) (4) and endotoxin (b) (4) (b) (4) (b) (4) test results also met the acceptance criteria for sterility, endotoxin, and mycoplasma ("not detected"; polymerase chain reaction (PCR) test method).

The firm conducted additional PPQ runs of CF to reduce the residual impurity levels (for (b) (4) by additional (b) (4) and processing (b) (4) cell culture bags (b) (4) number of culture bags from (b) (4) per (b) (4) (b) (4) (amendment STN 125738/0.39). Batch analysis for these additional PPQ lots were provided in amendment STN 125738/0.49, and the lots met the release specifications for sterility, endotoxin, and mycoplasma as well as in-process microbial content acceptance criteria.

The controls to prevent contamination are in place: Controls for raw materials, including single-use product contact equipment, accessories, container closure systems, reagents, buffers, and media, appeared acceptable with respect to sterility assurance, endotoxin, and mycoplasma (STN 125738/0 and amendments STN 125738/0.21, 0.29, and 0.47). Based on the information provided in the original BLA submission and amendment STN 125738/0.29, the firm appeared to have disinfectants qualified to clean facility, surfaces of equipment and other surfaces (e.g., surfaces of containers and accessories). Changeover procedures between batches are also in place. Open manipulations are performed in the qualified biological safety cabinets that are re-qualified biannually.

The environmental monitoring performance qualification (EMPQ) of the classified manufacturing areas (Grade (b) (4)) appeared acceptable (refer to the original BLA submission and amendment STN 125738/0.29). The firm has an acceptable EM

program in place. The air in the facility flows from clean areas to less clean areas (acceptable pressure cascade), and the flow diagrams for product, samples, waste, materials, and personnel appeared acceptable. All the product contact process equipment, and non-product contact and QC equipment appeared qualified. For the on-site evaluation of the facility and equipment for manufacturing, refer to EIR for the KGI PLI.

Acceptable labeling, tracking, and segregation procedures appear to be in place. The firm validated chain of custody (COC) and chain of identity (COI) procedures (VP439-R included in the original BLA submission) and associated electronic/computer systems, which appeared acceptable.

Information on the aseptic process validation of CF DS and DP manufacturing as a worst-case manufacturing scenario, which was provided in the original BLA submission and amendments (STNs 125738/0.16, 0.29, 0.34, and 0.39), appeared acceptable. Additional (b) (4) (performed to reduce the critical impurity levels) were also simulated with the (b) (4) and results met the acceptance criteria (amendment STN 125738/0.44). Aseptic process simulation (APS) is conducted biannually and growth promotion testing on the incubated containers is performed (amendments STN 125738/0.29 and 0.44).

The cold shipper (b) (4) for the shipment of IS at 2-8°C and the (b) (4) for the shipment of CF DP and NF DP at ≤-150°C were qualified as per the International Safe Transit Association (ISTA) and applicable ASTM guidelines (BLA 125738/0 and amendment STN 125738/0.29). (b) (4) was qualified for a maximum (b) (4) for the IS shipment at 2-8°C and (b) (4) for a maximum of (b) (4) shipment of a (b) (4) These shipment durations simulated the worst-case scenarios and included (b) (4) (b) (4) at the KGI warehouse.

At (b) (4) testing was performed on the (b) (4) bags according to the method described in Annex C.2 of (b) (4) Viral integrity of the bags at (b) (4) is also verified: For the (b) (4) (b) (4) (b) (4) (b) (4) The firm states in section 3.2.P.2 that the bags were shown to be resistant to this challenge.

The (b) (4) method was validated for container closure integrity testing (CCIT) on the (b) (4) bags shipped from KGI as outlined in (b) (4) at (b) (4) (refer to the original BLA submission and amendment STN 125738/0.29). This integrity test method was used only during the stability studies (amendments STN 125738/0.29 and 0.35) and will not be used in the future. The PPQ bags placed on stability were shipped to (b) (4) at different time points of

the storage/stability study and tested for the bag's integrity. All the tested bags passed the CCIT ("no growth" as per (b) (4)).

Sterility and endotoxin testing on CF DP, NF DP, and IS stability lots were performed at the beginning (b) (4) and end of the shelf-life. Long-term stability studies for PPQ lots were conducted for up to 12 weeks for CF DP (12 weeks shelf-life), 15 weeks for NF DP, and 18 weeks for IS. The results of the long-term stability studies met the acceptance criteria for sterility and endotoxin at release and end of the shelf-life of CF DP and NF DP (amendments STN 125738/0.19 and 0.35). For IS, there were stability studies up to (b) (4) weeks (maximum) and results met the acceptance criteria for sterility at the beginning and for sterility and endotoxin at (b) (4) months (amendment STN 125738/0.19).

B. RECOMMENDATION

I. APPROVAL

There are no outstanding issues for the information under DMPQ's purview. Therefore, from DMPQ's review standpoint, approval of this BLA is recommended for the manufacture of omidubicel at Gamida Cell Kiryat Gat Israel, (b) (4) Kiryat Gat, Israel.

II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Primary Level Review (Rabia Ballica, Facility and CMC Reviewer)	Concur	
Secondary Level Review (Lori Peters, Branch I Chief)	Concur	
Tertiary Level Review (Carolyn Renshaw, Division Director)	Concur	

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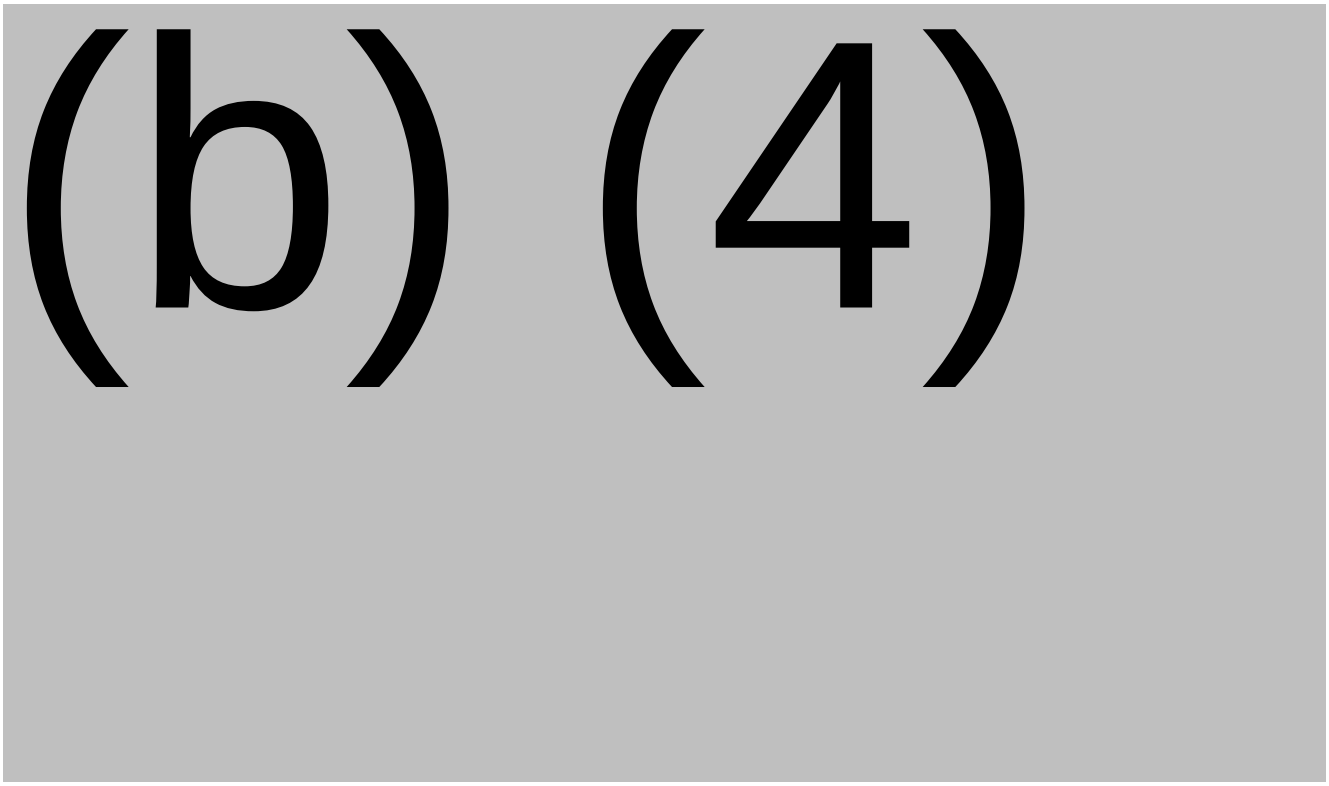
Module 3

