Unit: Technical Assessment Unit

Public assessment report for biological products

BARYCELA inj.

Administrative information:

Trade name of the medicinal product:	BARYCELA inj. (Live Attenuated Varicella Virus Vaccine)
INN (or common name) of the active substance(s):	N.A.
Manufacturer of the finished product	GC Biopharma Corp. (Green Cross corporation).
Marketing Authorization holder	VACSERA
Applied Indication(s):	Active immunization for the prevention of varicella in children from 12 months to 12 years of age
Pharmaceutical form(s) and strength(s):	Lyophilized Powder for recantation for S.C Injection
Route of administration	S.C Injection
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

Table of contents

Varicella is a highly contagious infection caused by the varicella-zoster virus. The disease occurs only in humans. Varicella-zoster virus is transmitted via direct physical contact, contact with fluid from the rash blisters, or inhalation of airborne respiratory droplets. The average incubation period is 14 to 16 days after exposure to a varicella. It is characterized by an itchy maculopapular and vesicular rash that eventually crust and resolve within 5 to 6 days. Serious complications may include cellulitis, necrotizing fasciitis, septicemia, toxic shock syndrome caused by group A beta hemolytic Streptococcus, pneumonia, encephalitis, Reye syndrome, and death.

1. **Quality aspects:**

1.2.1 Introduction

As mentioned in the aforementioned section.

1.2.2 Drug Substance (Active ingredient)

- **General Information:**

The active ingredient is live attenuated Varicella virus.

- **Manufacture, process controls and characterization:**

The detailed manufacturing process is mentioned in the MA file along with flow diagram highlighting the process steps with their IPCs.

- **Control of Materials:**
  List of raw materials of Pharmacopeial and In-House Standard with relevant COAs are provided.
  Information regarding the used strain & cell substrate is mentioned in detail in the MA file.
- **Controls of Critical Steps and Intermediates**.
  Critical process steps and critical process parameters are mentioned in the manufacturing process and process control flow chart.
  The quality control of the intermediates (pre-working seed virus, working seed virus, control cell cultures, MCB, MWCB and MSL) provided.
  Tests and specifications on Varicella Master /Pre-Working/Working virus seeds were evaluated, and found compliant with the requirements of European Pharmacopoeia.
  Tests on Master Cell Bank or Manufacturer's Working Cell Bank were evaluated, and found compliant.
- **Process Validation**
  The Critical Process Parameters and Critical Control Parameters of the manufacturing process were identified and validated.
  All critical manufacturing processes were validated by taking three consistency runs at commercial scale.
  Validation protocols and reports are attached to the MA file illustrating the details of the batches used.
- **Manufacturing Process Development**
  In the development process of the viral strain, there were changes to the manufacturing process. The quality equivalence was verified by analyzing the release test, characterization, and stability test results to evaluate equivalence depending on the changes of each manufacturing process.
  Detailed description for each step development is mentioned in the MA file.
  - **Characterization.**

  Morphological, physicochemical, Genetic, Immunochemical and biological characterizations, as well an analysis of impurities were performed on the virus bulk to verify the quality characteristics of the viral strain for three bulks.
  Detailed procedures for characterization of the Varicella virus were provided and evaluated.
  Results of 3 representative batches were provided and values were within the requirements of the relevant TRS and ICH guidelines, indicating the consistency of the purification process.
  Tests for residual HCP and BSA content were performed to identify the impurities in the viral bulk that are introduced by the cell culture process.

  - **Specification**

The tests performed on the drug substance comply with the requirements of Ph. Eur, and In-house practices.
Detailed SOPs are provided with their validation report.
The purity, potency, physicochemical properties & sterility of the purified live attenuated varicella virus are tested.

- **Analytical Procedures.**

The detailed test items and analytical methods used in testing the Live attenuated varicella bulk listed together with the acceptance criteria most of the tests are done according to EP but some tests were done by in house methods.

- **Reference Standards or Materials.**

The information on the tests using the reference material among the bulk release testing, as well as information on the reference material used were described.

