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Applicant	Merck Sharp & Dohme Corp.
Established Name	Varicella Virus Vaccine Live
Trade Name	VARIVAX
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	VARIVAX is a suspension for injection supplied as a single-dose vial of lyophilized vaccine to be reconstituted using the accompanying sterile diluent. A single dose after reconstitution is 0.5 mL.
Dosage Form and Route of Administration	Subcutaneous injection
Dosing Regimen	Single dose of entire amount of reconstituted vaccine (Lyophilized preparation with ≥ 1350 plaque-forming units of live attenuated varicella virus (Oka/ Merck strain).
Indication and Intended Population	Prevention of Varicella in healthy subjects 12 months of age and older.
Purpose of Supplement	Addition of intramuscular route of administration.

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GLOSSARY

AE	Adverse Event
BLA	Biological License Application
CI	Confidence Interval
CSR	Clinical Study Report
ELISA	Enzyme Linked Immunosorbent Assay
GMT	Geometric Mean Titer
gpELISA	Glycoprotein Enzyme Linked Immunosorbent Assay
IM	Intramuscular
IR	Information Request
IU	International Unit
LLOQ	Lower Limit of Quantification
mIU	Milli International Unit
MMR II	Measles Mumps Rubella Vaccine Brand Name
PFU	Plaque-Forming Units
PPS	Per-Protocol Set
rHA	Recombinant Human Albumin
SAE	Serious Adverse Event
sBLA	Supplemental BLA
SC	Subcutaneous

1. Executive Summary

VARIVAX is a live virus vaccine indicated for active immunization for the prevention of varicella in individuals 12 months of age and older. The approved route of administration of VARIVAX is subcutaneous injection. Merck submitted an efficacy supplement (STN 103552/6277) to the Biological License Application (BLA) for VARIVAX to include immunogenicity and safety data to add intramuscular (IM) as a new route of administration of the vaccine. Safety and immunogenicity data from clinical study V205C-011 was submitted and reviewed to support this application.

V205C-011 is a Phase IIIb, open label, randomized, comparative, multicenter study of the immunogenicity and safety of MMR 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. A single dose (entire volume of the reconstituted vaccine) of MMR II is administered concomitantly with a single dose of VARIVAX. Blood samples were taken before vaccination and at Day 42 post-vaccination to assess immunogenicity. The primary endpoints were antibody response rates at 42 days post-vaccination for subjects initially seronegative to measles (< 255 mIU/mL), mumps (< 10 ELISA Ab units/mL), rubella (< 10 IU/mL) or varicella (< 1.25 gpELISA units/mL).

The estimated differences of seroconversion rates (among the subjects who were initially seronegative to measles, mumps, rubella or varicella, respectively) between the IM group and the SC group (i.e. IM group – SC group), stratified by region, were -1.89% (95% CI: -5.28%, 1.29%), -0.33% (95% CI: -2.67%, 2.00%), -0.02% (95% CI: -2.42%, 2.43%) and 2.93% (95% CI: -2.18%, 8.06%) for measles, mumps, rubella and varicella, respectively. For all four antigens, the lower

bounds of the two-sided 95% CIs were greater than the pre-defined non-inferiority margin of -10%, implying that the immune response of the IM route was non-inferior to that of the SC route. In addition, the safety and reactogenicity profiles of the two treatment groups were similar throughout the 42-day post-vaccination safety follow-up.

In summary, the IM route co-administration of VARIVAX and MMR II showed a similar immunogenicity, reactogenicity, and safety profile compared to the SC route. Therefore, I consider the safety and immunogenicity data to support licensure of the administration of VARIVAX via IM route.

2. Clinical and Regulatory Background

VARIVAX is a live virus vaccine indicated for active immunization for the prevention of varicella in individuals 12 months of age and older. VARIVAX is a lyophilized preparation with ≥ 1350 plaque-forming units (PFU) of a live attenuated varicella virus (Oka/Merck strain). In Europe (17 countries including France and Germany), the vaccine license was obtained in 2003 for the refrigerator-stable formulation. VARIVAX is currently recommended only for SC administration.

The applicant submitted this efficacy supplement STN 103552/6277 to the BLA for VARIVAX vaccine, to include immunogenicity and safety data to support intramuscular (IM) as a new route of administration of the vaccine.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The applicant did not submit the dataset in 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 such that the statistical review can be performed.

3.2 Compliance With Good Clinical Practices And Data Integrity

No substantial issues were found during the review of this BLA.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

Please refer to review memos from other review disciplines.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

This statistical review focuses on the clinical safety and immunogenicity data collected in the Phase IIIb study V205C-011. The applicant also submitted clinical safety and immunogenicity data

collected in the Phase IIIb study V221-036. Of note, study V221-036 evaluated the immunogenicity and safety of ProQuad when administered by IM route or SC route to healthy children aged 12 to 18 months. Based on an internal discussion, only study V205C-011 is considered relevant to support the IM route of the VARIVAX vaccine, hence, this memo focuses solely on study V205C-011.