3.2.S DRUG SUBSTANCE

(b) (4)

5 pages have been determined to be not releasable: (b)(4)



3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

Omidubicel is comprised of the CF cell suspension and the NF cell suspension, both derived from the same umbilical CBU. Each cell fraction is formulated as a single dose cell suspension for infusion. Prior to intravenous administration to the patient, the CF DP and NF DP bags are thawed and diluted with IS (b) (4).

Patient administration starts with the diluted CF DP followed by the diluted NF DP.

The CF is (b) (4) hematopoietic CD34+ progenitor cells suspended in approximately **20 mL** of cryopreservation solution (CS10) and filtered through a (b) (4) filter during transfer into one 250 mL (b) (4) bag (from (b) (4) . The CF DP is a yellowish suspension.

The NF is (b) (4) hematopoietic mature myeloid and lymphoid cells suspended in approximately **10 mL** of cryopreservation solution and filtered through a (b) (4) filter during transfer into one 50 mL (b) (4) bag. The NF DP is a reddish suspension.

The IS is a colorless to yellowish clear solution that is composed of 8% w/v HSA and 6.8% w/v dextran. IS is filtered into 50 mL (filled with (b) (4) IS) and 250 mL (filled with (b) (4) IS) (b) (4) bags (for NF DP and CF DP, respectively) using a (b) (4) filter.

3.2.P.2.5 Microbiological Attributes

DS, DP, and IS are aseptically manufactured (open operations in BSCs and the rest of operations in the closed systems). Aseptic processing was initially validated with (b) (4) media fill runs and then it is re-qualified (b) (4) . For the review and evaluation of the aseptic process validation, refer to section **3.2.P.3.5**. CF DP, NF DP, and IS are manufactured (filtered into bags) in BSCs (ISO (b) (4) .

In-process controls for microbiological content (mycoplasma, endotoxin, and sterility) of CF (b) (4) are in place as tabulated along with test methods and their acceptance criteria in section **3.2.S.2.4**.

A quality control (QC) sample is taken from the CF (b) (4) cell suspension prior to its filtration. QC sample filtration is performed following the completion of the CF (b) (4) cell suspension filtration, using the filter that is used for the filtration of the CF (b) (4) suspension. The QC sample is tested for mycoplasma*, sterility, and endotoxin. *Mycoplasma testing performed on (b) (4) (b) (4) is an in-process test, but it is reported as a release test on the CF DP CoA.

Release-for-infusion:

Prior to preparing the patient for infusion, transplant centers receive a release-for-infusion (RFI) certificate issued by Gamida. This certificate is issued based on the following information:

1. The CoA for omidubicel CF includes results of all product release tests, except the results for the final product sterility and CFU (colony forming unit) on harvest day (a product attribute associated with potency matrix). The firm refers to the June 11, 2021 written responses to justify this time point of releasing the product without a sterility test result. In FDA's response letter, OTP accepted the proposed testing schedule for sterility testing. The firm also refers to (b) (4) (b) (4) for situations where a cell therapy product needs to be released based on in-process testing results. For this product, it is noted that the aseptic process validation is critical to accept this sterility testing schedule.
2. Final CoAs for omidubicel NF and IS batch(es) include the results for the product quality attributes and microbiological attributes (sterility and endotoxin).

Upon receipt of the shipment, the transplant center must also confirm that the product arrived with adequate shipping conditions by reviewing the temperature data upon receipt and confirming that the temperature upon receipt was ≤-150°C (indicated on the data logger).

The RFI certificate is uploaded to the Gamida assist platform as soon as available (within (b) (4) of manufacturing completion, which is typically around the earliest possible time of product receipt by the transplant center if shipped immediately).

Receipt of the RFI certificate for the patient-specific batch of omidubicel must be confirmed prior to the preparation of omidubicel for transplantation.

Release for shipment is based on acceptable results of Day 0 (for mycoplasma, sterility, and endotoxin testing on Day (b) (4) selection process), Day (b) (4) (for endotoxin testing on Day (b) (4) of the (b) (4) process), and Day (b) (4) (sterility testing on Day (b) (4) of the (b) (4) (b) (4) process).

In the event the sterility test result is positive following the product infusion based on the RFI certificate, the firm has an action plan that includes an investigation and reporting to the FDA.

Release testing on the final products IS, CF DP, and NF DP:

For the release testing, sterility and endotoxin testing performed on the IS and the cell fractions (CF, NF) prior to freezing. Acceptance criterion is "no growth" for sterility and (b) (4) for endotoxin. Mycoplasma is performed on the (b) (4) of the CF during (b) (4) as an in-process test, but this test is reported as a release test. Rapid contamination testing is also performed to release the CF DP, because the sterility test results are not available at the time of release.

Microbial test methods and acceptance criteria (specifications) for CF DP:

Test	Method	Acceptance Criteria Release (pre freeze)	Acceptance Criteria Post thaw
Rapid contamination test	(b) (4)	Not detected	NA
Sterility – Bacteria, yeast, and molds	(b) (4)	No growth*	No growth
(b) (4) content	(b) (4)	Absence	NA
***Endotoxin content of the (b) (4) CF to ensure limit of (b) (4) EU/kg/hour	(b) (4)	For patients 4 kg-29 kg: (b) (4) For patients above 29 kg: (b) (4)	NA

NA = Not applicable
EU = Endotoxin Unit; (b) (4)
*The result is not available at the time the product is released.

***Note that upon the Division of Biological Standards and Quality Control (DBSQC) reviewer's request, the release specifications for the endotoxin content are also updated in terms of EU/mL, which was provided in the amendment **STN 125738/0.47**:

- For patient weight of 11 – 29 kg: (b) (4) for CF DP, (b) (4) for NF DP, and (b) (4) for IS

- For patient weight of 29 – 166 kg: (b) (4) for CF DP, (b) (4) for NF DP, and (b) (4) for IS

Microbial test methods and acceptance criteria for NF DP:

Test	Method	Acceptance Criteria
Sterility – Bacteria, yeast, and molds	(b) (4)	No growth
Endotoxin content of the (b) (4) NF to ensure limit of (b) (4) EU/kg/hour	(b) (4)	For patients 4kg- 29kg: (b) (4) For patients above 29kg: (b) (4)

Microbial test methods and acceptance criteria (specifications) for IS:

Test	Method	Acceptance Criteria
Sterility – Bacteria, yeast, and molds	(b) (4)	No growth
Endotoxin	(b) (4)	For patients 4 kg – 29 kg: (b) (4) For patients above 29 kg: (b) (4)

Container closure integrity test method was validated (section **3.2.P.7**), and the container closure integrity of the shipped (b) (4) freezing bags was evaluated during the IS stability studies (section **3.2.P.8**).

