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| Application Type | BLA Supplement |
| STN | 125108/1128 |
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| Division / Office | DVRPA /OVRR |
| Committee Chair | Julianne C. M. Clifford, Ph.D. |
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| Priority Review | No |
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| Applicant | Merck Sharp & Dohme Corp. |
| Established Name | Measles, Mumps, Rubella and Varicella Virus Vaccine Live |
| (Proposed) Trade Name | ProQuad: measles, mumps, rubella and varicella vaccine (live) |
| Pharmacologic Class | Vaccine |
| Formulation(s), including Adjuvants, etc | Measles Virus Vaccine Live, active; Mumps Virus Vaccine Live, active; Rubella Virus Vaccine Live, active; Varicella Virus Vaccine Live, active |
| Dosage Form and Route of Administration | Subcutaneous injection |
| Dosing Regimen | Two-dose schedule with at least one month between first and the second dose |
| Indications and Intended Population | Active immunization against measles, mumps, rubella and varicella in healthy children aged 12 to 18 months |
| Purpose of Supplement | Addition of intramuscular route of administration |

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**GLOSSARY**

| | |
|---|---|
| Ab | Antibody |
| AE | Adverse Event |
| BLA | Biological License Application |
| BS | Blood Sample |
| CI | Confidence Interval |
| CSR | Clinical Study Report |
| ELISA | Enzyme Linked Immunosorbent Assay |
| gpELISA | Glycoprotein Enzyme Linked Immunosorbent Assay |
| IM | Intramuscular |
| IR | Information Request |
| PFU | Plaque Forming Units |
| rHA | Recombinant Human Albumin |
| SAE | Serious Adverse Event |
| SC | Subcutaneous |
| $TCID_{50}$ | 50% Tissue Culture Infective Dose |

## 1. Executive Summary

ProQuad is a combined live virus vaccine for vaccination against measles, mumps, rubella and varicella viruses in individuals 12 months of age and older. The approved route of administration of ProQuad is subcutaneous injection. Merck submitted an efficacy supplement (STN 125108/1128) to the Biological License Application (BLA) for ProQuad to include immunogenicity and safety data to add intramuscular (IM) as a new route of administration of the vaccine. Safety and immunogenicity data from Study V221-036 was submitted to support the application.

V221-036 is a Phase IIIb, open-label, randomized, comparative, multicenter study of the immunogenicity and safety of ProQuad when administered by the intramuscular (IM) route or subcutaneous (SC) route to healthy children aged 12 to 18 months of age. The first dose (0.5 mL) of ProQuad was administered at Visit 1 (Day 0) and the second dose (0.5 mL) was administered at Visit 2 (Day 30). Subjects were randomized into one of the two groups. In group 1, both doses were administered by the IM route and in group 2, both the doses were administered by the SC route. Three blood samples were collected from subjects participating in the study. The first blood sample (BS1) was taken at the time of visit 1, before the first vaccination; the second blood sample (BS2) was taken between Day 30 and 44 after the first vaccination, before or at Visit 2, and before the second vaccination; the third blood sample was collected between 42 and 56 days after the second vaccination, before or at the time of Visit 3. The primary endpoints were the seroconversion rates at six weeks post-dose 2 among subjects initially seronegative to measles (< 255 mIU/mL), mumps (< 10 ELISA Ab units/mL), rubella (< 10 IU/mL) or varicella (< 1.25 gpELISA units/mL). Seroconversion for measles, mumps, rubella and varicella is defined as achieving antibodies higher than the serostatus cutoff of the corresponding antigen.

The estimated differences of seroconversion rates (among subjects who were initially seronegative to measles, mumps, rubella or varicella, respectively) between the IM group and the SC group (i.e.,

IM group – SC group), stratified by region, were 0% (95% CI: -2.5%, 2.6%), 0.1% (95% CI: -3.0%, 3.3%), 0.7% (95% CI: -2.3%, 4.1%) and 0.7% (95% CI: -2.1%, 4.1%) for measles, mumps, rubella and varicella, respectively. For all four antigens, the lower bounds of the two-sided 95% CIs were greater than the pre-defined non-inferiority margin of -10%, implying that the immune response of the IM route was non-inferior to that of the SC route. In addition, the safety and reactogenicity profiles of the two treatment groups were similar throughout the 28-day post-vaccination safety follow-up after both doses.

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

## 2. Clinical and Regulatory Background

Proquad was first developed as a frozen vaccine to be stored at -15$^0$C or colder until use. The applicant later developed a refrigerator-stable formulation. ProQuad is indicated for individuals from 12 months of age who should receive two doses of ProQuad with an interval of at least one month or a single dose of a ProQuad followed by a second dose of a monovalent varicella vaccine to ensure optimal protection against varicella.

The applicant submitted this efficacy supplement STN 125108/1128 to the BLA for the refrigerator-stable formulation of ProQuad to include immunogenicity and safety data to support intramuscular (IM) as a new route of administration of the vaccine.

## 3. Submission Quality and Good Clinical Practices

### 3.1 Submission Quality and Completeness

The applicant did not submit the datasets in CDISC format since the study started on January 20, 2005, before it was required to submit the datasets in CDISC format. The submitted datasets did not contain detailed data descriptions and variable definitions. Multiple information requests regarding the detailed data definitions were communicated with the applicant such that the statistical review could be performed.

### 3.2 Compliance With Good Clinical Practices And Data Integrity

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

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

Please refer to review memos from other review disciplines.

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

### 5.1 Review Strategy

This statistical review focuses on the clinical safety and immunogenicity data collected in the Phase IIIb study V221-036. The applicant also submitted clinical safety and immunogenicity data collected in Phase IIIb study V205C-011. Of note, study V205C-011evaluated the immunogenicity

and safety of MMR II and VARIVAX when administered concomitantly by IM route or SC route at two separate injection sites to healthy children aged 12 to 18 months. Based on an internal discussion with the clinical reviewer, only study V221-036 is considered relevant to support the IM route of the ProQuad vaccine, hence, this memo focuses solely on study V221-036.

