BLA Clinical Review Memorandum

Application Type	Biologics License Application
STN	125748/0
CBER Received Date	June 4, 2021
PDUFA Goal Date	June 4, 2022
Division / Office	DVRPA/OVRR
Priority Review (Yes/No)	No
Reviewer Name(s)	Robin Wisch, MD, Nadine Peart Akindele, MD
Review Completion Date / Stamped Date	June 3, 2022
Supervisory Concurrence	Anuja Rastogi, MD, MHS 1st Level Supervisory Review Clinical Review Staff, Immediate Office of Director DVRPA, OVRR, CBER Douglas Pratt, MD, MPH 2nd Level Supervisory Review Associate Director, Medical Affairs DVRPA, OVRR, CBER
Applicant	GlaxoSmithKline Biologicals, SA
Established Name	Combined Measles, Mumps, and Rubella (MMR) Live (Attenuated) Viral Vaccine
(Proposed) Trade Name	PRIORIX
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants	Each dose (approximately 0.5 mL) contains not less than 3.4 log10 Cell Culture Infective Dose 50% (CCID50) of measles virus, 4.2 log10 CCID50 of mumps virus, and 3.3 log10 CCID50 of rubella virus. Each dose also contains 32 mg of anhydrous lactose, 9 mg of sorbitol, 9 mg of amino acids, and 8 mg of mannitol. Each dose may also contain residual amounts of neomycin sulphate (≤25 µg) from the manufacturing process.
Dosage Form(s) and Route(s) of Administration	Dosage form: Suspension Route of Administration: Subcutaneous
Dosing Regimen	The first dose is administered at 12 through 15 months of age. The second dose is administered at 4 through 6 years of age. If PRIORIX is not administered according to this schedule and 2 doses of measles-, mumps- and rubella-virus vaccine are recommended for an individual, there should be a minimum of 4 weeks between the first and second dose. PRIORIX may be administered as a second dose to individuals who have received a first dose of another measles, mumps and rubella virus-containing vaccine.
Indication(s) and Intended Population(s)	Active immunization for the prevention of measles, mumps, and rubella in individuals 12 months of age and older.
Orphan Designated (Yes/No)	No

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Glossary

ACIP	Advisory Committee on Immunization Practices
AE	adverse event
Am	amendment
ATP	According-to-Protocol
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CCID50	cell culture infective dose 50%
CDC	Centers for Disease Control and Prevention
CDP	clinical development plan
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CRO	contract research organization
D	diphtheria
DTaP-IPV	diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine
DTaP	diphtheria, tetanus, acellular pertussis
DTP	diphtheria, tetanus, pertussis
eCRF	electronic case report form
(b) (4)	
ED50	endpoint dilution 50%
ELISA	enzyme-linked immunosorbent assay
EOS	end of study
EOSL	end of shelf-life
EU	ELISA unit
ER	emergency room
FHA	filamentous hemagglutinin
GCP	Good Clinical Practice
GMC	geometric mean concentration
GMT	geometric mean titer
GSK	GlaxoSmithKline Biologicals
HAV	Havrix, a hepatitis A vaccine
Hib	Haemophilus influenzae type b
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IDMC	Independent Data Monitoring Committee
IgG	immunoglobulin G
IM	intramuscular
IND	investigational new drug application
iPSP	initial Pediatric Study Plan
IR	Information Request
IU	international unit
LAR	legally acceptable representative
MAE	medically attended event
med potency	medium potency
Merck	Merck & Co., Inc.
MedDRA	Medical Dictionary for Regulatory Activities
min potency	minimum potency
mIU	milli-international unit
MLI	Measles-like illness

MMR	measles, mumps, rubella
NOCD	new onset chronic disease
PCV7	Prevnar 7, a 7-valent pneumococcal conjugate vaccine
PCV13	Prevnar 13, a 13-valent pneumococcal conjugate vaccine
PeRC	Pediatric Review Committee
PFS	prefilled syringe
(b) (4)	
PREA	Pediatric Research Equity Act
PRN	pertactin
(b) (4)	
PT	preferred term
PTx	pertussis toxoid
PV	poliovirus
RoA	route of administration
SAE	serious adverse events
SC	subcutaneous
SOC	System Organ Class
SRR	seroresponse rate
T	tetanus
TCID50	Tissue Culture Infectious Dose 50%
TVC	Total Vaccinated Cohort
URI	upper respiratory tract infection
US	United States
USPI	United States Package Insert
VV	Varivax, a varicella vaccine
VZV	varicella zoster virus
WC/WC	whole content reconstitution/whole content administration
WFI	water for injection

1. Executive Summary

An original Biologics License Application (BLA) has been submitted by GlaxoSmithKline Biologicals (GSK) for a candidate measles, mumps, and rubella (MMR) live vaccine (PRIORIX) with a proposed indication for active immunization for the prevention of measles, mumps, and rubella in individuals 12 months of age and older.

The Applicant has submitted data from 6 randomized clinical studies as part of this BLA to support the safety and effectiveness of PRIORIX in comparison to United States (US)-licensed M-M-R II vaccine [Merck & Co., Inc. (Merck)]. M-M-R II is the only trivalent combined MMR vaccine licensed in the US (since 1978) and recommended for routine vaccination by the Advisory Committee on Immunization Practices (ACIP); thus, M-M-R II was the active comparator in all studies in the PRIORIX US Clinical Development Plan (CDP).

Five Phase 3 trials provide the primary data for the intended indication in individuals 12 months of age and older, as well as clinical data to support manufacturing consistency (lot consistency). One Phase 2 trial provided data to justify the formulation of the mumps potency used in the Phase 3 studies. These 6 trials (MMR-157, MMR-158, MMR-159, MMR-160, MMR-161, and MMR-162) enrolled participants ≥12 months of age at more than 400 sites in 11 countries, including the US.

Studies MMR-160, MMR-161, MMR-162, and MMR-157 evaluated a single dose of MMR vaccine in participants 12 through 15 months of age. Two Phase 3 studies assessed a second dose of MMR vaccine in older populations: study MMR-158 enrolled participants 4 through 6 years of age, and study MMR-159 enrolled participants ≥7 years of age. All studies evaluated safety (local and systemic adverse reactions, unsolicited adverse reactions, adverse events of specific interest and serious adverse events) descriptively. In all studies, except MMR-159, age-appropriate ACIP-recommended routine vaccinations were concomitantly administered.

Phase 3 study MMR-160 evaluated both lot consistency and non-inferiority to M-M-R II in terms of immunogenicity. Phase 3 study MMR-161 evaluated the immunogenicity of PRIORIX at an end of shelf-life (EOSL) potency compared to M-M-R II and was the only study to administer 2 doses of MMR vaccine, spaced 6 weeks apart. Phase 3 study MMR-162 was primarily a safety study used to define maximum release potency limits. Phase 3 studies MMR-158 and MMR-159 evaluated the non-inferiority of PRIORIX compared to M-M-R II as a second MMR dose after an MMR containing vaccine, in terms of immunogenicity. Phase 2 study MMR-157 compared three lots of PRIORIX with different mumps potencies in a US population.

