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BLA Clinical Review Memorandum

Application Type	Biologics License Application Prior Approval Supplement
STN	BLA 125108/1128 ProQuad - MMRV 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, MPH Associate Director, Medical Affairs, DVRPA, OVRR, CBER
Applicant	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Established Name	MMRV Virus Vaccine
Proprietary Name	ProQuad
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc.	Each dose (approximately 0.5 mL) contains not less than 3.00 $\log_{10}$ tissue culture infectious doses $TCID_{50}$ of measles virus; 4.30 $\log_{10}$ $TCID_{50}$ of mumps virus; 3.00 $\log_{10}$ $TCID_{50}$ of rubella virus; and not less than 3.99 $\log_{10}$ PFU of Oka/Merck varicella virus. Each dose also contains 20 mg of sucrose, 16 mg of sorbitol, 11 mg of hydrolyzed gelatin, 2.5 mg of urea; 2.3 mg of sodium chloride, 1.4 mg of sodium phosphate, 0.38 mg of monosodium L glutamate, 0.25 mg of recombinant human albumin, 0.13 mg of sodium bicarbonate, 94 mcg of potassium phosphate, 58 mcg of potassium chloride; and residual components from the manufacturing process: MRC 5 cells including DNA and protein; ≤5 mcg of neomycin, ≤0.5 mcg of bovine calf serum, and other buffer and media ingredients. 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	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 1 month should elapse between a dose of a measles containing vaccine and a dose of ProQuad. At least 3 months should elapse between a dose of varicella-containing vaccine and ProQuad.
Indication(s) and Intended Population(s)	Active immunization for the prevention of measles, mumps, rubella, and varicella in children 12 months through 12 years of age
Orphan Designated (Yes/No)	No

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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 ProQuad. In the submission, data from study, V221-036 is summarized. This study compares the immunogenicity and safety of ProQuad 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 ProQuad.

Study V221-036, conducted in France, evaluated the immunogenicity and safety of ProQuad when administered by the IM route as compared to the SC route. In this study, to align with the currently accepted CBER criteria to assess a non-inferior immune response to measles, mumps, and rubella antigens, post hoc analyses using the non-inferiority success criterion that the lower limit (LL) of the 2-sided 95% CI for difference (IM group – SC group) in seroresponse rate (SRR) be ≥-5% was performed. After measuring the vaccine antigen-specific antibody responses to measles, mumps, rubella, and varicella viruses by enzyme-linked immunosorbent assay (ELISA) at 30 days post-vaccination dose 1, this criterion was met for all vaccine antigens, except rubella virus which only narrowly missed meeting the criterion (-5.5%). Seroresponse rates for varicella virus met the accepted criterion for success in non-inferiority for intramuscular administration compared to subcutaneous administration (LL of the 95% CI for difference in SRR >-10%). The additional analysis of SRR demonstrated that the immune responses elicited by IM administration 30 days post-vaccination dose 1 were robust, with all vaccine antigens achieving a LL of the 95% CI for SRR of >90%. GMTs measured by ELISA at 30 days post-dose 1 vaccination were 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 response between the two routes of administration.

Safety data were reviewed from 405 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 Day 0 to Day 28 post-dose 1 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. Of the 6 reported SAEs in study V221-036 none were considered related to the study vaccination. The clinical reviewer agreed with the assessment of the investigator that none of these SAEs were likely related to study vaccination. 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

Individual vaccines were licensed for SC use in the US for measles in 1963, mumps in 1967, and rubella in 1969. The combination measles, mumps and rubella vaccine M-M-R™ was licensed in 1971, with a modified vaccine containing the more immunogenic rubella strain RA 27/3 (M-M-R II) licensed in 1978. In 1995, Varivax was approved, followed by the approval of the quadrivalent vaccine ProQuad in 2005.

The Advisory Committee on Immunization Practices (ACIP) currently recommends vaccination with MMR vaccine for all children as soon as possible on reaching age 12 months, and a second dose of MMR vaccine for all children aged 4 through 6 years before entering kindergarten or first grade. The ACIP also recommends a third dose of a mumps-virus containing vaccine for persons previously vaccinated with 2 doses of a mumps-virus containing vaccine (M-M-R II or ProQuad) who are identified by public health authorities as being part of a group or population at increased risk for acquiring mumps because of a mumps outbreak. 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

ProQuad (Measles, Mumps, Rubella and Varicella Virus Vaccine Live) is indicated for active immunization for the prevention of measles, mumps, rubella, and varicella in children 12 months through

12 years of age. It is administered as a 0.5-mL dose in two doses with the first dose administered at 12 through 15 months of age and the second dose administered at 4 through 6 years of age.

2.3 Safety and Efficacy of Pharmacologically Related Products

2.4 Previous Human Experience with the Product

The IM RoA was added to ProQuad's SmPC on July 31, 2013. Since then, over (b) (4) doses of ProQuad 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 V221-036 was used to support the IM RoA in the EU SmPC for ProQuad in 2013. 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 V221-036 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 2006 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): V221-036
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 9 of 34 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 2006. 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 measles, mumps, rubella and varicella viruses induced by ProQuad 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 ProQuad after two doses 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#125108/1128 Amendments (Ams) were reviewed (listed by modules):

- Am 0: sections 1, 2 and 5
- Am 1: section 1
- Am 2: sections 1 and 5
- Am 3: sections 1 and 5
- Am 4: sections 1 and 5
- Am 5: section 1
- Am 6: sections 1
- Am 7: sections 1 and 5
- Am 8: sections 1
- Am 9: sections 1 and 5
- Am 10: sections 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)
V221-036 (NCT00402831)	France	Phase 3, randomized, open-label, multicenter, active comparative, parallel-group study to evaluate the immunogenicity and safety of ProQuad when administered by IM route vs. SC route	Healthy children 12 through 18 months of age (2 dose: 1st dose at Day 0, 2nd dose at Day 30)	ProQuad by IM route: 202 (201) ProQuad by SC route: 203 (200)

Source: Adapted from STN 125108/1128, 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 V221-036

NCT00402831
"An open, randomised, comparative, multicentre study of the immunogenicity and safety of ProQuad® when administered by intramuscular (IM) route or subcutaneous (SC) route to healthy children aged 12 to 18 months."

Study Overview: This Phase 3 study conducted in France was designed to evaluate the non-inferiority of the humoral immune response to ProQuad when administered as 2 doses by IM route compared to 2 doses administered by SC route in children 12 through 18 months of age. The primary immunogenicity objective was assessed 42 days after 2nd dose which was administered 30 days after the 1st dose. The secondary immunogenicity objective assessed the immune responses 30 days after the 1st dose. The first participant was enrolled in the study on October 6, 2006, and the last study visit was on May 11, 2007.

6.1.1 Objectives

Primary Objectives

1. To demonstrate that two doses of ProQuad administered by the IM route is as immunogenic as two doses of ProQuad administered by the SC route to healthy children 12 through 18 months of age in terms of antibody response rates to measles, mumps and rubella as measured by ELISA and to varicella as measured by gpELISA at 42 days following the second dose of ProQuad.

   Endpoint: Antibody response rates to measles, mumps, rubella and varicella measured six weeks after the second dose of ProQuad in both groups (Visit 3).

   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 antibody 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 gpELISA units/mL (gpELISA) in children whose baseline varicella antibody titer was <1.25 gpELISA units/mL.

Statistical Criteria 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 V221-036 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%. Additionally, the interval used in the study was a non-US licensed interval for the administration of ProQuad as the interval between varicella-containing vaccines has only been studied at 3 months.

Secondary Objectives (Descriptive)

1. To describe the antibody response rates to measles, mumps, rubella and varicella 30 days after the first dose of ProQuad administered by the IM or SC route.

   Endpoint: Antibody response rates to measles, mumps, rubella and varicella measured four weeks after the first dose of ProQuad in both groups (Visit 2).

   Seroresponse Definitions: see in Primary Objectives above

2. To describe the antibody titers to measles, mumps, rubella and varicella 30 days after the first dose of ProQuad and 42 days after the second dose of ProQuad, both administered by the IM or SC route.