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

The following documents submitted to the sBLA are reviewed:

125108/1128.0 (Submitted on April 29, 2022)
Module 5: Clinical Study Reports
- V221-036 Clinical Study Report

125108/1128.1 (Submitted on June 23, 2022)
Module 1.11.4: Clinical Information Amendment

125108/1128.4 (Submitted on July 15, 2022)
Module 1.11.4: Clinical Information Amendment

125108/1128.5 (Submitted on August 17, 2022)
Module 1.11.4: Clinical Information Amendment

125108/1128.8 (Submitted on October 24, 2022)
Module 1.11.4: Clinical Information Amendment

125108/1128.9 (Submitted on November 17, 2022)
Module 1.11.4: Clinical Information Amendment

125108/1128.10 (Submitted on December 6, 2022)
Module 1.11.4: Clinical Information Amendment

125108/1128.11 (Submitted on December 16, 2022)
Module 1.11.4: Clinical Information Amendment

125108/1128.12 (Submitted on January 11, 2023)
Module 1.11.4: Clinical Information Amendment

125108/1128.13 (Submitted on January 12, 2023)
Module 1.11.4: Clinical Information Amendment

125108/1128.14 (Submitted on January 20, 2023)
Module 1.11.4: Clinical Information Amendment

125108/1128.15 (Submitted on January 31, 2023)
Module 1.11.4: Clinical Information Amendment

125108/1128.17 (Submitted on February 3, 2023)
Module 1.11.4: Clinical Information Amendment

125108/1128.18 (Submitted on February 10, 2023)
Module 1.11.4: Clinical Information Amendment

125108/1128.21 (Submitted on February 22, 2023)
Module 1.11.4: Clinical Information Amendment

### 5.3 Table of Studies/Clinical Trials

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

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

| Study | N | Age | Description |
|---|---|---|---|
| V221-036 | 405 | 12 months – 18 months | A Phase IIIb, open-label, randomized, comparative, multicenter 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 |

*Source: Summarized by the reviewer based on clinical study report (CSR) of V221-036.*

## 6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

### 6.1 Trial V221-036

#### 6.1.1 Objectives

***Primary Objectives***

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 to 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.

***Secondary Objectives***

• 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.

• 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.

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

### 6.1.2 Design Overview

Approximately 380 healthy children of either gender aged between 12 and 18 months were planned to be enrolled in ~40 centers in France and to be randomized in a 1:1 ratio into one of the two parallel groups, namely:

Group 1: a first dose of ProQuad administered by the IM route at 12 to 18 months of age and a second dose of ProQuad administered by the IM route 30 days later.

Group 2: a first dose of ProQuad administered by the SC route at 12 to 18 months of age and a second dose of ProQuad administered by the SC route 30 days later.

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

- The first blood sample (BS1) was to be collected after the subject's eligibility had been verified and the consent form was signed in the seven days prior to vaccination (Day 0) or at the time of the first visit.

- The second blood sample (BS2) was to be collected between Day 30 and Day 44 after first vaccination, before or at the time of Visit 2, and before the second vaccination.

- The third blood sample (BS3) was to be collected between Day 42 and Day 56 after the second vaccination or at the time of visit 3.

The randomization was stratified by center. Sera were analyzed for measles, mumps and rubella antibody titer by ELISA and for varicella antibody titer by gpELISA.

### 6.1.3 Population

Healthy male or female infants aged 12 to 18 months (From the $12^{th}$ month birthday to one day prior to the $19^{th}$ month birthday).

### 6.1.4 Study Treatments or Agents Mandated by the Protocol

ProQuad is a lyophilized vaccine including powder and diluent for suspension for injection stored in separate vials. After reconstitution, one dose (0.5 mL) contains

- Measles virus Enders' Edmonston strain (live attenuated) not less than 3.00 $\log_{10}$ $TCID_{50}$
- Mumps virus Jeryl Lynn (Level B) strain (live attenuated) not less than 4.30 $\log_{10}$ $TCID_{50}$
- Rubella virus Wistar RA 27/3 strain (live attenuated) not less than 3.00 $\log_{10}$ $TCID_{50}$
- Varicella virus Oka/Merck strain (live attenuated) not less than 3.99 $\log_{10}$ PFU

where $TCID_{50}$ denotes the 50% Tissue culture infective dose and PFU is the abbreviation for plaque forming units.

### 6.1.6 Sites and Centers

This was a multicenter study (33 of the planned 41 centers in France recruited subjects). As planned in the protocol, the centers were divided into 3 regions based on geographical locations.

### 6.1.7 Surveillance/Monitoring

Please refer to the clinical reviewer's memo.

### 6.1.8 Endpoints and Criteria for Study Success

Immunogenicity Endpoints

Primary Endpoints

Measles, mumps and rubella antibody titers were measured by ELISA and varicella antibody titers were measured by gpELISA.

The primary immunogenicity analyses are based on the antibody response rates to measles, mumps, rubella and varicella measured 42 days following the second dose of ProQuad in both groups (BS3).

- The response rate for measles is the percentage of subjects with measles antibody titers ≥ 255 mIU/mL in subjects whose baseline measles antibody titer (BS1) is < 255 mIU/mL.

- The response rate for mumps is the percentage of subjects with mumps antibody titers ≥ 10 ELISA Ab units/mL in subjects whose baseline mumps antibody titer (BS1) is < 10 ELISA Ab units/mL.

- The response rate for rubella is the percentage of subjects with rubella antibody titers ≥ 10 IU/mL in subjects whose baseline rubella antibody titer (BS1) is < 10 IU/mL.

- The response rate for varicella is the percentage of subjects with varicella antibody titers ≥ 5 gpELISA units/mL in subjects whose baseline varicella antibody titer (BS1) is < 1.25 gpELISA units/mL.

The Group 1 (IM) response rates will be considered as non-inferior to the Group 2 (SC) response rates if for each valence (measles, mumps, rubella, and varicella), the 95% two-sided Confidence Interval (CI) around the difference in response rates (i.e. Group 1 – Group 2) excludes a decrease of 10% or more (i.e., the non-inferiority margin is -10%). Success in this study would be declared if noninferiority criteria are met for all four valences.