3.2.P.3 Manufacture

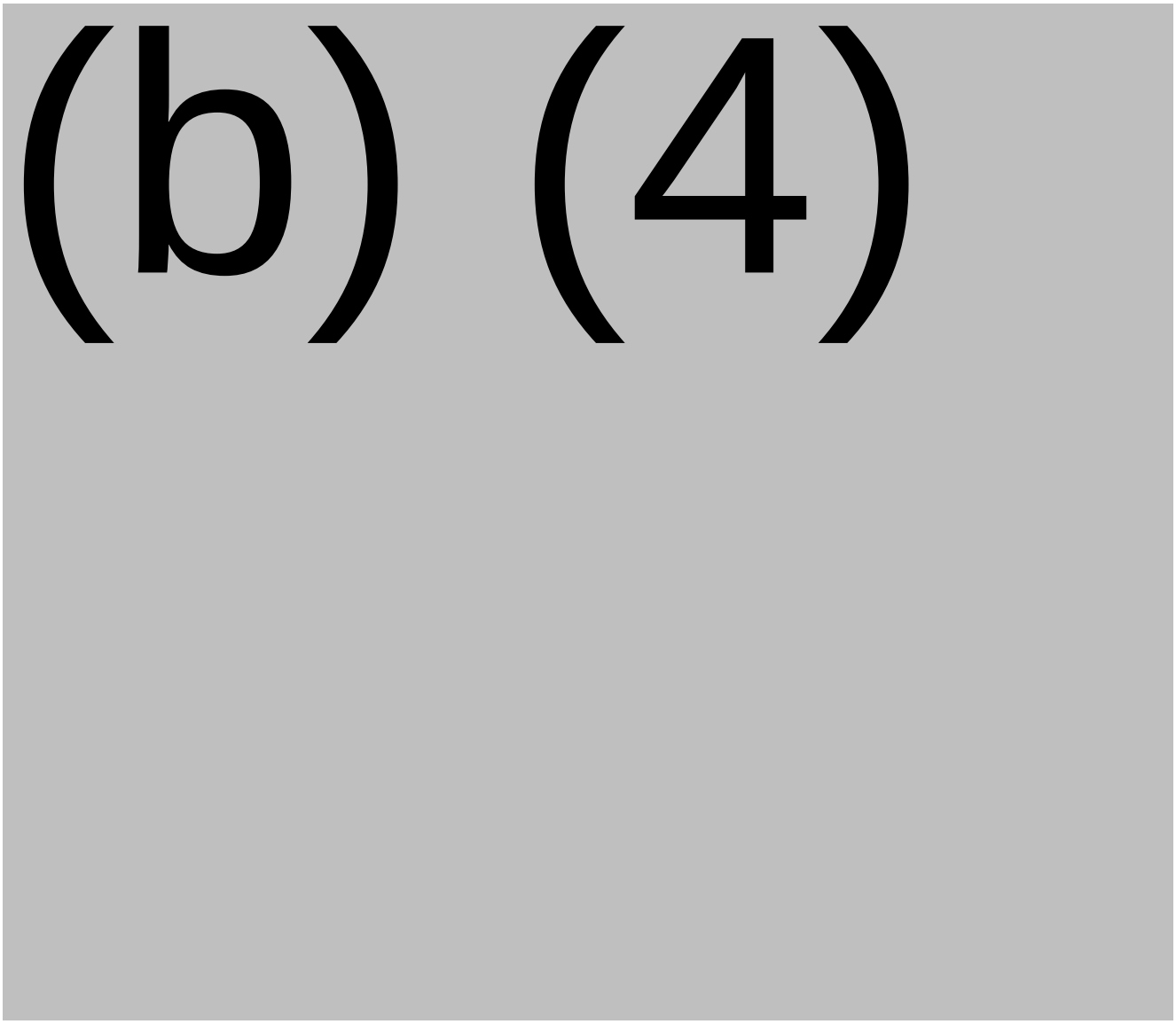
3.2.P.3.1 Manufacturer(s)

Refer to section **3.2.A.1** for a complete list of all manufacturing facilities.

3.2.P.3.3 Description of Manufacturing Process

(b) (4)

37 pages have been determined to be not releasable: (b)(4)



3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

CF stability

Long-term stability studies of omidubicel CF DP were planned for up to **12 weeks**. **Sterility and endotoxin will be tested at the beginning** (b) (4) **and end of the planned storage** (12 weeks shelf-life).

The stability sample was thawed, reconstituted, and held **for 2 hours at 15 – 25°C prior to testing** (for sterility and other tests) to simulate actual conditions.

Data from the interim timepoint T1 (6 weeks) were available at the time of BLA submission and met all acceptance criteria (including sterility) as detailed below.

PPQ stability testing lots:

- T1 stability (shelf-life 6 weeks): (b) (4) (b) (4) Batch (b) (4) was added as a replacement for (b) (4) due to an OOS (out of specification) result.
- T2 stability (shelf-life 12 weeks): (b) (4)

Pre-freeze sterility results for T1 and T2 PPQ lots met an acceptance criterion of "no growth". Endotoxin results also met an acceptance criterion of (b) (4) at the (b) (4) (b) (4) timepoint. The firm provided a justification for this endotoxin criterion, which is under OTP review.

Sterility results after the end of shelf for T1 PPQ lots met the acceptance criterion (no growth). Sterility results at the end of shelf for **T2 PPQ lots** were provided in amendments **STN 125738/0.35 and 0.49**: The final stability data (T2, 12 weeks) met the acceptance criterion for sterility ("no growth") at the end of shelf-life.

NF stability

The stability studies were conducted to demonstrate physical, chemical, biological, and microbiological NF stability through the proposed shelf-life of **fifteen (15) weeks** when stored at the intended long-term storage condition of **≤-150°C**.

Lots placed on long-term stability are listed as follows:
(b) (4) (PPQ with a **T1-shelf-life of 9 weeks +/- 3 days**), (b) (4) (PPQ-T1 shelf-life), (b) (4) (PPQ-T1 shelf-life), (b) (4) (T1 shelf-life), (b) (4) (with a **T2 shelf-life of 15 weeks** (b) (4)), (b) (4) (T2 shelf-life) and (b) (4) (T2 shelf-life).

*Batch (b) (4) was added as a replacement for (b) (4) due to an OOS result. The investigation concluded that inadequate sample handling was part of the root cause for the OOS result; therefore, an additional batch (b) (4) was placed on stability and all results at T1 were within the specifications.

The procedures for the long-term stability study are as follows:

The 50 mL cryopreservation bag is filled with 10 mL of the NF DP and frozen for the cryo-storage. Prior to testing, the NF DP bag is thawed and reconstituted (b) (4) with IS following the same procedure used at the transplant center. The reconstituted NF DP is held at ambient temperature (15 – 25°C) for 30 minutes (T1) and 1 hour (T2) before sampling for testing. This holding time is performed to simulate the maximum time span between thawing and completion of administration of omidubicel NF DP at the transplant center. The NF DP is tested immediately after thawing and reconstitution. Note that for the T1 and T2 PPQ stability lots, sterility is performed on PPQ lots at pre-

freeze timepoint (t=0) and at the end of shelf-life (9 weeks for T1 lots and 15 weeks for T2 lots).

