BLA Clinical Review Memorandum

Application Type	Biologics License Application Prior Approval Supplement
STN	BLA 103552/6277 VARIVAX - Varicella Virus Vaccine
CBER Received Date	April 29, 2022
PDUFA Goal Date	February 27, 2023
Division / Office	DVRPA/OVRR
Priority Review	No
Reviewer Name	Nadine Peart Akindele, MD Clinical Review Staff-Immediate Office of Director DVRPA, OVRR, CBER
Review Completion Date / Stamped Date	February 27, 2023
Supervisory Concurrence	Anuja Rastogi, MD, MHS, Branch Chief, Clinical Review Staff-IOD DVRPA, OVRR, CBER Douglas Pratt, MD, MP, Associate Director, Medical Affairs DVRPA, OVRR, CBER
Applicant	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Established Name	Varicella Virus Vaccine
Proprietary Name	VARIVAX
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc.	Each dose (approximately 0.5 mL) contains a minimum of 1,350 plaque-forming units (PFU) of Oka/Merck varicella virus. Each dose also contains approximately 18 mg of sucrose, 8.9 mg hydrolyzed gelatin, 3.6 mg of urea, 2.3 mg of sodium chloride, 0.36 mg of monosodium L-glutamate, 0.33 mg of sodium phosphate dibasic, 57 mcg of potassium phosphate monobasic, and 57 mcg of potassium chloride. The product also contains residual components of MRC-5 cells including DNA and protein and trace quantities of neomycin and bovine calf serum from MRC-5 culture media. The product contains no preservative.
Proposed Dosage Form(s) and Route(s) of Administration	Dosage form: Suspension Route of administration: Subcutaneous and Intramuscular
Dosing Regimen	Children (12 months to 12 years of age): The first dose is administered at 12 to 15 months of age but may be given anytime through 12 years of age. The second dose is administered at 4 to 6 years of age. At least 3 months should elapse between a dose of varicella containing vaccine and VARIVAX. Adolescents (≥13 years of age) and Adults: Two doses of VARIVAX are administered at a minimum interval of 4 weeks
Indication(s) and Intended Population(s)	Active immunization for the prevention of varicella in individuals 12 months of age and older.
Orphan Designated (Yes/No)	No

Table of Contents

Glossary

ACIP	Advisory Committee on Immunization Practices
AE	adverse event
Am	Amendment
BLA	Biologics Licensing Application
CBER	Center for Biologics Evaluation and Research
$CCID_{50}$	cell culture infectious dose 50%
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
ELISA	enzyme linked immunosorbent assay
EU	European Union
FAS	Full Analysis Set
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GMT	geometric mean titer
GMTR	geometric mean titer ratio
gpELISA	glycoprotein ELISA
IgG	immunoglobulin G
IM	intramuscular
IND	Investigational New Drug
IU	International unit
LL	lower limit
mIU	mili-International unit
mL	milliliter
MRL	Merck Research Laboratory
OBPV/DPV	Office of Biostatistics and Pharmacovigilance/Division of Pharmacovigilance
PFU	plaque forming units
PPS	Per Protocol Set
PPS1	Per Protocol Set Post-dose 1
PPS2	Per Protocol Set Post-dose 2
PREA	Pediatric Research Equity Act
rHA	recombinant human albumin
RoA	route of administration
SAE	serious adverse event
SC	subcutaneous
SmPC	Summary of Product Characteristics
SRR	seroresponse rate
$TCID_{50}$	tissue culture infectious dose 50%
USPI	US Prescribing Information
WFI	water for injection

1. Executive Summary

With the submission of this Biologics Licensing Application (BLA) Supplement, Merck & Co. Inc. (Merck, the Applicant), presents data from one clinical study to support the approval for the inclusion of the intramuscular (IM) route of administration (RoA) to the US Prescribing Information (USPI) for VARIVAX. In the submission, data from study, V205C-011 is summarized. This study compares the immunogenicity and safety of VARIVAX after IM administration to the immunogenicity and safety of the vaccine when administered by the subcutaneous (SC) route, which is the currently approved route of administration for VARIVAX.

Study V205C-011, conducted in France and Germany, evaluated the immunogenicity and safety of M-M-R II and VARIVAX when administered concomitantly by the IM route as compared to when administered concomitantly by the SC route. In this study, the primary immunogenicity objective of non-inferiority of the immune responses for the IM route as compared with the SC route was evaluated by measuring the vaccine antigen-specific antibody responses to measles, mumps, rubella, and varicella viruses measured by enzyme-linked immunosorbent assay (ELISA) at 6 weeks post-vaccination. The pre-specified non-inferiority criterion for success of a lower limit (LL) of the 2-sided 95% confidence interval (CI) for the difference (IM group – SC group) in seroresponse rate (SRR) of >-10%, was met, demonstrating non-inferiority of the IM route as compared to the SC route. To align with the currently accepted CBER criteria to assess a non-inferior immune response to measles, mumps, and rubella antigens, a post hoc analyses using the stricter success criterion that the LL of the 2-sided 95% CI for difference in SRR be ≥-5% were also performed. This criterion was met for all vaccine antigens, except measles virus which only narrowly missed meeting the criterion (-5.28%). The additional analysis of SRR demonstrated that the SRR 42 days post-vaccination was robust when administered by the IM route, with measles, mumps and rubella antigens achieving a LL of the 95% CI for SRR of >90%. Geometric mean titers (GMTs) measured by ELISA were also descriptively evaluated and were overall comparable for all vaccine antigens between the IM group and the SC group, which further supported the similarity in the immune responses between the two routes of administration.

Safety data were reviewed from 752 vaccine recipients enrolled in the clinical trial. Overall, the most frequently reported solicited local adverse reactions included injection site erythema and pain. Injection site adverse reactions followed from Day 0 to Day 42 post-vaccination were overall more common in the participants in the SC group as compared to the IM group. The most frequently reported solicited systemic adverse reaction was pyrexia. Rates and types of reported adverse events (AEs) across groups were similar and included common clinical events that are often reported in the evaluated age population. Only one of the 5 reported serious adverse events (SAEs) in study V205C-011 was considered related to the study vaccination. This was described as a case of otitis media of moderate intensity occurring in a child who had received the vaccines by the SC route. An underlying concomitant illness could have been an alternate explanation and otitis media is listed in the current USPI for M-M-R II. The clinical reviewer agreed with the assessment of the investigator that the SAE was possibly related to the study vaccine. No participants died during the study or discontinued from the study due to an AE.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

1.2 Patient Experience Data

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☐	Patient-reported outcome	

☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☒	If no patient experience data were submitted by Applicant, indicate here.	

Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Conditions Studied

In 1995, VARIVAX was approved, followed by the approval of the quadrivalent vaccine ProQuad in 2005.

The ACIP currently recommends 2 doses of varicella vaccine; preschool-aged children should receive the first dose at 12 through 15 months and school-aged children should receive the second dose at age 4 through 6 years, though the second dose may be administered earlier provided >3 months have elapsed after the first dose.

2.2 Currently Available, Pharmacologically Unrelated Treatments/Interventions for the Proposed Indication

VARIVAX [Varicella virus vaccine live (Oka/Merck)] is indicated for active immunization for the prevention of varicella in individuals 12 months of age and older. It is administered as a 0.5-mL dose. For children (12 months through 12 years of age), the first dose is administered at 12 to 15 months of age and the second dose is administered at 4 through 6 years of age with a minimum interval of 3 months between doses. For adolescents (≥13 years of age) and adults, two doses are administered at a minimum interval of 4 weeks.

2.3 Safety and Efficacy of Pharmacologically Related Products

2.4 Previous Human Experience with the Product

The IM RoA was added to VARIVAX's SmPC on April 2, 2008. Since then, over (b) (4) doses of VARIVAX have been distributed within European countries.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

July 26, 2021: WRO provided for the Type C Meeting request submitted by Merck on March 12, 2021 (CRMTS #13218, STN 101069/5766).

- CBER agrees that data generated in V205C-011 and V221-036 may support inclusion of intramuscular RoA in the USPI for M-M-R II, VARIVAX, and ProQuad pending complete review of the data.
    - CBER notes that the lower bound of the 95% CI of ≥-5% for differences in seroconversion rates to demonstrate non-inferiority are typically requested for demonstration of non-inferiority for measles, mumps and rubella antigens, and that the clinical significance of a narrow miss on this criterion will be considered in the context of the entirety of supporting data.
    - CBER requests that a post hoc non-inferiority comparison using the first dose of ProQuad is included in study V221-036 due the off-label use of the vaccine in this study, with an interval between dose 1 and 2 of 30 days.
- CBER requests a reactogenicity dataset generated from the participant diary be submitted along with raw datasets that are available due to the limited dataset submissions proposed by Merck related to the duration of time that has passed since the studies were completed.

February 14, 2022: CBER acknowledges the Agreed iPSP with the justification for a partial waiver with rationale revised as follows:

- 505.B. (a)(5)(B)(iii)(I): the drug or biological product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group; and
- 505.B. (a)(5)(B)(iii)(II): the drug or biological product is not likely to be used in a substantial number of pediatric patients in that age group

2.6 Other Relevant Background Information

In the US, M-M-R II, VARIVAX, ProQuad and Priorix (GSK, Measles, Mumps, and Rubella Vaccine, Live) are the only vaccines in the ACIP-recommended pediatric immunization schedule administered by the subcutaneous route of administration. Data obtained from the study of HIV vaccine in rhesus macaques (Ols et al. 2020) as well as clinical trial data from adults receiving hepatitis B vaccine (Wahl et al. 1987), hepatitis A vaccine (Fisch et al. 1996), herpes zoster vaccine (Diez-Domingo et al. 2014), influenza vaccine (Cook et al. 2005), and Tick-borne encephalitis virus (Hopf et al. 2016); and children receiving varicella vaccine (i.e., VARIVAX) (Dennehy et al. 1991) and diphtheria toxin vaccine (Mark et al. 1999), indicate that, in general, the intramuscular route of vaccine administration does not appear to adversely affect innate or adaptive immune responses when compared to the subcutaneous route. In addition, current clinical recommendations concerning immunization practice do not require re-immunization when a vaccine indicated for the SC route is erroneously given IM (ACIP) (Kroger et al. 2022).