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

The following documents submitted to the sBLA are reviewed

103552/6277.0 (Submitted on April 29, 2022)

Module 5: Clinical Study Reports

- V205C-011 Clinical Study Report

103552/6277.5001 (Submitted on June 27, 2022)

Module 1.11.4: Clinical Information Amendment

103552/6277.5003 (Submitted on July 15, 2022)

Module 1.11.4: Clinical Information Amendment

103552/6277.5004 (Submitted on August 17, 2022)

Module 1.11.4: Clinical Information Amendment

103552/6277.5007 (Submitted on October 24, 2022)

Module 1.11.4: Clinical Information Amendment

103552/6277.5008 (Submitted on November 17, 2022)

Module 1.11.4: Clinical Information Amendment

103552/6277.5009 (Submitted on December 6, 2022)

Module 1.11.4: Clinical Information Amendment

103552/6277.5010 (Submitted on December 16, 2022)

Module 1.11.4: Clinical Information Amendment

103552/6277.5012 (Submitted on January 12, 2023)

Module 1.11.4: Clinical Information Amendment

103552/6277.5013 (Submitted on January 20, 2023)

Module 1.11.4: Clinical Information Amendment

103552/6277.5014 (Submitted on January 31, 2023)

Module 1.11.4: Clinical Information Amendment

103552/6277.5016 (Submitted on February 3, 2023)

Module 1.11.4: Clinical Information Amendment

103552/6277.5017 (Submitted on February 10, 2023)

Module 1.11.4: Clinical Information Amendment

103552/6277.5020 (Submitted on February 22, 2023)
Module 1.11.4: Clinical Information Amendment

5.3 Table of Studies/Clinical Trials

One clinical study was submitted to support the licensure of administration of VARIVAX in IM route.

Table 1: Clinical Study supporting the licensure of administration of VARIVAX in IM route

Study	N	Age	Description
V205C-011	752	12 months – 18 months	A Phase IIIb, open label, randomized, comparative, multicenter study of the immunogenicity and safety of MMR II manufactured with recombinant Human Albumin and VARIVAX when administered concomitantly by IM route or SC route at two separate injection sites in healthy subjects 12 to 18 months of age.

Source: Summarized by the reviewer based on clinical study report (CSR) of V205C-011 submitted in sBLA 103552/6277.0.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Clinical Study V205C-011

6.1.1 Objectives

Primary Objectives

- To demonstrate that, when given concomitantly with VARIVAX by the same route at 12-18 months of age at separate injection sites, a single dose of MMR II rHA administered by IM route is as immunogenic as a single dose of MMR II rHA 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,

and/ or:
- To demonstrate that, when given concomitantly with MMR II rHA by the same route at 12-18 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.

Secondary Objectives

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

6.1.2 Design Overview

In this trial, approximately 700 subjects were to be randomized in a 1:1 ratio into two parallel groups, stratified by region, both receiving a single dose of MMR II and a single dose of VARIVAX by IM or SC route. Namely,

- Group 1: a single dose of MMR II and a single dose of VARIVAX administered by IM route
- Group 2: a single dose of MMR II and a single dose of VARIVAX, both vaccines administered by SC route.

Two blood samples were to be collected from subjects in the study:

- The first blood sample was to be collected after the subject's eligibility had been verified and the consent form was signed in the seven days prior to vaccination (Day 0) or at the time of the first visit.
- The second blood sample was to be collected at Visit 2 (Day 42 to Day 56) postvaccination, before or at the time of the second visit.

Sera were analyzed for measles, mumps and rubella antibody titer by ELISA and for varicella antibody titer by gpELISA. The recruitment period was planned to last six months.

6.1.3 Population

Healthy male or female infants aged 12 to 18 months (From 1st birthday to one day prior to 19th month).

6.1.4 Study Treatments or Agents Mandated by the Protocol

A single dose of MMR II rHA, a lyophilized preparation of combined live attenuated measles virus (more attenuated Enders' Edmonston strain), live attenuated mumps virus (Jeryl LynnTM [Level B] strain) and live attenuated rubella virus (Wistar RA 27/3 strain).

A single dose of VARIVAX, a lyophilised preparation with ≥ 1350 plaque-forming units (PFU) of a live attenuated varicella virus (Oka/ Merck strain).

For group 1, both vaccines were administered by IM route at two separate injection sites. For group 2, both vaccines were administered by SC route at two separate injection sites. The vaccines were administered at Day 0.