Available stability results were reported as follows:
Sterility results at pre-freeze point met the acceptance criterion (no-growth) for all the T1 and T2 lots listed above. Sterility results of T1 lots at the shelf-life (following thawing) also met the acceptance criteria. Results of T2 lots for the end of shelf (following thawing) were submitted with **STN 125738/0.19** and **STN 125738/0.49**: The final stability data (T2, 15 weeks) met the acceptance criteria for sterility ("no growth") at the end of shelf-life.

Endotoxin results also met the acceptance criteria for the samples at the (b) (4) timepoint (b) (4)

The firm also provided interim data for NF DP batches stored at ≤-150°C **for 7 – 14 days** in that sterility met the acceptance criterion.

IS stability

All IS stability studies were conducted in both IS presentations: (b) (4) 50 and (b) (4) 250 freezing bags.

PPQ stability for **18 weeks** was evaluated for the following lots (also listed in VP387-R): (b) (4)

(b) (4) lots were used for (b) (4) hr in-use (interim) stability.

PPQ lots met the acceptance criteria for sterility (no growth) at release and at the interim testing points and endotoxin (for patients 4 kg – 29 kg: (b) (4) EU/mL; for patients above 29 kg: (b) (4) EU/mL) at t=0 timepoint.

CCIT performed on the IS stability lots

VP387-R Stability of the Infusion Solution Product within Expiry Date Manufactured during the PPQ Study at Kiryat Gat (KGI) **Interim Report** (Version:2.0; Expiration Date: 27-May-2022)

The following stability lots were listed for the evaluation:
IS Stability **Batch**(b) (4) for NF and CF (b) (4) included **CCIT**
IS Stability **Batch**(b) (4) for NF and CF (b) (4) included **CCIT**
IS Stability **Batch**(b) (4) for NF and CF (b) (4) included **CCIT**

The stability study included testing at five stability timepoints for the IS, that consists of two components: IS-CF for reconstitution of CF DP and IS-NF intended for reconstitution of NF DP:
(T0) - Release post manufacturing
(T1) - Four (4) weeks post manufacturing
(T2) - Ten (10) weeks post manufacturing
(T3) - Twelve (12) weeks post manufacturing
(T4) - Eighteen (18) weeks post manufacturing
(T5) - (b) (4) post manufacturing

This interim report summarizes available results (obtained for the T0 to T4 stability testing points).

Each batch of IS were filled in (b) (4) 50 mL bags (filled with (b) (4) mL of IS) and (b) (4) 250 mL bags (filled with (b) (4) mL of IS). Results were as follows:

ISCF and ISNF: All results obtained for the T0 to T4 stability timepoints met the stability testing acceptance criteria.

CCIT using the (b) (4) test method was performed at release and expiry in addition to sterility testing on the bags. Also, CCIT was performed at interim timepoints as summarized below.

- Stability data for IS PPQ Batch 1 stored at 2 – 8°C in 250 mL bags at T1 (4 weeks) to T4 (18 weeks) - CCIT met the acceptance criteria (no growth based on the immersed bags/no microbial infiltration) at 4, 12, and 18 wks. The 10 weeks timepoint was not performed because of the bag leakage.
- Stability data for IS PPQ Batch 2 stored at 2 – 8°C in 250 mL bags at T1 (4 weeks) to T4 (18 weeks) - CCIT met the acceptance criteria.
- Stability data for IS PPQ Batch 3 stored at 2 – 8°C in 250 mL bags at T1 (4 weeks) to T4 (18 weeks) - CCIT met the acceptance criteria

Reviewer's comment: *For the final report for CCIT testing, refer to section* ***3.2.P.7.*** *For the complete IS stability data, refer to the review of amendment* ***STN 125738/0.5*** *in this section (3.2.P.8). The final report VP487-R was provided in amendment* ***STN 125738/0.19*** *and reviewed below.*

STN 125738/0.19

VP387-R Stability of the Infusion Solution Product within Expiry Date Manufactured during the PPQ Study at Kiryat Gat (KGI)-**Final Report** (Version:3.0; Effective Date: 29-Aug-2022)

This final report summarizes the results obtained for the T0 to T5 stability testing points:
IS-CF and IS-NF: All results obtained for the T0 to T5 stability timepoints have met the stability acceptance criteria.

Stability batches evaluated:
(b) (4)

The package integrity testing on the IS-CF and IS-NF batches that was performed as per (b) (4) and used the (b) (4) test method met the acceptance criterion of "no growth" at the timepoints of T1 (4 weeks) - T4 (18 weeks). One deviation, Dev-0000370, occurred, and this deviation was summarized under the review of interim report earlier in this section.

Sterility results at T0 (release) and T5 (shelf-life) met the acceptance criterion of "no growth" (b) (4) Endotoxin results also met the acceptance criterion of (b) (4) at T0 (release) and T5 (shelf-life).

The IS shelf-life is set to five months, based on the data gathered in the leachable study #CHBS-16780. This study evaluated the data beyond five months (b) (4)
(b) (4)

Reviewer's comment: *The batches appeared to be stable with respect to sterility and endotoxin, and the package integrity was maintained during the storage period. The information provided in this report matches the information provided in amendment* ***STN 125738/0.35****. OTPOTP*

STN 125738/0.35

This amendment was submitted in response to OTP IR's and contained stability data (for CCIT, sterility, and endotoxin) and the data is summarized below:

In section **3.2.P.8** of the amendment, the CCIT results were reported for the following IS batches:

50 mL bag (b) (4) IS PPQ batches for CCIT, endotoxin, and sterility testing:
(b) (4)

250 mL (b) (4) IS bag PPQ batches for CCIT, endotoxin, and sterility testing:
(b) (4)

Reviewer's comment: *The batches listed above were reported in the interim report* ***VP387-R*** *and ongoing stability studies were summarized in this section. In this interim report, the results for T1-T4 stability data points were reported and results for the T5*

timepoint (b) (4) *were not available. With this amendment, the firm provided the complete results*.

The firm provided the results of CCIT performed on 50 and 250 mL (b) (4) bags filled with IS (the batches listed above). These results covered the CCIT timepoints of 4, 10, 12, 18, (b) (4) and results met the acceptance criterion of "no growth" for the microbial immersion integrity test method. Sterility was performed at T=0 and T5= (b) (4) (b) (4) and met its acceptance criterion of "no growth". Endotoxin results met the acceptance criterion of (b) (4) at T1 (4 weeks) -T5 (b) (4) timepoints as well as for T=0 timepoint, except for T2=10 weeks for (b) (4) (for 50 mL bags) due to a deviation Dev-0000370 in that leakage was observed because of inadequate tubing connection.

In section 3.2.P.8 of the amendment, the firm also provided data for the complete stability data for CF DP and NF DP stability data (PPQ lot stability data). In the original BLA submission, the results for T2 stability data were not provided because they were not available.

T2 (12 weeks) stability data for CP DP that was stored at ≤-150°C: Results at pre-freeze and 12 weeks (+/-1week) timepoints met the acceptance criterion of "no growth". Note 12 weeks is the recommended shelf-life for CF DP.

This amendment did not contain T2 stability data (15 weeks) for NF DP.

Reviewer's comment: *The T2 stability results were provided in amendment* ***STN 125738/0.49*** *and summarized earlier in this section (3.2.P.8.1)*.

VP382-R Verification of Stability of the Infusion Solution Product within Expiry Date in the Frame of Comparability Runs at Kiryat Gat Facility – **Interim Report** (Version:1.0; Effective Date: 16-May-2022).

Study period: August 2021-April 2022.

(b) (4) were tested for the time points of T=0, T-4 weeks, T2=12 weeks, T3= (b) (4)

All results for NF and CF presentations (50-250mL) met the acceptance criteria for endotoxin (b) (4) at the timepoints above and sterility (no growth) at t=0 (release). Note this study was planned to continue for (b) (4) weeks, and therefore, sterility and other results at the (b) (4) weeks timepoint were not available at the time of the submission.