   Endpoint:
   - Antibody titers to measles, mumps, rubella and varicella measured four weeks after the first dose of ProQuad (Visit 2) and six weeks after the second dose of ProQuad (Visit 3) in both groups.
   - Rates of participants with varicella antibody titers ≥1.25 gpELISA units/mL in participants whose baseline varicella antibody titer was <1.25 gpELISA units/mL, four weeks after the first dose of ProQuad (Visit 2) and six weeks after the second dose of ProQuad (Visit 3) in both groups (Not discussed in this memorandum).

3. To describe the safety profile of each of the two doses of ProQuad, both administered either by the IM or SC route.

   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
  - Zoster-like rash
  - Other systemic AEs
- From Day 0 to study end
  - SAEs.

Primary Hypotheses: The IM route would be non-inferior to the SC route for the four vaccine antigens tested.

6.1.2 Design Overview

Study V221-036 was a Phase 3, open-label, randomized, comparative, multicenter study with two parallel groups. Overall, participants were randomized 1:1 to receive administration of ProQuad by either IM or SC RoA.

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

- Visit 1 (Day 0, at 12 through 18 months of age): Blood sampling, vaccination with 1st dose of ProQuad by either IM or SC route, 20-minute post-vaccination safety monitoring.
- Visit 2 (Between Day 30 and 44 post-Visit 1, at 13 through 14 months of age): Blood sampling and diary card transcription, vaccination with 2nd dose of ProQuad by either IM or SC route
- Visit 3 (Between Day 42 and 56 post-Visit 2, at 14 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 the following criteria: Healthy participants of either gender affiliated to a health social security system, 12 through 18 months of age (from 1st birthday to one day prior to 19th month), negative clinical history of measles, mumps, rubella, varicella and zoster, consent form signed by both holders of the parental authority or by the legal representative properly informed about the study, holder(s) of the parental authority or 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 and/or varicella vaccine either alone or in any combination.
- Any recent (≤30 days) exposure to measles, mumps, rubella, varicella and/or zoster involving:
  - Continuous household contact, or
  - Playmate contact (generally >1 hour of play indoors), or
  - Hospital contact (in same 2- to 4-bed room or adjacent beds in a large ward or face-to-face contact with an infectious staff member or individual), or
  - In the case of varicella, contact with a newborn whose mother had onset of varicella 5 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 seizure disorder.
- Any known blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the hematopoietic and lymphatic systems.

- Any severe thrombocytopenia or any other coagulation disorder that would contraindicate intramuscular injection.
- Prior known sensitivity/allergy to any component of the vaccine including neomycin, sorbitol or gelatin.
- 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 10 kg) within the previous 30 days] or other immunosuppressive therapy.
- Any previous (≤150 days) receipt of immunoglobulin or any blood-derived product or scheduled to be administered through Visit 3.
- Any recent (≤7 days) tuberculin test or scheduled tuberculin test through Visit 3.
- Any recent (≤30 days) receipt of an inactivated or a live vaccine or scheduled vaccination through Visit 3.
- Any medical condition which, in the opinion of the investigator, might interfere with the evaluation of the study objectives.
- Any recent (≤30 days) participation or scheduled participation in any other clinical trial through Visit 3.

Reasons for Study Withdrawal

Participants were free to discontinue the study for the following reasons:

- At the participant's holder(s) of the parental authority or legal representative's request.
- If, in the investigator's opinion, continuation in the study would be detrimental to the participant's well-being.
- At the specific request of Sanofi Pasteur MSD.

6.1.4 Study Treatments or Agents Mandated by the Protocol

ProQuad

- Dose and RoA: 0.5 mL, IM or SC
- Formulation:
  - Measles virus (Enders' Edmonston/Moraten strain) ≥3 $\log_{10}$ cell culture infectious dose 50% ($CCID_{50}$)
  - Mumps virus (Jeryl Lynn strain) (b) (4) $\log_{10}$ $CCID_{50}$
  - Rubella virus (Wistar RA 27/3 strain) ≥3 $\log_{10}$ $CCID_{50}$
  - Varicella virus (Oka/Merck strain) ≥3.99 $\log_{10}$ $CCID_{50}$
  - Excipients: Sucrose, Hydrolyzed gelatin, Sodium chloride, Sorbitol, Monosodium glutamate, Sodium phosphate, sodium bicarbonate, Potassium phosphate, Potassium chloride, (b) (4), Neomycin, (b) (4) urea.
- Presentation: Lyophilized pellet in a vial for reconstitution with WFI
- Lot: 0652834

Reviewer Comment:

The formulation and reconstitution methods for ProQuad are the same, irrespective of RoA (IM route or SC).

6.1.5 Directions for Use

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.

6.1.6 Sites and Centers

There were 41 centers in France (including 8 sites that did not enroll participants) with a total of 411 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 within 24 hours of the investigator becoming aware of the event. MAPI-NAXIS was the Contract Research Organization employed to oversee on-site monitoring and data verification.

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 AEs, 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, varicella-like or zoster-like), and mumps-like symptoms were recorded from Day 0 to 42 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 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, three 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.

In this study, revaccination with the currently licensed vaccine was not 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.

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 190 participants in each group for a total sample size of 380 participants. This assumed 20% non-evaluable participants for the measles, mumps, and rubella analyses (assuming 15% 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 25% non-evaluable participants for the varicella analyses (assuming 15% 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 152 evaluable participants per group for the measles, mumps, and rubella analyses, and 142 evaluable participants per group for the varicella analyses, providing a 98.9% and 93.0% power for each analysis, respectively, and a 90.1% 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.

For each primary criterion, the estimate of the between-groups difference in response rates (IM – SC) stratified by region was calculated together with its two-sided 95% CI. If the lower bound of the CI was >-10 percent, the IM group response rate was concluded to be non-inferior to the SC group response rate.

For each secondary criterion, descriptive statistics for antibody response rates were provided by group, for each vaccine antigen, per region and for all participants with two-sided 95% CIs for the Per Protocol Set Post-dose 1 (PPS1) and FAS. The GMT were calculated with their two-sided 95% CI by group, and for each vaccine antigen for each visit for the respective analysis set:

- Visit 1: PPS1, Per Protocol Set Post-dose 2 (PPS2), FAS
- Visit 2: PPS1, FAS
- Visit 3: PPS2, FAS

GMTRs were performed for the FAS in participants initially seronegative to each vaccine antigen

Descriptive safety analyses were performed for AEs with separate summaries of injection-site adverse reactions, systemic AEs, SAEs, and withdrawals, including relationship to vaccine for each.

Missing Data

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

Protocol Amendments

No protocol amendments were made to the study protocol during the course of the study.

Changes in the Conduct of the Study and Planned Analyses

The following changes from the protocol have been implemented in the analyses:

1. To take into consideration the baseline serostatus of participants for each vaccine antigen, subsets of the PPSs were defined.
2. In addition, the subset of participants with all four valences initially seronegative was analyzed to be consistent with the previous study.
3. To have a complete description of antibody titers, GMTR with 95% CI and 4-fold increase were to be provided in participants initially seropositive.
4. If Visit 3 was not performed, and there was no blood sampling available for that visit, the deviation “Absence of immunogenicity evaluation after first vaccination/blood sampling 2 not done” led to exclusion from the PPS for the analysis of the immunogenicity criteria after the first injection and after the second injection.

5. Some limits for the interval between vaccination and blood sample or first and second vaccinations leading to exclusion were changed:
    a. The deviations leading to exclusion were as follows:
        i. an interval between first vaccination and the second blood sampling was <28 days (28 days instead of 30 days).
        ii. an interval between second vaccination and the third blood sampling was <35 days (35 days instead of 42 days).
        iii. An interval between second vaccination and the third blood sampling was >63 days (63 days instead of 56 days).
        iv. An interval between first and second vaccination <28 or >44 days (28 days instead of 30 days).

Please see the statistical review memo for further discussion.

6.1.10 Study Population and Disposition

A total of 411 participants were enrolled in the study. The first participant was enrolled in the study on October 6, 2006, and the last study visit was on May 11, 2007.

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 dose of the study vaccine and who had safety follow-up data at the corresponding time-point. Participants were analyzed according to the route actually used for vaccination. There were two Safety sets described:

- Safety Set with safety follow-up data Post-dose 1.
- Safety Set with safety follow-up data Post-dose 2.