6.1.6 Sites and Centers

This was a multicenter study (39 centers in France and 33 in Germany). As planned in the protocol, centers were divided into 9 regions (4 in France and 5 in Germany) according to their geographic localizations and their recruitments for the purpose of performing the statistical analyses.

6.1.7 Surveillance/Monitoring

Please refer to the clinical review.

6.1.8 Endpoints and Criteria for Study Success

Immunogenicity Endpoints

The primary endpoints were antibody response rates and geometric mean antibody titers (GMT) at 6 weeks post-vaccination for subjects initially seronegative to measles (< 255 mIU/mL), mumps (< 10 ELISA Ab units/mL), rubella (< 10 IU/mL) or varicella (< 1.25 gpELISA units/mL).

Antibody response rates are defined as follows:

- a) Response rates for measles was the percentage of subjects with antibody titers ≥ 255 mIU/mL among subjects whose baseline measles antibody titers were < 255 mIU/mL.
- b) Response rates for mumps was the percentage of subjects with antibody titers ≥ 10 ELISA antibody units/mL among subjects whose baseline mumps antibody titers were < 10 ELISA antibody units/mL.
- c) Response rates for rubella was the percentage of subjects with antibody titers ≥ 10 IU/mL among subjects whose baseline rubella antibody titers were < 10 IU/mL.
- d) Response rates for varicella was the percentage of subjects with antibody titers ≥ 5 gpELISA units/mL among subjects whose baseline varicella antibody titers were < 1.25 gpELISA units/mL.

In relation to the first primary objective of the study (MMR II manufactured with rHA), non-inferiority of Group 1 (IM) compared to Group 2 (SC) will be demonstrated as following:

The Group 1 (IM) response rates will be considered non-inferior to the Group 2 (SC) response rates if, for each valence (measles, mumps and rubella), the two-sided Confidence Interval (CI) around the difference in response rates (Group 1 – Group 2) excludes a decrease of 10% or more (i.e., the non-inferiority margin).

In relation to the second primary objective (VARIVAX) of the study, the non-inferiority of Group 1 (IM) compared to Group 2 (SC) will be demonstrated as following:

The Group 1 (IM) varicella response rate will be considered non-inferior to the Group 2 (SC) varicella response rate if the two-sided CI around the difference in response rates (Group 1 – Group 2) excludes a decrease of 10% or more (i.e., the non-inferiority margin).

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

Safety Endpoints

The safety endpoints included

- From Day 0 to Day 4:
 - Solicited injection-site adverse reactions
 - Injection site erythema
 - Injection site swelling
 - Injection site pain.

- From Day 0 to Day 42
 - Other injection site adverse reactions,
 - Systemic adverse reactions
 - Rectal temperature $\geq 39.4^{\circ}\text{C}$ or if missing, axillary temperature $\geq 38.5^{\circ}\text{C}$.
 - Rectal temperature $\geq 38.0^{\circ}\text{C}$ or if missing, axillary temperature $\geq 37.1^{\circ}\text{C}$.
 - Injection site rashes
 - Measles/Measles-like rash
 - Rubella/Rubella-like rash
 - Varicella/Varicella-like rash
 - Mumps/mumps-like illness

- From the time of the consent form was signed to Visit 2 (Day 42):
 - Serious adverse events.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Analysis Sets

Randomized Set

Randomized set included all the subjects if a randomization number was assigned.

Full Analysis Set

Full analysis set was defined in accordance with the intent-to-treat principle. It included all randomized subjects who received at least one of the study vaccines with a postvaccination immunogenicity evaluation. Subjects were analyzed according to the administration route from the randomization.

Per Protocol Set

Per Protocol set was defined as all randomized subjects excluding subjects with protocol violation which may interfere with immunogenicity evaluation.

Such protocol violations include the following:

- non-respect of inclusion criteria or violation of non-inclusion criteria which may interfere with the immunogenicity evaluation,
- non-respect of the randomization scheme,
- absence of pre-vaccination immunogenicity evaluation,
- absence of postvaccination immunogenicity evaluation,
- non-respect of the postvaccination blood sampling schedule (i.e. 42 to 56 days after V1),

- intake of excluded medication which may interfere with the immunogenicity evaluation, between inclusion visit and postvaccination blood sample,
- injection of excluded vaccine between inclusion visit and postvaccination blood sample.

For the Per Protocol Immunogenicity analysis

1. PPS with only subjects with baseline (BS1) measles antibody titers < 255 mIU/mL (i.e., initially seronegative to measles)
2. PPS with only subjects with baseline (BS1) mumps antibody titers < 10.0 ELISA Ab units/mL (i.e., initially seronegative to mumps)
3. PPS with only subjects with baseline (BS1) rubella antibody titers < 10.0 IU/mL (i.e., initially seronegative to rubella)
4. PPS with only subjects with baseline (BS1) varicella antibody titers < 1.25 gpELISA units/mL (i.e., initially seronegative to varicella)

Safety Set

All subjects who received at least one of the study vaccines and who had safety follow-up data. Subjects were analyzed according to the route actually used for vaccination.