Deviations: There was one deviation, Dev-0000371, that impacted (b) (4) and (b) (4) at the 4 weeks timepoint (T1). For this timepoint, the testing laboratory for the product quality attributes (sterility and endotoxin are not included) was not instructed to test the bags separately (for each of IS-CF and IS- NF bags separately), but this

deviation did not impact the outcome and results were acceptable. Both IS-NF and IS-CF were within specifications at all timepoints, indicating that both IS-CF and IS-NF remain stable until T3 of 24 weeks.

***Reviewer's comment**: The final report of VP382-R was provided in amendment **STN125738/0.19**. For the complete results for the stability studies described in the interim report, refer to the review of the final report below*.

STN 125738/0.19

VP-382-R Verification of Stability of the Infusion Solution Product within Expiry Date in the Frame of Comparability Runs at Kiryat Gat Facility–Report (Version:2.0; Effective Date: 29-Aug-2022).

Sterility at the end of shelf-life was unavailable because the study at (b) (4) was decommissioned (refer to the interim report). Sterility result at release (T=0) was "no growth". Endotoxin results met the acceptance criteria of (b) (4) at the test timepoints of T1 (4 weeks), T2 (12 weeks), T3 (b) (4) and T4 (b) (4)

***Reviewer's comment:** The evaluation of the results for the quality attributes other than endotoxin and sterility and the overall success of this study for comparability analysis (Comparability of the data generated at (b) (4) with the data generated at KGI) is deferred to the OTP reviewers. Refer to the OTP CMC review memo*.

VP349-R Verification of Stability of the Infusion Solution Product within Expiry Date (Version:1.0; Effective Date: 19-May-2022)

Reviewer's comment:
*-According to **the protocol (#VP349)**, the stability verification study was planned to continue for (b) (4) weeks after the manufacturing date, which ensures the maximum claimed expiry date of the IS CF & NF ((b) (4) weeks), but the (b) (4) weeks was skipped because Gamida decommissioned the project at the (b) (4) contract site (b) (4). The study at (b) (4) was concluded after completion of timepoint T4 (b) (4) weeks) and no testing was performed for timepoint T5 ((b) (4) weeks). In accordance with this decision, no further testing is planned, and **this document is considered the final report**. Also note that this study was conducted for comparability analysis, which is under the OTP purview. The stability studies reported in VP349 are summarized below and the results met the acceptance criteria for sterility.*
-Deviations occurred and was investigated. The deviations did not appear to have any impact on the study outcome.

-**Note this stability study was designed to test sterility and endotoxin (under DMPQ purview) and other stability indicating parameters (under OTP purview), not for the CCIT evaluation. CCIT was evaluated in a separate study that was documented in **VP387-R.

Long-term IS stability study design described in **VP349-R**:
Three of the four IS batches were used for long-term stability assessment according to the stability verification study design (T0, T1= 4 weeks, T2= 12 weeks, T3= (b) (4) weeks, T4= (b) (4) weeks; T5= (b) (4) weeks)

The sterility test at the release of the IS at T0 is performed in accordance with the (b) (4) (b) (4) requirements (i.e., (b) (4) bags of IS-CF and (b) (4) bags of IS-NF testing). Acceptance criteria is no growth.

Endotoxin is tested as per (b) (4) Acceptance criterion is (b) (4)

Visual inspection is performed as outlined in (b) (4)
Acceptance criteria is colorless to yellowish clear solution, free of visible particles.

Lots used and timepoints for the study are as follows: (b) (4)
(b) (4) the timepoints of 0 weeks, 4 weeks, 12 weeks, (b) (4) weeks, and (b) (4) weeks.

Results: The results obtained for all (b) (4) batches met the acceptance criteria for sterility at release (result at (b) (4) weeks was not available because of decommissioning) and endotoxin at all timepoints tested. The stability verification study appeared to maintain a shelf-life of (b) (4) weeks for the IS product stored at 2 – 8°C (August 2021-April 2022).

Deviations: Three deviations from the protocol were reported during this study as detailed below. One of these deviations was classified as major (NC-798962 under OTP purview) while others were defined as minor.

- NC-776060 – During visual inspection of (b) (4), a leakage was observed for one of the samples designated for sterility testing at (b) (4) Therefore, IS (b) (4) was sent for sterility testing instead of IS (b) (4) Sterility testing showed no growth
- NC-765454 – During preparation of the HSA/dextran infusion solution batch (b) (4) according to NLGE-2482, the (b) (4) of the 50 mL IS NF bag #1 cryopreservation bag was sealed off (b) (4)
  As a result, the spike adaptor could not be connected to the bag. The mistake in sealing was most likely due to the operators' error regarding the sealing location of the IS bags (which is different from the sealing location of the CF and NF bags). An additional bag was prepared using the remaining volume originally to be used as a retain sample. The volume of the IS-NF bag was transferred to a new container to be used as retain sample.
- NC- 798690 – The temperature of refrigerator (b) (4) used for the storage of the IS retain samples, was out-of-specification (OOS) of 2 – 8° C for approximately (b) (4) The investigation concluded no impact on the IS retain samples based on R&D data indicating that IS is stable at room temperature for (b) (4)

Conclusion: The firm concluded based on the results obtained in this study that the IS product, when stored in specified conditions at 2 – 8°C, is stable according to all relevant parameters (appearance, (b) (4) HSA identity, dextran identity, HSA Assay, HSA impurities, endotoxin, and sterility), over the time period assessed up to (b) (4) **weeks**. Sterility and endotoxin results met the acceptance criteria. OTPOTP

***Reviewer's comment on the information provided in amendment STN 125738/0.19 (summary)*:**

In this amendment, the firm reported the complete stability results. The information/results (which were not included in the original BLA) are as follows:

-T2 stability lots of CF DP met the acceptance criteria for sterility at the end of shelf-life (12 week), except for (b) (4) *that was replaced with another PPQ lot,* (b) (4) (b) (4) *was invalidated due to an OOS result.*

-T2 stability lots for NF DP met the acceptance criterion for sterility at the end of shelf-life (15 weeks).

***Reviewer's comment:** The proposed shelf-life and storage conditions, with respect to microbial quality and/or sterility assurance, appeared acceptable. Deficiencies were resolved through IRs.*

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

Facility Table

Manufacturing and testing facilities are listed in the table below.

Location	Activity	Most Recent Inspection
Gamida Cell Kiryat Gat Israel (b) (4)	-Drug substance (DS) manufacturing and in-process testing (excluding endotoxin, mycoplasma (b) (4) PCR and sterility testing) -Drug product (DP) manufacturing and release and stability testing (including appearance, identity and potency testing)	CBER PLI (b) (4) VAI

1 page has been determined to be not releasable: (b)(4)

KGI Facility Design

The KGI facility is located on the (b) (4) floor and half of the (b) (4) floor of an existing building. The area of the facility is approximately (b) (4) This facility is (b) (4) (b) (4) manufacturing facility.