Secondary Endpoints

The secondary immunogenicity endpoints include:

- The antibody response rates to measles, mumps, rubella and varicella measured 30 days following the first dose of ProQuad (BS2) in both groups.

- The antibody titers to measles, mumps, rubella and varicella measured 30 days following the first dose of ProQuad (BS2) and 42 days following the second dose of ProQuad (BS3) in both groups.

- The percentage of subjects with varicella antibody titers ≥ 1.25 gpELISA units/mL in subjects whose baseline varicella antibody titer (BS1) is < 1.25 gpELISA units/mL is used as a secondary definition of seroconversion following the first and the second dose of ProQuad.

Safety Endpoints

The safety endpoints include:

- From Day 0 to Day 4 following each dose: Solicited injection-site adverse reactions including
    - injection site erythema,
    - injection site swelling,
    - injection site pain.
- From Day 0 to Day 28 following each dose: Unsolicited injection-site adverse reactions and systemic adverse events including
    - other injection-site adverse reactions (May include injection site erythema, injection site swelling, injection site pain 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 adverse events.

- From Day 0 to the last visit of the concerned subject:
    - serious adverse events.

### 6.1.9 Statistical Considerations & Statistical Analysis Plan

Analysis Sets

Randomized Set

The Randomized Set included all randomized subjects. A subject was considered as randomized if a randomization number has been assigned.

Full Analysis Set (FAS)

The Full Analysis Set included all randomized subjects who received at least one dose of the study vaccine and with any post-vaccination immunogenicity evaluation. Subjects were analyzed according to the route of administration from randomization.

All subjects with serology results at Visit 2 (BS2) or at Visit 3 (BS3) were included in the analysis using the Full Analysis Set regardless of the antibody titers at baseline (BS1).

Per Protocol Set (PPS)

The Per Protocol Sets included all randomized subjects who had valid immunogenicity results pre- and post-dose for at least one antigen, excluding subjects with protocol violation(s) which may interfere with the immunogenicity evaluation at the corresponding time point. Specifically,

- **PPS1** included all randomized subjects excluding subjects with protocol violation(s) which may interfere with the Post-dose 1 immunogenicity evaluation.

- **PPS2** included all randomized subjects excluding subjects with protocol violation(s) which may interfere with the Post-dose 2 immunogenicity evaluation.

The following subsets of subjects were distinguished for the Per Protocol immunogenicity analyses:

The PPS1 consisted of 5 subsets, namely:

- PPS1 with only subjects initially seronegative to measles (measles antibody titers < 255 mIU/mL at baseline);
- PPS1 with only subjects initially seronegative to mumps (mumps antibody titers < 10 ELISA Ab units/mL at baseline);
- PPS1 with only subjects initially seronegative to rubella (rubella antibody titers <10 IU/mL at BS1);
- PPS1 with only subjects initially seronegative to varicella (varicella antibody titers <1.25 gpELISA units/mL at baseline);
- PPS1 with subjects initially seronegative to measles, mumps, rubella and varicella.

Five similar subsets were defined for PPS2 analogously.

Safety Set

The Safety Set included all subjects who received at least one dose of the study vaccines and who had safety follow-up data at the corresponding time point. The Safety Set consisted of 2 subsets, namely:

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

Subjects in the safety set were analyzed according to the actual route of vaccination at the corresponding time point.

Sample Size

The power for this study has been calculated using the Farrington and Manning method.

It was expected that up to 20% of subjects enrolled in the study would be non-evaluable for the analyses of the measles, mumps and rubella immunogenicity endpoints based on the Per Protocol set, due to lost to follow-up or protocol deviations up to dose 2 (15%) and the assumption that 5% of subjects would have pre-vaccination measles antibody titers ≥255 mIU/mL, 5% of subjects would have pre-vaccination mumps antibody titers ≥ 10 ELISA antibody units/mL and 5% of subjects would have pre-vaccination rubella antibody titers ≥10 IU/mL.

It was also expected that up to 25% of subjects enrolled in the study would be non-evaluable for the varicella response rate analysis based on the Per Protocol set, due to lost to follow-up or protocol deviations up to dose 2 (15%) and the assumption that 10% of subjects would have pre-vaccination varicella antibody titers ≥1.25 gpELISA units/mL.

Consequently, 190 subjects per group would result in 152 evaluable subjects per group for the measles, mumps and rubella analyses and 142 evaluable subjects per group for the varicella analyses using the Per Protocol set. With 152 evaluable subjects in Group 1 and Group 2, assuming that the true response rates to measles, mumps and rubella in Group 2 are 97%, 97% and 97%, respectively, and that there is no difference between groups, the study will have approximately 98.9% power to declare non-inferiority for each of the measles, mumps and rubella antigens using a one-sided 2.5% type I error rate and a -10% non-inferiority margin.

With 142 evaluable subjects in Group 1 and Group 2, assuming that the true response rate to varicella in Group 2 is 95% and no difference between groups, the study will have approximately 93.0% power to declare non-inferiority for the varicella response rate using a one-sided 2.5% type I error rate and a -10% non-inferiority margin.

The overall power of the study will be around 90% for the success of the primary objective.

Analysis of Immunogenicity

The non-inferiority analysis of Group 1 response rates compared to Group 2 response rates was performed based on the stratified Miettinen and Nurminen confidence interval. The stratification was done by geographical regions with weights proportional to the numbers of subjects within each region. The region and the corresponding center numbers are provided in Table 2. For each valence, the estimated between-group difference in response rates (Group 1 - Group 2) was calculated together with its two-sided 95% CI. If the lower bound of the CI was greater than -10% (i.e., the non-inferiority margin), it would be concluded that the Group 1 response rate is non-inferior to the Group 2 response rate for that particular valence.

Antibody response rates Post-dose 2 (subsets of PPS2) would be described by group for each valence, per region and for all subjects, together with their two-sided 95% CIs.