Sample Size

The power for this study was calculated for the first step of the Hochberg procedure (i.e., success of both primary objectives) using the Farrington and Manning method.

It was expected that up to 15% of subjects enrolled in the study would be non-evaluable for the MMR II analyses using the Per-Protocol set, due to the number of subjects lost to follow-up or with protocol deviations (10%) and assuming that 5% of subjects would have pre vaccination measles antibody titers ≥ 255 mIU/mL, 5% of subjects would have pre vaccination mumps antibody titers ≥ 10.0 ELISA antibody units/mL and 5% of subjects would have pre vaccination rubella antibody titers ≥ 10.0 IU/mL.

It was also expected that up to 20% of subjects enrolled in the study would be non-evaluable for the VARIVAX analyses using the Per-Protocol set, due to the number of subjects lost to follow-up or with protocol deviations (10%) and assuming that 10% of subjects would have pre vaccination varicella antibody titers ≥ 1.25 gpELISA units/mL.

Consequently, 350 subjects would result in 297 evaluable subjects per group for the MMR II analyses and 280 evaluable subjects per group for the VARIVAX analyses using the Per Protocol approach. With 297 evaluable subjects in each of Group 1 and Group 2, assuming that the true response rates to measles, mumps and rubella in Group 2 are 95%, 95% and 95% respectively and no difference between groups, the study will have approximately 99.9% power to declare noninferiority for each of the measles, mumps and rubella response rates using a one-sided 2.5% type I error rate and a 10% non-inferiority margin. The overall power for the MMR II primary objective is therefore 99.8%. With 280 evaluable subjects in each of Group 1 and Group 2, assuming that the true response rate to varicella in Group 2 is 85% and no difference between groups, the study will have approximately 90.4% power to declare non-inferiority for the varicella response rate using a one-sided 2.5% type I error rate and a 10% non-inferiority margin. The overall

power of the study will be 90.2% for success of the two primary objectives at the first step of the Hochberg procedure.

In case of failure of one primary objective at the first step of the Hochberg procedure, the power of the study for the remaining objective would decrease from 99.8% to 99.4% for MMR II or from 90.4% to 84.6% for VARIVAX due to the adjustment of the type I error rate at the second step of the procedure.

Analysis of Immunogenicity

The immunogenicity analysis of the primary objectives for specific antigens was performed based on the corresponding PPS. For example, to analyze the primary objective related to measles, the PPS with subjects seronegative to measles at baseline was used. The immunogenicity analyses for the secondary objectives were performed on both FAS and PPS.

The analysis for the demonstration of the non-inferiority of Group 1 response rates compared to Group 2 response rates was based on the stratified Miettinen and Nurminen confidence interval (CI). The stratification was done by region that were defined based on geographic locations with weight proportional to the number of subjects in each region. The region and the corresponding center numbers are provided in Table 2.

Table 2: Centers considered for each region for stratified analysis

Region	Center Number
Region 1	2, 9, 18, 19, 20, 22, 24, 25, 28, 30, 31, 41
Region 2	3, 17
Region 3	4, 5, 10, 11, 14, 15, 27, 29, 33, 34, 36, 39, 43
Region 4	1, 7, 12, 13, 21, 26, 32, 35, 37, 38, 40, 42
Region 5	54, 55, 56, 57, 58, 64
Region 6	59, 60, 61, 63
Region 7	51, 52, 53, 62, 65, 67, 68, 69, 87
Region 8	70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81
Region 9	82, 83, 84, 85, 86

Source: Section 2.3.3 of Statistical analysis plan of V205C-011, submitted in sBLA 103552/6277.0.

For immunogenicity analyses, data points lower than the Lower Limit of Quantification (LLOQ) were replaced by half of the LLOQ. The values higher than the upper limit of quantification (ULOQ) were replaced by the ULOQ.

Sensitivity analysis

A sensitivity analysis was performed using the method without stratification proposed by Miettinen and Nurminen. For each primary objective, the estimate of the between-group difference in response rates (Group 1 - Group 2) will be calculated with its two-sided CI.

Multiplicity Adjustment

Since the study could be declared successful if either one or both primary endpoints were reached, an adjustment of the type I error was necessary. The multiplicity was adjusted using the method proposed by Hochberg (1988).

Overall, four hypotheses were tested, namely, three hypotheses for the MMR II rHA primary objective (one hypothesis per strain) and one hypothesis for the VARIVAX (one hypothesis per strain) objective. The following procedure was implemented:

1st Step: All two-sided 95% CIs for the 4 valences (Group 1 – Group 2) were calculated. If the smallest lower bound was greater than -0.10 (-10%) then the non-inferiority was demonstrated for both primary objectives.