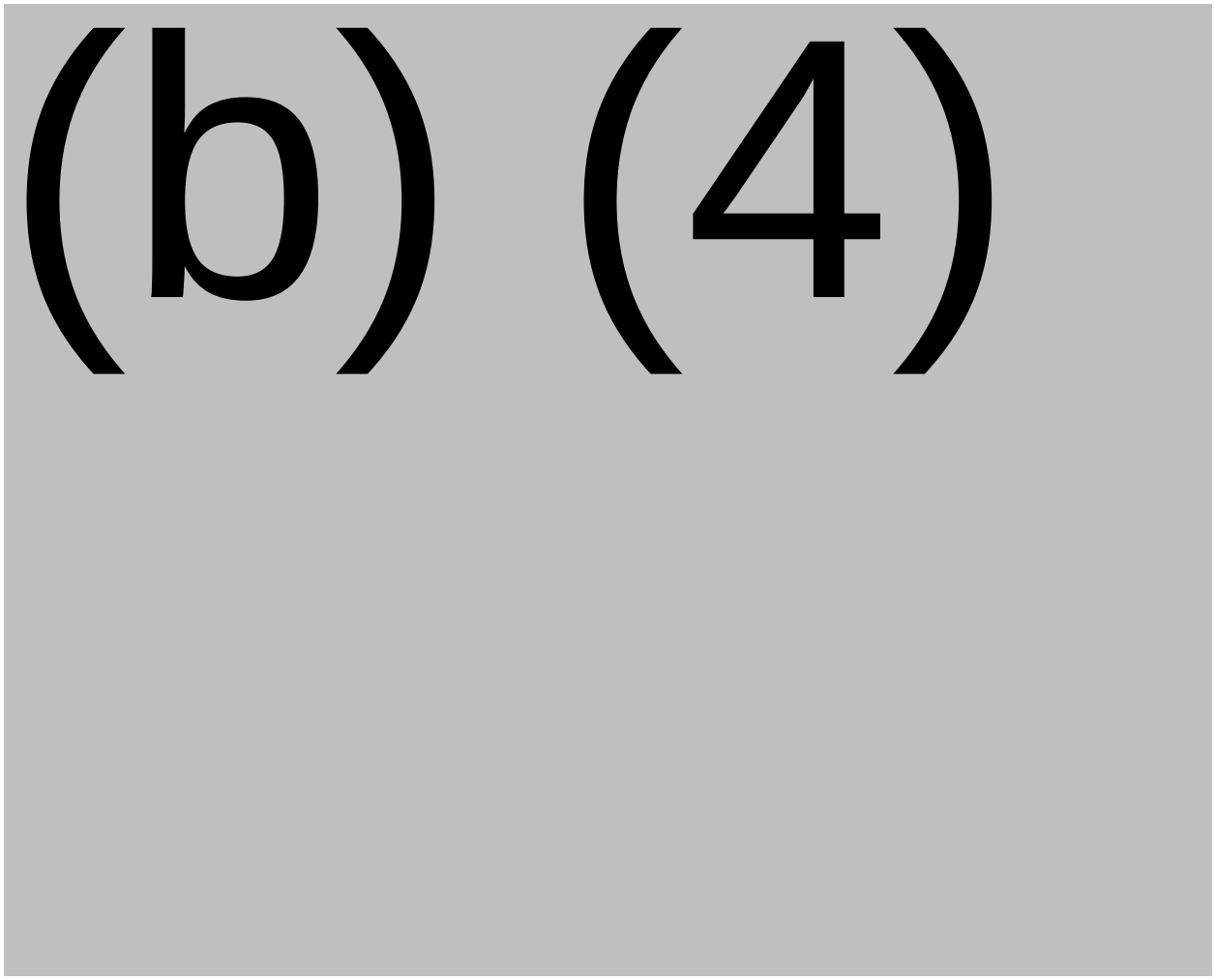
The facility is designed to contain (b) (4) manufacturing (b) (4) (b) (4) (b) (4) Each (b) (4) is designed to include (b) (4) (b) (4) (b) (4) (b) (4) and qualified for production of CF and NF. The site capacity for production will be (b) (4)

(b) (4) will be used to manufacture omidubicel (CF, NF, and IS) DP and the clinical product (b) (4)

(b) (4) consists of (b) (4) Grade (b) (4) rooms, which are dedicated to CF and NF manufacturing (rooms (b) (4) There is also a separate Grade (b) (4) room, which is dedicated to IS manufacturing (b) (4) surrounded by Grade (b) (4) Grade (b) (4) and controlled non-classified (CNC) rooms.

Manufacturing areas are listed with room classifications and numbers, and manufacturing activities in the table below:

(b) (4)



Reviewer's comment:

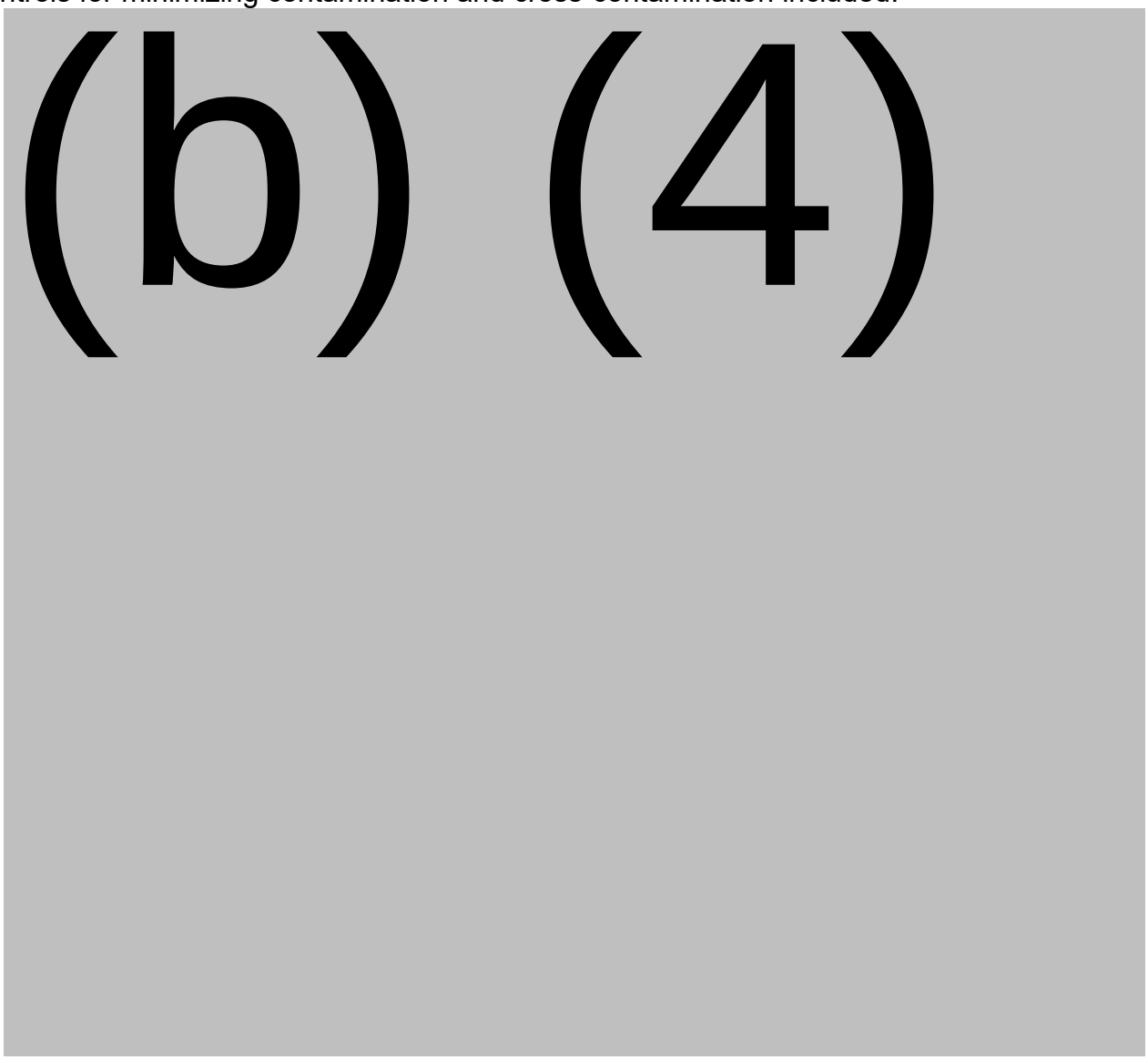
- *The room classifications listed in the table above appeared acceptable for their intended use*.
- *A facility layout depicting offices, QC, warehouse, production, support, and gowning areas is provided*.
- *The firm provided a diagram for manufacturing area classifications along with their pressure differentials (pressure cascade), which appeared acceptable*. *The clean areas have higher pressure compared to the surrounding areas, and air flows from clean areas to less clean areas*.
- *Manufacturing flow diagrams for waste, sample, raw material, product, and personnel appeared unidirectional*.
- *Air exchange rates appeared acceptable: Minimum air changes are designed at a rate of* (b) (4) *for ISO* (b) (4) *(Grade* (b) (4) *at rest and Grade* (b) (4) *in operation), and* (b) (4) *for ISO* (b) (4) *(Grade* (b) (4) *in operation).*
- *For additional information on the summarized information above, refer to the **EIR** for the **KGI PLI**.*