Study V205C-011 was used to support the IM RoA in the EU SmPC for VARIVAX in 2008. The study was conducted in recognition of the importance of providing a choice to healthcare practitioners with

respect to RoA, and in an effort to align and harmonize the prescribing information with other products by including both IM and SC RoA. The Applicant is proposing that, similar to the EU, inclusion of both IM and SC routes of administration would support clinicians in allowing flexibility in their approach to vaccination, and inclusion of IM dosing would align the RoA for these measles, mumps, rubella and varicella vaccines with other pediatric vaccines. The Applicant proposed that conduct of the study satisfies the 21 CFR 312.120, Guidance for Industry and FDA Staff, *FDA Acceptance of Foreign Clinical Studies Not conducted Under an Investigational New Drug (IND) application*.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission of this BLA was adequately organized to accommodate the conduct of a complete review without unreasonable difficulty, however due to the submission of legacy datasets, multiple information requests were communicated to the Applicant to clarify and verify, the dataset used for study V205C-011 analyses to support the non-inferiority evaluation. See Sections 4.5 and 5.2 for additional details.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Safety and immunogenicity data from one study was provided in this application to support the change in the USPI to add the IM RoA. The clinical trial was approved by an Ethics Committee; followed the International Council on Harmonisation Good Clinical Practice (GCP) guidelines; conformed to the Declaration of Helsinki; and informed, written consent was obtained from all participants or legal guardians as per GCP requirements and contained all the essential elements as stated in 21 CFR 50.25. There were no potential or actual issues regarding the conduct of the study. Because the trial was conducted in 2005, conduct of bioresearch monitoring inspections were of limited utility and not considered for this application.

3.3 Financial Disclosures

Covered clinical study (name and/or number): V205C-011
Was a list of clinical investigators provided? ☒ Yes ☐ No (Request list from applicant)
Total number of investigators identified: _____
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 00
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0 Is an attachment provided with details of the disclosable financial interests/arrangements? ☐ Yes ☒ No (Request details from applicant) Is a description of the steps taken to minimize potential bias provided? ☒ Yes ☐ No (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 36 Is an attachment provided with the reason? ☒ Yes ☐ No (Request explanation from applicant)

Reviewer Comment
Form FDA 3454, Certification: Financial Interests and Arrangements of Clinical Investigators, includes a list of 36 of 94 clinical investigators for whom required financial information could not be obtained, due to not returning information after attempts were made to contact. The Applicant conducted a due diligence process by which efforts were made to contact investigators by at least two methods to have them submit a Financial Disclosure Form if one was not previously available. Additionally, an internal search by the Applicant was performed to determine whether an investigator had a proprietary or financial interest in Merck Sharp & Dohme Corp. Significant Payments of Other Sorts search was not able to be performed as records were not retroactively available from 2005. These clinical trials were conducted by these investigators over 15 years ago limiting the Applicant's ability to retrieve the remaining financial data, however it is not expected that financial bias impacted the studies performed to support the addition of IM RoA to the USPI.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

4.2 Assay Validation

The methods to measure antibody responses were validated under BLA 101069 (M-M-R II) and BLA 103552 (VARIVAX). No changes were made to the assays. In a response to an Information Request dated July 8, 2021, the Applicant confirmed that the same assays used to support prior approvals for the M-M-R II, VARIVAX, and ProQuad were used to support this current BLA supplement and were performed at Merck Research Laboratory (MRL). This is documented in the CBER CMC Type C meeting memorandum dated August 26, 2021. Review of each of the assays after submission of this Application revealed no new concerns with regards to the validation or the use of the serological assays used to measure the immune responses to measles, mumps, rubella or varicella in the submitted study.

4.4.1 Mechanism of Action

Immune responses against varicella viruses induced by VARIVAX were measured by enzyme-linked immunosorbent assays (ELISAs). Immunoglobulin G (IgG) antibodies measured by the ELISAs used in clinical studies described have been shown to correlate with the presence of neutralizing antibodies that have been associated with protection.

4.5 Statistical

The Applicant did not submit the datasets in the Clinical Data Interchange Standards Consortium (CDISC) format since the study started on January 20, 2005, before it was required to submit the datasets in CDISC format. The submitted datasets did not contain detailed data descriptions and variable definitions. Multiple information requests regarding the detailed data definitions were communicated with the Applicant for the statistical review to be performed which clarified and resolved the questions surrounding the datasets.

4.6 Pharmacovigilance

The Office of Biostatistics and Pharmacovigilance/Division of Pharmacovigilance (OBPV/DPV) review of the post-marketing safety data from the EU, where the IM route of administration is approved for use, did not reveal any new or unlabeled safety concerns. Given the number of syncope reports associated with administration of ProQuad reported to the Vaccine Adverse Event Reporting System, the temporal association of post-vaccination syncope, and prior documentation in the literature that syncope may be

triggered by vaccination, the OBPV reviewer recommended the addition of the term Syncope to the Warnings and Precautions and Post-Marketing Experience of the USPI Section 6.2.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

This BLA supplement included clinical data from 1 clinical trial to support the non-inferiority and safety of the IM RoA as compared to the SC RoA of VARIVAX as a first dose in children 12 through 18 months of age.

The clinical, labeling, and financial disclosure information sections of the application were reviewed with detailed analyses of the study reports and pertinent line listings, case report forms, and datasets. ACIP vaccine recommendations for the prevention of measles, mumps, rubella and varicella viruses and current US surveillance data were also reviewed.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The following STN#103552/6277 Amendments (Am) were reviewed (listed by modules):

- Am 0: section 1
- Am 1: sections 1 and 5
- Am 2: sections 1 and 5
- Am 3: sections 1 and 5
- Am 4: section 1
- Am 5: section 1
- Am 6: section 1 and 5
- Am 7: section 1
- Am 8: section 1 and 5
- Am 9: section 1
- Am 10: section 1
- Am 11: section 1
- Am 12: section 1
- Am 13: section 1
- Am 14: section 1
- Am 15: section 1
- Am 16: section 1
- Am 17: section 1
- Am 18: section 1
- Am 19: section 1
- Am 20: section 1

5.3 Table of Studies/Clinical Trials

Table 1. Clinical Trials Submitted in Support of Intramuscular Route of Administration

Study Number	Countries	Description	Population (Schedule)	Study Groups: #Vaccinated (Completed)
V205C-011 (NCT00432523)	France and Germany	Phase 3, randomized, open-label, multicenter, active comparative, parallel-group study to evaluate the immunogenicity and safety of M-M-R II and VARIVAX when administered concomitantly by IM route vs. SC route	Healthy children 12 through 18 months of age (1 dose at Day 0)	M-M-R II and VARIVAX by IM route: 374 (373) M-M-R II and VARIVAX by SC route: 378 (377)

Source: Adapted from STN 103552/6277, 101069/5846, Amendment 0, Module 5, Tabular Listings
Abbreviations: IM=intramuscular, SC=subcutaneous

5.5 Literature Reviewed (if applicable)

Centers for Disease Control and Prevention (CDC). (2013). Morbidity and Mortality Weekly Report: MMWR. U.S. Dept. of Health, Education, and Welfare, Public Health Service, CDC. https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6204a1.htm.

Cook, I. F., Barr, I., Hartel, G., Pond, D., & Hampson, A. W. (2006). Reactogenicity and immunogenicity of an inactivated influenza vaccine administered by intramuscular or subcutaneous injection in elderly adults. *Vaccine*, *24*(13), 2395–2402. https://doi.org/10.1016/j.vaccine.2005.11.057

Dennehy, P. H., Reisinger, K. S., Blatter, M. M., & Veloudis, B. A. (1991). Immunogenicity of subcutaneous versus intramuscular Oka/Merck varicella vaccination in healthy children. *Pediatrics*, *88*(3), 604–607.

Diez-Domingo, J., Weinke, T., Garcia de Lomas, J., Meyer, C. U., Bertrand, I., Eymin, C., Thomas, S., & Sadorge, C. (2015). Comparison of intramuscular and subcutaneous administration of a herpes zoster live-attenuated vaccine in adults aged ≥50 years: a randomised non-inferiority clinical trial. *Vaccine*, *33*(6), 789–795. https://doi.org/10.1016/j.vaccine.2014.12.024

Fisch, A., Cadilhac, P., Vidor, E., Prazuck, T., Dublanchet, A., & Lafaix, C. (1996). Immunogenicity and safety of a new inactivated hepatitis A vaccine: a clinical trial with comparison of administration route. *Vaccine*, *14*(12), 1132–1136. https://doi.org/10.1016/0264-410x(96)00044-8

Hochberg, Y. (1988). A sharper Bonferroni procedure for multiple tests of significance. *Biometrika*, *75*(4), 800-802. https://sci2s.ugr.es/keel/pdf/algorithm/articulo/1988-Hochberg-BIO.pdf

Hopf, S., Garner-Spitzer, E., Hofer, M., Kundi, M., & Wiedermann, U. (2016). Comparable immune responsiveness but increased reactogenicity after subcutaneous versus intramuscular administration of tick borne encephalitis (TBE) vaccine. *Vaccine*, *34*(17), 2027–2034. https://doi.org/10.1016/j.vaccine.2015.12.057

Kroger, A., Bahta, L., & Hunter, P. (2022). General Best Practice Guidelines for Immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP). Updated March 15, 2022. https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/administration.html

Mark, A., Carlsson, R. M., & Granström, M. (1999). Subcutaneous versus intramuscular injection for booster DT vaccination of adolescents. *Vaccine*, *17*(15-16), 2067–2072. https://doi.org/10.1016/s0264-410x(98)00410-1Ols, S., Yang, L., Thompson, E. A., Pushparaj, P., Tran, K., Liang, F., Lin, A., Eriksson, B., Karlsson Hedestam, G. B., Wyatt, R. T., & Loré, K. (2020). Route of Vaccine Administration Alters Antigen Trafficking but Not Innate or Adaptive Immunity. *Cell reports*, *30*(12), 3964–3971.e7. https://doi.org/10.1016/j.celrep.2020.02.111

Wahl, M., & Hermodsson, S. (1987). Intradermal, subcutaneous or intramuscular administration of hepatitis B vaccine: side effects and antibody response. *Scandinavian journal of infectious diseases*, *19*(6), 617–621. https://doi.org/10.3109/00365548709117195

6. Discussion of Individual Studies/Clinical Trials

6.1 Study V205C-011

NCT00432523
"An open, randomised, comparative, multicentre study of the immunogenicity and safety of M-M-R™II manufactured with recombinant human albumin (rHA) and VARIVAX® when administered concomitantly by intramuscular (IM) route or subcutaneous (SC) route at two separate injection sites in healthy subjects 12 to 18 months of age."

Study Overview: This Phase 3 study, conducted in France and Germany, was designed to evaluate the non-inferiority of M-M-R II and VARIVAX, in terms of safety and humoral immune responses 42 days following one dose of each vaccine, when administered concomitantly by the IM route as compared to SC route in children 12 through 18 months of age. The first participant was enrolled in the study on January 20, 2005, and the last study visit was on September 5, 2005.

6.1.1 Objectives

Primary Objectives

Success in this study could be declared if either one or both primary objectives were reached:

1. To demonstrate that, when given concomitantly with VARIVAX by the same route at 12 through 18 months of age at separate injection sites, a single dose of M-M-R II administered by IM route is as immunogenic as a single dose of M-M-R II administered by SC route in terms of response rates to measles, mumps and rubella as measured by enzyme linked immunosorbent assay (ELISA) at 42 days following vaccination.