The *FAS* consisted of all randomized participants who received at least one study vaccine and with any post-vaccination immunogenicity evaluation. Participants were analyzed according to the theoretical RoA issued from the randomization.

The *PPS* for one valence, included all participants with valid immunogenicity criteria pre- and post-dose for that valence and no protocol violation (below) leading to the exclusion from the PPS for that valence. There were two PPS sets described:

- One for the analysis of the immunogenicity criteria Post-dose 1 (PPS1), with five subsets as follows:
    - PPS1 with only participants initially seronegative to measles (measles antibody titers <255mIU/mL at Baseline).
    - PPS1 with only participants initially seronegative to mumps (mumps antibody titers <10 ELISA Ab units/mL at Baseline).
    - PPS1 with only participants initially seronegative to rubella (rubella antibody titers <10 IU/mL at Baseline).
    - PPS1 with only participants initially seronegative to varicella (varicella antibody titers <1.25 gpELISA units/mL at Baseline).
    - PPS1 with participants initially seronegative to measles, mumps, rubella and varicella.

- A second for the analysis of the immunogenicity criteria Post-dose 2 (PPS2), with five subsets.
    - PPS2 with only participants initially seronegative to measles (measles antibody titers <255 mIU/mL at Baseline).

- PPS2 with only participants initially seronegative to mumps (mumps antibody titers <10 ELISA Ab units/mL at Baseline).
- PPS2 with only participants initially seronegative to rubella (rubella antibody titers <10 IU/mL at Baseline).
- PPS2 with only participants initially seronegative to varicella (varicella antibody titers <1.25 gpELISA units/mL at Baseline).
- PPS2 with participants initially seronegative to measles, mumps, rubella and varicella.

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

- Non-adherence to the inclusion criteria or violation of non-inclusion criteria which may interfere with the immunogenicity evaluation.
- Non-adherence to the randomization scheme.
- Absence of pre-vaccination immunogenicity evaluation (Visit 1 blood sampling).
- Absence of post-vaccination immunogenicity evaluation (Visit 2 or 3 blood sampling).
- Post-vaccination blood sampling outside of pre-specified schedule (i.e., more than 14 days before the first dose for Visit 1, 28 to 44 days after the first dose for blood sampling 2, 35 to 63 days after the second dose for blood sampling 3, after first dose for blood sampling 1 or after second dose for blood sampling 2).
- Injection of non-study vaccine between inclusion visit and post-vaccination blood sample (blood sampling 2 or blood sampling 3).
- Non-adherence to the vaccination schedule.
- Intake of excluded medication which may interfere with the immunogenicity evaluation, between first vaccination and blood sampling 3.
- Non-compliance with vaccine administration (i.e., first or second vaccination not done, undefined route for first or second vaccination, more than 30 minutes between interval reconstitution and vaccination, incomplete injection or route for first injection different from route for second injection).
- Exposure to measles, mumps, rubella, varicella or zoster.
- Seropositivity to measles, mumps, rubella, varicella at blood sampling 1.

6.1.10.1.1 Demographics

The demographics of study V221-036 are demonstrated in Table 2.

Table 2. Demographic and Baseline Characteristics, Randomized Set, Study V221-036

Characteristic	Intramuscular N=202	Subcutaneous N=203
Sex	--	--
Male:Female ratio	97:105	109:94
% male:% female	48.0%:52.0%	53.7%:46.3%
Age, months	--	--
Mean age (SD)	13.7 (1.4)	13.7 (1.5)
Median age	13.3	13.3
Age range	11.9-18.0	11.7-18.3
Country, n (%)	--	--
France	202 (100%)	203 (100%)

Characteristic	Intramuscular N=202	Subcutaneous N=203
Region (Geographic)	--	--
Region 1[a]	71 (35.1%)	76 (37.4%)
Region 2[b]	68 (33.7%)	63 (31.0%)
Region 3[c]	63 (31.2%)	64 (31.5%)

Source: Adapted from STN 125108/1128 Study V221-036, Clinical Study Report, Text Table 8, Text Table 4
N: total number of participants in the group. n indicates number of participants fulfilling the item followed by the calculated percentage in parentheses (%).
a. North-East, Center, and South-West
b. North-West
c. South-East

The median age at vaccination in the Randomized Set was 13.7 months, with a range of 11.7 to 18.3 months. Overall, the majority were male (50.9%), though there were fewer males (48.0%) than females (52.0%) in the IM group. Among the 405 randomized participants, centers were classified for statistical analyses in three regions, based on geographic location in France. There were 147 (36.3%) participants enrolled into Region 1 (North-East, Centre and South-West), 131 (32.3%) participants were enrolled into Region 2 (North-West) and 127 (31.4%) participants were enrolled into Region 3 (South-East). Similar demographics were seen findings in the FAS.

> Reviewer Comment
> Four participants (1, IM group; 3, SC group) were enrolled and vaccinated, but were excluded from the PPS because they did not meet inclusion criteria for age which stated that participants should be between their 12th month birthday to one day before their 19th month birthday at the time of vaccination.

There were 201 participants that received vaccination via the IM route and 203 participants that received vaccination via the SC route. In the FAS, the majority of participants were seronegative at baseline for these antigens across groups (IM vs. SC): measles (99.0% vs. 99.0%), mumps (99.0% vs. 98.5%) and varicella (90.0% vs. 90.6%). For rubella, the proportion across groups (IM vs. SC) that were seronegative were 83.6% vs. 90.6%.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

A total of 171 (42.2%) participants had at least one personal medical history. This was similar between groups. The majority participants reported a history with a System Organ Class (SOC) of *Infections and Infestations* (29.2%, IM group vs. 28.6%, SC group), followed by *Gastrointestinal disorders* (11.9%, IM group vs. 14.8%, SC group).

6.1.10.1.3 Participant Disposition

A total of 411 participants were enrolled in the study. Six were screened and not randomized (1, SAE [see Section 6.1.12.4]; 1 lost to follow up; 4, inability to obtain blood sample) and 405 were randomized and vaccinated (Randomized Set). Of the 405 participants, 202 were randomly allocated to the IM group and 203 to the SC group. All participants, except for 1, were included in the FAS. The one participant that was excluded from the FAS was lost to follow-up and did not provide postvaccination serology samples (blood sample 2 or blood sample 3). All 405 randomized participants were included in the Safety Set post-dose 1, while 401 (99.0%) were included in the Safety Set post-dose 2. There were 4 participants (1, IM group; 3, SC group) that were excluded from the Safety Set post-dose 2 due to not having safety data after receiving the second dose.

Of the 405 participants randomized and vaccinated, 4 (1.0%) withdrew from the study: one participant in the IM group (lost to follow up) and three participants in the SC group (2, lost to follow up; 1, last visit

not done/non-compliance with study protocol). There were no participants who withdrew due to an AE. Of those vaccinated 401 (99.0%) completed the study.

> Reviewer Comment
> Although 4 participants did not complete the study to Visit 3, there were 7 participants who attended Visit 3, but did not have a blood sample taken. Three of these participants, (1 in the IM Group and 2 in the SC Group) attended Visit 3 but blood samples were not taken (no reason is provided for not obtaining the sample but all three were excluded from the PPS). For the 4 participants that did not complete the study, the reason that blood sample number 3 was not taken varied: one in the IM Group and 2 in the SC Group were lost to follow-up after the second dose of ProQuad; one in the SC Group did not come to Visit 3 and was considered non-compliant with the study.

Of the 405 participants in the Randomized Set, 178 (44.0%) had at least one protocol deviation. Protocol deviations leading to exclusion from PPS1 and PPS2 occurred in 174 (43.0%) and 176 (43.5%) of participants, respectively. Common protocol deviations are included in Table 3, below.