2nd Step: If the smallest lower bound was lower than or equal to -0.10 (-10%) then the corresponding non-inferiority was not demonstrated (i.e., if it was a M, M or R valence, the objective for MMR II rHA was not reached; if it was the Varicella valence, the VARIVAX objective was not reached). Then the two-sided 97.5% CI(s) 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.

Interim Analysis

None

Analysis of Safety

The proportions were calculated and tabulated. Subjects who received the dose via a route which they were not randomized to would be analyzed according to the actual route of administration.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

A total of 776 healthy infants aged 12-18 months were enrolled from 39 centers in France and 33 centers in Germany. Among them, 752 were randomly allocated to either the IM group (374 subjects) or the SC group (378 subjects).

6.1.10.1.1 Demographics

The demographic and baseline characteristics in the randomized set are described in Table 3. The demographic and baseline characteristics were generally well balanced across treatment arms and were similar in Per-Protocol set and Safety set.

Table 3: Demographic and Baseline Characteristics (Randomized Set)

Characteristic	Group 1 (IM) (N=374)	Group 2 (SC) (N=378)	Total N=752
Sex n (%)			
Male	206 (55.1%)	210 (55.6%)	416 (55.3%)
Female	168 (44.9%)	168 (44.4%)	336 (44.7%)
Age, months			
Mean age (SD)	13.79 (1.72)	13.69 (1.59)	13.74 (1.66)
Median age	13.19	13.14	13.17
Age range	12.02-18.96	11.96-18.86	11.96-18.96
Country n (%)			
France	178 (47.6%)	189 (50.0%)	367 (48.8%)
Germany	196 (52.4%)	189 (50.0%)	385 (51.2%)
Region n (%)			
Region 1 ^a	47 (12.6%)	51 (13.5%)	98 (13.0%)
Region 2 ^a	39 (10.4%)	39 (10.3%)	78 (10.4%)
Region 3 ^a	35 (9.4%)	40 (10.6%)	75 (10.0%)
Region 4 ^a	57 (15.2%)	59 (15.6%)	116 (15.4%)
Region 5 ^b	37 (9.9%)	33 (8.7%)	70 (9.3%)
Region 6 ^b	44 (11.8%)	42 (11.1%)	86 (11.4%)
Region 7 ^b	27 (7.2%)	27 (7.1%)	54 (7.2%)
Region 8 ^b	66 (17.6%)	63 (16.7%)	129 (17.2%)
Region 9 ^b	22 (5.9%)	24 (6.3%)	46 (6.1%)

Source: Adapted from Text Table 3, Text Table 7 of the CSR of Study V205C-011, submitted in sBLA 103552/6277.0)

- a. Region indicates France
- b. Region indicates Germany

6.1.10.1.3 Subject Disposition

The subject disposition of V205C-011 is provided in Table 4. One subject (Subject (b) (6) randomized in the SC group (Group 2) received both vaccines by IM route thus was analyzed for safety in the IM group (Group 1). The dropouts were generally balanced across the treatment arms. The proportion of subjects retained in the per protocol set from the exposed set were also generally comparable across treatment arms.

Table 4: Subject Dispositions (Randomized set)

	Group 1 (IM) (N=374)	Group 2 (SC) (N=378)	Total N=752
Randomized Set	374	378	752
Full Analysis Set (FAS)	370 (98.9%)	375 (99.2%)	745 (99.1%)
FAS for Measles	369 (98.7%)	374 (98.9%)	743 (98.8%)
FAS for Mumps	370 (98.9%)	375 (99.2%)	745 (99.1%)
FAS for Rubella	369 (98.7%)	374 (98.9%)	743 (98.8%)
FAS for Varicella	369 (98.7%)	375 (99.2%)	744 (98.9%)
Per Protocol Sets (PPS)			
PPS for Measles	349 (93.3%)	363 (96.0%)	712 (94.7%)
PPS for Mumps	349 (93.3%)	363 (96.0%)	712 (94.7%)
PPS for Rubella	321 (85.8%)	318 (84.1%)	639 (85.0%)
For Varicella, subjects with baseline varicella antibody titers < 1.25 gpELISA units/mL	336 (89.8%)	345 (91.3%)	681 (90.6%)
Safety Set (actual route)	375	377	752

Source: Adapted from Text Table 6 of CSR V205C-011, submitted in sBLA 103552/6277.0.

One subject in each group was not vaccinated according to the protocol (Subject (b) (6) in the IM group received the diluent of MMR II only and Subject (b) (6) in the SC group received MMR II by deep SC); these subjects were excluded from the safety analyses.