   Endpoint: SRRs to measles, mumps, rubella and varicella measured 42 days following vaccination in both groups.

   Seroresponse Definitions:

   - For measles, a post-vaccination anti-measles antibody titer ≥255 mili-International Units (mIU)/mL (ELISA) in children whose baseline anti-measles antibody titer was <255 mIU/mL.
   - For mumps, a post-vaccination anti-mumps antibody titer ≥10 ELISA units/mL (ELISA) in children whose baseline anti-mumps antibody titer was <10 ELISA units/mL.
   - For rubella, a post-vaccination anti-rubella antibody titer ≥10 IU/mL (ELISA) in children whose baseline anti-rubella antibody titer was <10 IU/mL.
   - For varicella, a post-vaccination anti-varicella antibody titer ≥5 glycoprotein (gp) ELISA units/mL (gpELISA) in children whose baseline varicella antibody titer was <1.25 gpELISA units/mL.

Statistical Criterion for Success: The LL of the CI, adjusted for multiplicity, on the group difference in SRRs (IM – SC) for each vaccine antigen was >-10%.

2. To demonstrate that, when given concomitantly with M-M-R II by the same route at 12 through 18 months of age at separate injection sites, a single dose of VARIVAX administered by IM route is as immunogenic as a single dose of VARIVAX administered by SC route in terms of response rate to varicella as measured by glycoprotein ELISA (gpELISA) at 42 days following vaccination.

   Endpoint: SRRs to measles, mumps, rubella and varicella measured 42 days following vaccination in both groups.

   Statistical Criterion for Success: The LL of the CI, adjusted for multiplicity, on the group difference in SRRs (IM – SC)] for each vaccine antigen was >-10%.

   Reviewer Comment
   Based on the CBER CMC Type C meeting memorandum dated August 26, 2021, the assay methods to measure antibody response in study V205C-011 were previously validated under BLA 101069 (M-M-R II) and BLA 103552 (VARIVAX) and were performed at MRL. The study was conducted outside of the US and was not conducted under IND. The study was not designed to meet the stricter non-inferiority criterion for measles, mumps and rubella antigens which is ≥-5%.

Primary Hypotheses: The IM route would be non-inferior to the SC route for both vaccines (M-M-R-II and VARIVAX) for the four vaccine antigens tested.

Secondary Objectives (Descriptive)

1. To summarize the antibody titers to measles, mumps, rubella and varicella at 42 days following vaccination in children 12 to 18 months of age immunized with M-M-R II rHA and VARIVAX administered concomitantly at two separate injection sites by the same route IM or SC.

   Endpoint:
   - GMT of antibodies to measles, mumps, rubella and varicella measured 42 days following vaccination in both groups.
   - The percentage of participants with varicella antibody titers ≥1.25 gpELISA units/mL in children whose baseline varicella antibody titer was <1.25 gpELISA units/mL (Not discussed in this memorandum).

2. To evaluate the safety profiles of M-M-R II and VARIVAX administered concomitantly at two separate injection sites by the same route, IM or SC.

   Endpoint:
   - From Day 0 to Day 4 following each dose: Solicited Injection-site adverse reactions-
     - Injection-site erythema
     - Injection-site swelling
     - Injection-site pain
   - From Day 0 to Day 28 following each dose: injection-site adverse reactions and systemic AEs-
     - Injection-site adverse reactions, including injection-site erythema, injection-site swelling, injection-site pain and injection site rashes starting from Day 5 to Day 28
     - Rectal temperature ≥38.0°C (or, if missing, axillary temperature ≥37.1°C)
     - Rectal temperature ≥39.4°C (or, if missing, axillary temperature ≥38.5°C)
     - Measles-like rash
     - Mumps-like illness

  - Rubella-like rash
  - Varicella-like rash
  - Other systemic AEs

- From Day 0 to study end
  - SAEs

6.1.2 Design Overview

Study V205C-011 was a Phase 3, open-label, randomized, comparative, multicenter study with two parallel groups. Overall, participants were randomized 1:1 to receive concomitant administration of M-M-R II and VARIVAX at different body sites by either IM or SC RoA.

All study participants had two study visits that had the following major study activities:

- Visit 1 (Day 0, at 12 through 18 months of age): Blood sampling, vaccination with both vaccines by either IM or SC route, 15-to-20-minute post-vaccination safety monitoring.
- Visit 2 (Between Day 42 and 56, at 13 through 20 months of age): Blood sampling and diary card transcription.

6.1.3 Population

Eligibility Criteria

Individuals were eligible for inclusion if they met all of the following criteria: Healthy participants of either gender, 12 through 18 months of age (from 1st birthday to one day prior to 19th month of age), consent form signed by both parent(s)/ legal representative properly informed about the study, parent(s)/legal representative able to understand the protocol requirements and to fill in the diary card.

Individuals were not eligible for inclusion in the study if they met any of the following exclusion criteria:

- Prior receipt of measles, mumps, rubella or varicella vaccine either alone or in a combination vaccine.
- Known or suspected clinical history of infection with measles, mumps, rubella, varicella or zoster.
- Any recent (≤30 days) exposure to measles, mumps or rubella.
- Any recent (≤30 days) exposure to varicella or zoster involving:
  - continuous household contact, or
  - playmate contact (generally >1 hour of play indoors), or
  - hospital contact (in same two- to four-bed room or adjacent beds in a large ward or face-to-face contact with an infectious staff member or individual), or
  - contact with a newborn whose mother had onset of varicella five days or less before delivery or within 48 hours after delivery,
- Any recent (≤3 days) history of febrile illness (rectal temperature ≥38.0°C).
- Any severe chronic disease.
- Active untreated tuberculosis.
- Known personal history of seizures.
- Any known blood dyscrasia, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems.
- Any severe thrombocytopenia or any other coagulation disorder that would have contraindicated intramuscular injection.
- Any immune impairment or humoral/cellular deficiency, neoplastic disease or depressed immunity including those resulting from corticosteroid (any long-term [≥14 days] administration of systemic corticosteroid therapy given daily or on alternate days at high doses [≥2 mg/kg/day

prednisone equivalent or ≥20 mg/day if weight more than 10kg] within the previous 30 days) or other immunosuppressive therapy.
- Any recent tuberculin test (≤7 days) or scheduled tuberculin test through Visit 2.
- Any previous (≤150 days) receipt of immune serum globulin or any blood-derived products or scheduled to be administered through Visit 2.
- Any recent receipt of any inactivated vaccine in the past 14 days or any live vaccine in the past 30 days.
- Prior known sensitivity/allergy to any component of the vaccines including neomycin, sorbitol or gelatin.
- True allergy to egg proteins (anaphylactic or anaphylactoid reaction after ingesting eggs),
- Any medical condition which, in the opinion of the investigator, might interfere with the evaluation of the study objectives.
- Participant that, in the investigator's opinion, was likely to be lost to follow-up or to comply poorly with the study requirements.
- Any recent participation (≤30 days) or scheduled participation in any other clinical study through Visit 2.

Reasons for Study Withdrawal

Participants could discontinue the study for any of the following reasons:
- At the request of the parent(s)/ legal representative,
- If, in the investigator's opinion, further participation in the study would be detrimental to the participant's well-being,
- At the specific request of Sanofi Pasteur MSD.

In all cases, the reason for withdrawal was recorded in the CRF and in the participants' medical records. The participant was followed-up to establish whether the reason was an AE, and, if so, this was reported in accordance with the mandatory procedures.

As far as possible, examinations scheduled at Visit 2 were to be performed on all participants who had received the study vaccines including those who did not complete the study according to the protocol. The investigator had to make every effort to contact participants lost to follow-up.

6.1.4 Study Treatments or Agents Mandated by the Protocol

M-M-R II
- Dose and RoA: 0.5 mL, IM or SC
- Formulation:
  - Measles virus (Enders' Edmonston/Moraten strain) ≥1,000 tissue culture infectious dose 50% ($TCID_{50}$)
  - Mumps virus (Jeryl Lynn strain) ≥12,500 $TCID_{50}$
  - Rubella virus (Wistar RA 27/3 strain) ≥1,000 $TCID_{50}$
  - Excipients: Sorbitol, Sodium phosphate, (b) (4), Sucrose, Hydrolysed gelatine, Medium 199 with (b) (4) salts, Minimum Essential Medium, (b) (4) (b) (4) L-glutamate, Neomycin, (b) (4) (b) (4) rHA.
- Presentation: Lyophilized pellet in a vial for reconstitution with water for injection (WFI)
- Lot: 0644172

VARIVAX:
- Dose and RoA: 0.5 mL, IM or SC
- Formulation:
  - Varicella virus (Oka/Merck strain) ≥1,350 plaque forming units (PFU)

- Excipients: Sucrose, Hydrolysed gelatin, Urea, Sodium chloride, Monosodium L-glutamate, Anhydrous disodium phosphate, Potassium dihydrogen phosphate, Potassium chloride, neomycin.

- Presentation: Vial of lyophilized vaccine for reconstitution with WFI
- Lot: HV20550

Reviewer comment:
Both M-M-R II and VARIVAX had the same formulation and reconstitution methods for the IM and SC routes.

6.1.5 Directions for Use

M-M-R II: The lyophilized antigen was provided in a vial and was to be reconstituted using the entire volume of sterile water from the provided diluent vial using a needle and syringe (provided by Merck). The investigator was then to agitate the vial to mix thoroughly, and to withdraw the entire amount of the reconstituted vaccine into the syringe.

VARIVAX: The lyophilized antigen was provided in a vial and was to be reconstituted using the entire volume of sterile water from the provided pre-filled syringe. The investigator was then to agitate the vial to mix thoroughly, and to withdraw the entire amount of the reconstituted vaccine into the syringe.

6.1.6 Sites and Centers

There were 72 centers in France (39 sites, including four sites that did not enroll participants) and Germany (36 sites) with a total of 776 participants enrolled in the study.

6.1.7 Surveillance/Monitoring

Surveillance

An Ethics Committee approved the protocol and the study. The study was sponsored by Sanofi Pasteur MSD S.N.C. who ensured appropriate reporting of SAEs to the French or German Sanofi Pasteur MSD Pharmacovigilance Department. (b) (4) was the Contract Research Organization employed to oversee data monitoring.

Safety Monitoring

After vaccination, participants were monitored at the study site for 15 to 20 minutes to monitor for immediate injection-site adverse reactions/systemic adverse reactions. Solicited injection-site adverse reactions (injection site redness, swelling and/or pain) were recorded in a provided diary card from Day 0 to Day 4. Systemic adverse reactions, including rectal temperature ≥39.4ºC and ≥38.0ºC (or axillary temperature ≥38.5ºC and ≥37.1ºC, respectively, if rectal temperature was missing), rash (at either injection site or elsewhere, characterized as measles-like, rubella-like, or varicella-like), and mumps-like symptoms, were recorded from Day 0 to 42 in a diary card. Other systemic events were also recorded in the diary card. SAEs included hospitalizations or visits to physicians and were recorded from the time the consent for was signed until Visit 2. For AEs and SAEs, relationship to the vaccine were also recorded from Day 0 to the last study visit.