Immunogenicity Analyses
Effectiveness of PRIORIX was inferred by demonstration of vaccine-specific antibody responses to measles, mumps, and rubella virus following administration of PRIORIX that were non-inferior to responses observed following M-M-R II, assessed using validated immunological assays. Both PRIORIX and M-M-R II contain the same strains for mumps (Jeryl-Lynn or a Jeryl-Lynn-derived strain) and rubella (Wistar 27/3 strain) and a similar lineage of measles strain derived from the Edmonston strain (Schwarz strain at GSK and Edmonston-Enders strain at Merck). Unless otherwise specified, immunogenicity objectives were to establish non-inferiority to MMR II as determined by the following: 1) lower limit (LL) of the two-sided 95% confidence interval (CI) of the seroresponse rate (SRR) difference (PRIORIX minus M-M-R II) of ≥-5% for each vaccine antigen; and 2) LL of the two-sided 95% CI of the geometric mean concentration (GMC) ratio (PRIORIX over M-M-R II) of ≥0.67 for each vaccine antigen.

Study MMR-160 was the main study evaluating the non-inferiority of PRIORIX compared to M-M-R II as a first MMR dose in healthy individuals 12 through 15 months of age. Non-inferiority was determined as described above with additional criteria of a seroresponse rate ≥90% for all vaccine antigens. The co-primary objectives to demonstrate immunological non-inferiority of PRIORIX to M-M-R II, were met. Secondary objectives evaluated concomitant vaccination with Varivax (VV), Havrix (HAV), and Prevnar 13 (PCV13). Lack of immune interference with concomitantly administered routine pediatric vaccines (VV, HAV, and PCV13) in PRIORIX as compared to M-M-R II was also demonstrated.

Study MMR-158 evaluated the non-inferiority of PRIORIX compared to M-M-R II as a second MMR dose in healthy individuals 4 through 6 years of age in participants who received study vaccine with or without administration of concomitant vaccines. Non-inferiority was determined as described above, though using the LL of the two-sided 97.5% CI. The primary objectives to demonstrate non-inferiority of PRIORIX to M-M-R II in terms of seroresponse rate and GMCs, when administered either with diphtheria, tetanus, acellular pertussis, and inactivated poliovirus (DTaP-IPV) and VV or alone, were met. Secondary objectives evaluated concomitant vaccination with DTaP-IPV and VV vaccines. Lack of immune interference with concomitantly administered routine pediatric vaccines (DTaP-IPV and VV) in PRIORIX as compared to M-M-R II was also demonstrated.

Study MMR-161 evaluated the End of Shelf Life (EOSL) potency for each antigen in PRIORIX in healthy 12 through 15-month-olds who received a first dose of either minimum potency PRIORIX, medium potency PRIORIX, or M-M-R II. Non-inferiority was determined as described above, though the LL of the two-sided 97.5% CI was used and the additional criteria of the seroresponse rate being ≥90% for all vaccine antigens was measured. The primary objectives to demonstrate non-inferiority of medium potency PRIORIX to M-M-R II as measured by ELISA for measles, mumps and rubella were met. Secondary objectives descriptively evaluated the immunogenicity of a second dose of MMR vaccine, where study participants who received a first dose of either PRIORIX or M-M-R II, received targeted release potency PRIORIX or M-M-R II, respectively, 6 weeks later. Immune responses to PRIORIX or M-M-R II as a second dose were comparable among children enrolled in the US.

Study MMR-162 primarily evaluated non-inferiority of PRIORIX as compared to M-M-R II with regard to fever when administered at a potency used to define each antigen's maximum release limits when administered as a first dose to healthy 12 through 15-month-olds. Safety analyses are described below. The descriptive secondary immunogenicity analyses demonstrated comparable SRRs and point estimates for GMCs to the measles, mumps and rubella vaccine components.

Study MMR-159 demonstrated the non-inferiority of PRIORIX compared to M-M-R II as a second MMR dose in healthy individuals ≥7 years of age. Non-inferiority was determined as described above for the primary objective (GMCs) and the first secondary objective (SRR). The study met its predefined criteria for success for the primary objective and the first co-secondary objective.

Study MMR-157 was an exploratory Phase 2 study conducted in the US to descriptively assess the immunogenicity and safety of three lots of PRIORIX with different mumps virus potencies. The results supported the target mumps potency of >4.2 log10 CCID50 to be used in Phase 3 trials.

Safety Analyses
Post-vaccination safety data were reviewed from over 12,000 PRIORIX recipients who were enrolled in the six randomized clinical trials. Overall, the most frequently reported solicited local adverse reactions included injection site pain and erythema. The most frequently reported solicited systemic adverse reactions were irritability/fussiness in 12 through 15-month-olds, drowsiness in 4 through 6-year-olds, and fever in participants 7 years and older. Across all studies, there were two PRIORIX recipients and one M-M-R II recipient who died of causes unrelated to study vaccination. Rates of reported serious

adverse events (SAEs) and the types of SAEs across groups were similar and included clinical events that are often reported in the evaluated populations.

In study MMR-162, the primary objectives were to evaluate the incidence of fever at a potency used to define each antigen's maximum release limits when administered as a first dose to 12 through 15-month-old children. The co-primary safety objectives, to demonstrate that the two-sided 95% UL of the difference in fever rates (PRIORIX minus M-M-R II) did not exceed 5% for fever >39.0°C and 10% for fever ≥38.0°C, were met.

Overall, the safety profile was similar to M-M-R II across all studies.

Lot Consistency
The Applicant satisfactorily demonstrated consistency of lot performance in Study MMR-160 based on pair-wise comparisons of GMCs and SRRs of three different lots of PRIORIX. Safety profiles across lots were also consistent.

Concomitant Vaccination
The safety and effectiveness of PRIORIX when administered concomitantly with ACIP-recommended routine childhood vaccines, PCV13, HAV, and VV in 12 through 15-month-olds and VV and DTaP-IPV in 4 through 6-year-olds, were evaluated in all relevant studies for the appropriate age groups as compared to M-M-R II concomitantly administered with the respective vaccines. Non-inferiority of PRIORIX to M-M-R II in terms of immune response for each antigen in the concomitantly administered vaccines was demonstrated. No evidence of immune interference to the antibody responses to the PRIORIX vaccine virus antigens and the antibody responses to the concomitantly administered vaccines was observed. Additionally, no notable increase in frequency or severity of reported adverse events (AEs) with concomitant administration was observed in PRIORIX as compared to M-M-R II.

Pediatric Assessment and Pediatric Research Equity Act
Under the Investigational New Drug Application (IND), the Applicant submitted an initial Pediatric Study Plan (iPSP) on July 6, 2016, and an Agreed iPSP on January 6, 2017, which included a request for waiver of pediatric studies in infants <12 months of age. FDA concurred with the Agreed iPSP, acknowledged the plan to request the partial waiver, and provided a letter of agreement to the Applicant on January 26, 2017.

Under the Biologics License Application (BLA), the final Pediatric Study Plan was presented to the Pediatric Review Committee (PeRC) on April 26, 2022. Safety and effectiveness of PRIORIX have not been established in individuals younger than 12 months of age in the US. The Applicant's request for a partial waiver for those less than 12 months of age was accepted by PeRC because the candidate vaccine does not represent a meaningful therapeutic benefit and is not likely to be used in this age group. PeRC agreed that the pediatric assessment for PRIORIX was complete.