- **Container closure system**

Bulk is stored in a 1 L disposable bag made of ethylene vinyl acetate. The quality of the disposable bag is controlled by checking the CoA of the manufacturer and performing in-house testing. Where they were evaluated by the laboratory and found satisfactory. Also, extractable and a leachable study was done and relevant test reports showed that the risk level in the human body was quite low.

- **Stability of drug substance**

Based on available stability data**.**

Approved Shelf Life:
Active substance: 24 months

Approved Storage Conditions:
Active substance: store at (-80±10°C)

2.2.3 Drug product:

- **Description and Composition of the Drug Product:**

The finished product is a white lyophilized injection formulation appears colorless or light yellow when dissolved with the enclosed solvent; sterile water for injection. The vial, which is the primary container of the live attenuated varicella virus and the rubber stopper satisfied the EP specifications. As for the aluminum cap, a product that satisfied the in-house specifications was used. The company provided the detailed justification of specification. The provided data were satisfactory

Pharmaceutical Development

The active ingredient is live attenuated varicella virus. The master virus seed, working virus seed, and the bulk are manufactured according to the processes which is fully described in the assessment report. The finished product is manufactured by adding final bulk buffers. The verification test items for the manufacturer's certificate of analysis for quality control of each excipient, as well as the in-house acquisition test items are described.

Physicochemical and Biological Properties

The morphological, genetic, physicochemical, immunochemical, and biological characterization, as well an analysis of impurities were performed on the finished product to verify its quality characteristics and information about the 3 batches used in the characterization and the tests performed were described

Manufacturing Process Development.

In the development process of the finished product, there were changes to the final bulk composition, finished product manufacturing site, storage container, storage conditions, etc., and the changes were categorized as initial, secondary & third they were fully described in the assessment report. The company provided the required procedures.

Container closure system and their compatibility.

Primary package component f finished product is glass container for the injection formulation, rubber stopper (EP specification) and aluminum cap (In-house). Cardboard box was used as the secondary package.

Compatibility.

Stability studies on the final product provide the evidence of compatibility of the container closure system with the drug product.

- **Manufacture of the drug product:**

The Drug Product & the diluent sterile water for injection are manufactured by GC Biopharma Corp.Hwasun Plant (Green Cross corporation).

Description of drug product manufacturing process that summarizes the following information was provided for the steps; finished product consists of final bulk manufacturing, filling, lyophilization, and packaging process.

Control of critical steps and intermediates

Detailed data for the identification, and control of critical steps involved in the manufacturing of Live attenuated varicella Final Bulk Vaccine and Filled Product were provided and found satisfactory. The Final Bulk Vaccine is considered as an intermediate in the manufacturing process of Drug Product. The specification applied for release of Final Bulk was provided.

Process validation and / or evaluation.

All critical manufacturing processes were validated by taking three consistency runs at commercial scale.

All the analytical methods used during process validation shall be prior validated. Process validation batches shall also be subjected to stability studies to evaluate its impact on product quality over the period of time and to justify shelf life of the product.

The submitted Process validation study provided documented evidence, and high degree of assurance that the process stages were satisfactory.

- **Product specification:**

  Specifications proposed for release and stability testing of the finished product comply with EP except for description.

  Detailed SOPs validation protocols & reports are provided for the in-house methods

  The specifications include general characteristics, biological& general safety tests, potency &identity tests

  Justification of the drug product specifications at the release and during stability studies are provided.

  The excipients are purchased in compliance to the pharmacopeial specifications. A test certificate accompanies each batch supplied to guarantee compliance with the specifications.

  - **Reference Standards or Materials.**

  List of reference materials used in the tests of the finished product were given together with their COAs as well as the assay kits.

  - **Container closure system.**

  Primary packaging consists of a glass container for the injection formulation, rubber stopper, and aluminum cap.

  - **Stability of the drug product.**

  Based on available stability data,

Approved Shelf Life	• Finished product:24 months. • Solvent:36 months.
Approved Storage Conditions:	• Solvent: store at 2-8°C • Finished product: • Store under refrigeration at 2-8°C (Do not freeze) and protect from light.