Immunogenicity Monitoring

In total, two blood samples were collected for analysis. MRL (Wayne, PA, United States) personnel performing the serology assays were blinded with respect to the vaccination group. If the volume of serum was insufficient, antibody titration was carried out in the following order of priority: varicella IgG antibody > mumps IgG antibody > measles IgG antibody > rubella IgG antibody.

Revaccination with the currently licensed vaccine was offered to participants who did not reach the protocol defined response levels of antibody titers to one or more of the viral components of the vaccines 42 days following the final study vaccination if parent(s)/legal representative agreed. The decision to offer revaccination was based solely on the results of the assays conducted by MRL and revaccination was performed outside of the study.

6.1.8 Endpoints and Criteria for Study Success

See Section 6.1.1.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample Size

The target enrollment was 350 participants in each group for a total sample size of 700 participants. This assumed 15% non-evaluable participants for the M-M-R II analyses (assuming 10% would be lost-to-follow up or have protocol deviations and 5% would have pre-vaccination titers above the predefined seroresponse thresholds in Section 6.1.1) and 20% non-evaluable participants for the VARIVAX analysis (assuming 10% would be lost-to-follow up or have protocol deviations and 10% would have pre-vaccination titers above the predefined seroresponse thresholds in Section 6.1.1). This would result in 297 evaluable participants per group for the M-M-M II analyses, and 280 evaluable participants per group for the VARIVAX analyses, providing a 99.9% and 90.4% power for each analysis and a 90.2% overall power of the study to meet the predefined criteria.

Methods

The immunogenicity analysis of the primary and secondary criteria was performed on the Per Protocol Set (PPS, main analysis) and on the Full Analysis Set (FAS, supportive analysis). Descriptive statistics were also provided for participants seropositive at inclusion in the PPS.

Since success in this study could be declared if either one or both primary objectives were reached, an adjustment of the type one error rate was necessary. For a two-hypothesis testing, the largest observed p-value was compared to the overall type one error rate (one-sided 0.025 for this study). If the largest p-value led to the rejection of the null hypothesis (largest p-value <0.025) then the two null hypotheses were rejected, and success was declared for the two primary objectives. If the largest p-value did not allow rejection of the null hypothesis (largest p-value ≥0.025) then the associated primary objective was not met, and the smaller p-value was compared to half of the overall type one error rate (one-sided 0.025/2 in this study) in a second step. Success of the remaining objective was declared according to the results of this comparison. Due to the use of CI instead of p-values and the presence of three hypotheses in the M-M-R II primary objective (one hypothesis per valence):

- All two-sided 95% CIs for the 4 valences (IM – SC) were calculated. If the smallest lower bound was >-0.10 (-10%) then the two objectives were reached,
- If the smallest lower bound was ≤-0.10 (-10%) then the corresponding objective was not met, and the two-sided 97.5% CIs associated with the other primary objective was calculated. The lower bound(s) was compared to -0.10 (-10%) and the conclusion was drawn on this base.

  Reviewer Comment

  Although two hypothesis testing was performed, the FDA statistical reviewer determined that the Hochberg method (Hochberg 1988) used in this study to adjust for multiplicity is more powerful compared to the Bonferroni correction and was an appropriate step to take to account for the two hypotheses evaluated.

Descriptive statistics were provided by group for pre- and post-vaccination results. The GMT were calculated with their two-sided 95% CI by group on the antibody titers of measles, mumps, rubella and varicella measured at baseline and 42 days following vaccination. Descriptive analyses were performed for AEs with separate summaries of injection-site adverse reactions and systemic AEs.

Missing Data

Missing data was not imputed for continuous variables (i.e., immunogenicity).

Protocol Amendments

No substantial protocol amendments were made to the study protocol.

Changes in the Conduct of the Study and Planned Analyses

1. Ten post-vaccination (Day 42) samples initially tested negative for anti-measles and anti-rubella IgG when measured by ELISA because these samples were not placed into the test wells. Following sample retesting, the original results were considered invalid and replaced by the retest results.
2. Prior to performing the analysis:
    a. To clarify the Per Protocol analysis, 4 subsets of the PPSs were defined to include participants with baseline seropositive status to each vaccine antigen
    b. Six other subsets of the PPS were added for completeness
        i. PPS with those initially seronegative to measles, mumps, rubella and varicella
        ii. PPS with those initially seropositive to measles
        iii. PPS with those initially seropositive to mumps
        iv. PPS with those initially seropositive to rubella
        v. PPS with those initially seropositive to varicella
3. Four-fold increase of individual titers between pre- and post-vaccination ratios of GMT (GMTR) were to be calculated in participants initially seropositive from the PPS.
4. A stratified analysis by country of the primary criteria was to be performed, additionally to the within country estimates already planned in the protocol. The statistical methodology was the same as defined for the primary analysis.

Reviewer Comment

The reviewer agrees that ten post-vaccination sample re-testing (Change #1 above) was appropriate.

Please see the statistical review memo for further discussion.

6.1.10 Study Population and Disposition

A total of 776 participants were enrolled in the study. The first participant was enrolled in the study on January 20, 2005, and the last study visit was on September 5, 2005.

6.1.10.1 Populations Enrolled/Analyzed

The *Randomized Set* was defined as all randomized participants. A participant was considered as randomized if a randomization number was assigned.

The *Safety Set* was defined as all participants who received at least one of the study vaccines and for whom safety follow-up data were available. Participants were analyzed according to the route actually used for vaccination.

The *FAS* consisted of all randomized participants who received at least one study vaccine and for whom a post-vaccination immunogenicity evaluation was available. Participants were analyzed according to the theoretical RoA allocated by the randomization procedure.

The *PPS* was defined as all randomized participants excluding participants with protocol violation which might have interfered with the immunogenicity evaluation.

Protocol violations which led to exclusion from the PPS were as follows:

- non-adherence to the inclusion criteria or violation of exclusion criteria which may interfere with the immunogenicity evaluation.
- non-adherence to the randomization scheme.
- absence of pre-vaccination immunogenicity evaluation.
- absence of post-vaccination immunogenicity evaluation.
- non-adherence to the post-vaccination blood sampling schedule (i.e., 42 to 56 days after Visit 1).
- intake of excluded medication which may interfere with the immunogenicity evaluation, between inclusion visit and post-vaccination blood sample.
- injection of non-study vaccine between inclusion visit and post-vaccination blood sample.

6.1.10.1.1 Demographics

The demographics of study V205C-011 are demonstrated in the table below.

Table 2. Demographic and Baseline Characteristics, Randomized Set, Study V205C-011

Characteristic	Intramuscular N=374	Subcutaneous N=378
Sex	--	--
Male:Female Ratio	206:168	210:168
% male:% female	55.1%:44.9%	55.6%:44.4%
Age, months	--	--
Mean age (SD)	13.8 (1.7)	13.7 (1.6)
Median age	13.2	13.1
Age range	12.0-19.0	12.0-18.9
Country, n (%)	--	--
France	178 (47.6%)	189 (50.0%)
Germany	196 (52.4%)	189 (50.0%)
Region	--	--
Region 1[a]	47 (12.6%)	51 (13.5%)
Region 2[a]	39 (10.4%)	39 (10.3%)
Region 3[a]	35 (9.4%)	40 (10.6%)
Region 4[a]	57 (15.2%)	59 (15.6%)
Region 5[b]	37 (9.9%)	33 (8.7%)
Region 6[b]	44 (11.8%)	42 (11.1%)
Region 7[b]	27 (7.2%)	27 (7.1%)
Region 8[b]	66 (17.6%)	63 (16.7%)
Region 9[b]	22 (5.9%)	24 (6.3%)

Source: Adapted from STN 101069/5846 and STN 103552/6277, Study V205C-011, Clinical Study Report, Text Table 3, Text Table 7
N: total number of participants in the group. n indicates number of participants fulfilling the item followed by the calculated percentage in parentheses (%);
a. Region indicates France
b. Region indicates Germany

The median age at vaccination in the Randomized Set was 13.2 months, with a range of 12 to 19 months. Overall, the majority of participants were male (55.3%). Demographic and baseline characteristics were

overall similar between groups. Among the 752 randomized participants, 367 (48.8%) participants were recruited in France, with 178 French participants (47.6%) in the IM group and 189 (50.0%) in the SC group. There were 385 (51.2%) participants recruited in Germany, with 196 (52.4%) German participants in the IM group and 189 (50.0%) in the SC group. French centers were classified for statistical analyses in four regions (Region 1 to Region 4) and German centers in five regions (Region 5 to Region 9). In France, a majority of the French participants were enrolled in Region 4 (15.4%) and in Germany, a majority of the German participants were enrolled in Region 8 (17.2%).

> Reviewer Comment
> The range of ages presented are rounded to the nearest whole number and included age range between 11.96 to 18.96 months. One participant was 11 months and 362 days old and was not excluded from the PPS which was used for the primary analysis, though the eligibility criteria required that participants be at least 12 months (from 1st birthday). The clinical reviewer does not consider that exclusion of this participant would change the conclusions of the study.

There were 374 participants that received vaccination via the IM route and 378 participants that received vaccination via the SC route. In the Randomized Set, participants were seronegative at baseline at similar rates between IM and SC groups for measles (97.3% vs. 98.1%), mumps (97.3% vs. 97.9%) and varicella (94.1% vs. 93.4%), while there were slightly more participants in the IM group as compared to the SC group who were seronegative for rubella (89.6% vs. 85.7%).

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

A total of 289 (38.4%) participants had at least one personal medical antecedent/intercurrent disease. The majority participants reported a history with a System Organ Class (SOC) of *Infections and Infestations* (21.9%, IM group vs. 19.8%, SC group), followed by *Skin and subcutaneous tissue disorders* (8.8%, IM group vs. 9.8%, SC group).

6.1.10.1.3 Participant Disposition

A total of 776 participants were enrolled in the study. Twenty-four were screened and not randomized and 752 were randomized and vaccinated (Randomized Set), all of which were included in the Safety Set. One participant that was randomized into the SC group, received both vaccines by the IM route and so was analyzed for safety in the IM group and excluded from the PPS.

Of the 752 vaccinated participants, two (0.3%) withdrew from the study: one participant in the IM group ("personal reason") and one in the SC group (lost to follow-up). For both of these withdrawn participants, safety data was collected by phone at the time of Visit 2 (Day 42 post-vaccination). There were no participants who withdrew due to an AE. Of those vaccinated 750 (99.7%) completed the study.