Clinical Reviewer Recommendation
The totality of clinical data presented in this application support approval of PRIORIX vaccine for active immunization for the prevention of measles, mumps, and rubella in individuals 12 months of age and older.

1.1 Demographic Information: Sub-group Demographics and Analysis Summary

For each study, the demographic characteristics were reviewed.

Immunogenicity
All Phase 3 studies were conducted in multiple regions and countries. Descriptive analyses were performed to ensure that the immune response was consistent across countries and consistent with the overall population of each study. No notable differences were observed in the safety outcomes and immune responses of the two MMR vaccines in different countries. The immune responses to measles, mumps, and rubella for vaccine recipients of all age categories enrolled in the US were comparable to the immune responses in the overall study population. Immune responses were also consistent between vaccines when analyzed by gender and race.

Safety
Descriptive summary safety data of solicited symptoms were reported by country, gender, and race (geographic ancestry). In general, there were no clinically meaningful differences between males and females or between the study and comparator vaccine groups. Similarly, there were no suggestions of clinically relevant differences of the reactogenicity profile of the two vaccines by race.

1.2 Patient Experience Data

Patient experience data were not submitted as part of this application.

Table 1. 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 Condition(s) Studied

Measles
Measles is a highly contagious viral illness seen primarily in children that is caused by measles virus, a negative sense single-stranded RNA virus. The virus is transmitted by respiratory droplets and airborne spread and disease is characterized by cough, coryza, conjunctivitis, fever and a pathognomonic maculopapular rash that typically occurs around 14 days from the time of exposure (McLean et al., 2013). Common complications from measles include pneumonia and diarrhea, which can lead to significant morbidity and mortality (Moss et al., 2017), however other complications include neurological manifestations including acute encephalitis and subacute sclerosing panencephalitis, the latter of which typically presents 10 years after acute infection and results in severe neurologic devastation and death (Patterson et al., 2020).

Prior to 1963, when the first measles vaccine became available, measles caused hundreds of deaths each year in the US (Bloch et al., 1985). National vaccination campaigns have substantially reduced the number of those affected and in the US by 2000, resulted in elimination of measles (defined as no endemic transmission in 12 months). Measles cases continue to occur, with 49 reported cases in the US in 2021 (CDC, 2022a), though cases are primarily among unvaccinated communities and those traveling from regions with low vaccination rates. Globally, measles still causes over 140,000 deaths world-wide, primarily affecting children under 5 years of age (WHO, 2019a). Children under 5 years, pregnant women, immunocompromised individuals, and older adults are at highest risk for measles complications and death.

Mumps
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 (McLean et al., 2013). Prior to routine vaccination in 1977, mumps occurred almost universally, primarily in school aged children (Collins et al., 1929). Still, sporadic outbreaks continue to occur globally, even among vaccinated communities raising concerns for waning immunity and vaccine efficacy (Su et al., 2020). In the US, 154 cases were reported in 2021 (CDC, 2022b)

Rubella
Rubella, caused by rubella virus, is also a viral illness seen in childhood, which after transmission through respiratory droplets or nasopharyngeal secretions, manifests clinically with rash, low-grade fever, lymphadenopathy, and malaise. Although infections are often mild or subclinical, complications including thrombocytopenic purpura (more so in children) and encephalitis (more so in adults) can occur (McLean et al., 2013).

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 (Miller et al., 1982). Prior to licensure of a vaccine in the US in 1969, there were an estimated 12.5 million rubella cases occurring with approximately 2,000 cases of encephalitis. At that time there were over 11,250 fetal deaths due to spontaneous or therapeutic abortions, 2,100 infants who were stillborn or died soon after birth, and over 20,000 infants born with CRS (CDC, 2020). Despite the availability of the vaccine and international efforts to prevent disease, globally, rubella remains the leading vaccine-preventable cause of birth defects (WHO, 2019b). In the United States, rubella no longer spreads endemically and today, less than 10 cases are reported each year (CDC, 2022c).

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Currently, there is no recommended therapeutic option that directly targets and treats infections with measles, mumps, or rubella viruses. Primary efforts are centered around prevention via vaccination.

2.3 Safety and Efficacy of Pharmacologically Related Products

Primary prevention against all three viruses is provided in the US by M-M-R II, manufactured by Merck, Sharp & Dohme Corp, which was first licensed in 1978 (Lievano et al., 2012). M-M-R II is indicated for active immunization for the prevention of measles, mumps, and rubella in individuals 12 months of age and older and is administered at a dose of 0.5 mL per dose, subcutaneously. The ACIP currently recommends a two-dose series to be administered first at 12 through 15 months and then at 4 through 6 years. Information regarding the safety and effectiveness of the M-M-R II vaccine is described in the US Prescribing Information (USPI).

2.4 Previous Human Experience with the Product (Including Foreign Experience)

PRIORIX is a combined trivalent vaccine intended to prevent measles, mumps, and rubella in individuals 12 months of age and older. It was first authorized for use in Germany in 1997 and is currently licensed in over 100 countries. The potency of the formulation may vary across countries in which it is authorized for use.

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

Regulatory Pathway to Licensure:
The basis of the licensure approach relied on establishing non-inferiority of the antibody immune response towards measles, mumps, and rubella viruses after administration of PRIORIX as compared to that of a US-licensed combination vaccine, Merck's M-M-R II.

Major Regulatory Activity:
The following timeline provides the major regulatory activity associated with this BLA

- December 2011: Type B, End-of-Phase 2 (EOP2) Meeting
    - Overall safety database size/US sample size agreed upon and serologic assays discussed
- April 2012, June 6, 2017, May 1, 2020: Type C Meetings
    - Thresholds for seroresponse, respective assays, and the EOSL potency agreed upon
    - Agreement that reproductive toxicity studies were not needed
    - Clinical; nonclinical; and chemistry, manufacturing, and controls (CMC) related development and licensure plans discussed
    - Preliminary concurrence obtained regarding the diluent presentation for the ungraduated prefilled syringe (PFS). In Phase 2 studies an ungraduated PFS was used for the water for injection and in Phase 3 studies an unmeasured vial was used instead.
- October 2020: Type B, Pre-BLA Meeting
    - This meeting was held to seek CBER's concurrence on the clinical (immunogenicity and safety) data supporting review of a BLA submission.
    - An Integrated Summary of Effectiveness and an Integrated Summary of Safety were determined to not be needed because each clinical study contained a different potency, the concomitant vaccines administered varied by study population, and the participants in the different trials varied in age.
    - Preliminary discussion on content of USPI, including post-marketing non-US safety data

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.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Safety and immunogenicity data from six studies were provided in this application (MMR-157, MMR-158, MMR-159, MMR-160, MMR-161, and MMR-162) to support licensure of PRIORIX. All MMR US CDP clinical trials were approved by Ethics Committees; followed the International Council on Harmonisation (ICH)-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. Potential or actual issues regarding the conduct of the study were investigated and, where possible, corrective and preventive actions were taken.

Bioresearch monitoring (BIMO) inspections were issued for 4 clinical study sites that participated in the conduct of study MMR-158 and MMR-160. The inspections did not reveal substantive issues that impact the data submitted in this application.