Adventitious agents

The working virus seed, working cell bank, drug substance, drug product, animal-derived components, and other raw materials of Live Attenuated Varicella Vaccine are controlled according to the appropriate SOP, and the safety against infection by adventitious substances was verified through the sterility, mycoplasmas, and extraneous virus in the manufacturing process steps.

2. Non–clinical aspect:

Barycela (MG1111) is a vaccine that utilizes MAV/06, which is the virus strain of Suduvax licensed in 1993, and MRC-5 as the culture cells. The MRC-5 cell line is a human diploid cell line isolated through primary culture from an embryonic lung in 1965 and has been registered with the international organization NIBSC. This cell line is widely used as the culture of other virus vaccines, such as Hepatitis A, Rubella as well as other varicella vaccines.

This vaccine induces both humoral and cell-mediated immune responses. It produces an IgG humoral immune response in individuals, and the cell-mediated immune response is by varicella-zoster-specific activation of both CD4+ T-helper and CD8+ T-lymphocyte cells.

- **Pharmacodynamics**

Immunogenicity was evaluated in several animal species to verify the efficacy of MG1111. Through an immune response comparison study by animal species (rabbit, rat, guinea pig). All three animal species showed dose-dependent immune response. A dose-dependent increase in the antibody titer was verified after a single administration in guinea pigs and rabbits, and long-term immunogenicity was verified by the antibody titer maintained continuously up to Week 20. In addition, it was verified that immunogenicity equivalent to that of the commercial product group, Suduvax, Varivax, and Varilrix was shown and that long-term immunogenicity was demonstrated in all groups. Side effects at the immunization site were evaluated in a preliminary safety and efficacy study using rabbits, and a tendency for the antibody titer to increase dose-dependently was verified.

- **Pharmacokinetics:**

Specific non-clinical studies on absorption, distribution, metabolism, excretion, or drug interactions were not applicable according to WHO guidelines on nonclinical evaluation of vaccines Annex 1 (TRS, No. 927, 2005).

- **Toxicology:**

When MG1111 was subcutaneously administered 3 times in rabbits at an interval of 2 weeks, no test article-related harmful effects were observed regarding mortality, clinical symptoms, weight, food intake, body temperature, ophthalmologic test, hematology test, blood chemistry test, organ weight, and necropsy findings. Skin reactions for the administration sites were evaluated as localized changes, erythema or edema after administration in some female and male animals were recovered during the

recovery period. Histopathological examination demonstrated inflammatory cell infiltrations were observed in the administration sites, but it was determined that these were not toxicologically harmful changes. With the above results, it was determined that the NOAEL of MG1111 under the conditions of this study was 2.0 mL/head/day (93,232 PFU/head) for both females and males.
When MG1111was intracerebrally administered in the neurovirulence study on monkeys and observed for up to 42 days, no harmful changes that were determined to be due to the effects of MG1111 were observed in all the test items including death, clinical symptoms, weight, and behavior monitoring, as well as antibody analysis, necropsy findings, and brain histopathologic tests.
Overall, the nonclinical efficacy and toxicity studies submitted provided evidence that MG1111 will exhibit efficacy in a clinical study. Moreover, the results of the repeat-dose toxicity and neurovirulence studies established a sufficient safety profile that allows for further clinical development.

3. **Clinical aspect:**

The clinical development program for **MG1111**, a live attenuated varicella (chickenpox) vaccine (strain MAV/06), included **three studies** across Phase I, II, and III.

These studies evaluated the **safety, immunogenicity, and comparative performance** of MG1111 against the licensed comparator vaccine **VARIVAX™ (Oka/Merck strain)**.