> Reviewer Comment
> In the original protocol, the Applicant stated in pre-specified plans in the case of participant withdrawal, that: "As far as possible, all examinations scheduled at the second visit (V2) must be performed on all participants who received the study vaccine but do not complete the study according to protocol. The investigator must make every effort to contact participants lost to follow-up." Due to the pre-specified plan for this scenario and the small number of participants that withdrew from the study, the clinical reviewer does not believe that inclusion of these participants in the safety analysis should affect the overall conclusion of the study.

Of the 752 participants in the Randomized Set, 144 (19.1%) had at least one protocol deviation and 121 had at least one other condition leading to exclusion from at least one PPS. Common protocol deviations are included in Table 3.

Table 3. Participant Disposition and Data Analyses, Randomized Set, Study V205C-011

Population, n (%)	Intramuscular N=374	Subcutaneous N=378
Enrolled	--	--
Randomized Set	374	378
Safety Set[a]	374	376
Full Analysis Set (FAS)	370 (98.9%)	375 (99.2%)
Per Protocol Set (PPS) [b]	--	--
Measles	351 (93.8%)	365 (96.6%)
Mumps	355 (94.9%)	367 (97.1%)
Rubella	351 (93.8%)	365 (96.6%)
Varicella	354 (94.6%)	364 (96.3%)
Participants excluded from the PPS (n, %)	--	--
Measles	23 (6.1%)	13 (3.4%)
Mumps	19 (5.1%)	11 (2.9%)
Rubella	23 (6.1%)	13 (3.4%)
Varicella	20 (5.3%)	14 (3.7%)
≥1 important protocol deviation[c]	--	--
Measles	23 (6.1%)	13 (3.4%)
Mumps	19 (5.1%)	11 (2.9%)
Rubella	23 (6.1%)	13 (3.4%)
Varicella	20 (5.3%)	14 (3.7%)

Population, n (%)	Intramuscular N=374	Subcutaneous N=378
Reason for exclusion from PPS	--	--
Received measles, mumps, rubella, and/or varicella vaccine prior to study vaccination	1 (0.3%)	0
Received a non-study live vaccine within 30 days or a non-study inactivated vaccine within 14 days prior to vaccination	1 (0.3%)	1 (0.3%)
Route of vaccination different from randomization	0	2 (0.5%)
Initial serostatus missing for all antigens (blood sample 1 (BS1) not done or no serology value at BS1)	3 (0.8%)	4 (1.1%)
Initial serostatus missing for measles	4 (1.1%)	1 (0.3%)
Initial serostatus missing for rubella	4 (1.1%)	1 (0.3%)
Initial serostatus missing for varicella	1 (0.3%)	2 (0.5%)
Six-week serology result missing for all antigens (blood sample 2 (BS2) not done or no serology value at BS2)	4 (1.1%)	3 (0.8%)
Six-week serology result missing or not evaluable for measles	1 (0.3%)	1 (0.3%)
Six-week serology result missing or not evaluable for rubella	1 (0.3%)	1 (0.3%)
Six-week serology result missing or not evaluable for varicella	1 (0.3%)	0
Pre-vaccination blood sample taken more than 14 days prior to vaccination	3 (0.8%)	1 (0.3%)
Post-vaccination blood sample outside of day range (>63 days)	5 (1.3%)	2 (0.5%)
Received a non-study vaccine between Day 0 and Day 42	1 (0.3%)	0
Subject having received diluent of MMR™II rHA vaccine only	1 (0.3%)	0
Measles seropositive at baseline	3 (0.8%)	2 (0.5%)
Mumps seropositive at baseline	7 (1.9%)	4 (1.1%)
Rubella seropositive at baseline	32 (8.6%)	49 (13.0%)
Varicella seropositive at baseline	18 (4.8%)	19 (5.0%)

Source: Adapted from STN 101069/5846 and STN 103552/6277Study V205C-011, Clinical Study Report, Text Table 2, Text Table 5, Text Table 6
N: total number of participants in the group. n indicates number of participants fulfilling the item followed by the calculated percentage in parentheses (%).
a. Subject (b) (6) randomized to SC route was vaccinated by IM route; this subject was included in IM route for the Safety Set. Two participants (subject (b) (6) in the IM group and subject (b) (6) in the SC group) were excluded from the safety analyses because of an error of vaccination. Both subjects reported a systemic adverse event of fever of moderate intensity (38.7°C and 38.9°C rectal respectively) that started at Day 21 and Day 29 post-vaccination and lasted for 1 and 2 days respectively.
b.PPS includes participants both seronegative and seropositive at baseline
c. Includes participants with important protocol violations that resulted in exclusion from the Per Protocol Set (PPS) analysis population.

Reviewer Comment

The overall number of protocol deviations experienced between each group was balanced. The Applicant did not include non-deltoid vaccine administration as a pre-defined protocol deviation. There were 2 participants (1 in each group) who received vaccination at a non-deltoid site (anterolateral thigh) and were included in study analyses. The current ACIP Best Practice Guidelines for Vaccine Administration includes both deltoid and the anterolateral site of IM and SC vaccine administration as recommended sites for vaccination of children 1 to 2 years of age. An additional participant who received SC injection by "deep SC injection" was also not considered a protocol deviation. The inclusion of these participants in study analyses is acceptable.

There were 745 (99.1%) participants included in the FAS.

The PPS subsets based on baseline serostatus included participants as follows:

- PPS of initially seronegative participants to Measles consisted of 712 (94.7%) participants
  - 349 (93.3%) participants in the IM group and 363 (96.0%) in the SC group.
- PPS of initially seronegative participants to Mumps consisted of 712 (94.7%) participants
  - 349 (93.3%) participants in the IM group and 363 (96.0%) in the SC group.
- PPS of initially seronegative participants to Rubella consisted of 639 (85.0%) participants
  - 321 (85.8%) participants in the IM group and 318 (84.1%) in the SC group.
- PPS of initially seronegative participants to Varicella consisted of 681 (90.6%) participants
  - 336 (89.8%) participants in the IM group and 345 (91.3%) in the SC group.
- PPS of initially seronegative participants to Measles + Mumps + Rubella consisted of 632 (84.0%) participants
  - 316 (84.5%) participants in the IM group and 316 (83.6%) in the SC group
- PPS of initially seronegative participants to Measles + Mumps + Rubella + Varicella consisted of 598 (79.5%) participants
  - 298 (79.7%) participants in the IM group and 300 (79.4%) in the SC group.

Reviewer comment

The baseline serostatus for each vaccine antigen was balanced between groups.

6.1.11 Immunogenicity Analyses

6.1.11.1 Analyses of Primary Endpoints

The first and second primary immunogenicity objectives were to demonstrate non-inferiority of IM RoA as compared to the SC RoA for M-M-R II and VARIVAX respectively. The two hypotheses testing strategy allowed for meeting just one of the objectives to achieve meeting the primary objective.

Non-Inferiority of SRRs 6 Weeks Post-Vaccination

The Visit 2 antibody response rates for participants initially seronegative (PPS) to each vaccine antigen are demonstrated in Table 4.

Table 4. Seroresponse Rates and Group Differences, Per Protocol Set, Study V205C-011

Antibody, n^1/n^2 (%)	Intramuscular N=374	Subcutaneous N=378	SRR Difference[a] (95% CI)
Anti-measles (mIU/mL)	329/349 (94.3%)	349/363 (96.1%)	-1.89% (-5.28, 1.29)
Anti-mumps (EU/mL)	341/349 (97.7%)	356/363 (98.1%)	-0.33% (-2.67, 2.00)
Anti-rubella (IU/mL)	315/321 (98.1%)	312/318 (98.1%)	-0.02% (-2.42, 2.43)
Anti-varicella (gpELISA unit/mL)	297/336 (88.4%)	295/345 (85.5%)	2.93% (-2.18, 8.06)

Source: Adapted from STN 101069/5846 and STN 103552/6277Study V205C-011, Clinical Study Report, Text Table 12
N: total number of participants in the group. n^1 indicates number of participants fulfilling the item and n^2 indicates number of participants in PPS seronegative at baseline for the seroresponse, followed by the calculated percentage in parentheses (%).
Abbreviations: ELISA=enzyme linked immunosorbent assay; EU=ELISA antibody Unit; gpELISA=glycoprotein ELISA; IU=International Unit; mIU=milli-International Unit; SRR=Seroresponse Rate: percentage of initially seronegative participants with concentration above seroresponse threshold for each assay
Assays: anti-measles IgG ELISA, anti-mumps IgG ELISA, anti-rubella IgG ELISA, anti-varicella IgG ELISA (For each assay - seroresponse thresholds are 255 mIU/mL, 10 EU/mL, 10 IU/mL and 5 gpELISA/mL for anti-measles, anti-mumps, anti-rubella and anti-varicella antibodies, respectively).
a. Defined as IM group SRR minus SC group SRR
Success criteria: the lower limit of the 2-sided 95% CI for the group difference in SRR (IM minus SC) must be >-10% for the respective vaccine antigen.

In the IM group, rates were 94.3%, 97.7%, 98.1%, and 88.4% as compared to those in the SC group, where rates were 96.1%, 98.1%, 98.1%, and 85.5% for SRRs against the measles, mumps, rubella, and varicella vaccine antigens, respectively.

For measles, mumps and rubella antigens, the lower bound of the 95% CI of the point estimates in SRR was >90% in both the intramuscular (91.3%, 95.5%, and 96.0%, respectively), and subcutaneous groups (93.6%, 96.1%, and 95.9%, respectively). For varicella the lower bound in the 95% CI of the point estimates in SRR was 84.5% in the IM group and 81.3% in the SC group.

When supplementary non-inferiority analyses were performed on the FAS either: 1) using a stratification by region, 2) without stratification, and 3) with stratification by country, the LL of the 95% CI remained >-10% for all vaccine antigens for all FAS analyses, indicating that the PPS results reflected the immunogenicity of the entire group.

> Reviewer Comment
> When evaluating the FAS descriptively by region, despite small percentage differences between the IM and SC groups in certain regions for measles and varicella antigens, the overall regional data remains comparable to the main PP analyses.

6.1.11.2 Analyses of Secondary Endpoints

The secondary immunogenicity objectives descriptively characterized the antibody responses to the measles, mumps, rubella and varicella, vaccine antigens in terms of GMTs and GMTRs.

Summary of Antibody Response in Terms of GMTs Post-Vaccination

The GMTs at baseline and Day 42 post-vaccination are descriptively provided in Table 5. The GMTs for each vaccine antigen were overall similar between groups.