3.3 Financial Disclosures

Table 2. Covered Clinical Studies

Covered clinical study (name and/or number): MMR-157, MMR-158, MMR-159, MMR-160, MMR-161, MMR-162
Was a list of clinical investigators provided? ☑ Yes ☐ No (Request list from applicant)
Total number of investigators identified*: 247
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): 8
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: 8 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): 0 Is an attachment provided with the reason? ☐ Yes ☐ No (Request explanation from applicant) N/A

*Source: STN 125748 Am 0 and Am 25 (Total number of investigators across all studies was clarified.)

Reviewer Comment: Form FDA 3454, Certification: Financial Interests and Arrangements of Clinical Investigators, includes a list of 128 clinical investigators for whom required financial information could not be obtained. Of these investigators, 120 (93.8%) were sub-investigators or coordinators. According to GSK's procedures for obtaining financial information, all investigators are requested to supply information upon commencement of their participation in the study. No investigator at the

start of his/her participation in the study had a financial interest in GSK and it is the Applicant's policy to not allow study participation if the investigator, their spouse or dependent children have a proprietary interest in the tested product. The Applicant conducted a due diligence process by which three documented attempts to collect available financial information in the form of a questionnaire were performed. Based on available information internal to GSK, the Applicant states that none of the investigators listed had disclosable interests including compensation potentially affected by the outcome of the study or a significant equity interest in the study sponsor (as per 21 CFR 54.2) and that these 128 investigators were listed because updated financial information (equity interest, proprietary interest, and/or payments of other sorts) could not be obtained in a timely manner. The clinical reviewer noted that some of the clinical trials conducted by these investigators were initiated over 10 years ago. The primary comments listed that precluded timely collection of the financial information was that the investigator was not located. No additional financial concerns were identified by the BIMO reviewer. It is not expected that financial bias impacted the studies performed to support licensure of PRIORIX.

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

4.1 Chemistry, Manufacturing, and Controls

Manufacturing process development, in-process testing, release and stability testing were reviewed and support licensure. Facility information and data provided in the BLA were reviewed by CBER CMC reviewers and found to be sufficient and acceptable.

4.2 Assay Validation

The potency tests for the final drug product and clinical serologic assays were adequate to support licensure as determined by CBER Product and Assay reviewers.

4.3 Nonclinical Pharmacology/Toxicology

The CBER Toxicology reviewer considered the nonclinical toxicology data to be adequate to support licensure.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Immune responses against measles, mumps, and rubella viruses induced by PRIORIX were measured by enzyme-linked immunosorbent assays (ELISAs). IgG antibodies measured by the ELISAs used in clinical studies of PRIORIX have been shown to correlate with the presence of neutralizing antibodies that have been associated with protection.

4.5 Statistical

The CBER Statistical reviewer concluded that the datasets and the analyses provided in this application were adequate to assess the safety and effectiveness of the candidate vaccine.

4.6 Pharmacovigilance

PRIORIX is currently marketed in all European Union countries as well as over 70 non-EU countries. Over 388 million doses have been distributed outside the US. The CBER Epidemiology/Pharmacovigilance reviewer did not identify any safety concerns or potential risks on review of the Periodic Benefit Risk Evaluation Report (PBRER) for PRIORIX which have not been previously described for MMR-containing vaccines or that would require a Risk Evaluation and

Mitigation Strategy or a new post-marketing requirement to evaluate safety. 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 adverse event reporting as required under 21 CFR 600.80.

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

5.1 Review Strategy

This BLA included clinical data from 6 trials (MMR-157, MMR-158, MMR-159, MMR-160, MMR-161, and MMR-162) to support immunogenicity (inferred effectiveness) and safety of PRIORIX compared to M-M-R II, as a first dose in children 12 through 15 months of age and as a second dose in children 4 through 6 years of age, as well as in individuals 7 years and older.

The clinical, labeling, and financial disclosure information sections of the application were reviewed with detailed analyses of the main trials' study reports and pertinent line listings, case report forms, and datasets. ACIP vaccine recommendations for the prevention of measles, mumps, and rubella 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#125748/0 Amendments (Am) were reviewed (listed by modules)

- Am 0: 1.1, 1.2, 1.6.3, 1.9, 1.14, 1.18, 2.2, 2.7, 5.2, 5.3, 5.4
- Am 3: 1.11.3
- Am 4: 1.11.3 and 5.3.5.1
- Am 6: 1.11.3
- Am 14: 1.11.1, 1.11.3, 2.5, 2.7.4, and 5.3.5.3
- Am 16: 1.11.3, 2.7.4, and 5.3.5.3
- Am 25: 1.11.3, 2.7.4, 5.3.5.1
- Am 26: 1.11.3 and 5.3.5.1
- Am 28: 1.11.3
- Am 29: 1.11.1
- Am 30: 1.11.1
- Am 31: 1.11.3, 5.3.5.4, and 5.3.6
- Am 32: 1.11.3, and 5.3.1.4
- Am 33: 1.11.3
- Am 34: 1.11.1
- Am 35: 1.11.3, 1.11.4
- Am 36: 11.11.1, 1.11.3
- Am 37: 1.11.1
- Am 38: 1.11.3
- Am 39: 1.11.1 and 5.3.5.4
- Am 40: 1.11.3
- Am 41: 1.17.1
- Am 42: 1.14
- Am 43: 1.14
- Am 44: 1.11.3
- Am 45: 1.14

5.3 Table of Studies/Clinical Trials

Table 3: Clinical Trials Submitted in Support of Safety and Efficacy

Study Number	Region	Description	Population (Schedule)	Study Groups: # Enrolled (# Exposed)
Trial # 1: MMR-160 Lot Consistency Immunogenicity Safety (NCT01702428)	US (including Puerto Rico) Estonia Finland Mexico Spain	Phase 3, observer-blind, randomized, controlled, consistency and non-inferiority study to evaluate the immunogenicity and safety of PRIORIX vs. MMR-II, as a first dose	Healthy children 12 through 15 months (1 dose at Day 0 with VV and HAV, and PCV13 in US only)	PRIORIX: 3,719 (3,714) Lot 1: 1,239 (1,239) Lot 2: 1,234 (1,232) Lot 3: 1,246 (1,243) M-M-R II: 1,291 (1,289)
Trial # 2: MMR-158 Immunogenicity Safety (NCT01621802)	US Republic of Korea Taiwan	Phase 3, observer-blind, randomized, controlled study to evaluate non-inferiority PRIORIX as a second dose vs. M-M-R II as a second dose	Healthy children 4 through 6 years (1 dose at Day 0 with VV and DTaP-IPV in a US-only sub-cohort)	PRIORIX: 2,918 (2,917) Sub-cohort 1: 802 (802) Sub-cohort 2: 796 (796) Sub-cohort 3: 1,320 (1,319) M-M-R II: 1,091 (1,090) Sub-cohort 1: 299 (298) Sub-cohort 2: 303 (303) Sub-cohort 3: 489 (489)
Trial # 3: MMR-161 Immunogenicity Safety (NCT01681992)	US (including Puerto Rico) Czech Republic Finland Malaysia Spain Thailand	Phase 3, observer-blind, randomized, controlled study to evaluate the immunogenicity and safety of PRIORIX at an end of shelf-life potency (established for each antigen) vs. MMR-II	Healthy children 12 through 15 months (2 doses: 1 at Day 0 with VV and HAV, and PCV13 in US only and 1 at Day 42)	PRIORIX: 2998 (2990) Min: 1497 (1493) Med: 1501 (1497) M-M-R II: 1530 (1526)
Trial # 4: MMR-162 Safety Immunogenicity (NCT02184572)	US (including Puerto Rico) Estonia Finland Taiwan	Phase 3, observer-blind, randomized, controlled study to evaluate the safety and immunogenicity of PRIORIX (at a potency used to define maximum release limits) vs. MMR-II, as a first dose	Healthy children 12 through 15 months (1 dose at Day 0 with VV and HAV, and PCV13 in US only)	PRIORIX: 1165 (1164) M-M-R II: 575 (572)
Trial # 5: MMR-159 Immunogenicity Safety (NCT02058563)	US Estonia Slovakia	Phase 3, observer-blind, randomized, controlled study to evaluate non-inferiority of PRIORIX as a second dose vs. M-M-R II as a second dose	Healthy children, adolescents, and adults ≥ 7 years primed with at least 1 dose of an MMR vaccine (1 dose at Day 0)	PRIORIX: 497 (454) M-M-R II: 497 (457)