Table 3. Participant Disposition and Data Analyses, Randomized Set, Study V221-036

Population, n (%)	**Intramuscular N=202**	**Subcutaneous N=203**
Enrolled	--	--
Randomized Set	202	203
Safety Set	--	--
Post-dose 1 (actual route)	202 (100%)	203 (100%)
Post-dose 2 (actual route)	201 (99.5%)	200 (98.5%)
Full Analysis Set (FAS)	201 (99.5%)	203 (100%)
Per Protocol Set Post-dose 1 (PPS1)	--	--
PPS1 Measles	153 (75.7%)	148 (72.9%)
PPS1 Mumps	152 (75.2%	149 (73.4%)
PPS1 Rubella	129 (63.9%)	133 (65.5%)
PPS1 Varicella	138 (68.3%)	136 (67.0%)
Per Protocol Set Post-dose 2 (PPS2)	--	--
PPS2 Measles	153 (75.7%)	147 (72.4%)
PPS2 Mumps	152 (75.2%)	148 (72.9%)
PPS2 Rubella	129 (63.9%)	132 (65.0%)
PPS2 Varicella	138 (68.3%)	134 (66.0%)
Participants excluded from the PPS1 (n, %)	--	--
Measles	49 (24.3%)	55 (27.1%)
Mumps	50 (24.8%)	54 (26.6%)
Rubella	73 (36.1%)	70 (34.5%)
Varicella	64 (31.7%)	67 (33.0%)
Participants excluded from the PPS2 (n, %)	--	--
Measles	49 (24.3%)	56 (27.6%)
Mumps	50 (24.8%)	55 (27.1%)
Rubella	73 (36.1%)	71 (35.0%)
Varicella	64 (31.7%)	69 (34.0%)
≥1 important protocol deviation[a]	--	--
Subjects with at least one protocol deviation leading to exclusion from the PPS1	87 (43.1%)	87 (42.9%)
Subjects with at least one protocol deviation leading to exclusion from the PPS2	87 (43.1%)	89 (43.8%)

Population, n (%)	Intramuscular N=202	Subcutaneous N=203
Reason for exclusion from PPS	--	--
Age out of range (<12 months)	1 (0.5%)	3 (1.5%)
At least one vaccine administration in a different route from randomization	1 (0.5%)	1 (0.5%)
Subject number re-attributed	1 (0.5%)	0
Site not respecting the randomization procedure	37 (18.3%)	36 (17.7%)
Initial serostatus missing for all antigens (blood sample 1 (BS1) not done)	1 (0.5%)	0
Four-week post-dose 1 serology result missing for all antigens (blood sample 2 (BS2) not done)[b]	2 (1.0%)	0
Six-week post-Dose 2 serology result missing for all antigens (blood sample 3 (BS3) not done)[c]	2 (1.0%)	5 (2.5%)
Interval between 1st vaccination and BS2 <28 days[b]	2 (1.0%)	3 (1.5%)
Interval between 1st vaccination and BS2 >44 days[b]	9 (4.5%)	9 (4.4%)
Interval between 2nd vaccination and blood sample 3 (BS3) <35 days[c]	2 (1.0%)	3 (1.5%)
Interval between 2nd vaccination and BS3 >63 days[c]	0	1 (0.5%)
Received a non-study vaccine between Visit 1 and BS3	1 (0.5%)	0
Interval between 1st and 2nd vaccination <28 or >44 days	11 (5.4%)	11 (5.4%)
Exposed to measles, mumps, rubella, varicella between the 1st vaccination and BS2	1 (0.5%)	2 (1.0%)
Exposed to measles, mumps, rubella, varicella between the 2nd vaccination and BS3[c]	1 (0.5%)	1 (0.5%)
Measles seropositivity before 1st vaccination [d]	1 (0.5%)	2 (1.0%)
Mumps seropositivity before 1st vaccination [e]	1 (0.5%)	3 (1.5%)
Mumps seropositivity before 1st vaccination [f]	32 (15.8%)	19 (9.4%)
Varicella seropositivity before 1st vaccination [g]	19 (9.4%)	19 (9.4%)

Source: Adapted from STN 125108/1128 Study V221-036, Clinical Study Report, Text Table 3, Text Table 7, Table 16, 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. Includes subjects with important protocol violations that resulted in exclusion from the Per Protocol Set (PPS) analysis population.

b. Exclusion from the PPSs for the analysis of the immunogenicity criteria after 1st vaccination only.

c. Exclusion from the PPSs for the analysis of the immunogenicity criteria after 2nd vaccination only.

d. Deviations leading to exclusion from PPS – measles.

e. Deviations leading to exclusion from PPS – mumps.

f. Deviations leading to exclusion from PPS – rubella.

g. Deviations leading to exclusion from PPS – varicella.

Reviewer Comment

The overall number of protocol deviations experienced between each group was balanced. The main reason for excluding participants from a PPS was lack of appropriate randomization procedure, i.e., investigators from three centers of the South-east geographic region did not randomize some participants chronologically. Due to difficulties in retrospectively assessing when the procedure was followed correctly in these centers, a total of 73 participants (37 participants, IM group; 36 participants, SC group) were excluded.

Two participants (1 in each group) received a non-study vaccination (both received Prevnar and Pentavac, the latter of which is not a US-licensed vaccine). The first participant (IM group) received both vaccines 6 days prior to their Visit 3 blood sampling. This participant was included

in the immunogenicity analyses for all vaccine virus antigens, except fur rubella virus due to being seropositive for rubella at baseline. The second participant (SC group) received both vaccines on the day of the Visit 3 blood sampling. This participant was included in all immunogenicity analyses. Injection of non-study vaccine between inclusion visit and post-vaccination blood sample (including both blood sampling 2 and blood sampling 3) was considered a protocol violation (Section 6.1.10.1), however due to the proximity of administration of these vaccines to the Visit 3 blood draw as well as the low likelihood of the vaccine components in Prevnar and Pentavac (diphtheria toxoid, tetanus toxoid, pertussis, poliovirus and *Haemophilus influenzae* type b) to interfere with the immunologic response to measles, mumps, rubella, or varicella antigens, the clinical reviewer does not believe exclusion of these participants in the immunogenicity analyses would have affected the study results.

6.1.11 Immunogenicity Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Non-Inferiority of Antibody Response 6 Weeks Post-Dose 2

The primary immunogenicity objective was to demonstrate non-inferiority of two doses of ProQuad, administered via the IM route as compared to when administered via the SC route at 42 days post-vaccination dose 2.

The Visit 3 antibody response rates for participants initially seronegative (PPS) to each vaccine antigen are demonstrated in Table 4.

Table 4. Seroresponse Rates and Group Differences Post-Dose 2, Per Protocol Set, Study V221-036

Antibody, n^1/n^2 (%)	Intramuscular N=202	Subcutaneous N=203	SRR Difference[a] (95% CI)
Anti-measles (mIU/mL)	153/153 (100%)	147/147 (100%)	0.0% (-2.5, 2.6)
Anti-mumps (EU/mL)	151/152 (99.3%)	147/148 (99.3%)	0.1% (-3.0, 3.3)
Anti-rubella (IU/mL)	129/129 (100%)	131/132 (99.2%)	0.7% (-2.3, 4.1)
Anti-varicella (gpELISA unit/mL)	138/138 (100%)	133/134 (99.3%)	0.7% (-2.1, 4.1)

Source: Adapted from STN 125108/1128 Study V221-036, Clinical Study Report, Table 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 criterion: the lower limit of the 2-sided 95% CI for the group difference in SRR (IM group minus SC group) must be >-10% for the respective vaccine antigen.

In the IM group, rates were 100%, 99.3%, 100%, and 100% as compared to those in the SC group, where rates were 100%, 99.3%, 99.2%, and 99.3% for SRRs against the measles, mumps, rubella, and varicella vaccine antigens, respectively.

For measles, mumps, rubella and varicella antigens the lower bound of the 95% CI of the point estimates in SRR after the 2nd dose was >90% in both the intramuscular (97.6%, 96.4%, 97.2%, and 97.4%, respectively) and subcutaneous (97.5%, 96.3%, 95.9%, and 95.9%, respectively) groups.

For each vaccine antigen, when stratified by region, the LL of the 95% CI for the group difference (IM group minus SC group) in SRR was >-10%, and so the criterion for primary objectives was met.

When supplementary non-inferiority analyses were performed on the FAS either: 1) using a stratification by region and 2) without stratification, 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.

6.1.11.2 Analyses of Secondary Endpoints

The first secondary immunogenicity objective was to describe the antibody response rates to measles, mumps, rubella and varicella 30 days after the first dose of ProQuad administered by the IM or SC route. The second secondary immunogenicity objective was to describe the antibody titers to measles, mumps, rubella and varicella 30 days after the first dose of ProQuad and 42 days after the second dose of ProQuad, both administered by the IM or SC route.