Table 5. Geometric Mean Titers at Baseline and 6 Weeks After First Dose, Per Protocol Set, Study V205C-011

Antibody	Intramuscular N=374	Subcutaneous N=378
Anti-measles (mIU/mL)	n=349 (93.3%)	n=363 (96.0%)
Baseline[a]	62.9 (61.5, 64.3)	62.3 (61.1, 63.5)
Visit 2[b]	2396.4 (2117.7, 2711.8)	2560.6 (2278.5, 2877.7)
Anti-mumps (EU/mL)	n=349 (93.3%)	n=363 (96.0%)
Baseline	5.0	5.0
Visit 2	86.4 (78.7, 95.0)	89.8 (82.6, 97.6)
Anti-rubella (IU/mL)	n=321 (85.8%)	n=318 (84.1%)
Baseline	5.0	5.0
Visit 2	97.2 (88.6, 106.7)	94.4 (85.7, 104.0)
Anti-varicella (gpELISA unit/mL)	n=336 (89.8%)	n=345 (91.3%)
Baseline	0.6	0.6
Visit 2	9.8 (9.2, 10.5)	9.2 (8.6, 9.8)

Source: Adapted from STN 101069/5846 and STN 103552/6277 Study V205C-011, Clinical Study Report, After Text Table 108, After Text Table 111, After Text Table 114, After Text Table 117, Text Table 11
N: total number of participants in the group. n indicates number of participants fulfilling the item followed by the calculated percentage in parentheses (%).
Abbreviations: ELISA=enzyme linked immunosorbent assay; EU=ELISA antibody Unit; GMT=Geometric Mean Titer; GMTR=Geometric Mean of individual Titers Ratios; gpELISA=glycoprotein ELISA; IU=International Unit; mIU=milli-

International Unit; SRR=Seroresponse Rate: percentage of initially seronegative participants with concentration above seroresponse threshold for each assay
Assays: anti-measles IgG ELISA, anti-mumps IgG ELISA, anti-rubella IgG ELISA, anti-varicella IgG ELISA
a. Baseline blood sampling was defined as blood sample collected prior to Visit 1 vaccination
b. Visit 2 blood sampling was planned for 42 days post-vaccination. Fourty-two to 56 days was the accepted range of days that this blood sampling could be completed.

6.1.11.3 Subpopulation Analyses

Antibody responses were descriptively evaluated by country and were overall similar. An exploratory analysis was also performed demonstrating that the LL of the 95% CI was >-10% for all vaccine antigens for participants enrolled in France and Germany.

For each vaccine antigen, when stratified by region, the LL of the 95% CI for the group difference (IM minus SC) was >-10%, and so the criteria for both primary objectives were met. When the data was analyzed without stratification by region or with stratification by country, the LL of the 95% CI remained >-10% for all vaccine antigens.

6.1.11.4 Dropouts and/or Discontinuations

Approximately 96.6% of enrolled participants completed the study. Immunogenicity analyses excluded participants with missing or non-evaluable measurements. A summary of the dropouts and discontinuations from the study are provided in Section 6.1.10.1.3.

6.1.11.5 Post Hoc Analyses

CBER Non-inferiority Criteria

The Applicant also interpreted the primary objective of non-inferiority of SRRs 6 weeks post-vaccination using the stricter criterion of a LL of the 95% CI for the group difference in SRR (IM minus SC) ≥-5%. Review of the data using this interpretation demonstrated that this criterion was met for mumps, rubella, and varicella and marginally missed the criterion for measles (LL 95% CI of -5.28, see Table 4).

> Reviewer Comment
> CBER requested the analysis using a stricter success criterion to align with CBER's current approach for assessment of non-inferior immune responses to measles, mumps, and rubella antigens. Based on the totality of immunogenicity data submitted as part of this BLA supplement, including measles GMT responses and SRRs (LL of the 95% CI for SRR >90% in both the IM and SC groups), the post hoc analyses with stricter success criteria supports the acceptability of the use of the IM route of administration.

Subgroup analyses – Sex

The applicant also conducted a subgroup analysis of immunogenicity based on sex. This did not reveal any major differences in the immune response after intramuscular administration of M-M-R II or VARIVAX as compared to subcutaneous administration.

Immunogenicity by Baseline Serostatus

The Applicant additionally explored the SRRs and GMTs in participants that were seronegative to either three (measles, mumps, and rubella) or four (measles, mumps, rubella and varicella) antigens. The SRRs and GMTs were similar to the primary and secondary analysis and comparable between groups. Additional descriptive analyses were performed for participants who were seropositive for each vaccine antigen at baseline. Due to the small number of participants in this analysis set (between 2 to 20 participants per vaccine antigen), the analysis resulted in wide confidence intervals, limiting interpretation.

6.1.12 Safety Analyses

6.1.12.1 Methods

Safety data surveillance is described in Section 6.1.7. Ninety-nine percent of participants completed the study and the safety follow up.

For the entire Safety Set, safety follow up through at least 42 days for 681 (90.6%) participants (IM group, 342 and SC group, 338); 28 through 42 days for 47 (6.3%) participants (IM group, 20 and SC group, 27), and less than 28 days for 22 (2.9%) participants (11 participants in each group). Two (0.3%) participants (participant (b) (6) in the IM group, and participant (b) (6) in the SC group) had a safety follow-up with an unknown duration.

6.1.12.2 Overview of Adverse Events

Safety Overview

Safety data were overall comparable between the two groups (Table 6). At least one AE was reported in 83.7% of those in the IM group and 86.4% of those in the SC group within 42 days post-vaccination; There were 190 (50.8%) participants in the IM group and 202 (53.7%) participants in the SC group that developed a vaccine-related reaction to M-M-R II and 173 (46.3%) participants in the IM group and 210 (55.9%) in the SC group that developed a vaccine related reaction to VARIVAX.

Table 6. Proportion of Participants Reporting at Least One Adverse Event Following Vaccination, Safety Set, Study V205C-011

AE Type: Monitoring Period[a]	Intramuscular N=374 % (n/N)	Subcutaneous N=376 % (n/N)
Solicited Injections-site reactions[b]: 0-4 days	--	--
At MMR injection-site	15.5% (58/374)	21.5% (81/376)
At VARIVAX injection-site	15.2% (57/374)	22.6% (85/376)
Solicited Systemic reaction from Day 0 to Day 42	--	--
Measles-like rash[c]	2.9% (11/374)	2.7% (10/376)
Rubella-like rash[c]	2.7% (10/374)	2.7% (10/376)
Varicella-like rash[c]	0.5% (2/374)	3.2% (12/376)
Mumps-like illness: 0-42 days	0	0.3% (1/376)
Fever (temperature ≥38.0°C): 0-42 days	66.5 (248/373)	66.8 (250/374)
Other systemic adverse event from Day 0 to Day 42[d]	62.8% (235/374)	59.8% (225/376)
AEs leading to study w/d: Entire study period	0	0
SAEs: Entire study period	0.3% (1/374)	1.1% (4/376)
Deaths: Entire study period	0	0

Source: Adapted from STN 101069/5846 and STN 103552/6277 Study V205C-011, Clinical Study Report, Text Table 18, Text Table 19, Text Table 21, Text Table 23, Text Table 26, Text Table 27, After Text Table 203, After Text Table 206
Participants were analyzed according to the route actually used for vaccination.
Abbreviations: AE=Adverse Event; N=total number of participants in the group; n= number of participants who experienced the event; SAE=serious adverse event; w/d=withdrawal
Temperature 38.0 ºC=100.4 ºF
a. Monitoring Period: time interval that the relevant type of AE was monitored for post-vaccination
b. Solicited local included pain, redness, and swelling at injection site
c. Testing to distinguish between rash caused by wild-type or vaccine virus was not performed. Reports of measles-, rubella- and varicella-like rash included 3 reports of measles, 1 report of rubella, and 1 report of varicella, all with onset within 15 days post-vaccination.
d. The rates of "other systemic adverse events" reported in these tables include the rates of participants who experienced solicited systemic rashes. See the subsection titled "Unsolicited AEs" below for a report of the systemic events excluding the rates of solicited systemic rashes (unsolicited adverse events).

Solicited Adverse Reactions

Solicited reactions are described in Table 7 below.

Local Reactions

Between Day 0 to Day 4 post-vaccination, participants in the IM group experienced less frequent injection-site reactions with at least one injection-site adverse reaction reported in 15.5% and 21.5% of participants in the IM and SC groups, respectively. The most frequently reported M-M-R II injection site reaction was injection-site erythema (10.4% and 16.2% of participants in the IM and SC groups, respectively). This was followed by injection-site pain (IM, 7.0%; SC, 7.2%) and injection-site swelling (IM, 1.9%; SC, 5.3%). Similarly, for VARIVAX, the order of most frequent injection-site reactions was erythema (IM, 8.8%; SC 16.8%), pain (IM, 7.0%; SC, 8.5%), and swelling (IM, 3.2%; SC, 4.8%). Reactions to either vaccine persisted for no more than 2.5 days.

> Reviewer Comment
> Although local injection site reactions to vaccination occurred at lower rates in the IM group as compared to the SC group between Day 0 and Day 4, the open label design and small study size make it difficult to interpret the significance of these findings. The higher rates of local reactions at the injection site in SC group participants may be expected given the superficial RoA compared to the IM RoA.

Between Day 0 to Day 42, injection-site reactions reported following M-M-R II and VARIVAX occurred less frequently in the IM group (15.8% and 20.9%, respectively) as compared to the SC group (25.8% and 34.3%, respectively). Injection-site rash occurred only in participants in the SC group (2.7%) and included varicella-like injection-site rashes (2 at M-M-R II injection-site, 7 at VARIVAX injection- site and 1 at both injection-sites). Across groups, injection-site adverse reactions were mostly graded as mild (non-severe) and had a diameter of ≤2.5 cm.

Systemic Reactions

Non-injection site rashes occurred at similar rates in both groups for measles- and rubella-like rashes (2.9% and 2.7% in the IM group and 2.7% and 2.7% in the SC group, respectively), however, varicella-like rash occurred less frequently in the IM group (0.5%) as compared to the SC group (3.2%). All rashes were graded as mild to moderate in severity in both groups, and none were reported as severe. The median onset of all rashes was between 5 and 11 days with a median duration of 3 to 6 days in both groups. There was one case of a mumps-like illness (moderate unilateral parotitis) that occurred in the SC group on Day 16 post-vaccination and lasted for 10 days.

Fever occurred at similar rates between groups (IM, 66.5%; SC, 66.8%) and was considered related to M-M-R II (IM, 40.9%; SC, 39.6%) and/or VARIVAX (IM, 32.4%; SC, 33.2%) at similar rates as well. The mean maximal temperature in both groups was 38.6°C (±0.8). Temperature 39.5-40.0°C occurred in 11.8% of participants in the IM group and 11% of participants in the SC group. Median vaccine-related fever onset was 8.0 days in both the IM and SC groups with a range 0 to 42 days in the IM group and 0 to 39 days in the SC group, and fever occurring between Day 5 and Day 12 post-vaccination occurred in 8.4% and 11.7% of participants in the IM and SC groups, respectively with a mean temperature of 38.2°C (±0.8) in both groups. Fever generally resolved in 2 days in both groups.