6.1.11 Immunogenicity Analyses

6.1.11.1 Analyses of Primary Endpoints

The primary immunogenicity endpoints were the response rates to measles, mumps, rubella and varicella measured 42 days following vaccination in both groups. A summary of seroconversion rates is described in Table 5. For each of the antigens, the seroconversion rates were comparable in each group. The 95% CIs of the seroconversion rate differences were computed using the stratified MN method, with region as the stratum. Since the lower bounds of all the four confidence intervals of the seroconversion rate differences were greater than -10%, the noninferiority criteria were met for all four antigens.

As a sensitivity analysis, seroconversion rate difference with 95% CIs were also computed based on the non-stratified MN method and the results are summarized in Table 6. For all four antigens, the 95% CI obtained based on stratified and non-stratified confidence intervals were similar.

Table 5: Summary of response rates to Measles, Mumps, Rubella and Varicella 42 days post-vaccination for subjects initially seronegative to Measles, Mumps, Rubella or Varicella (Antigen specific PPS)

Antigen	Group 1 (IM) N	Group 2 (IM) Response Rate n (%)	Group 2 (SC) N	Group 2 Response Rate n (%)	Difference Group 1 (IM) – Group 2 (SC)	95% CI (Stratified by region)
Measles (≥ 255 mIU/mL)	349	329 (94.3)	363	349 (96.1)	-1.89%	(-5.28, 1.29)
Mumps (≥ 10 IU/mL)	349	341 (97.7)	363	356 (98.1)	-0.33%	(-2.67, 2.00)
Rubella (≥ 10 IU/mL)	321	315 (97.7)	318	312 (98.1)	-0.02%	(-2.42, 2.43)
Varicella (≥ 5 gpELISA units/mL)	336	297 (88.4)	345	295 (85.5)	2.93%	(-2.18, 8.06)

Source: Adapted from Text Table 12 of CSR V205C-011, submitted in sBLA 103552/6277.0.

The seroconversion rate difference is computed using stratified MN method with regions considered as strata.

Table 6: Estimates of seroconversion rate difference and 95% CI using the non-stratified MN method

Antigen	Difference of Group 1 (IM) - Group 2 (SC)	95% CI (non-stratified)
Measles (≥ 255 mIU/mL)	-1.87%	(-5.24, 1.31)
Mumps (≥ 10 IU/mL)	-0.36%	(-2.76, 1.93)
Rubella (≥ 10 IU/mL)	0.02%	(-2.37, 2.43)
Varicella (≥ 5 gpELISA units/mL)	2.89%	(-2.21, 8.00)

Source: Adapted from After Text Table 93 of CSR V205C-011, submitted in sBLA 103552/6277.0.

Reviewer's Comment: I verified the applicant's reported results for non-stratified analysis based on the analysis and tabulation datasets submitted by the applicant. I computed the stratified MN confidence interval using the scoreci function of the ratesci package in R. The results are summarized in Table 7. Despite of some minor differences (<0.1%) between my results and the applicant's results, the final conclusions are the same.

Table 7: Estimated difference and 95% CI confidence interval of stratified MN method computed by the reviewer.

Antigen	Estimated Difference (Group 1 (IM) -Group 2 (SC))	95% CI
Measles	-1.87%	(-5.24, 1.28)
Mumps	-0.32%	(-2.66, 1.99)
Rubella	-0.02%	(-2.41, 2.43)
Varicella	2.93%	(-2.17, 8.04)

Source: Computations by the reviewer based on the datasets submitted for study V205C-011 in sBLA 103552/6277.0.

6.1.11.2 Analyses of Secondary Endpoints

For both the groups, the GMT results for all four antigens at 42 days following vaccination among subjects initially seronegative to measles, mumps, rubella or varicella are presented in Table 8. For all antigens, the GMTs were similar between groups.

Table 8: Summary of GMT to Measles, Mumps, Rubella and Varicella at 42 days post-vaccination for subjects initially seronegative to Measles, Mumps, Rubella or Varicella (Antigen specific PPS)

Antigen	Group 1 (IM) n	Group 1 (IM) GMT	Group 1 (IM) 95% CI	Group 2 (SC) n	Group 2 (SC) GMT	Group 2 (SC) 95% CI
Measles (mIU/mL)	349	2396.43	(2117.72, 2711.82)	363	2560.64	(2278.50, 2877.71)
Mumps (ELISA Ab units/mL)	349	86.42	(78.66, 94.95)	363	89.77	(82.57, 97.61)
Rubella (IU/mL)	321	97.22	(88.55, 106.73)	318	94.37	(85.67, 103.95)
Varicella (gpELISA units/mL)	336	9.83	(9.20., 10.50)	345	9.21	(8.62, 9.84)

Source: Adapted from Text Table 13 of CSR V205C-011, submitted in sBLA 103552/6277.0.