Table 2: Centers considered for each region for stratified analysis

| Region | Center Number |
|---|---|
| Region North-East and South-West | 11, 15, 17, 18, 22, 24, 25, 40, 41, 42, 46, 48 |
| Region North-West | 21, 26, 28, 29, 30, 31, 32, 34, 37, 43, 44, 49 |
| Region South-East | 16, 19, 20, 33, 35, 38, 45, 47, 50 |

*Source: Section 2.3.3 of the Statistical Analysis Plan submitted in sBLA 125108/1128.0.*

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

Sensitivity analysis

A non-stratified analysis was performed using the method without stratification proposed by Miettinen and Nurminen.

Multiplicity Adjustment

No adjustment of the significance level for multiplicity was required since the two-sided 95% CI around the difference in response rate must meet the non-inferiority criteria for all four valences to meet the success criteria.

Interim analysis

None.

Analysis of Safety

The safety analysis would be performed on the Safety Sets (Post-dose 1 and Post-dose 2). Proportions would be calculated within the subjects vaccinated and providing safety follow-up (e.g., exposed to the risk of experiencing an event).

In case of a vaccine injection mistake (e.g., undefined route, inconsistent route at second vaccination compared to first vaccination, mis-reconstitution), the subject would not be included in the analysis at that time point.

### 6.1.10 Study Population and Disposition

#### 6.1.10.1 Populations Enrolled/Analyzed

A total of 405 healthy infants aged 12-18 months were enrolled from 33 centers in France and were randomly allocated to either the IM group (202 subjects) or the SC group (203 subjects).

#### 6.1.10.1.1 Demographics

The demographic and baseline characteristics in the safety set post dose 1 are described in Table 3. In the SC group, the percentage of female participants (45.8%) was slightly lower compared to the percentage of male participants (54.2%). The demographic and baseline characteristics were otherwise generally balanced across treatment arms and were similar in the safety set post-dose 2, per protocol set post-dose 1 and per protocol set post-dose 2.

Table 3: Demographic and Baseline Characteristics (Safety Set Post-Dose 1)

| | Group 1 (IM) (N=202) | Group 2 (SC) (N=203) | Total (N=405) |
|---|---|---|---|
| Sex n (%) | | | |
| Male | 96 (47.5) | 110 (54.2) | 206 (50.9) |
| Female | 106 (52.5) | 93 (45.8) | 199 (49.1) |
| Age, months | | | |
| Mean age (SD) | 13.71 (1.44) | 13.66 (1.53) | 13.68 (1.48) |
| Median age | 13.3 | 13.3 | 13.3 |
| Age range | 11.9-18.0 | 11.7-18.3 | 11.7-18.3 |
| Region n (%) | | | |
| Region 1 (North-East, Center, South-West) | 71 (35.1) | 76 (37.4) | 147 (36.3) |
| Region 2 (North-West) | 67 (33.2) | 64 (31.5) | 131 (32.3) |
| Region 3 (South-West) | 64 (31.7) | 63 (31.0) | 127 (31.4) |

*Source: Adapted from After Text Table 13 and After Text Table 25 of the CSR of Study V221-036, submitted in sBLA 125108/1128.0.*

#### 6.1.10.1.3 Subject Disposition

The subject disposition information of V221-036 is provided in Table 4. The dropouts were generally balanced across the treatment arms. The proportion of subjects retained in the per protocol sets from the randomized set were also generally comparable across treatment arms.

Table 4: Subject Dispositions (Randomized Set)

| | Group 1 (IM) (N=202) | Group 2 (SC) (N=203) | Total (N=405) |
|---|---|---|---|
| Randomized Set | 202 | 203 | 405 |
| Full Analysis Set (FAS) | 201 (99.5) | 203 (100) | 404 (99.8) |
| Per Protocol Set Post-dose 1 | | | |
| PPS1 – measles | 153 (75.7) | 148 (72.9) | 301 (74.3) |
| PPS1 – mumps | 152 (75.2) | 149 (73.4) | 301 (74.3) |
| PPS1 – rubella | 129 (63.9) | 133 (65.5) | 262 (64.7) |
| PPS1 – varicella | 138 (68.3) | 136 (67.0) | 274 (67.7) |
| Per Protocol Sets Post-dose 2 | | | |
| PPS2 – measles | 153 (75.7) | 147 (72.4) | 300 (74.1) |
| PPS2 – mumps | 152 (75.2) | 148 (72.9) | 300 (74.1) |
| PPS2 – rubella | 129 (63.9) | 132 (65.0) | 261 (64.4) |
| PPS2 – varicella | 138 (68.3) | 134 (66.0) | 272 (67.2) |
| Safety Set Post-dose 1 | 202 (100) | 203 (100) | 405 (100) |
| Safety Set Post-dose 2 | 201 (99.5) | 200 (98.5) | 401 (99.0) |

*Source: Text Table 7 of the CSR of Study V221-036, submitted in sBLA 125108/1128.0.*

### 6.1.11 Immunogenicity Analyses

#### 6.1.11.1 Analyses of Primary Endpoints

The primary immunogenicity endpoints were the response rates to measles, mumps, rubella and varicella measured 42 days following the second dose of ProQuad in both groups. A summary of seroconversion rates is described in Table 5. The seroconversion rates were higher than 99% for all antigens in both IM and SC groups. The 95% CIs of the seroconversion rate differences were computed using the stratified MN method with region as stratum and are provided in Table 6. Since the lower bounds of all four confidence intervals were greater than -10%, the noninferiority criteria were met for all four antigens.

As a sensitivity analysis, the seroconversion rate difference with 95% CIs were summarized in Table 7 based on the non-stratified MN method. For all four antigens, the 95% CIs obtained based on the stratified and non-stratified methods were similar.