Reports of measles, rubella and varicella

Testing to distinguish between rash caused by wild-type or vaccine virus was not performed. Reports of measles-, rubella- and varicella-like rash included 3 reports of measles, 1 report of rubella, and 1 report of varicella, all with onset within 15 days post-vaccination.

- Measles:

- A 13-month-old female participant (SC group), with no known exposure to a case of Measles experienced a measles-like rash with macules too numerous to count (>300) beginning on 10 days post-vaccination, reportedly lasting 3 days. The participant had a fever (maximum rectal temperature of 38.2°C) that developed 9 days post-vaccination. The investigator concluded that this event was possibly related to M-M-R II.
- A 12-month-old female participant (SC group), with no known exposure to a case of Measles experienced a measles-like rash with macules too numerous to count (>300) beginning the day of vaccination, reportedly lasting 2 days. The participant reported intermittent rhinitis 1 day post-vaccination and fever beginning 4 days post-vaccination (maximum rectal temperature of 39.2°C) and lasting 2 days. The investigator concluded that this event was possibly related to M-M-R II.
- A 12-month-old female participant (IM group), with no known exposure to a case of Measles experienced a measles-like rash with macules too numerous to count (>300) beginning 15 days post-vaccination, reportedly lasting 1 day. The participant had a fever beginning on the same day the rash developed (maximum rectal temperature of 40.2°C) lasting for 2 days. The investigator concluded that this event was not related to M-M-R II.

- Rubella:
  - A 12-month-old female participant (SC group), with no known exposure to a Rubella case experienced a rubella-like rash with macules too numerous to count (>300) beginning 14 days post-vaccination. The participant had a fever beginning on the day of vaccination (maximum rectal temperature of 38.4°C), lasting 3 days. The investigator concluded that this event was possibly related to M-M-R II.
- Varicella:
  - A 12-month-old male participant (SC group), with no known exposure to a Varicella case experienced an injection site varicella-like rash with 4 vesicles beginning 9 days post-vaccination. The participant had a fever beginning 1-day post-vaccination (maximum rectal temperature of 38.7°C) lasting 1 day and a fever beginning 11 days post-vaccination lasting 1 day. The investigator concluded that this event was probably related to VARIVAX.

Reviewer comment

Of the five events described above, the investigator concluded that the event was possibly related to study vaccination for 2 events of measles and 1 event of rubella and that it was probably related to the 1 event of varicella. In only one event reported as measles, does the investigator conclude that this event was not related to study vaccination. In a response to an Information Request (STN 103552/6277, Amendment 17) the Applicant did not provide additional data, such as testing to distinguish whether these cases were caused by wild-type or vaccine virus. The clinical reviewer has reviewed each case, and in regard to the measles and rubella cases, the timing of rash and fever onset in proximity to study vaccination does raise the possibility that these rash and fever cases are related to the study vaccination. However, given the majority of children were seronegative for measles and rubella prior to study enrollment, and the possibility of exposure to a case of measles or rubella before or after study vaccination, paired with the number of lesions, timing of disease onset and the known small risk of primary vaccine failure associated with one dose of a measles or rubella containing vaccines (CDC, 2013), it is also reasonable to consider that these were possible cases of wild-type Measles and Rubella disease that occurred shortly after vaccination and were not related to study vaccination. The varicella

case occurred only at the injection-site and consisted of very few lesions consistent with a varicella-like rash that can occur post-vaccination. The reviewer agrees with the investigator that this case was probably related to the study vaccination.

Table 7. Proportion of Participants Reporting Solicited Reactions Following Vaccination, Safety Set, Study V205C-011

Solicited Adverse Reaction	Intramuscular N=374	Subcutaneous N=376
Local (injection site)	--	--
Pain[a], % (n/N)	--	--
Any	7.0% (26/374)	7.2% (27/376)
Mild	5.1% (19/374)	5.9% (22/376)
Moderate	1.9% (7/374)	1.3% (5/376)
Severe	0	0
Erythema, % (n/N)	--	--
Any	10.4% (39/374)	16.2% (61/376)
≤2.5 cm	8.8% (33/374)	13.0% (49/376)
>2.5 to ≤5.0 cm	0.8% (3/374)	3.2% (12/376)
>5.0 cm	0	0
Missing	0.8% (3/374)	0
Swelling, % (n/N)	--	--
Any	1.9% (7/374)	5.3% (20/376)
≤2.5 cm	1.1% (4//374)	2.9% (11/376)
>2.5 to ≤5.0 cm	0.5% (2/374)	1.1% (4/376)
>5.0 cm	0	0
Missing	0.3% (1/374)	1.3% (5/376)
Injection-site rash of interest[b], % (n/N)	0	0
Systemic	--	--
Measles-like rash, % (n/N)	2.9% (11/374)	2.9% (11/376)
Rubella-like rash, % (n/N)	2.9% (11/374)	2.6% (10/376)
Varicella-like rash, % (n/N)	0	2.9% (11/376)
Mumps-like illness[c], % (n/N)	0	0.3% (1/376)
Fever (temperature ≥38ºC), % (n/N) [d]	--	--
Any Fever[e]	66.5 (248/373)	66.8 (250/374)

Solicited Adverse Reaction	Intramuscular N=374	Subcutaneous N=376
38.0-38.5°C	20.4% (76/373)	22.2% (83/374)
>38.5-39.0°C	17.4% (65/373)	16.6% (62/374)
>39.0-39.5°C	14.2% (53/373)	13.4% (50/374)
>39.5-40.0°C	11.8% (44/373)	11.0% (41/374)
≥40.01°C	2.7% (10/373)	3.7% (14/374)

Source: Adapted from STN 101069/5846 and STN 103552/6277 Study V205C-011, Clinical Study Report, After Text Table 170, After Text Table 214, After Text Table 219, After Text Table 224, After Text Table 206
Subjects were analyzed according to the route actually used for vaccination.
Abbreviations: AE=Adverse Event; N=total number of participants in the group; n= number of participants who experienced the event; SAE=serious adverse event
Temperature 38.0 ºC =100.4 ºF
a. Pain grade: mild- awareness of symptom but easily tolerated, moderate- definitely acting like something is wrong, severe- extremely distressed or unable to do usual activities
b. Injection-site rash of interested included measles, rubella, and varicella-like rashes
c. Mumps-like illness was defined as mumps-like symptoms such as swollen parotid
d. Based on the maximal recorded temperature between Day 0 and 42, only includes temperatures (rectal or axillary) that were measured by the participant. No adjustments were performed.
e. In the IM Group 92.3% of fevers were documented using the rectal route of measurement and 7.7% of fevers were documented only by the axillary route of measurement. In the SC Group 89.6% of fevers were documented using the rectal route of measurement and 10.4% of fevers were documented only by the axillary route of measurement.

Unsolicited AEs

Overall, AEs from Day 0 to Day 42 were similar across groups, with at least one systemic AE, excluding fever, occurring in 66.5% of participants in the IM group and 66.8% of participants in the SC group. Vaccine related systemic AEs were reported in 9.1% and 11.7% of IM and SC group participants, respectively.

Most common vaccine-related systemic AEs by MedDRA System Organ Class and Preferred Term were reported at rates <10%, including *Infections and Infestations,* nasopharyngitis (<1.1%) and either *Skin and Subcutaneous Tissue Disorders,* including general, morbilliform, rubelliform, or vesicular rash (<2.1%) which were most frequently reported (>1%). Severe vaccine-related AEs occurred in <0.3% of participants.

> Reviewer comment
> To determine the rate of unsolicited AEs, the sponsor provided a response to an Information Request under STNs 103552/6277, Amendment 17, in which the rates of solicited systemic rashes of interest were excluded from the determination of systemic AEs. Rates of unsolicited AEs were 60.7% in the IM group and 56.1% in the SC group. The events described were most frequently (>1%) conditions that commonly occur in the pediatric group of 12 through 18 months of age.

6.1.12.3 Deaths

There were no deaths reported in this study.

6.1.12.4 Nonfatal Serious Adverse Events

SAEs were reported by five participants, one in the IM group and 4 in the SC group. One reported SAE, in the SC group, was considered related to administration of both M-M-R II and VARIVAX, while the other four SAEs were considered unrelated. The SAE considered related to the study vaccination was described as a case of otitis media of moderate intensity at Day 5 post-vaccination that developed as a complication of purulent rhinitis in a 14.5-month-old male. He was admitted to the hospital and received treatment with antibiotics (cefpodoxime). He was discharged after 1 day in the hospital. It was assessed

by the investigator and the Applicant as being possibly related to both vaccines, though a plausible alternative etiology due to an underlying concomitant illness exists.

Reviewer Comment
In a response to an Information Request under STNs 103552/6277 and 125108, Amendment 17, the Applicant concludes that no other information is available on the reason the participant was hospitalized. The clinical reviewer agrees with the investigator's assessment that the SAE of otitis media requiring hospitalization was possibly associated with study vaccinations due to close temporality. Otitis media is listed in the current USPI for M-M-R II.

6.1.12.7 Dropouts and/or Discontinuations

No participants were withdrawn due to an adverse event.

Table 8. Proportion Disposition, Randomized Set, Study V205C-011

Population	Intramuscular % (n/N)	Subcutaneous % (n/N)
Enrolled[a]	N=374	N=378
Vaccinated	100% (374/374)	100% (378/378)
Completed study	99.7% (373/374)	99.7% (377/378)
Withdrawal due to	0.3% (1/374)	0.3% (1/378)
Consent withdrawal	0	0
Lost to follow-up	0	0.3% (1/378)
Personal reason	0.3% (1/374)	0
Protocol deviation	18.4% (69/374)	19.8% (75/378)
Non-serious AE	83.7% (313/374)	86.0% (325/378)
Serious AE	0.3% (1/374)	1.1% (4/378)
Death	0	0

Source: Adapted from STN 101069/5846 and STN 103552/6277 Study V205C-011, Clinical Study Report, Text Table 2, Text Table 5, Text Table 18
Abbreviations: AE=Adverse Event; N=total number of participants in the group; n= number of participants who experienced the event; SAE=serious adverse event; w/d=withdrawal
a. A total of 776 participants were enrolled in this study. 24 participants were enrolled but not randomized

6.1.13 Study Summary and Conclusions

Study V205C-011 was designed as a comparative immunogenicity and safety study of M-M-R II and VARIVAX in children 12 through 18 months of age. Participants received these two study vaccines concomitantly by either the IM or SC route. The primary objectives were to demonstrate non-inferiority of one dose of each study vaccines by IM route as compared to the SC route for M-M-R II (1st primary objective) and VARIVAX (2nd primary objective) at 6 weeks post-vaccination in terms of SRRs. Both primary objectives were met. For measles, mumps and rubella antigens, the LL of the 95% CI for SRR was >90% and for varicella the LL of the 95% for SRR was 84.5% after intramuscular administration in initially seronegative participants in each group. For all vaccine antigens, the descriptive summary of GMTs 6 weeks post-vaccination demonstrated comparable humoral immune responses between the IM and SC routes and no evidence of immune interference with concomitant administration of the two vaccines by either route. Post hoc analyses using the CBER criterion for success in non-inferiority for measles, mumps, and rubella viruses (LL of the 95% CI for difference in SRR ≥-5%) were met for mumps, rubella, and varicella and marginally missed the criterion for measles (LL of the 95% CI of -5.28). Despite this narrow miss of this success criterion, the acceptability of the immune response after IM administration is supported by the proportions of those achieving seroresponse 42 days post-vaccination and the similar GMTs for measles in both groups.