Reviewer's Comment: I have independently verified these immunogenicity results based on the datasets submitted by the applicant.

6.1.12 Safety Analyses

6.1.12.1 Solicited Adverse Events

The safety analysis was performed on the safety set. One subject in each group was not vaccinated according to the protocol (Subject (b) (6) in the IM group received the diluent of MMR II only and Subject (b) (6) in the SC group received MMR II by deep SC); these subjects were excluded from the safety analyses. As a result, 374 subjects in the SC group and 376 subjects in the IM group were considered for the safety analysis.

A summary of solicited injection site reactions is provided in Table 9. The proportions of subjects experiencing at least one solicited injection site AEs were generally numerically higher in the SC group compared to the IM group. Solicited local injection site AEs at MMR II injection site were slightly higher in the SC (21.5%) group compared to the IM group (15.5%). Similar trend was also observed at the VARIVAX injection site; solicited local injection site was slightly higher at in the SC group (22.6%) compared to the IM group (15.2%). For both vaccines, between day 0 and day 4, injection site erythema was the most common solicited injection site AE. The percentage of participants who experienced MMR injection-site erythema was slightly higher in the SC group (16.2%) compared to the IM (10.4%). Similar trend was observed at the VARIVAX injection site; 22.6% subjects in SC group and 15.2% subjects in IM group experienced injection-site erythema. Of note, during the post-vaccination monitoring period (0-42 days) varicella-like injection site rash was observed for 8 and 3 subjects respectively at the VARIVAX injection site and MMR injection site respectively. All of these varicella-like injection site rashes were reported in the SC group.

Table 9: Injection site solicited adverse events (Safety Set)

	Group 1 IM N=374 [n (%)]	Group 2 SC N=376 [n (%)]
Solicited Local Injection-site AE (Days 0 to 4)		
at MMR Injection site	58 (15.5)	81 (21.5)
Injection site Erythema	39 (10.4)	61 (16.2)
Mild (≤ 2.5 cm)	33 (8.8)	49 (13.0)
Moderate (> 2.5 cm to ≤ 5 cm)	3 (0.8)	12 (3.2)
Severe (> 5 cm)	0 (0.0)	0 (0.0)
Missing	3 (0.8)	0 (0)
Injection site Pain	26 (7.0)	27 (7.2)
Mild	19 (5.1)	22 (5.9)
Moderate	7 (1.9)	5 (1.3)
Severe	0	0
Injection site Swelling	7 (1.9)	20 (5.3)
Mild (≤ 2.5 cm)	4 (1.1)	11 (2.9)
Moderate (> 2.5 cm to ≤ 5 cm)	2 (0.5)	4 (1.1)
Severe (> 5 cm)	0 (0)	0 (0)
Missing	1 (0.3)	5 (1.3)
at VARIVAX Injection site	57 (15.2)	85 (22.6)
Injection site Erythema	33 (8.8)	63 (16.8)
Mild (≤ 2.5 cm)	30 (8.0)	48 (12.8)
Moderate (> 2.5 cm to ≤ 5 cm)	2 (0.5)	14 (3.7)
Severe (> 5 cm)	0 (0.0)	0 (0.0)
Missing	1 (0.3)	1 (0.3)
Injection site Pain	26 (7.0)	32 (8.5)
Mild	18 (4.8)	27 (7.2)
Moderate	8 (2.1)	5 (1.3)
Severe	0 (0.0)	0 (0)
Injection site Swelling	12 (3.2)	18 (4.8)
Mild (≤ 2.5 cm)	6 (1.6)	13 (3.5)
Moderate (> 2.5 cm to ≤ 5 cm)	4 (1.1)	2 (0.5)
Severe (> 5 cm)	0 (0.0)	0 (0)
Missing	2 (0.5)	3 (0.8)

Source: Text Table 19 and Text Table 21, After Text Table 170 and After Text Table 174 of CSR of V205C-011 submitted in sBLA 103552/6277.0.

To quantify the intensity of swelling and erythema, the maximum largest diameter of the injection site AE was reported.

Table 10 summarizes the systemic adverse reactions occurring between Day 0 and Day 42 in each treatment group. The rates of systemic adverse reactions were similar in both treatment groups. The numbers reported for non-injection site rashes include cases of potential clinical disease, including: 3 measles cases, 1 rubella case, and 1 varicella case. Based on the response to a CBER Information

Request (STN 103552/6277.5017), additional information was not available on the methods used to diagnose these clinical cases, including but not limited to, clinical serological testing and/or PCR testing results. Of note, 1 participant in the SC group experienced mumps-like illness. Similar percentage of subjects experienced Fever $\geq 38.0^{\circ}\text{C}$ for IM group (66.3%) and SC group (66.5%) . The percentage of fever is defined within the population who had valid temperature measurements. One participant in the IM group and two participants in the SC group did not have temperature measurements and were excluded from the denominator, resulting in N=373 and N=374, respectively.