Summary of Antibody Responses 30 Days Post-Dose 1

Antibody response rates for participants initially seronegative (PPS) to each vaccine antigen were comparable between groups and are as follows: In the IM group, rates were 100%, 97.4%, 98.4%, and 98.6% as compared to those in the SC group, where rates were 97.3%, 91.3%, 100%, and 98.5% for SRRs against the measles, mumps, rubella, and varicella vaccine antigens, respectively.

For measles, rubella and varicella antigens the lower bound of the 95% CI of the point estimates in SRR after the 1st dose was >90% in both the intramuscular (97.6%, 94.5%, and 94.9%, respectively) and subcutaneous (93.2%, 97.3%, and 94.8%, respectively) groups. This was not seen for the SRR to mumps in the SC group, where the LL of the 95% CI for SRR was 85.5%, while it was seen in the IM group, where the LL of the 95% CI for SRR was 93.4%.

Summary of GMTs Post-Dose 1

The GMTs at baseline, 30 days post-vaccination 1 (Visit 2) and 42 days post-vaccination 2 are descriptively provided in Table 5. The GMTs for each vaccine antigen were overall similar between groups.

When the antibody titers to all vaccine antigens were summarized for both vaccination doses on the FAS, the results were overall similar to that of the PPS and the results between groups were comparable.

Table 5. Geometric Mean Titers at Baseline, 4 Weeks Post-Dose 1; and 6 Weeks Post-Dose 2, Per Protocol Set, Study V221-036

Antibody	Intramuscular N=202	Subcutaneous N=203
Anti-measles (mIU/mL)	n=153 (75.7%)	n=148 (72.9%)
Baseline[a]	60.6 (59.7, 61.6)	62.2 (60.4, 64.0)
Visit 2[b]	4058.7 (3643.1, 4521.8)	3327.0 (2835.4, 3903.9)
Visit 3[c]	3953.7 (3497.2, 4469.9)	3748.6 (3270.9, 4296.0)
Anti-mumps (EU/mL)	n=152 (75.2%)	n=149 (73.4%)
Baseline[a]	5.0 (5.0, 5.0)	5.0 (5.0, 5.0)
Visit 2[b]	120.0 (102.2, 140.9)	101.9 (84.2, 123.2)
Visit 3[c]	157.9 (138.6, 180.0)	168.8 (146.9, 194.0)
Anti-rubella (IU/mL)	n=129 (63.9%)	n=133 (65.5%)
Baseline[a]	5.0 (5.0, 5.0)	5.0 (5.0, 5.0)
Visit 2[b]	46.9 (39.7, 55.4)	50.9 (44.9, 57.7)
Visit 3[c]	92.8 (82.4, 104.5)	94.2 (83.2, 106.6)

Antibody	Intramuscular N=202	Subcutaneous N=203
Anti-varicella (gpELISA unit/mL)	n=138 (68.3%)	n=136 (67.0%)
Baseline[a]	0.6 (0.6, 0.6)	0.6 (0.6, 0.6)
Visit 2[b]	25.0 (22.5, 27.7)	23.6 (20.9, 26.7)
Visit 3[c]	358.1 (300.1, 427.4)	261.8 (216.7, 316.4)

Source: Adapted from STN 125108/1128 Study V221-036, Clinical Study Report, Table 55, Table 56, Table 57, Table 58, Table 63, Table 64, Table 65, Table 66, Text Table 5, Table 21
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 Titer Ratio; 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
201 and 203 participants completed Visit 1, 200 and 203 participants completed Visit 2, and 200 and 198 participants completed Visit 3 in IM group and SC group, respectively
a. Baseline blood sampling was defined as blood sample collected prior to Visit 1 vaccination
b. Visit 2 blood sampling was planned for 30 days post-vaccination. 30 to 44 was the accepted range days that this blood sampling could be completed. Range of days participants completed this blood sampling was 22 to 114 days.
c. Visit 3 blood sampling was planned for 42 days post-vaccination. 42 to 56 was the accepted range days that this blood sampling could be completed. Range of days participants completed this blood sampling was 20 to 85 days.

6.1.11.3 Subpopulation Analyses

No subpopulation analyses were performed.

6.1.11.4 Dropouts and/or Discontinuations

Approximately 97.6% 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 Table 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 dose 2 using the stricter criterion of a LL of the 95% CI for the group difference in SRR (IM group minus SC group) for measles, mumps, and rubella ≥-5%. Review of the data (Table 4) using this interpretation demonstrated that this criterion was met for all four vaccine antigens post-dose 2.

The Applicant then provided a post hoc analysis of the secondary objective of SRRs 30 days post-dose 1 using the criterion of a LL of the 95% CI for the group difference in SRR (IM group minus SC group) ≥-5%. Review of the data using this interpretation demonstrated that this criterion was met for measles (LL 95% CI: 1.3), mumps (LL 95% CI: 1.0), and varicella (LL 95% CI: -3.8) post-dose 1, but marginally missed the criterion for rubella (LL 95% CI: -5.5) (Table 6).

Table 6. Seroresponse Rates and Group Differences Post-Dose 1, Per Protocol Set, Study V221-036

Antibody	Intramuscular n^1/n^2(%)	Subcutaneous n^1/n^2(%)	SRR Difference[a] (95% CI)
Anti-measles (mIU/mL)	153/153 (100%)	144/148 (97.3%)	2.7% (1.3, 6.8)
Anti-mumps (EU/mL)	148/152 (97.3%)	136/149 (91.3%)	6.1% (1.0, 12.1)
Anti-rubella (IU/mL)	127/129 (98.4%)	133/133 (100%)	-1.6% (-5.5, -1.3)[b]
Anti-varicella (gpELISA unit/mL)	136/138 (98.6%)	134/136 (98.5%)	0.0% (-3.8, 3.9)

Source: Adapted from STN 125108/1128, Amendment 0, Summary of Clinical Efficacy, Table 2.7.3
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).
Response rates were defined as:
Measles antibody titer ≥255 mIU/mL in subjects with baseline titer <255 mIU/mL.
Mumps antibody titer ≥10 ELISA Ab units/mL in subjects with baseline titer <10 ELISA Ab units/mL.
Rubella antibody titer ≥10 IU/mL in subjects with baseline titer <10 IU/mL.
Varicella antibody titer ≥5 gpELISA units/mL in subjects with baseline titer <1.25 gpELISA units/mL.
a. Defined as IM group SRR minus SC group SRR
b. The rubella response narrowly missed the -5% margin in the post hoc analysis.
Success criterion: the lower limit of the 2-sided 95% CI for the group difference in SRR (IM group minus SC group) must be >-10% for the respective vaccine antigen.

Reviewer Comment

CBER requested the analyses 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 rubella GMT responses and SRRs post-dose 1 (LL of the 95% CI for SRR >90% in both the IM and SC groups after each dose), the post hoc analyses with stricter success criterion would support 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 ProQuad as compared to subcutaneous administration.

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.

Median time between Visit 1 and Visit 2 were comparable between groups: 35 days in both the IM group and the SC group. Median time between Visit 2 and Visit 3 was also comparable between groups: 46 days in the IM group and 47 days in the SC group. Median safety follow-up duration in the Randomized Set for the entire study was 85 days. All 405 randomized participants received both vaccinations and had safety follow-up data post-vaccination dose 1 occurring at least 28 days post-vaccination. Four hundred and one (99.0%) of participants (201, IM group; 200, SC group) had safety follow-up data post-vaccination dose 2: three participants were lost to follow-up, and one was non-compliant with the protocol (last visit not done). After dose 2, safety follow-up duration was at least 28 days for 399 (98.5%)

participants, it was less than 28 days for 2 (0.5%) participants. Four (1.0%) participants (1 in the IM group and 3 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 7 and Table 8). At least one AE was reported in 80.7% of those in the IM group and 86.2% of those in the SC group within 28 days post-vaccination dose 1, while 74.6% and 72.0% of participants in the IM and SC groups, respectively experienced at least one AE; There were 105 (52.0%) participants in the IM group and 114 (56.2%) participants in the SC group that developed a vaccine-related reaction to ProQuad by Day 28 post-vaccination dose 1, and 70 (34.8%) and 85 (42.5%) participants in the IM and SC group that developed a vaccine-related reaction to ProQuad by Day 28 post-vaccination dose 2.