The safety profile of the vaccines when administered via the IM route were similar to the safety profile when administered via the SC route, potentially showing less local reactogenicity though this cannot be confirmed given the open label design and the small sample size.

Overall, the results of study V205C-011 support the safety and effectiveness of administration of M-M-R II and VARIVAX administered by the IM route.

7. Integrated Overview of Efficacy

In the context of the Applicant's proposed changes to Sections 6 and 14 of the USPI, pooled analyses of immunogenicity data were not informative because data were from one study. The immunogenicity data from Study V205C-011 were described in Section 6.1 of this clinical memorandum.

8. Integrated Overview of Safety

In the context of the Applicant's proposed changes to Sections 6 and 14 of the USPI, pooled analyses of safety data were not informative because data were from one study. The safety data from Study V205C-011 were described in Section 6.1 of this clinical memorandum.

9. Additional Clinical Issues

9.1 Special Populations

Sections 4 and 8 of the proposed prescribing information submitted to the BLA included information presented in Sections 9.1.1 through 9.1.5 of this memorandum.

9.1.1 Human Reproduction and Pregnancy Data

The intramuscular administration of VARIVAX was not evaluated in pregnant individuals. The data in Section 8.1 of the USPI of VARIVAX comply with the requirements of the Pregnancy and Lactation Labeling Rule.

9.1.2 Use During Lactation

The intramuscular administration of VARIVAX was not evaluated in lactating individuals. The data in Section 8.1 of the USPI of VARIVAX comply with the requirements of the Pregnancy and Lactation Labeling Rule.

9.1.3 Pediatric Use and PREA Considerations

Pediatric Research Equity Act (PREA) requirements applied to this application because of the evaluation of a new RoA (IM). The Applicant requested that the assessment of VARVIVAX in infants less than 12 months of age be waived based on the following sections of the Food, Drug, and Cosmetics Act (FD&C Act):

- 505B(a)(5)(B)(iii)(I): the drug or biological product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group
- 505B(a)(5)(B)(iii)(II): the drug or biological product is not likely to be used in a substantial number of pediatric patients in that age group

Additionally, the Applicant requested an extrapolation of the data obtained in the pediatric age groups studied to individuals ≥19 months to 16 years of age based on the following:

- There is no biologically plausible reason to anticipate a difference in immunogenicity for the IM route versus the SC route in older children and adolescents.

- Live attenuated viral vaccine immunogenicity and safety via the IM route are not expected to differ across pediatric age groups, requiring switching from one route to the other.

The Applicant's request for a partial waiver in infants less than 12 months of age and extrapolation to children ≥19 months to 16 years of age was presented to FDA's Pediatric Review Committee (PeRC) on December 13, 2022. PeRC agreed with the partial waiver and extrapolation request.

9.1.4 Immunocompromised Patients

The intramuscular administration of VARIVAX was not evaluated in immunocompromised individuals. The current USPI includes a warning in Section 4.2 stating the following:

Do not administer VARIVAX to individuals who are immunodeficient or immunosuppressed due to disease or medical therapy.

Disseminated varicella disease and extensive vaccine-associated rash have been reported in individuals who are immunosuppressed or immunodeficient who were inadvertently vaccinated with a varicella-containing vaccine.

9.1.5 Geriatric Use

The intramuscular administration of VARIVAX was not evaluated in the geriatric population.

10. Conclusions

Study V205C-011 enrolled and vaccinated 752 children, 12 through 18-months of age, who received 1 dose of M-M-R II and VARIVAX administered concomitantly, by either the intramuscular or subcutaneous route. This study demonstrated that intramuscular administration is appropriate for the proposed indication of VARIVAX, which is supported by the demonstration of non-inferiority of the antibody responses in terms of SRRs as measured by ELISA for antibodies to varicella virus as compared to those elicited by the SC route, which is the current US-approved route of administration. In descriptive analyses, intramuscular administration of the vaccine elicited antibody responses to all vaccine virus antigens in terms of GMTs that were comparable to those elicited by subcutaneous route.

The safety data collected regarding the IM RoA was overall similar to the known and accepted safety profile for the SC route. The intramuscular route was generally well tolerated and in the submitted study, was less reactogenic when compared to the SC route, however the small samples size and open-label design of the trial may limit the generalizability of these findings. No safety signals were detected that would require further assessment in post-marketing safety studies. The safety data reported during the post-marketing surveillance of the IM route of administration of VARIVAX used outside the US are also supportive of the overall safety of this route of administration.

The data provided in the application support the safety and effectiveness of the IM route of administration of VARIVAX. With this approval, Section 2 Dosage and Administration of the USPI will include both the intramuscular and subcutaneous administration routes.

11. Risk-Benefit Considerations and Recommendations

11.1 Risk-Benefit Considerations

Table 9. Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Measles is a highly contagious viral disease primarily affecting children. Common complications from measles include pneumonia and diarrhea, which can lead to significant morbidity and mortality. Measles still causes over 140,000 deaths world-wide, with the highest disease incidence by age occurring among children under 5 years of age. Children under 5 years, pregnant women, immunocompromised individuals, and adults are at highest risk for measles complications and death. • Mumps is an acute viral illness that results in inflammation of the salivary glands and most often presents as parotitis. Other manifestations of the infection include orchitis (in post-pubertal males), oophoritis (in post-pubertal females), and meningoencephalitis. • Rubella is a viral disease primarily affecting children, which manifests clinically with rash, low-grade fever, lymphadenopathy, and malaise. Fetal infection, particularly in the first trimester, can result in miscarriages, stillbirths, and Congenital Rubella Syndrome (CRS), the latter of which can present with cataracts, hearing loss, mental retardation, and congenital heart defects.	• Prevention of these highly infectious childhood diseases by vaccination helps to avert widespread serious morbidity and mortality, especially for high-risk individuals, including pregnant women and their unborn fetuses, children <5 years of age, and immunocompromised individuals. • Addition of the IM RoA increases ease of administration of these vaccines for all populations.
Unmet Medical Need	• In the US, M-M-R II, VARIVAX, ProQuad, and Priorix are the only vaccines in the ACIP-recommended pediatric immunization schedule administered by the SC RoA. • Current clinical recommendations concerning immunization practice do not require re-immunization when a vaccine indicated for the SC route is erroneously given IM.	• An alternative option for RoA aligns these vaccines with the current pediatric schedule and provides options for administration of the vaccines.
Clinical Benefit	• The immunogenicity of the IM RoA of VARIVAX administered as a first dose was evaluated in a clinical trial as compared to the SC route. A total of 752 children ages 12 through 18 months off age participated in this trial. In the trial 374 received the vaccine via the IM route and 378 received the vaccine via the SC route. • The effectiveness of VARIVAX the IM RoA in varicella was inferred from antigen specific serological responses compared to responses induced by the SC RoA. Immunological evaluations included non-inferiority of immunogenicity of VARIVAX in terms of SRR after a first dose in varicella-naïve children, 12 through 18 months of age.	• M-M-R II and VARIVAX given by IM route elicited immune responses that were non-inferior to those elicited by the SC route demonstrated by similar antibody response rates to measles, mumps, rubella, and varicella 42 days postvaccination. Lower bounds of the 95% CI for SRR >90% for measles, mumps and rubella and comparable geometric mean antibody titers for all vaccine antigens further support this conclusion.
Risk	• The rates of solicited injection site and systemic adverse reactions (AR) after IM administration were as follows: local erythema 10.4; local pain 7%; local swelling 1.9%; Most solicited ARs were reported as mild or moderate with none reporting Grade 3/severe solicited local ARs with exception of fever ≥40°C which occurred in 2.5% of children. The rates of reported SAEs were low (<1%). There were no deaths throughout the entire study period. • The IM RoA is approved in all EU countries. Over (b) (4) doses have been distributed in the EU. Post-marketing safety data from the EU did not identify safety concerns or risks that have not been previously described for other MMRV-containing vaccines. • The most common risks of IM RoA were described above.	• The data from the clinical study adequately characterizes the safety of the IM RoA. Overall, the safety results were comparable to those of the SC route. The safety profile of the IM RoA is acceptable for its intended use. • The post-marketing safety experience outside the US provides additional reassurance regarding the safety of the IM RoA.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	• The most common risks of VARIVAX vaccination were described above.	• The risks of the IM RoA are adequately characterized in the USPI. Routine pharmacovigilance to monitor AEs in accordance with 21 CFR 600.80 is anticipated to be sufficient.

11.2 Risk-Benefit Summary and Assessment

The overall clinical benefit of the intramuscular RoA of VARIVAX in individuals 12 months of age and older in prevention of varicella is favorable compared to the risks associated with vaccination by this route. Data submitted to this application establish the safety and effectiveness of the intramuscular RoA for VARIVAX among individuals in the age groups for which it is indicated. The safety of the intramuscular RoA of VARIVAX is adequately described in the prescribing information and the Applicant's routine pharmacovigilance is adequate for monitoring AEs post-marketing.

11.3 Discussion of Regulatory Options

The effectiveness of the intramuscular RoA of VARIVAX is based on determination of non-inferior antibody responses compared to the currently approved RoA, which is the SC route, for which effectiveness for the prevention of clinical disease has previously been demonstrated in children.

Safety data and analyses provided in the submission do not raise concerns such that other regulatory options need to be considered.

11.4 Recommendations on Regulatory Actions

Based on the clinical data provided in the application, the clinical reviewer recommends approval of intramuscular RoA of VARIVAX for the prevention of varicella in individuals 12 months of age and older.

11.5 Labeling Review and Recommendations

The prescribing information was reviewed and specific comments on the labeling were provided by CBER to the Applicant. All issues were satisfactorily resolved.

11.6 Recommendations on Postmarketing Actions

No post-marketing requirements or post-marketing commitments are needed or recommended. As recommended by OBPV/DPV, the clinical reviewer agrees with the pharmacovigilance activities as proposed by the Applicant in the pharmacovigilance plan which include routine pharmacovigilance through signal detection and AE reporting as required under 21 CFR 600.80.