Study Number	Region	Description	Population (Schedule)	Study Groups: # Enrolled (# Exposed)
Trial # 6: MMR-157 Immunogenicity Safety (NCT00861744)	US (including Puerto Rico)	Phase 2, observer-blind, randomized, controlled study to evaluate the immunogenicity and antibody persistence (descriptive analysis) of PRIORIX (3 lots with different mumps potencies) vs. M-M-R II, as a first dose	Healthy children 12 through 15 months (1 dose at Day 0 with HAV, VV, PCV7)	PRIORIX: 914 (912) Lot 1: 304 (304) Lot 2: 305 (304) Lot 3: 305 (304) M-M-R II: 310 (308)

Source: Adapted from STN 125748/0, Module 5.2, Tabular Listing of All Clinical Studies
Abbreviations: VV=Varivax, HAV=Havrix; PCV13=Prevnar 13; DTaP-IPV= diphtheria, tetanus, acellular pertussis, and inactivated poliovirus; Min=minimum potency PRIORIX; Med=medium potency PRIORIX; US=United States.

5.4 Literature Reviewed

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6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1 (Study MMR-160)

NCT01702428
"A Phase 3a, randomized, observer-blind, controlled, multinational consistency study to evaluate the immunogenicity and safety of GSK's MMR vaccine (PRIORIX) compared to Merck's MMR vaccine (M-M-R II), as a first dose, both concomitantly administered with Varivax, Havrix, and Prevnar 13 (subset of children) to healthy children 12 through 15 months of age."

Study Overview: This study was designed to evaluate consistency of the immune response to three different lots of PRIORIX (manufactured to target potencies) and to evaluate the immunogenicity and safety of PRIORIX compared to M-M-R II, when both are used as a first dose in children at 12 through 15 months of age with concomitant vaccinations. In the US, concomitant vaccines[1] were Varivax (VV), Havrix (HAV), and Prevnar 13 (PCV13), and at sites outside the US, concomitant vaccines were VV and HAV.

6.1.1 Objectives

Primary Objectives
The co-primary objectives were assessed in a hierarchical manner according to the order presented below.[2] A co-primary objective can only be met if the statistical criteria for that objective are met as well as the statistical criteria for all previous co-primary objectives.

1. To demonstrate the consistency of three manufacturing lots of PRIORIX vaccine in terms of SRRs to measles, mumps, and rubella viruses at Day 42.
   Endpoint: Seroresponse to measles, mumps, and rubella viruses
   Seroresponse Definition (across all studies in this BLA):
   - For measles, a post-vaccination anti-measles virus antibody concentration ≥200 mIU/mL (enzyme-linked immunosorbent assay [ELISA], (b) (4) among children who were seronegative (antibody concentration <150 mIU/mL) before vaccination.
   - For mumps, a post-vaccination anti-mumps virus antibody concentration ≥10 ELISA unit (EU)/mL (ELISA, (b) (4) among children who were seronegative (antibody concentration <5 EU/mL) before vaccination.
   - For rubella, a post-vaccination anti-rubella virus antibody concentration ≥10 IU/mL (ELISA, (b) (4) among children who were seronegative (antibody concentration <4 IU/mL) before vaccination.

   Statistical Criteria for Success: For each pair-wise comparison, the two-sided 95% CI on the lot difference in SRRs is within the [-5%, 5%] margin for antibodies to measles, mumps, and rubella viruses.

   Reviewer Comment:
   The immune responses were assessed at 43 days post-vaccination and included serology endpoints of GMCs and seroresponse rates. ELISA thresholds were chosen based on agreement with seroresponse thresholds of the respective neutralizing/inhibition assay and further validated by a significant difference between serostatus. CBER agreed with this approach.

1 Varivax, Varicella Virus Vaccine Live manufactured by Merck Sharp & Dohme Corp.; Havrix, Hepatitis A Vaccine, Inactivated, manufactured by GlaxoSmithKline Biologicals; Prevnar 13, Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein) manufactured by Wyeth Pharmaceuticals, Inc.
2 All criteria were assessed for each assay (ELISA) separately. With the exception of anti-pneumococcal antibodies, the criteria were specific to children seronegative for the assay at pre-vaccination.

2. To demonstrate the consistency of three manufacturing lots of PRIORIX vaccine in terms of GMCs for antibodies to measles, mumps, and rubella viruses at Day 42.
   Endpoint: Measles, mumps, and rubella virus antibody concentrations
   Statistical Criteria for Success: For each pair-wise comparison, the two-sided 95% CI on the lot ratio is within the [0.67, 1.5] margin for antibodies to measles, mumps, and rubella viruses.

3. To demonstrate the non-inferiority of PRIORIX (for the three pooled lots) compared to M-M-R II vaccine (for the two pooled lots) in terms of SRRs to measles, mumps, and rubella viruses at Day 42.
   Endpoint: Seroresponse to measles, mumps, and rubella viruses
   Statistical Criteria for Success: The lower limit of the two-sided 95% CI on the group difference (pooled PRIORIX lots minus pooled M-M-R II lots) in SRR is ≥-5% for antibodies to measles, mumps, and rubella viruses.

4. To demonstrate the non-inferiority of PRIORIX (for the three pooled lots) compared to M-M-R II vaccine (for the two pooled lots) in terms of GMCs for antibodies to measles, mumps, and rubella viruses at Day 42.
   Endpoint: Measles, mumps, and rubella virus antibody concentrations
   Statistical Criteria for Success: The lower limit of the two-sided 95% CI on GMC ratio (pooled PRIORIX lots over pooled M-M-R II lots) is ≥0.67 for antibodies to measles, mumps, and rubella viruses.

5. To demonstrate an acceptable immune response for PRIORIX in terms of SRRs to measles, mumps, and rubella viruses at Day 42.
   Endpoint: Seroresponse to measles, mumps, and rubella viruses
   Statistical Criteria for Success: The lower limit of the two-sided 95% CI for the SRR for the pooled PRIORIX lots is ≥90% for antibodies to measles, mumps, and rubella viruses.