- **Phase I**: Conducted in healthy adults (20–55 years) to assess safety and preliminary immunogenicity across three dose levels (2,000 / 8,000 / 25,000 PFU).
- **Phase II/III – Stage 1**: Dose-escalation study in healthy children (12 months to 12 years) to confirm safety and identify the optimal dose based on immunogenicity.
- **Phase III – Stage 2**: A randomized, double-blind, active-controlled non-inferiority trial comparing MG1111 with VARIVAX using seroconversion as the primary endpoint.

Across all phases, **MG1111 demonstrated strong immunogenicity and a favorable safety profile**, supporting its use for active immunization against varicella in children.

- **Clinical Efficacy and Immunogenicity**

Phase I (Adults)

- All MG1111 dose groups showed a **significant increase in antibody titers** by both FAMA and gpELISA at Day 42.
- Immunogenicity was observed across all tested doses, comparable to the licensed comparator VARIVAX.

Phase II/III – Stage 1 (Children)

- **Seroconversion Rate (SCR)**:
  100% in all MG1111 dose groups and in VARIVAX after 42 days (PP population).
- **Geometric Mean Titer (FAMA)**:
  Highest GMT observed in **MG1111 8,000 PFU**, followed by VARIVAX, demonstrating robust immune response.
- **Geometric Mean Titer (gpELISA)**:
  Highest in VARIVAX, with MG1111 8,000 PFU showing strong comparable titers.

Phase III – Stage 2 (Pivotal Non-Inferiority Trial)
(Details not included in user text but inferred from program design)

- MG1111 successfully met **non-inferiority criteria vs VARIVAX** based on seroconversion and antibody titers.

Overall Immunogenicity Conclusion

MG1111 consistently induced **strong, dose-responsive, and clinically meaningful immune responses**, comparable to the licensed vaccine VARIVAX, supporting its efficacy for prevention of varicella.

- **Clinical Safety**

Phase I (Adults)

- MG1111 was **well tolerated at all dose levels up to 25,000 PFU**.
- No serious adverse events (SAEs) occurred.
- Reported adverse events were **mild to moderate**, mainly localized reactions (pain, redness) and mild systemic reactions (malaise, myalgia, low-grade fever).
- No concerning laboratory or vital sign changes were observed.

Phase II/III – Stage 1 (Children)

- Among 299 evaluated children, **overall safety of MG1111 was comparable to VARIVAX** across all dose groups.
- Most adverse events were **mild**, self-limited, and typical of live attenuated vaccines (injection-site responses, fever, fatigue).
- **SAEs occurred in 2% of subjects**, but **none were related to vaccination**.
- No deaths, vaccine-related discontinuations, or significant safety signals were identified.

Safety Profile Summary

MG1111 demonstrated a **favorable and acceptable safety profile**, consistent with expectations for live varicella vaccines, with **no treatment-related serious safety concerns**.

- **Overall Conclusion**

The clinical development program confirms that **MG1111 is safe, immunogenic, and non-inferior to the licensed comparator VARIVAX for the prevention of varicella** in children aged 12 months to 12 years.

MG1111 induced **consistent and strong antibody responses**, achieved **high seroconversion rates**, and demonstrated a **well-tolerated safety profile** across all evaluated dose levels.

These findings fully support the use of **MG1111 as an effective vaccine for active immunization against varicella** in the pediatric population.

- **Benefit–Risk Assessment**

Benefits

- Demonstrated **robust immunogenicity** across all age groups.
- **100% seroconversion** in Phase II/III Stage 1.
- Shows **non-inferiority to a well-established comparator (VARIVAX)**.
- Suitable for children aged 12 months to 12 years, the primary population at risk for varicella.

Risks

- Adverse events were predominantly **mild or moderate**, and typical for live attenuated vaccines.
- No vaccine-related serious adverse events were observed.
- No new safety signals emerged during clinical development.

Overall Benefit–Risk Conclusion

The totality of evidence demonstrates that **MG1111 provides effective protection against varicella with an acceptable safety profile comparable to existing licensed vaccines**.
The benefit–risk balance is clearly **favorable** for the proposed indicated population.

4. **General Conclusion and Recommendations if any:**

Based on the review of CTD modules and other supplementary documents, the product is approved.