Table 5: Antibody response rates for Measles, Mumps, Rubella and Varicella 42 days after the Second dose of ProQuad for subjects initially seronegative to Measles, Mumps, Rubella or Varicella (antigen specific Per Protocol Set Post-Dose 2)

| | Group 1 (IM) N | Group 1 (IM) Response Rate n (%) | Group 1 (IM) 95% CI | Group 2 (SC) N | Group 2 (SC) Response Rate n (%) | Group 2 (SC) 95% CI |
|---|---|---|---|---|---|---|
| Measles | 153 | 153 (100) | [97.6, 100] | 147 | 147 (100) | [97.5, 100] |
| Mumps | 152 | 151 (99.3) | [96.4, 100] | 148 | 147 (99.3) | [96.3, 100] |
| Rubella | 129 | 129 (100) | [97.2, 100] | 132 | 131 (99.2) | [95.9, 100] |
| Varicella | 138 | 138 (100) | [97.4, 100] | 134 | 133 (99.3) | [95.9, 100] |

*Source: Text Table 12 of the CSR of V221-036 submitted in sBLA 125108/1128.0.*

Table 6: Estimates of seroconversion rate difference and 95% CI using the stratified MN method (antigen specific Per Protocol Set Post-Dose 2)

| | Group Difference | 95% CI |
|---|---|---|
| Measles | 0.00% | [-2.5, 2.6] |
| Mumps | 0.10% | [-3.0, 3.3] |
| Rubella | 0.70% | [-2.3, 4.1] |
| Varicella | 0.70% | [-2.1, 4.1] |

*Source: Text Table 12 of the CSR of V221-036 submitted in sBLA 125108/1128.0.*
*The seroconversion rate difference is computed using the stratified MN method with regions considered as strata.*

Table 7: Estimates of seroconversion rate difference and 95% CI using the non-stratified MN method (antigen specific Per Protocol Set Post-Dose 2)

| | Group Difference | 95% CI |
|---|---|---|
| Measles | 0.00% | [-2.5, 2.6] |
| Mumps | 0.00% | [-3.0, 3.1] |
| Rubella | 0.80% | [-2.2, 4.2] |
| Varicella | 0.70% | [-2.0, 4.1] |

*Source: Table 43 of the CSR of V221-036 submitted in sBLA 125108/1128.0.*

*Reviewer's Comment:*

*Two participants (1 in each group) received non-study vaccinations (both received Prevnar and Pentavac). The first participant (IM group, PATID* (b) (6) *received these vaccines 6 days prior to their Visit 3 blood sampling. This participant was included in the immunogenicity analyses for all vaccine virus antigens, except for rubella virus due to being seropositive for rubella at baseline. The second participant (SC group, PATID* (b) (6) *received these vaccines on the day of the Visit 3 blood sampling. This participant was included in all immunogenicity analyses. Injection of non-study vaccines between inclusion visit and post-vaccination blood sample (including both blood sampling 2 and blood sampling 3) was considered as a protocol violation, however, due to the proximity of administration of these vaccines to the Visit 3 blood*

*draw as well as the likely inability 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. From the statistical perspective, even if these two subjects were excluded from the per protocol set for immunogenicity analyses, the noninferiority criteria would have been unaffected.*

*I have independently verified the results related to the non-stratified analysis using BinomDiffCI function of DescTools package of the R software.*

*I verified the stratified MN confidence interval using the scoreci function of the ratesci package in R. The summary of results is provided in Table 8. Despite of some minor differences (<0.1%) between my results and the applicant's results, the final conclusions are the same.*

Table 8: Estimated seroconversion rate difference and 95% CI, stratified MN method, computed by the reviewer. (Antigen specific Per Protocol Set Post-Dose 2)

| | Group Difference | 95% CI |
|---|---|---|
| Measles | 0.0% | - |
| Mumps | 0.1% | [-3.0, 3.3] |
| Rubella | 0.7% | [-2.3, 4.2] |
| Varicella | 0.7% | [-2.1, 4.1] |

*Source: Computations by the reviewer based on the datasets submitted for study V221-036 in sBLA 125108/1128.0.*

*Of note, since 100% of the subjects in both groups achieved seroconversion for measles, the scoreci function was not able to produce a CI. Upon further investigation, this was because the denominator is 0, preventing from further iterative calculations, based on the formula provided in Miettinen and Nurminen (1985). It was further noted that since the seroconversion rates were 100% in both groups across regions consistently, which would suggest that the non-stratified MN CI is appropriate. Since the lower limit of the non-stratified MN confidence interval of the seroconversion rate difference is -2.5% (Table 7), the noninferiority criterion was met.*

*Furthermore, I performed a sensitivity analysis by assuming that 1 subject from each region of each treatment group did not achieve seroconversion for measles, thereby eliminating the possibility of denominator being 0 to enable the use of the stratified MN method, to represent worse outcomes than the actually observed data, and evaluate whether the noninferiority criterion would be met for worse scenarios. In each of these six scenarios, I used the stratified MN method to compute the seroconversion rate difference between groups with the 95% CI and summarized the results in Table 9. Across the 6 scenarios, the smallest value of the lower limits is -5.4% and the highest of the upper limits is 3.8%, suggesting that the noninferiority criteria would have been met for all 6 scenarios. Scenarios 1, 2, and 3 are more extreme in terms of demonstrating non-inferiority of the IM group versus SC group compared to what was observed in this V221-036 study. Since noninferiority criteria would have been met for these three cases, it can be concluded that noninferiority is demonstrated for measles in this clinical study.*

Table 9: Estimated seroconversion rate differences and confidence intervals in different scenarios related to measles based on stratified MN method computed by the reviewer – Sensitivity analysis.

| | Group 1 (IM) Region 1 | Group 1 (IM) Region 2 | Group 1 (IM) Region 3 | Group 2 (SC) Region 1 | Group 2 (SC) Region 2 | Group 2 (SC) Region 3 | Estimated Difference (95% CI) |
|---|---|---|---|---|---|---|---|
| Sample Size (N) | 64 | 65 | 24 | 72 | 55 | 20 | |
| Seroconversion (n) | | | | | | | |
| Scenario 1 | 63 | 65 | 24 | 72 | 55 | 20 | -0.7 (-4.0, 1.8) |
| Scenario 2 | 64 | 64 | 24 | 72 | 55 | 20 | -0.6 (-4.0, 2.0) |
| Scenario 3 | 64 | 65 | 23 | 72 | 55 | 20 | -0.6 (-5.4, 2.0) |
| Scenario 4 | 64 | 65 | 24 | 71 | 55 | 20 | 0.7 (-1.9, 3.8) |
| Scenario 5 | 64 | 65 | 24 | 72 | 54 | 20 | 0.7 (-1.7, 3.8) |
| Scenario 6 | 64 | 65 | 24 | 72 | 55 | 19 | 0.7 (-1.7, 3.8) |