Secondary Objectives

6. To demonstrate non-inferiority of the pooled PRIORIX groups compared to the pooled M-M-R II groups in terms of SRR and GMC for antibodies to VZV at Day 42 (in a subset of children enrolled in the US).
   Endpoints: Immunogenicity of Varivax in terms of seroresponse to VZV and VZV antibody concentrations (b) (4)
   Seroresponse Definition:
   - For varicella, post-vaccination anti-VZV antibody concentration ≥75 mIU/mL among children who were seronegative (antibody concentration <25 mIU/mL) before vaccination.
     Statistical Criteria for Success:
     - The lower limit of the two-sided 95% CI for the group difference (pooled PRIORIX lots minus pooled M-M-R II lots) in SRRs for antibodies to VZV is ≥-10%.
     - The lower limit of the two-sided 95% CI on the GMC ratio (pooled PRIORIX lots over pooled M-M-R II lots) is ≥0.67 for antibodies to VZV.

7. To demonstrate non-inferiority of the pooled PRIORIX groups compared to the pooled M-M-R II groups in terms of GMC for antibodies to hepatitis A virus at Day 42 (in a subset of children enrolled in the US).
   Endpoint: Hepatitis A virus antibody concentrations (b) (4)
   Statistical Criterion for Success: The lower limit of the two-sided 95% CI for the group GMC ratio (pooled PRIORIX lots over pooled M-M-R II lots) for antibodies to hepatitis A virus (post-dose 1) is ≥0.5.

8. To demonstrate non-inferiority of the pooled PRIORIX groups compared to the pooled M-M-R II groups in terms of antibodies to *Streptococcus pneumoniae* (13 serotypes), at Day 42 (in a subset of children administered Prevnar 13 in the US).
   Endpoint: Pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) IgG antibody concentrations as measured by an (b) (4) assay which was shown to be comparable to the (b) (4) in a bridging study.
   Statistical Criteria for Success: The lower limit of the two-sided 95% CI for the group GMC ratio (pooled PRIORIX lots over pooled M-M-R II lots) for antibodies to *S. pneumoniae* serotypes (13 endpoints) is ≥0.5.

9. To assess the immunogenicity of Havrix with respect to the SRRs for antibodies to hepatitis A virus in the pooled PRIORIX groups in contrast to the pooled M-M-R II vaccine groups at Day 42 (in a subset of children enrolled in the US).
   Endpoint (Descriptive): Seroresponse to Hepatitis A virus
   Seroresponse Definition:
   - For hepatitis A virus, post-vaccination concentration equal to or above the cut-off of 15 mIU/mL in children below the assay cut-off of 15 mIU/mL before vaccination, or ≥2-fold increase in antibody concentration in children ≥15 mIU/mL before vaccination.

10. To assess safety and reactogenicity of PRIORIX and M-M-R II when concomitantly administered with Varivax, Havrix (to all children), and Prevnar 13 (only to children enrolled in the US).
    Endpoints (Descriptive):
    - Solicited local and general symptoms.
      - Occurrence of solicited local symptoms in terms of injection site redness, pain, and swelling from Day 0 to Day 3 after vaccination.
      - Occurrence of solicited general symptoms in terms of drowsiness, loss of appetite, and irritability from Day 0 to Day 14 after vaccination.
      - Occurrence of solicited general symptoms in terms of fever (temperature ≥38.0°C/100.4°F), rash, parotid/salivary gland swelling, any sign of meningism (including febrile convulsions) from Day 0 to Day 42 after vaccination.
      - Unsolicited adverse events.
        - Occurrence of unsolicited symptoms, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification, from Day 0 to Day 42 after vaccination.
      - Adverse events of specific interest.
        - Occurrence of new onset chronic disease (NOCD) (e.g., autoimmune disorders, asthma, type I diabetes, vasculitis, celiac disease, conditions associated with subacute or chronic thrombocytopenia and allergies) and AEs prompting emergency room (ER) visits from Day 0 through the end of study (EOS).
      - Serious adverse events.
        - Occurrence of SAEs from Day 0 through the EOS.

6.1.2 Design Overview

Study MMR-160 was an observer-blind, randomized, controlled, multi-center, multi-country, consistency study with five parallel groups. Overall, participants were randomized 3:1 to receive PRIORIX or M-M-R II. Within each group, participants were randomized 2:2:2:1:1 to receive one of the three PRIORIX lots (sub-groups identified as PRIORIX Lot 1, PRIORIX Lot 2, and PRIORIX Lot 3) or one of the two M-M-R II lots (sub-groups identified as M-M-R II Lot 1 and M-M-R II Lot 2), respectively. The two lots of M-M-R II were analyzed as pooled lots. The study design for the lot-to-lot consistency evaluation of the

three PRIORIX lots was double-blinded, while the comparison of the pooled lots of PRIORIX versus the pooled M-M-R II lots was observer-blinded.

All study participants had three study visits (Days 0, 42, and 180) that had the following major study activities:

- Day 0: Visit 1 at 12 through 15 months of age. Blood sampling; single vaccination with either one of the three PRIORIX lots or one of two M-M-R II active control lots, along with the concomitantly administered vaccines Varivax and Havrix (to all children) and Prevnar 13 (only to children enrolled in the US)
- Day 42: Visit 2 at 13-17 months of age. Blood sampling and diary card transcription
- Day180: Visit 3 at 18-22 months of age. Safety follow-up

The study duration was approximately six months starting at Visit 1 (Day 0) and ending with Visit 3 (Day 180).

Reviewer Comments:

1. The Applicant included two lots of the M-M-R II vaccine to obtain more representative data on this licensed comparator. The Applicant analyzed data from both M-M-R II lots as pooled lots for all analyses. The three PRIORIX lots were analyzed as pooled lots for the safety and immunogenicity noninferiority assessments after first demonstrating consistency across the three lots.
2. While the study was conducted in a double-blind fashion for the lot-to-lot consistency evaluation, it was conducted in an observer-blind fashion (blinding the researchers but not the participant to the treatment) for the comparison of PRIORIX lots versus M-M-R II lots due to the potential color differences of each vaccine, therefore dedicated unblinded staff were responsible for reconstitution and administration of study vaccines.

6.1.3 Population

Eligibility Criteria

Individuals were eligible for inclusion if they met all the following criteria: males or females between 12 and 15 months of age at the time of vaccination; parent(s) or legally acceptable representative(s) (LAR(s)) could and would, comply with the protocol requirements; written informed consent was obtained from the parent(s)/LAR(s) of the child; and the participant was in stable health. For US participants only, the child previously received a 3-dose series of Prevnar 13 with the last dose at least 60 days prior to study entry.

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

- Child in care (defined as a child placed under the control or protection of an agency, organization, institution, or entity by the courts, the government, or a government body).
- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) during the period starting 30 days before the day of study vaccination (i.e., 30 days prior to Day 0) or planned use during the entire study period.
- Concurrently participating in another clinical study, in which the child had been or would be exposed to an investigational or a non-investigational product (pharmaceutical product or device).
- Chronic administration (defined as 14 or more consecutive days) of immunosuppressants or other immune-modifying drugs during the period starting 180 days prior to the first vaccine dose or any planned administration of immunosuppressive and immune-modifying drugs during the entire study. For corticosteroids, this meant prednisone, ≥0.5 mg/kg/day or equivalent. Inhaled and topical steroids were allowed.