Table 7. Proportion of Participants Reporting at Least One Adverse Event Following First Vaccination, Safety Set, Study V221-036

AE Type: Monitoring Period[a]	Intramuscular N=202 % (n/N)	Subcutaneous N=203 % (n/N)
Immediate: 30 minutes	--	--
Solicited Injections-site reactions[b]: 0-4 days	15.3% (31/202)	21.7% (44/203)
Injection-site reactions: 0-28 days	3.0% (6/202)	8.9% (18/203)
Injection-site measles-like rash	0	0
Injection-site rubella-like rash	0	0.5% (1/203)
Injection-site varicella-like rash	0	0.5% (1/203)
Injection-site zoster-like rash	0	0
Solicited systemic reactions from Day 0 to Day 28	--	--
Measles-like rash	0.5% (1/202)	2.0% (4/203)
Rubella-like rash	3.0% (6/202)	3.0% (6/203)
Varicella-like rash	1.0% (2/202)	0.5% (1/203)
Zoster-like rash	0	0
Fever (temperature ≥38.0°C): 0-28 days	62.8% (125/199)	68.3% (136/199)
Other systemic adverse events[d] from Day 0 to Day 28	60.4% (122/202)	59.6% (121/203)
AEs leading to study w/d: Day 0 to Visit 2	0	0
SAEs: Day 0 to Visit 2	1.0% (2/202)	1.0% (2/203)
Deaths: Day 0 to Visit 2	0	0

Source: Adapted from STN 125108/1128 Study V221-036, Clinical Study Report, Text Table 20, Text Table 26, Table 93, Table 95

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

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).

Table 8. Proportion of Participants Reporting at Least One Adverse Event Following Second Vaccination, Safety Set, Study V221-036

AE Type: Monitoring Period[a]	Intramuscular N=201 % (n/N)	Subcutaneous N=200 % (n/N)
Immediate: 30 minutes	--	--
Solicited Injections-site reactions[b]: 0-4 days	20.4% (41/201)	29.5% (59/200)

AE Type: Monitoring Period[a]	Intramuscular N=201 % (n/N)	Subcutaneous N=200 % (n/N)
Injection-site reactions: 0-28 days	0	0.5% (1/200)
Injection-site measles-like rash	0	0.5% (1/200)
Injection-site rubella-like rash	0	0
Injection-site varicella-like rash	0	0
Injection-site zoster-like rash	0	0
Solicited systemic adverse event from Day 0 to Day 28	67.7% (136/201)	61.1% (122/200)
Measles-like rash	0	1.0% (2/200)
Rubella-like rash	2.0% (4/201)	1.0% (2/200)
Varicella-like rash	0	2.0% (4/200)
Zoster-like rash	0	0
Mumps-like illness: 0-28 days	0.5% (1/201)	0
Fever (temperature ≥38.0°C): 0-28 days	50.0% (98/196)	47.2% (92/195)
Other systemic adverse events[d] from Day 0 to Day 28	56.7% (114/201)	49.0% (98/200)
AEs leading to study w/d: Visit 2 to Visit 3	0	0
SAEs: Visit 2 to Visit 3	0.5% (1/201)	0.5% (1/200)
Deaths: Visit 2 to Visit 3	0	0

Source: Adapted from STN 125108/1128 Study V221-036, Clinical Study Report, Text Table 21, Text Table 27, Table 94, Table 96
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
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 9 and Table 10 below.

Local Reactions Post-Dose 1

From Day 0 to Day 4 post-vaccination dose 1, participants in the IM group experienced less frequent injection-site reactions with at least one injection-site adverse reaction reported in 15.3% and 21.7% of participants in the IM and SC groups, respectively. The most frequently reported injection site reactions were injection-site pain (10.9%, IM group; 5.9%, SC group) and injection-site erythema (5.0%, IM group; 14.3%, SC group). Injection-site swelling occurred least frequently in both groups (IM, 1.0%; SC, 3.9%).

> Reviewer Comment
> Though 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.

Injection-site reactions reported from Day 0 to Day 28 occurred less frequently in the IM group (17.8%) as compared to the SC group (28.6). Six and 18 participants in the IM and SC groups, respectively, reporting an injection-site reaction during the reporting period, which was most often reported to be injection site erythema (4 participants vs. 13 participants in the IM and SC groups, respectively). An injection-site rash occurred only in participants in the SC group (1.0%). These were described as rubella-like (1 participant) and varicella-like (1 participant) injection rashes.

Table 9. Proportion of Participants Reporting at Least One Adverse Event Following First Vaccination, Safety Set, Study V221-036

Solicited Adverse Reaction	Intramuscular N=202	Subcutaneous N=203
Local (injection site)	--	--
Pain[a], % (n/N)	--	--
Any	10.9% (22/202)	5.9% (12/203)
Mild	8.9% (18/202)	3.9% (8/203)
Moderate	2.0% (4/202)	2.0% (4/203)
Erythema, % (n/N)	--	--
Any	5.0% (10/202)	14.3% (29/203)
≤2.5 cm	4.5% (9/202)	12.8% (26/203)
to >2.5 to ≤5.0 cm	0	1.5% (3/203)
>5.0 cm	0	0
Missing	0.5% (1/202)	0
Swelling, % (n/N)	--	--
Any	1.0% (2/202)	3.9% (8/203)
≤2.5 cm	1.0% (2/202)	3.9% (8/203)
Measles-like rash, % (n/N)	0	0
Rubella-like rash, % (n/N)	0	0.5% (1/203)
Varicella-like rash, % (n/N)	0	0.5% (1/203)
Systemic Events	--	--
Measles-like rash, % (n/N)	0.5% (1/202)	2.0% (4/203)
Rubella-like rash, % (n/N)	3.0% (6/202)	3.0% (6/203)
Varicella-like rash, % (n/N)	1.0% (2/202)	0.5% (1/203)
Mumps-like illness[b], % (n/N)	0.5% (1/202)	0
Fever (temperature ≥38ºC), % (n/N)[c]	--	--
Any Fever[d]	62.8% (125/199)	68.3% (136/199)
38.0-38.5°C	21.1% (42/199)	17.6% (35/199)
>38.5-39.0°C	18.1% (36/199)	21.6% (43/199)
>39.0-39.5°C	14.1% (28/199)	18.1% (36/199)
>39.5-40.0°C	7.0% (14/199)	9.0% (18/199)
≥40.01°C	2.5% (5/199)	2.0% (4/199)

Source: Adapted from STN 125108/1128 Study V221-036, Clinical Study Report, Text Table 24, Table 109, Table 111, Table 113, Table 101, Table 103, Table 105, Table 115, Text Table 20, Table 95

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. 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

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.

d. In the IM Group 96.0% of fevers were documented using the rectal route of measurement and 4.0% of fevers were documented only by the axillary route of measurement. In the SC Group 99.3% of fevers were documented using the rectal route of measurement and 0.7% of fevers were documented only by the axillary route of measurement.

Local Reactions Post-Dose 2

All injection-site reactions occurred between Day 0 and Day 4 after vaccination dose 2. From Day 0 to Day 4 post-vaccination dose 2, participants in the IM group experienced less frequent injection-site reactions with at least one injection-site adverse reaction was reported in 20.4% and 29.5% of participants in the IM and SC groups, respectively. The most frequently reported injection site reaction was injection-site erythema (15.4% and 27.0% of participants in the IM and SC groups, respectively). This was followed by injection-site pain (IM, 10.0%; SC, 10.0%) and injection-site swelling (IM, 6.0%; SC,

12.5%). Only 1 participant (SC group) reported an injection site reaction between Day 0 and Day 28 post-vaccination this participant reported an injection site rash of interest, which was described as a measles-like rash.

In both groups, after both dose 1 and dose 2, injection-site reactions were most commonly reported as mild intensity or with a diameter of ≤2.5 cm. There was one report of severe intensity injection site pain in a participant in the IM group after dose 2.