*Source: Computations by the reviewer based on the datasets submitted for study V221-036 in sBLA 125108/1128.0.*
*The seroconversion rate difference is computed using the stratified MN method with regions considered as strata.*

### 6.1.11.2 Analyses of Secondary Endpoints

The antibody response rates to all four antigens measured 4 weeks after the first dose of ProQuad are provided in Table 10. The antigen specific response rates were similar in both groups.

The antibody titers to all four antigens measured 4 weeks after the first dose of ProQuad and six weeks after the second dose of ProQuad are summarized in Table 11. The Post dose 2 GMTs were generally higher than the Post dose 1 GMTs except for Measles in the IM group, where the Post dose 1 GMT for Measles was 4058.7 mIU/mL and the Post dose 2 GMT was 3953.7 mIU/mL. The antigen specific GMTs were generally similar between both groups at each time point except that the GMT for Varicella Post dose 2 in the IM group (358.1 gpELISA units/mL) was slightly higher compared to the GMT for Measles Post dose 2 in the SC group (261.8 gpELISA units/mL).

The proportions of subjects with varicella antibody titers ≥ 1.25 gpELISA units/mL in subjects who were seronegative at baseline for varicella antigens at four weeks after the first dose of ProQuad and 6 weeks after the second dose of ProQuad are summarized in Table 12. For both groups, more than 99% of the subjects had varicella antibody titers ≥ 1.25 gpELISA units/mL at either time point.

Table 10: Antibody response rates for Measles, Mumps, Rubella and Varicella 4 weeks after the First dose of ProQuad for subjects initially seronegative to Measles, Mumps, Rubella or Varicella (antigen specific Per Protocol Set Post-Dose 1)

| | Group 1 (IM) N | Group 1 (IM) Response Rate n (%) | Group 1 (IM) 95% CI | Group 2 (SC) N | Group 2 (SC) Response Rate n (%) | Group 2 (SC) 95% CI |
|---|---|---|---|---|---|---|
| Measles | 153 | 153 (100) | [97.6, 100] | 147 | 144 (97.3) | [93.2, 99.3] |
| Mumps | 152 | 148 (97.4) | [93.4, 99.4] | 148 | 136 (91.3) | [85.5, 95.3] |
| Rubella | 129 | 127 (98.4) | [94.5, 99.8] | 133 | 133 (100) | [97.3, 100] |
| Varicella | 138 | 138 (98.6) | [94.9, 99.8] | 136 | 133 (99.3) | [94.8, 99.8] |

*Source: Text Table 13 of the CSR of V221-036 submitted in sBLA 125108/1128.0.*

Table 11: Summary of GMT to Measles, Mumps, Rubella and Varicella at 4 weeks after the first dose of ProQuad and 6 weeks after the second dose of ProQuad for subjects initially seronegative to Measles, Mumps, Rubella or Varicella (Antigen specific Per Protocol Sets)

| Antigen | Visit | Group 1 (IM) N | Group 1 (IM) GMT (95% CI) | Group 2 (SC) N | Group 2 (SC) GMT (95% CI) |
|---|---|---|---|---|---|
| Measles (mIU/mL) | Post-dose 1 | 153 | 4058.7 (3643.1, 4521.8) | 148 | 3327.0 (2835.4, 3903.9) |
| Measles (mIU/mL) | Post-dose 2 | 153 | 3953.7 (3497.2, 4469.9) | 147 | 3748.6 (3270.9, 4296.0) |
| Mumps (ELISA Ab units/mL) | Post-dose 1 | 152 | 120.0 (102.2, 140.9) | 149 | 101.9 (84.2, 123.2) |
| Mumps (ELISA Ab units/mL) | Post-dose 2 | 152 | 157.9 (138.6, 180.0) | 148 | 168.8 (146.9, 194.0) |
| Rubella (IU/mL) | Post-dose 1 | 129 | 46.9 (39.7, 55.4) | 133 | 50.9 (44.9, 57.7) |
| Rubella (IU/mL) | Post-dose 2 | 129 | 92.8 (82.4, 104.5) | 132 | 94.2 (83.2, 106.6) |
| Varicella (gpELISA units/mL) | Post-dose 1 | 138 | 25.0 (22.5, 27.7) | 136 | 23.6 (20.9, 26.7) |
| Varicella (gpELISA units/mL) | Post-dose 2 | 138 | 358.1 (300.1, 427.4) | 134 | 261.8 (216.7, 316.4) |

*Source: Text Table 14 and Text Table 15 of CSR of study V221-036 submitted in sBLA 125108/1128.0.*

Table 12: Rates of subjects with Varicella antibody titer ≥ 1.25 gpELISA units/mL 4 weeks after First dose and 6 weeks after second dose of ProQuad (Per Protocol Sets Post Dose 1 and Per Protocol Set Post Dose 2 for Varicella)

| | Group 1 (IM) N | Group 1 (IM) n (%) | Group 1 (IM) 95% CI | Group 2 (SC) N | Group 2 (SC) n (%) | Group 2 (SC) 95% CI |
|---|---|---|---|---|---|---|
| Post Dose 1 | 138 | 138 (100) | [97.4, 100] | 136 | 135 (99.3) | [96.0, 100] |
| Post Dose 2 | 138 | 138 (100) | [97.4, 100] | 134 | 133 (99.3) | [95.9, 100] |

*Source: Text Table 17 and Text Table 18 of CSR of study V221-036 of submitted in sBLA 125108/1128.0.*