In the IM Group 92.3% of fevers were based on the rectal route of measurement and 7.7% of fevers were based on the axillary route of measurement. In the SC Group 89.6% of fevers were based on the rectal route of measurement and 10.4% of fevers were based on the axillary route of measurement.

Table 10: Systemic Adverse Reactions occurring between Day 0 and Day 42 (Safety Set)

	Group 1 (IM) N=374 [n (%)]	Group 2 (SC) N=376 [n (%)]
Systemic Adverse Reactions	295 (78.9)	295 (78.5)
Measles-like rash	11 (2.9)	10 (2.7)
Rubella-like rash	10 (2.7)	10 (2.7)
Varicella-like rash	2 (0.5)	12 (3.2)
Mumps-like illness	0 (0.0)	1 (0.3)
Fever (Temperature $\geq 38.0^{\circ}\text{C}$)	248 (66.5)	250 (66.8)
38.00 - 38.50 $^{\circ}\text{C}$	76 (20.4)	83 (22.2)
38.51 - 39.00 $^{\circ}\text{C}$	65 (17.4)	62 (16.6)
39.01 - 39.50 $^{\circ}\text{C}$	53 (14.2)	50 (13.4)
39.51 - 40.00 $^{\circ}\text{C}$	44 (11.8)	41 (11.0)
$\geq 40.01^{\circ}\text{C}$	10 (2.7)	14 (3.7)

Source: Text Table 18, Text Table 23 and After Text Table 203 of CSR of V205C-011 submitted in sBLA 103552/6277.0. Table submitted in Page 2 of sBLA 103552/6277.5014 was based on the applicant's response to the information request sent on January 20, 2023.

The number of subjects who had fever were summarized based on subjects who had at least one temperature (rectal or axillary) $\geq 38.0^{\circ}\text{C}$, without adjustment, between Day 0 to Day 42.

One participant in the IM group and two participants in the SC group did not have temperature measurements and were excluded from the denominator, resulting in N=373 and N=374, respectively.

Reviewer's Comments: I have independently computed the numbers related to the safety analysis based on the submitted dataset submitted by the applicant.

6.1.12.2 Serious Adverse Events

Serious adverse events (SAE) observed from Day 0 to Visit 2 are summarized in Table 13. One subject in the IM group experienced at least one SAE compared to 4 subjects in the SC group. Out of the 4 subjects in the SC group, one subject each reported SAE related to MMR II and SAE related to VARIVAX.

Table 13: Serious Adverse events from Day 0 to Visit 2 (Safety Set)

	Group 1 (IM) N=374 [n (%)]	Group 2 (SC) N=376 [n (%)]
Any Serious Adverse Events	1 (0.3)	4 (1.1)
Any Death	0 (0)	0 (0)
Any Vaccine related SAE to MMR II	0 (0)	1 (0.3)
Any Vaccine related SAE to VARIVAX	0 (0)	1 (0.3)
Any withdrawal due to an adverse event	0 (0)	0 (0)

Source: Adapted from Text Table 7 of CSR of V205C-011 study submitted in sBLA 103552/6277.0

Reviewer's Comment: I have independently verified the SAE results based on the datasets submitted by the applicant.

6.1.12.3 Deaths

No deaths were reported in this study.

6.1.12.5 Adverse Events of Special Interest (AESI)

Please refer to clinical reviewer's memo.

6.1.12.6 Clinical Test Results

N/A.

6.1.12.7 Dropouts and/or Discontinuations

There were no dropouts due to AEs or SAEs.

7. INTEGRATED OVERVIEW OF EFFICACY

N/A.

8. INTEGRATED OVERVIEW OF SAFETY

N/A

9. ADDITIONAL STATISTICAL ISSUES

There are no additional statistical issues identified.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

The applicant submitted results from one Phase IIIb study, V205C-011, to support the authorization of intramuscular administration as a new route for the VARIVAX vaccine.

Noninferiority of the immune response induced by the intramuscular administration compared to that of the subcutaneous administration in terms of the seroconversion rate was demonstrated for both MMR II and VARIVAX vaccines in Study V205C-011.

The study also showed similar reactogenicity and safety profiles when MMR II and VARIVAX are administered by IM route compared to by SC route.

10.2 Conclusions and Recommendations

All success criteria for immunogenicity objectives were met in study V205C-011. The reactogenicity and safety profiles were similar in the subjects who received the vaccine by intramuscular route compared to the subjects who received the vaccine by subcutaneous route. I consider the immunogenicity data to support the licensure of intramuscular as a new route of administration for VARIVAX.