Table 10. Proportion of Participants Reporting at Least One Adverse Event Following Second Vaccination, Safety Set, Study V221-036

Solicited Adverse Reaction	Intramuscular N=201	Subcutaneous N=200
Local (injection site)	--	--
Pain[a], % (n/N)	--	--
Any	10.0% (20/201)	10.0% (20/200)
Mild	9.0% (18/201)	7.0% (14/200)
Moderate	0.5% (1/201)	3.0% (6/200)
Severe	0.5% (1/201)	0
Erythema, % (n/N)	--	--
Any	15.4% (31/201)1	27.0% (54/200)
≤2.5 cm	13.9% (28/201)	22.5% (45/200)
to >2.5 to ≤5.0 cm	1.0% (2/201)	4.5% (9/200)
Missing	0.5% (1/201)	0
Swelling, % (n/N)	--	--
Any	6.0% (12/201)	12.5% (25/200)
≤2.5 cm	5.0% (10/201)	11.0% (22/200)
>2.5 to ≤5.0 cm	1.0% (2/201)	1.0% (2/200)
Missing	0	0.5% (1/200)
Measles-like rash, % (n/N)	--	--
Rubella-like rash, % (n/N)	0	0
Varicella-like rash, % (n/N)	0	0
Systemic Events	--	--
Measles-like rash, % (n/N)	0	1.0% (2/200)
Rubella-like rash, % (n/N)	2.0% (4/201)	1.0% (2/200)
Varicella-like rash, % (n/N)	0	2.0% (4/200)
Mumps-like illness[b], % (n/N)	0.5% (1/201)	0

Solicited Adverse Reaction	Intramuscular N=201	Subcutaneous N=200
Fever (temperature ≥38ºC), % (n/N)[c]	--	--
Any Fever[d]	50.0% (98/196)	47.2% (92/195)
38.0-38.5°C	13.8% (27/196)	16.4% (32/195)
>38.5-39.0°C	18.4% (36/196)	10.8% (21/195)
>39.0-39.5°C	11.2% (22/196)	11.3% (22/195)
>39.5-40.0°C	5.6% 911/196)	7.2% (14/195)
≥40.01°C	1.0% (2/196)	1.5% (3/195)

Source: Adapted from STN 125108/1128 Study V221-036, Clinical Study Report, Text Table 25, Table 110, Table 112, Table 114, Table 102, Table 104, Table 106, Table 116, Table 96
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. 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. Mumps-like illness was defined as mumps-like symptoms such as swollen parotid
c. 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.
d. In the IM Group 96.0% of fevers were documented using the rectal route of measurement and 4.0% of fevers were documented only by the axillary route of measurement. In the SC Group 99.3% of fevers were documented using the rectal route of measurement and 0.7% of fevers were documented only by the axillary route of measurement.

Systemic Reactions Post-Dose 1

Non-injection site rashes between Day 0 to Day 28 occurred at similar rates in both groups 4.5%, IM group; 5.4%, SC group) with rubella-like rashes occurring most frequently (6 participants in each group) and no participants in either group reporting a zoster-like rash. All rashes were most commonly reported as mild to moderate in both groups, with no reports of severe cases. The median onset of all rashes was between 1.5 and 17 days with a median duration of 3 to 5 days in both groups. There was one case of a mumps-like illness (bilateral parotid gland enlargement, severe intensity) that occurred in the IM group between Day 13 and Day 28 post-vaccination and lasted for 15 days.

Fever occurred less frequently in the IM group (62.8%) as compared to the SC group (68.3%) and was considered related to ProQuad less frequently as well (IM, 35.6%; SC, 39.4%). The mean maximal temperature in both groups was 38.5°C (±0.8) between Day 0 and Day 28 post-vaccination dose 1. Temperature 39.5-40.0°C occurred in 7% of participants in the IM group and 9% of participants in the SC group. Median onset of fever was 8 days post-vaccination and fever ≥39.4°C occurring between Day 5 and Day 12 post-vaccination occurred in 13.1% and 11.1% of participants in the IM and SC groups, respectively with a mean maximal temperature of 38.2°C (±0.9) in both groups. Fever generally resolved in 2 days in both groups.

Post-Dose 2

Non-injection site rashes between Day 0 to Day 28 occurred at similar rates in both groups (2.0%, IM group; 4.0%, SC group) with rubella-like rashes occurring most frequently in the IM group (4 participants) and varicella-like rashes occurring most frequently in the SC group (4 participants) and no participants in either group reporting a zoster-like rash. All rashes were most commonly reported as mild to moderate in both groups, with no reports of severe cases. The median onset of all rashes was between 9 and 12.5 days with a median duration of 2 to 12 days in both groups. There was one case of a mumps-like illness in the same participant (IM group) that experienced a mumps-like illness after dose 1 (bilateral parotid gland enlargement, moderate intensity) that occurred on between Day 5 and Day 12 post-vaccination and lasted for 1 days.

Fever occurred less frequently at similar rates between groups (50% vs. 47.2%) after a second dose of ProQuad and was considered related to the vaccination at equal rates as well (16.9% vs. 17.0%). The mean maximal temperature in both groups was 38.3°C (±0.8). Temperature 39.5-40.0°C occurred in 5.6% of participants in the IM group and 7.2% of participants in the SC group. Median fever onset was 12- and 10-days post-vaccination in the IM and SC groups, respectively resolving after a median of 2 days. No mean temperature peak was seen after dose 2, though the mean maximal temperature of 37.8°C (±0.8) in both groups. In both groups, fever ≥39.4°C occurred less frequently between Days 5 and 12 post-vaccination after the second vaccine dose (IM, dose 1: 13.1% and dose 2: 4.1%; SC, dose 1: 11.1% and dose 2: 7.3%)

Unsolicited AEs

Post-Dose 1

Systemic AEs from Day 0 to Day 28 were similar between groups, with at least one systemic AE occurring in 60.4% of participants in the IM group and 59.6% of participants in the SC group.

The most common systemic AEs in all participants after dose 1 by MedDRA System Organ Class/Preferred Term were reported as follows: *Gastrointestinal disorders*/teething (IM, 9.4% and SC, 8.4%); *Infections and Infestations/*ear infections (IM, 10.9% and SC, 9.4%); and *Skin and Subcutaneous Tissue Disorders*/general rash, (IM, 4.5% and SC, 3.4%). Vaccine related systemic AEs other than fever were reported in 8.9% and 8.4% of IM and SC group participants, respectively. Severe vaccine-related AEs were reported in <2.0% of participants.

Post-Dose 2

Systemic AEs from Day 0 to Day 28 were similar between groups, with at least one systemic AE occurring in 56.7% of participants in the IM group and 49.0% of participants in the SC group

The most common systemic AEs in all participants after dose 2 by MedDRA System Organ Class/Preferred Term were as follows: *Gastrointestinal disorders*/teething (IM, 5.5% and SC, 6.0%); *Infections and Infestations*/ear infections (IM, 10.4% and SC, 11.0%) and *Skin and Subcutaneous Tissue Disorders*/rubelliform rash, (IM, 2.0% and SC, 1.5%) and eczema (IM, 2.0% and SC, 1.0%). Severe vaccine-related AEs were reported in <1.5% of participants. Vaccine related systemic AEs other than fever were reported in 6.0% and 5.0% of IM and SC group participants, respectively.

> Reviewer Comment
> To determine the rate of unsolicited AEs, the sponsor provided a response to an Information Request under STN 125108/1128 Amendment 17, in which the rates of solicited systemic rashes were excluded from the determination of systemic AEs. Rates of unsolicited AEs in the IM and SC groups were 58.4% and 56.7%, respectively, post dose 1 and 55.2% and 46.5%, respectively, post-dose 2. 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

Prior to Randomization

One 15-month-old male participant was diagnosed with viral encephalitis after informed consent was obtained but prior to randomization, baseline blood sampling, and vaccination. This participant was withdrawn from the study due to this SAE which was not considered related to the study vaccination.

Post-Dose 1

Between Visit 1 and Visit 2, SAEs were reported by four participants, two in each group. None of these events were considered related by the investigator as vaccine related. Of these events, there was one case of a simple febrile convulsion of moderate intensity that occurred in a 13-month-old male participant in the SC group, that started 31 days after the first dose of the vaccine. This participant was hospitalized and received antibiotics for associated diagnoses of tonsillitis and conjunctivitis. The convulsion resolved within 1 day and the participant was discharged from the hospital after 2 days.