*Reviewer's comments: I have independently verified these immunogenicity results based on the datasets submitted to sBLA 125108/1128.0 by the applicant.*

### 6.1.12 Safety Analyses

#### 6.1.12.1 Solicited Adverse Events

The Post-Dose 1 and Post-dose 2 safety analyses were performed on the Safety Set Post-Dose 1 and Safety Set Post-Dose 2, respectively. The summary of solicited local injection site reactions between day 0 to day 4 after Dose 1 and Dose 2 are provided in Tables 13 and 14, respectively. The proportions of subjects experiencing at least one solicited injection site AEs were generally numerically higher in the SC group compared to the IM group. Injection site erythema was reported by slightly more participants in the SC group (14.3%) compared to the IM group (5.0%) Post-Dose 1. A similar trend was observed for the Post-Dose 2 safety results; injection site erythema was reported by 27% participants in the SC group compared to 15.4% in the IM group. Injection site pain was reported by slightly more participants in the IM group (10.9%) compared to the SC group (5.9%) Post-Dose 1. However, similar percentages of subjects experienced injection site pain Post-Dose 2 in the IM group (10.0%) compared to the SC group (10.0%).

Table 13: Post-Dose 1 Solicited Local Injection site adverse events between Day 0 to Day 4 (Safety Set Post-Dose 1)

| | Group 1 (IM) N=202 [n (%)] | Group 2 (SC) N=203 [n (%)] |
|---|---|---|
| Any Solicited Local Injection-site AE (Days 0 to 4) | 31 (15.3) | 44 (21.7) |
| Injection site Erythema | 10 (5.0) | 29 (14.3) |
| Mild (≤ 2.5 cm) | 9 (4.5) | 26 (12.8) |
| Moderate (> 2.5 cm to ≤ 5 cm) | 0 (0) | 3 (1.5) |
| Severe (> 5 cm) | 0 (0) | 0 (0) |
| Missing | 1 (0.5) | 0 (0) |
| Injection site Pain | 22 (10.9) | 12 (5.9) |
| Mild | 18 (8.9) | 8 (3.9) |
| Moderate | 4 (2.0) | 4 (2.0) |
| Severe | 0 (0) | 0 (0) |
| Injection site Swelling | 2 (1.0) | 8 (3.9) |
| Mild (≤ 2.5 cm) | 2 (1.0) | 8 (3.9) |
| Moderate (> 2.5 cm to ≤ 5 cm) | 0 (0) | 0 (0) |
| Severe (> 5 cm) | 0 (0) | 0 (0) |
| Missing | 0 (0) | 0 (0) |

*Source: Table 87 of CSR of V221-036 submitted in sBLA 125108/1128.0.*

Table 14: Post-Dose 2 Solicited Local Injection site adverse events between Day 0 to Day 4 (Safety Set Post-Dose 2)

| | Group 1 (IM) N=201 [n (%)] | Group 2 (SC) N=200 [n (%)] |
|---|---|---|
| Any Solicited Local Injection-site AE (Days 0 to 4) | 41 (20.4) | 59 (29.5) |
| Injection site Erythema | 31 (15.4) | 54 (27.0) |
| Mild (≤ 2.5 cm) | 28 (13.9) | 45 (22.5) |
| Moderate (> 2.5 cm to ≤ 5 cm) | 2 (1.0) | 9 (4.5) |
| Severe (> 5 cm) | 0 (0) | 0 (0) |
| Missing | 1 (0.5) | 0 (0) |
| Injection site Pain | 20 (10.0) | 20 (10.0) |
| Mild | 18 (9.0) | 14 (7.0) |
| Moderate | 1 (0.5) | 6 (3.0) |
| Severe | 1 (0.5) | 0 (0) |
| Injection site Swelling | 12 (6.0) | 25 (12.5) |
| Mild (≤ 2.5 cm) | 10 (5.0) | 22 (11.0) |
| Moderate (> 2.5 cm to ≤ 5 cm) | 2 (1.0) | 2 (1.0) |
| Severe (> 5 cm) | 0 (0) | 0 (0) |
| Missing | 0 (0) | 1 (0.5) |

*Source: Table 88 of CSR of V221-036 submitted in sBLA 125108/1128.0.*

Summaries of systemic adverse reactions occurring between Day 0 and Day 28 Post-dose 1 and Post-Dose 2 are provided in Tables 15 and 16, respectively. At each time point, percentages of subjects who experienced at least one systemic adverse reaction were similar in both groups. The percentage of subjects who experienced fever ≥ 38.0º C was slightly lower for the IM group (62.8%) compared to the SC group (68.3%) in the Post-Dose 1 safety set. Similar proportions of subjects experienced fever ≥ 38.0º C in the IM group (50.0%) and SC group (47.2%) Post-Dose 2.

Among the subjects in the Safety set Post-dose 1, in the IM Group 96.0% of fevers were based on the rectal route of measurement and 4.0% of fevers were based on the axillary route of measurement; in the SC Group 99.3% of fevers were based on the rectal route of measurement and 0.7% of fevers were based on the axillary route of measurement.

Among the subjects in the Safety set Post-dose 2, in the IM Group 95.9% of fevers were based on the rectal route of measurement and 4.1% of fevers were based on the axillary route of measurement; in the SC Group 98.9% of fevers were based on the rectal route of measurement and 1.1% of fevers were based on the axillary route of measurement.