- Planned administration/administration of a vaccine not foreseen by the study protocol during the period starting 30 days prior to study vaccination/s and ending at Visit 2.
    - Note: Inactivated influenza vaccine and *Haemophilus influenzae* type b (Hib) conjugate vaccine may be given at any time, including the day of study vaccination (Influenza and Hib vaccines must be administered at a different body site location than the study vaccines).
- Any other age-appropriate vaccine may be given starting at Visit 2 and any time thereafter.
- Administration of immunoglobulins and/or any blood products during the period starting 180 days prior to study vaccination at Visit 1 or planned administration from the date of vaccination through the immunogenicity evaluation at Visit 2.
- History of measles, mumps, rubella, varicella/zoster, and/or hepatitis A disease.
- Known exposure to measles, mumps, rubella, and/or varicella/zoster during the period starting within 30 days prior to first study vaccination.
- Previous vaccination against measles, mumps, rubella, hepatitis A, and/or varicella virus.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- A family history of congenital or hereditary immunodeficiency.
- History of allergic disease or reactions likely to be exacerbated by any component of the vaccines, including hypersensitivity to neomycin, latex, or gelatin.
- Blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems.
- Acute disease at the time of enrollment. Acute disease is defined as the presence of a moderate or severe illness with or without fever. Fever is defined as temperature ≥38.0°C (100.4°F) by any age-appropriate route. All vaccines could be administered to persons with a minor illness such as diarrhea, mild upper respiratory tract infection (URI) without fever.
- Active untreated tuberculosis based on medical history.
- Any other condition which, in the opinion of the investigator, prevents the child from participating in the study.

  For US children only:
- Child that previously received a vaccination with Prevnar (heptavalent). Prior vaccination should be with 3 doses of Prevnar 13 only.
- Child that previously received a fourth dose of any pneumococcal conjugate vaccine.

6.1.4 Study Treatments or Agents Mandated by the Protocol

PRIORIX: investigational measles, mumps, and rubella vaccine

- Dose and route of administration (RoA): 0.5 mL subcutaneous (SC)
- Formulation: Measles virus (Schwarz strain) $\geq 10^{3.0}$ $CCID_{50}$; Mumps virus (RIT4385 strain) $\geq 10^{4.3}$ $CCID_{50}$; Rubella virus (Wistar RA 27/3 strain) $\geq 10^{3.0}$ $CCID_{50}$; anhydrous lactose; sorbitol; mannitol; amino acids; neomycin
- Presentation: Lyophilized pellet in a vial for reconstitution with water for injection
- Lots:
    - Lot 1: AMJRC455A
    - Lot 2: AMJRC456A
    - Lot 3: AMJRC457A

M-M-R II: comparator measles, mumps, and rubella vaccine

- Dose and RoA: 0.5 mL SC

- Formulation: Measles virus ≥1,000 tissue culture infectious dose 50% ($TCID_{50}$); Mumps virus ≥12,500 $TCID_{50}$; Rubella virus ≥1,000 $TCID_{50}$; sorbitol 14.5 mg; (b) (4) , sucrose 1.9 mg; (b) (4) , hydrolyzed gelatin 14.5 mg; recombinant human albumin ≤0.3 mg; fetal bovine serum <1 parts per million; other buffer and media ingredients; neomycin approximately 25 µg
- Presentation: Lyophilized pellet in a vial for reconstitution with water for injection (WFI)
- Lots:
  - Lot 1: H004594, J006933, H017980, J006564, 0682AE, H015824, J015488
  - Lot 2: G019547, J006564, H021002, H020866, J006933, 0498AE, H016132, J015222

Varivax:

- Dose and RoA: 0.5 mL SC
- Formulation: A minimum of 1350 plaque forming units Oka/Merck varicella virus; approximately 25 mg sucrose, 12.5 mg hydrolyzed gelatin, 3.2 mg sodium chloride, 0.5 mg monosodium L-glutamate, 0.45 mg sodium phosphate dibasic, 0.08 mg of potassium phosphate monobasic, 0.08 mg of potassium chloride; residual components of MRC-5 cells including DNA and protein; and trace quantities of sodium phosphate monobasic, ethylenediaminetetraacetic acid, neomycin, and fetal bovine serum
- Presentation: Vial of lyophilized vaccine for reconstitution with water for injection
- Lots: H004550, H019070, H012704, J004098, 0603AE, 0604AE

  Reviewer Comment: Both $CCID_{50}$ and $TCID_{50}$ are endpoint dilution tests for final determinations of virus potency. Although M-M-R II virus potency is reported as $TCID_{50}$ and PRIORIX virus potency is reported as $CCID_{50}$, both measure infectious doses and the final values can be interpreted on a similar scale.

Havrix

- Dose and RoA: 0.5mL intramuscular (IM)
- Formulation: 720 EU of hepatitis A virus antigen; 0.25 mg aluminum (as hydroxide); amino acid supplement (0.3% w/v); in a phosphate-buffered saline solution and polysorbate 20 (0.05 mg/mL)
- Presentation: Suspension in vial/prefilled syringe
- Lots: AHAVB666C, AHAVB668A, AHAVB573C, AHAVB646BA, AHAVVB738B

Prevnar 13

- Dose and RoA: 0.5mL IM
- Formulation: 2.2 µg of the purified saccharides 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 23F; 4.4 µg of the purified saccharide 6B; approximately 34 µg CRM197 carrier protein; 100 µg polysorbate 80; 295 µg succinate buffer; 125 µg aluminum as aluminum phosphate adjuvant
- Presentation: Suspension in vial/prefilled syringe
- Lots: F94001, H17427

6.1.5 Directions for Use

For this study, and all other Phase 3 studies included in this application, lyophilized PRIORIX vaccine in a vial was reconstituted with the entire volume of water for injection (WFI) diluent in a vial, and the entire contents of the reconstituted vaccine were withdrawn into a syringe. After the needle was changed, the total volume of reconstituted vaccine was administered subcutaneously via the syringe.

Reviewer Comment: As mentioned above, the Phase 3 clinical trials included in this application (MMR-158, MMR-159, MMR-160, MMR-161, and MMR-162) used Water for Injection (WFI)

diluent in a vial presentation to reconstitute the lyophilized PRIORIX vaccine, with instructions to inject the entire volume of diluent from the vial into the lyophilized vaccine vial and to withdraw and administer the whole content of reconstituted vaccine to the participant. A Type C Meeting (May 2020) was held to discuss the Applicant's proposed change to an ungraduated pre-filled syringe (PFS) diluent presentation for PRIORIX as part of the anticipated BLA. The sponsor's proposed change included the use of a diluent presentation of WFI in an ungraduated PFS that would be used to reconstitute the lyophilized vaccine in a vial with a whole content reconstitution and whole content administration (WC/WC) strategy for commercial use. The Applicant presented CMC data on volume loss and minimal/maximal potency titers with the Type C meeting package. Based on the information provided, CBER agreed that Phase 3 clinical data that had used WFI vial/vial presentation could be used to support the use of an ungraduated PFS presentation using a WC/WC strategy as the final presentation/administration approach for commercial use.

6.1.6 Sites and Centers

There were 92 sites in the United States (including Puerto Rico), Estonia, Finland, Mexico, and Spain with a total vaccinated cohort of 5,003 participants. There were 65 US sites with a total vaccinated cohort of 2,502 participants.