Post-Dose 2

Between Visit 2 and Visit 3, SAEs were reported by 2 participants, one in each group. Neither of these events were considered related by the investigator as vaccine related.

> Reviewer Comment
> After review of all listed case narratives of SAEs, both post-doses 1 and 2, the clinical reviewer agrees that none of the SAEs that occurred throughout the study were likely related to study vaccination.

6.1.12.7 Dropouts and/or Discontinuations

No participants that were vaccinated were withdrawn due to an adverse event.

Table 11. Participant Disposition, Randomized Set, Study V221-036

Population	Intramuscular N=202 % (n/N)	Subcutaneous N=203 % (n/N)
Enrolled[a]	--	--
Vaccinated	--	--
First dose	100% (202/202)	100% (203/203)
Second dose	100% (202/202)	100% (203/203)
Completed study	99.5% (201/202)	98.5% (200/203)
Withdrawal due to	0.5% (1/202)	1.5% (3/203)
Consent withdrawal	0	0
Lost to follow-up	0.5% (1/202)	1.0% (2/203)
Non-compliance with protocol	0	0.5% (1/203)
Protocol deviation	43.6% (88/202)	44.3% (90/203)
Non-serious AE	--	--
Post-dose 1	80.7% (163/202)	86.2% (175/203)
Post-dose 2	74.6% (150/201)	72.0% (144/200)
Serious AE	--	--
Post-dose 1	0.5% (1/202)	0.5% (1/203)
Post-dose 2	0.5% (1/201)	0.5% (1/200)
Death	0	0

Source: Adapted from STN 125108/1128 Study V221-036, Clinical Study Report, Text Table 3, Text Table 6, Table 16, Text Table 20, Text Table 21
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. A total of 411 participants were enrolled in this study. Six participants were enrolled but not randomized

6.1.13 Study Summary and Conclusions

Study V221-036 was designed as a comparative immunogenicity and safety study of ProQuad in children 12 through 18 months of age who received the study vaccine by either the IM or SC route. The primary objective to demonstrate non-inferiority of two doses of ProQuad by IM route as compared to the SC

route at 6 weeks post-vaccination in terms of SRRs was met, however due to the off-label use of ProQuad in this study (2 doses administered within 30 days), the data from the pre-specified primary analysis of post-dose 2 is not considered to be aligned with the approved dosage and administration in the current USPI. Most children in the US do not receive a second dose of ProQuad until 4-6 years of age, therefore the post-dose 1 comparisons of intramuscular administration as compared to subcutaneous administration are most relevant. 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 measles, mumps and varicella post dose 1, while the analyses marginally missed the criterion for rubella (LL 95% CI of -5.5). The evaluation of SRRs 30 days post vaccination dose 1 showed comparable results between both groups, with the LL of the 95% CI for SRR was >90% for all vaccine antigens after intramuscular administration, meeting the CBER acceptance criterion for seroresponse rates for measles, mumps and rubella viruses. Seroresponse rates for varicella virus met the accepted criterion for success in non-inferiority for intramuscular administration compared to subcutaneous administration (LL of the 95% CI for difference in SRR >-10%). The descriptive evaluation of GMTs post-vaccination dose 1 demonstrated comparable humoral immune responses between the IM and SC routes for all vaccine antigens.

The safety profile of ProQuad when administered via the IM route was 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 study V221-036 support the safety and effectiveness of ProQuad when administered as a first dose 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 V221-036 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 V221-036 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 ProQuad was not evaluated in pregnant individuals. The data in Section 8.1 of the USPI of ProQuad comply with the requirements of the Pregnancy and Lactation Labeling Rule.

9.1.2 Use During Lactation

The intramuscular administration of ProQuad was not evaluated in lactating individuals. The data in Section 8.1 of the USPI of ProQuad 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 ProQuad 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

The Applicant also requested than an assessment of ProQuad in children greater than 13 years of age to 16 years of age be waived based on the following:

- The existing vaccines for individuals 13 through 16 years of age are M-M-R II and Varivax therefore there is limited benefit for ProQuad in this age group.
- ProQuad is currently only indicated for use in individuals 12 months through 12 years of age
- The sponsor is only seeking to include the IM RoA for all age groups currently approved for use of ProQuad as indicated in the USPI.

Additionally, the Applicant requested an extrapolation of the data obtained in the pediatric age groups studied to individuals ≥19 months through 12 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 through 12 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 ProQuad was not evaluated in immunocompromised individuals. The current USPI includes a warning in Section 4.2 stating the following:

Do not administer ProQuad vaccine to individuals who are immunodeficient or immunosuppressed due to disease or medical therapy. Measles inclusion body encephalitis (MIBE), pneumonitis and death as a direct consequence of disseminated measles vaccine virus infection have been reported in immunocompromised individuals inadvertently vaccinated with measles-containing vaccine. In this population, disseminated mumps and rubella vaccine virus infection have also been reported. 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 ProQuad was not evaluated in the geriatric population.

10. Conclusions

Study V221-036 enrolled and vaccinated 405 children, 12 through 18-months of age, who received 2 doses of ProQuad administered intramuscularly or subcutaneously, 30 days apart. This study demonstrated that intramuscular administration is appropriate for the proposed indication of ProQuad, which is supported by the demonstration of non-inferiority of the antibody responses after the first dose in terms of SRRs as measured by ELISA for antibodies to measles, mumps, rubella and varicella as compared to those elicited by the SC route, which is the current US-approved route of administration. For all vaccine antigens, the LL of the 95% CI for SRR was >90% after the first dose administered intramuscularly. In a descriptive analysis, intramuscular administration of one dose of the vaccine also elicited antibody responses to all vaccine virus antigens in terms of GMTs that were comparable to those elicited by the 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 ProQuad 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 ProQuad. 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 12. 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. • Varicella, commonly known as chicken pox, is a disease often seen in children less than ten years of age, and manifests as a generalized, pruritic, erythematous vesicular rash with 250 to 500 lesions, often in varying stages of development. Complications such as secondary bacterial infections (e.g., pneumonia), encephalitis and acute cerebellar ataxia can lead to more guarded outcomes. After primary infection with varicella-zoster virus, the virus establishes latency in the sensory ganglia and, with waning cell mediated immunity, can manifest later in life or during times of immunosuppression, as Zoster, also known as shingles. This presents as a painful, dermatomal, vesicular rash, though in immunocompromised hosts, can be severe and disseminated.	• 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 ProQuad administered as a first dose was evaluated in a clinical trial as compared to the SC route. A total of 405 children ages 12 through 18 months off age participated in this trial. In the trial 202 received the vaccine via the IM route and 203 received the vaccine via the SC route. • The effectiveness of ProQuad the IM RoA in prevention of measles, mumps, rubella or varicella was inferred from antigen specific serological responses compared to responses induced by the SC RoA. Immunological evaluations included non-inferiority of immunogenicity of *** in terms of SRR after two doses in MMRV-naïve children, 12 through 18 months of age.	• In a post hoc analysis, administration of one dose of ProQuad by the 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 30 days postvaccination. Lower bounds of the 95% CI for SRR >90% and comparable geometric mean antibody titers further support this conclusion.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons

Risk	• The rates of solicited injection site and systemic adverse reactions (AR) after IM administration were as follows:
	  • Post dose 1: Local pain 10.9%; local erythema 5%; local swelling 1%;
	  • Post-dose 2: local erythema 15.4%; local pain 10%; local swelling 6%; Most solicited ARs were reported as mild or moderate with none reporting Grade 3/severe solicited local ARs after dose 1 and only 1 participant reporting Grade 3/severe after dose 2. The rates of reported SAEs were low (<1.5%). 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.

Risk Management	• The most common risks of ProQuad 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 ProQuad in individuals 12 months of age through 12 years of age in prevention of measles, mumps, rubella and 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 ProQuad among individuals in the age groups for which it is indicated. The safety of the intramuscular RoA of ProQuad 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 ProQuad 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 ProQuad for the prevention of measles, mumps, rubella and varicella in individuals 12 months of age through 12 years of age.

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.