Table 15: Post-dose 1 Systemic Adverse Reactions occurring between Day 0 and Day 28 (Safety Set Post Dose 1)

| | Group 1 (IM) N=202 [n (%)] | Group 2 (SC) N=203 [n (%)] |
|---|---|---|
| Any Systemic Adverse Reactions | 158 (78.2) | 167 (82.3) |
| Measles-like rash | 1 (0.5) | 4 (2.0) |
| Rubella-like rash | 6 (3.0) | 6 (3.0) |
| Varicella-like rash | 2 (1.0) | 1 (0.5) |
| Zoster/Zoster-like rash | 0 (0) | 0 (0) |
| Mumps-like illness | 1 (0.5) | 0 (0) |
| Fever (Temperature ≥ 38.0°C)* | 125 (62.8) | 136 (68.3) |
| 38.00 - 38.50°C | 42 (21.1) | 35 (17.6) |
| 38.51 - 39.00°C | 36 (18.1) | 43 (21.6) |
| 39.01 - 39.50°C | 28 (14.1) | 36 (18.1) |
| 39.51 - 40.00°C | 14 (7.0) | 18 (9.0) |
| ≥ 40.01°C | 5 (2.5) | 4 (2.0) |

*Source: Table 11 of CSR of V221-036 submitted in sBLA 125108/1128.0. Table submitted on Page 3 of sBLA 125108/1128.15 was based the applicant's response to the information request sent on January 20, 2023. The numbers of subjects who had fever were summarized based on subjects who had at least 1 temperature (rectal or axillary) ≥ 38.0°C, without adjustment, between Day 0 to Day 28 after each dose.*

** The percentage of fever is defined within the population who had valid temperature measurements. Three participants in IM group and four participants in SC group did not have temperature measurements and were excluded from the denominator, resulting in N=199 and N=199, respectively.*

Table 16: Post-dose 2 Systemic Adverse Reactions occurring between Day 0 and Day 28 (Safety Set Post Dose 2)

| | Group 1 (IM) N=201 [n (%)] | Group 2 (SC) N=200 [n (%)] |
|---|---|---|
| Any Systemic Adverse Reactions | 136 (67.7) | 122 (61) |
| Measles-like rash | 0 (0) | 2 (1.0) |
| Rubella-like rash | 4 (2.0) | 2 (1.0) |
| Varicella-like rash | 0 (0) | 4 (2.0) |
| Zoster/Zoster-like rash | 0 (0) | 0 (0) |
| Mumps-like illness | 1 (0.5) | 0 (0) |
| Fever (Temperature ≥ 38.0°C)* | 98 (50.0) | 92 (47.2) |
| 38.00 - 38.50°C | 27 (13.8) | 32 (16.4) |
| 38.51 - 39.00°C | 36 (18.4) | 21 (10.8) |
| 39.01 - 39.50°C | 22 (11.2) | 22 (11.3) |
| 39.51 - 40.00°C | 11 (5.6) | 14 (7.2) |
| ≥ 40.01°C | 2 (1.0) | 3 (1.5) |

*Source: Table 13 of CSR of V221-036 submitted in sBLA 125108/1128.0. Table submitted on Page 3 of sBLA 125108/1128.15 was based on the information request sent on January 20, 2023.*
*The numbers of subjects who had fever were summarized based on subjects who had at least 1 temperature (rectal or axillary) ≥ 38.0°C, without adjustment, between Day 0 to Day 28 after each dose.*

**The percentage of fever is defined within the population who had valid temperature measurements. Five participants in IM group and five participants in SC group did not have temperature measurements and were excluded from the denominator, resulting in N=196 and N=195, respectively.*

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

### 6.1.12.2 Serious Adverse Events

Serious adverse events (SAEs) observed from Day 0 to Visit 2 and Visit 2 to Visit 3 are summarized in Table 17 and Table 18, respectively. Two subjects in each group experienced SAEs between Day 0 and Visit 2. One subject in each group experienced SAEs between Visit 2 and Visit 3. The SAE observed in the SC group, between Visit 2 and Visit 3 was considered to be related to the vaccine by the investigator.

Table 17: Serious Adverse events from Day 0 to Visit 2 (Safety Set Post-dose 1)

| | Group 1 (IM) N=202 [n (%)] | Group 2 (SC) N=203 [n (%)] |
|---|---|---|
| Any Serious Adverse Events | 2 (1.0) | 2 (1.0) |
| Any Vaccine related SAE | 0 (0) | 0 (0) |
| Any withdrawal due to an adverse event | 0 (0) | 0 (0) |

*Source: Table 83 of CSR of V221-036 of submitted in sBLA 125108/1128.0.*

Table 18: Serious Adverse events from Day 2 to Visit 3 (Safety Set Post-dose 2)

| | Group 1 (IM) N=201 [n (%)] | Group 2 (SC) N=200 [n (%)] |
|---|---|---|
| Any Serious Adverse Events | 1 (0.5) | 1 (0.5) |
| Any Vaccine related SAE | 0 (0) | 1 (0.3) |
| Any withdrawal due to an adverse event | 0 (0) | 0 (0) |

*Source: Table 84 of CSR of V221-036 of submitted in sBLA 125108/1128.0.*

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

#### 6.1.12.3 Deaths

No deaths were reported in this study.

#### 6.1.12.5 Adverse Events of Special Interest (AESI)

Please refer to clinical reviewer's memo.

#### 6.1.12.6 Clinical Test Results

N/A.

#### 6.1.12.7 Dropouts and/or Discontinuations

There were no dropouts due to AEs or SAEs.

## 7. INTEGRATED OVERVIEW OF EFFICACY

N/A.

## 8. INTEGRATED OVERVIEW OF SAFETY

N/A.

## 9. ADDITIONAL STATISTICAL ISSUES

There are no additional statistical issues identified.

## 10. CONCLUSIONS

### 10.1 Statistical Issues and Collective Evidence

The applicant submitted results from one Phase IIIb study, V221-036, to support the authorization of intramuscular administration as a new route of the ProQuad vaccine.

Noninferiority of the immune response induced by the intramuscular administration compared to that of the subcutaneous administration in terms of the seroconversion rate was demonstrated for ProQuad in Study V221-036.

The study also showed similar reactogenicity and safety profiles when ProQuad was administered by the IM route compared to by the SC route.

## 10.2 Conclusions and Recommendations

All success criteria for immunogenicity objectives were met in study V221-036. The reactogenicity and safety profiles were similar in the subjects who received the vaccine by the intramuscular route compared to the subjects who received the vaccine by the subcutaneous route. I consider the immunogenicity data to support licensure of intramuscular as a new route of administration of ProQuad.