Prevention of cross-contamination

A risk assessment for the prevention of contamination and cross-contamination was conducted: “Risk Assessment for Contamination Control Strategy at Kiryat Gat GMP Facility” (**RA-045**). Key risk elements of the overall contamination prevention program were examined for potential failures and hazards:

- Facility related risks (facility design and critical systems)
- Personnel related risks
- Equipment related risks
- Process related risks
- Cleaning and disinfection related risks
- Raw materials related risks

Risks were assessed using a **FMEA** method, which defines the strategies and activities required to mitigate the risk of cross-contamination. Based on the risk assessment, controls for minimizing contamination and cross-contamination included:



(b) (4)

Reviewer's comment: *Additional manufacturing controls for the microbial content are summarized in section 3.2.P.2.5. Controls for the prevention of the contamination, which are described above, appeared acceptable. The adequacy of the controls was evaluated onsite during the KGI PLI. Refer to* ***EIR*** *for the* ***KGI PLI*****.**

Utilities

Water: The KGI facility does not have a water system. The facility (b) (4) (b) (4) . WFI is not **used directly in the manufacturing process** and is not in contact with product. WFI is used to (b) (4) and is stored at (b) (4) temperature in the warehouse.

Liquid Nitrogen (LN): LN is supplied by an approved supplier with a CoC that includes % nitrogen purity, dew point, and O2 level of the LN. The LN freezers and the CRF are connected to (b) (4) LN tanks that have a digital level display and a local alarm. The (b) (4) LN tanks used for the freezers are connected to a (b) (4) tank by (b) (4) (b) (4) The dedicated (b) (4) LN tank is stored (b) (4) with an independent level control and level control transmission to the LN supplier. There are also (b) (4) (b) (4) tanks for the manual refilling of the dry shippers. The (b) (4) LN tank is located (b) (4)

(b) (4)

(b) (4)

Environmental Monitoring (EM) Program and Qualification

EM in the manufacturing cleanrooms is carried out according to an approved sampling schedule. EM sampling is performed during production (operational monitoring), and at rest on a scheduled basis. The EM program includes both viable and non-viable sampling.

Airborne non-viable particulate monitoring is performed by measuring (b) (4) (b) (4) and will be performed routinely during manufacturing operations. **BSCs are** (b) (4) **monitored**. Viables for surface and air (active and passive), and personnel are monitored and will be monitored in the frequency summarized below.

All cleanrooms are classified in accordance with (b) (4) defined with respect to both the minimum number of sample locations and the sample size based on the required class. The monitoring locations are determined with regard to the risks (e.g., at locations posing the highest risk of contamination) and results obtained during the qualification of manufacturing areas. The maximum permitted airborne particle limit for each of the classified areas is determined according to the recommendations of the (b) (4) and complies with the **FDA guidelines.** The following information for the classified areas summarizes the information on the EM program and qualifications (VP236-R).

VP236-R Clean Room Microbiology Conditions Performance Qualification “In Operation”– Final Report (Version: 1.0; Effective Date: 05-Jul-2021)

Non-viable particulate monitoring

Alert and action levels for non-viable particulate monitoring (**VP236-R**):

(b) (4)

The monitoring frequency is performed according to the area classification and activity as detailed below.

(b) (4)

Reviewer's comment: *The alert and action levels for* (b) (4) *and the frequency of EM for the classified areas appeared acceptable*.

1 page has been determined to be not releasable: (b)(4)

Personnel monitoring

Sampling of personnel is performed using (b) (4) (b) (4) during manufacturing, following critical interventions, or when exiting the Grade (b) (4) processing area.

(b) (4)

In routine manufacturing, the limits in the table below apply for personnel monitoring:

Area Grade and sampling	Alert Limit Contact Plate	Action Limit Contact Plate
(b) (4)		

EM performance qualification (EMPQ):

(b) (4)

Reviewer's comment:

- *Microorganisms (flora) were identified during the EMPQ and listed in the report (Table 6). This list included* (b) (4) *Additional information on the EMPQ was provided in amendment* ***STN125738/0.29****.*
- *Based on the information provided in the reports* ***RP152*** *(EMPQ at rest that was submitted with amendment STN 125738/0.29) and* ***VP236-R*** *(EMPQ in operation that was provided in the original BLA submission),* (b) (4) (b) (4) *recovered) and* (b) (4) *) had the highest distribution percentage:* (b) (4) *during EMPQ at rest;* (b) (4) (b) (4) *during EMPQ in operation. These microorganisms recovered with the highest percentage appeared to be included in the disinfectant efficacy study.*

- *The information on the* (b) (4) *EMPQ in operation (associated report was not provided in amendment STN 125738/0.29), a follow-up on this ongoing* (b) (4) *qualification was recommended during the KGI **PLI**. Refer to **EIR** for the KGI PLI.*
- *Deviation #GC 006-20KG (DEV 0000174) and #DEV 0000080 occurred due to OOS results (see Section 10.1 of VP236-R) and associated additional information was provided in amendment STN 125738/0.29 that was reviewed below*.

STN 125738/0.29:

This amendment was submitted in response to **IR# 4**.

IR# 6.1-Report **VP236-R** ('Clean Room Microbiology Conditions Performance Qualification 'In Operation'– Final Report') indicated that microorganisms were identified in the facility during the EMPQ in operation as well as (b) (4) (refer to Tables 6 and 7 of the report). Therefore, a copy of the associated CAPAs along with the results of the CAPA effectiveness evaluation was requested under **IR# 6.1**. Under this IR item, a copy of the EM trend analysis conducted for the last three months for (b) (4) was also requested. The summary and evaluation of the response to IR# 6.1, is as follows:

The complete PQ of the HVAC system was performed in (b) (4) (*refer to Table 13 of the response*). Based on the completion of the "in operation" PQ study, routine monitoring sampling points, locations, and frequency were defined.

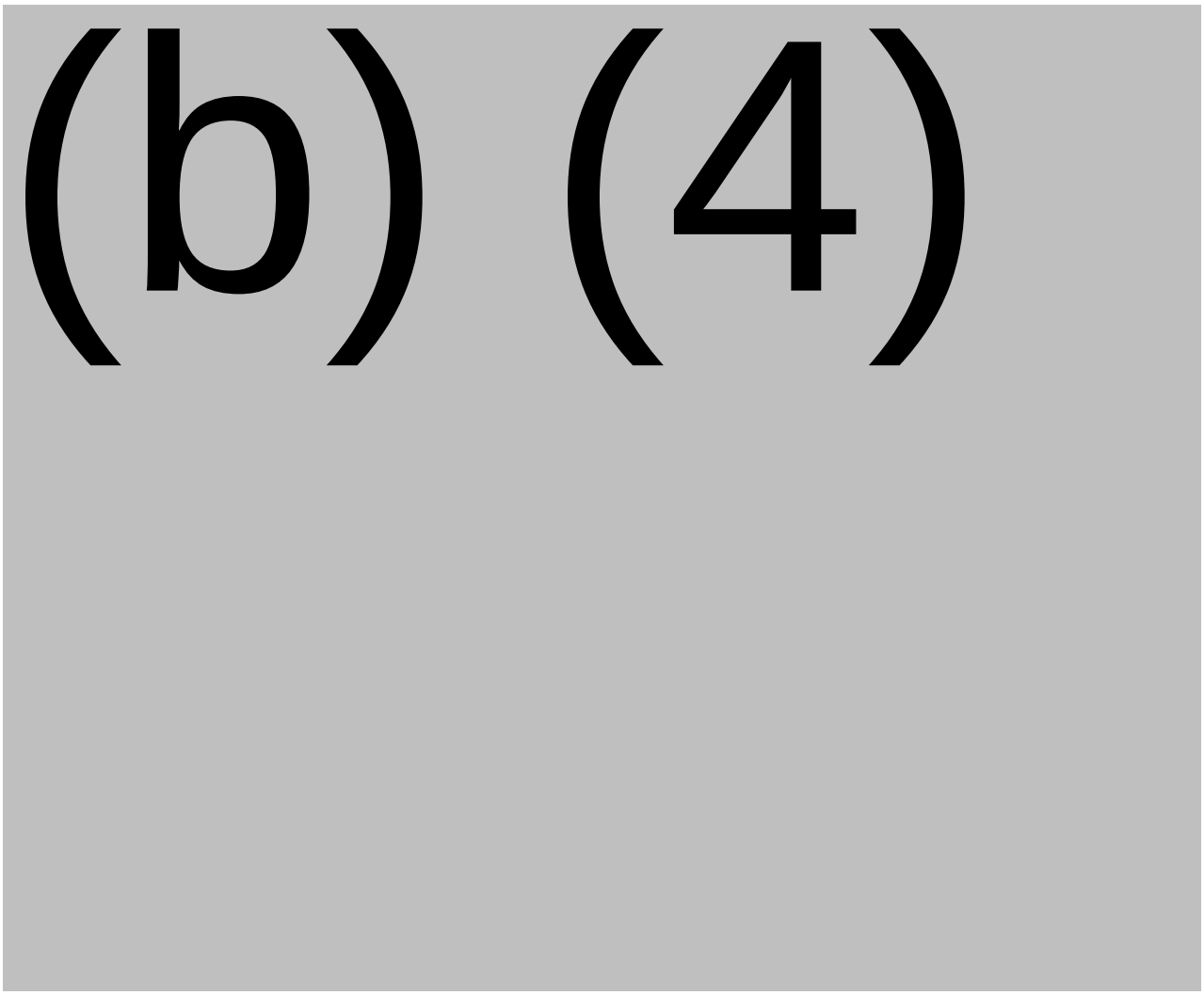
(b) (4) (Dev-0000279) and completed, but it was in progress for the approval at the time of this amendment submission.

***Reviewer's comment*:** *Because the report for the* (b) (4) *EMPQ was not submitted with this amendment, this stage qualification was followed up during the KGI **PLI**. Refer to EIR for the KGI PLI*.

During the performance of the "in-operation" EMPQ (b) (4) deviations occurred and were investigated and analyzed. Based on the root cause findings, CAPAs were issued and implemented (*as summarized in Table 10 of VP236-R*). The associated reports, Doc# Ys032021 and Doc# Ys022021, were provided and reviewed. A summary of the reviewed information is follows:

(b) (4)

1 page has been determined to be not releasable: (b)(4)



IR# 6.2- Because the report for EMPQ at rest (VP-152) was not provided in the original BLA submission, this report was requested. A summary and evaluation of this report is as follows:

The firm indicated that EMPQ at rest was performed according to Protocol #VP-149 (provided in this amendment), not according to protocol #VP-152 listed in Section 3.2.A.1 Facilities and Equipment. Protocol #VP-152 was a typographical error, and the section was updated to correct this error.

The results of the EMPQ at rest were summarized in report #RP152 Clean Room Performance Qualification (At Rest Conditions – Microbiology Baseline) – Final Report:

BSCs were sampled at the (b) (4) The viable monitoring at these locations yielded (b) (4) results, except for the (b) (4) sample of BSC (b) (4) and (b) (4) (b) (4) sample of the BSC (b) (4) (b) (4) BSC (b) (4) and BSC (b) (4) (b) (4) and the results met the acceptance limit (b) (4) results). Some locations in Grade (4) areas had high CFU counts that exceeded the

limits, such as for areas (b) (4)
(b) (4) A few locations in Grade (b) (4) areas had also high CFU counts, such as for (b) (4)
(b) (4)

The deviations related to the high CFU results were investigated and microorganisms were identified. The most common microorganisms identified were (b) (4)
(b) (4) (b) (4)
(b) (4) (b) (4) (b) (4)
The data suggested that environmental contaminants were brought in inadvertently by personnel.

The locations that exceeded the limits were further monitored and analyzed in the (b) (4) PQ.

***Reviewer's comment*:**

- *The firm's response appeared acceptable, and further follow-up on the EMPQ at rest and in operation and associated deviations was performed during the KGI **PLI**.*
- *Acceptable corrective actions appear to have been taken for the deviations such as training personnel for aseptic and good documentation procedures, and the locations that exceeded the limits were further monitored and analyzed in the (b) (4) PQ. Note the report for the (b) (4) PQ was not submitted with this amendment, and therefore, this stage PQ along with its deviations was evaluated during the KGI PLI.*
- *Microorganisms identified at the highest level such as (b) (4) were included in the new/updated disinfectantefficacy study.*

Efficacy Studies for Disinfectants

R-003 Gamida cell Ltd. **Interim Report** No. R-003 Disinfectants Efficacy "Disinfectants Efficacy by Recovery from Contaminated Coupons of: (b) (4)

Gamida's QA reviewed this interim report on 07/19/2021.

The purpose of this study was to determine the efficacy of the disinfectant reagents used for the sanitization of surfaces in the controlled KGI.

(b) (4)

6 pages have been determined to be not releasable: (b)(4)

(b) (4)

Reviewer's comment: *The firm provided a qualification report for each of the disinfectants used in the study. Results for all the disinfectants, which are listed along with their qualification reports in the table above, met the acceptance criteria and as recommended in* (b) (4) *The response appeared acceptable.*

The firm also clarified whether the (b) (4) solution and the (b) (4) which were listed in (b) (4) are the same solutions (*in response to **IR# 5.3***): (b) (4) (b) (4) (b) (4) are not the same solutions. In the study, (b) (4) is used as a placebo for the disinfectant solutions (positive and negative controls) for (b) (4) (b) (4)

Reviewer's comment: *The clarifications appeared acceptable.*

Equipment Qualification (IQ/OQ/PQ)

All the equipment qualifications were provided in **VP236-R** that was included in section 3.2.A.1 of the original BLA submission.

Critical process equipment qualification

(b) (4) (b) (4)

(b) (4)

26 pages have been determined to be not releasable: (b)(4)