6.1.7 Surveillance/Monitoring

Surveillance
Study oversight included Institutional Review Board or Independent Ethics Committee review and approval of the study protocol, any amendments, the informed consent, and other pre-approval information. A GSK Site Monitor conducted monitoring visits. Contract research organizations (CROs) were employed at study sites in Finland, Canada, and the US for various activities including sample management, site monitoring, and vaccine distribution. The study was subject to audit by GSK's R&D Global Quality Compliance - Clinical Development Quality Assurance department.

Safety Monitoring
Solicited local AEs (pain, redness, or swelling at injection site) were recorded from Day 0 to Day 3. Solicited systemic AEs of drowsiness, loss of appetite, and irritability were collected from Day 0 to Day 14. Solicited systemic AEs of varicella-like rash, measles/rubella-like rash, other rash (not measles/rubella-like nor varicella-like), fever (defined as temperature ≥38ºC/100.4ºF), parotid gland/salivary gland swelling, and meningism (including febrile convulsions) were collected from Day 0 to Day 42. All AEs occurring from Day 0 through 42 days after vaccination were recorded. Diary cards and remote data entry were used.

AEs of specific interest included NOCDs (e.g., autoimmune disorders, asthma, type I diabetes, vasculitis, celiac disease, conditions associated with sub-acute or chronic thrombocytopenia, and allergies) and conditions/AEs prompting ER visits. AEs of specific interest were reported throughout the study, through a minimum of six months post-vaccination, irrespective of whether considered possibly related to the treatment administration.

Unsolicited AEs, AEs of specific interest (i.e., NOCDs and AEs prompting an ER visit), medically attended events (MAEs), and SAEs were collected and recorded from the first receipt of study vaccine throughout the entire study (Day 0 to Day 180). MAEs were defined as an event for which the participant received medical attention such as hospitalization, an ER visit, or a visit with a medical provider for any reason, although routine well child visits were not recorded in the electronic case report form (eCRF).

SAEs that were related to the study vaccine(s) were collected and recorded from the time of the first study vaccination until the child was discharged.

The investigator assessed events of rashes and parotid/salivary gland swelling. In the case of a seizure, the investigator classified the level of diagnostic certainty according to the Brighton Collaboration Seizure Working Group's case definitions of generalized convulsive seizure as an AE following immunization.

Investigators followed participants with SAEs or participants who were withdrawn as result of an AE until the event had resolved, subsided, stabilized, disappeared, or until the event was otherwise explained, or the child was lost to follow-up. Those with other non-serious AEs were followed until resolution or study end unless they were lost to follow-up. Investigators followed children who were withdrawn due to SAE or AE until resolution of the event.

Immunogenicity monitoring

Table 4 includes the serological assays used in the measurement of immunogenicity endpoints.

Table 4. Summary of Serological Assays, Study MMR-160

Component	Method	Unit	Cut-Off	Thresholds	Kit/ Manufacturer	Location
Measles Virus Ab.IgG	ELISA	mIU/mL	150	200	(b) (4)	
Rubella Virus Ab.IgG	ELISA	IU/mL	4	10		
Mumps Virus Ab.IgG	ELISA	EU/mL	5	10		
Varicella Zoster Virus Ab.IgG	(b) (4)	mIU/mL	25	75		
Hepatitis A Virus Ab.IgG	(b) (4)	mIU/mL	15	--	In-house	GSK Biologicals
Streptococcus pneumoniae Polysaccharide 01 Ab.IgG	(b) (4)	µg/mL	0.08	0.35	In-house	GSK Biologicals
Streptococcus pneumoniae Polysaccharide 03 Ab.IgG	(b) (4)	µg/mL	0.075	0.35	In-house	GSK Biologicals
Streptococcus pneumoniae Polysaccharide 04 Ab.IgG	(b) (4)	µg/mL	0.061	0.35	In-house	GSK Biologicals
Streptococcus pneumoniae Polysaccharide 05 Ab.IgG	(b) (4)	µg/mL	0.198	0.35	In-house	GSK Biologicals
Streptococcus pneumoniae Polysaccharide 06A Ab.IgG	(b) (4)	µg/mL	0.111	0.35	In-house	GSK Biologicals
Streptococcus pneumoniae Polysaccharide 06B Ab.IgG	(b) (4)	µg/mL	0.102	0.35	In-house	GSK Biologicals
Streptococcus pneumoniae Polysaccharide 07F Ab.IgG	(b) (4)	µg/mL	0.063	0.35	In-house	GSK Biologicals
Streptococcus pneumoniae Polysaccharide 09V Ab.IgG	(b) (4)	µg/mL	0.066	0.35	In-house	GSK Biologicals
Streptococcus pneumoniae Polysaccharide 14 Ab.IgG	(b) (4)	µg/mL	0.16	0.35	In-house	GSK Biologicals

Component	Method	Unit	Cut-Off	Thresholds	Kit/ Manufacturer	Location
Streptococcus pneumoniae Polysaccharide 18C Ab.IgG	(b) (4)	µg/mL	0.111	0.35	In-house	GSK Biologicals
Streptococcus pneumoniae Polysaccharide 19A Ab.IgG	(b) (4)	µg/mL	0.199	0.35	In-house	GSK Biologicals
Streptococcus pneumoniae. Polysaccharide 19F Ab.IgG	(b) (4)	µg/mL	0.163	0.35	In-house	GSK Biologicals
Streptococcus pneumoniae Polysaccharide 23F Ab.IgG	(b) (4)	µg/mL	0.073	0.35	In-house	GSK Biologicals

Source: Adapted from STN 125748/0, Clinical Overview, Table 4
Abbreviations: Ab=antibody; (b) (4) ; ELISA=enzyme-linked immunosorbent assay; IgG=immunoglobulin G; IU-international unit

6.1.8 Endpoints and Criteria for Study Success

See Section 6.1.1.

6.1.9 Statistical Considerations and Statistical Analysis Plan

Sample Size
The target to enroll approximately 5,000 children assumed a 20% non-evaluable rate which would result in an evaluable population of 4,000 children, with an estimated 1,000 children in each PRIORIX lot group and 500 in each M-M-R II lot group.

Methods
To control the type I error below 2.5%, a hierarchical procedure was used for the primary and secondary objectives. Each co-primary objective could only be reached if all the associated criteria were met and all previous co-primary objectives had been reached, and the secondary objectives could only be assessed if all co-primary objectives had been met. No hierarchy between secondary objectives was made.

The analysis was performed in two steps which were combined in the final clinical report:

- A final analysis of immunogenicity data for measles, mumps, and rubella and solicited symptoms up to Day 42 was performed as soon as the immunogenicity and reactogenicity data up to Visit 2 were available and cleaned.
- A final analysis of immunogenicity data for the concomitantly administered vaccines, unsolicited AEs from Day 0 to Day 42 following vaccination, and SAEs and specific AEs covering the period from Day 0 to study end (including the 6-months safety follow-up) was performed at the end of the study.

Following unblinding for the analysis up to Day 42, accessibility to group attribution was limited to the statisticians until all study procedures pertaining to the active Phase and the six-month safety follow-up were completed for all children.

Descriptive immunogenicity analyses (for measles, mumps, and rubella) and safety analyses were repeated by country, gender, and race (geographic ancestry) if there were at least 50 participants per treatment group.

Only participants with a completed solicited AE section of the eCRF were considered for the analysis of solicited symptoms. Missing or non-evaluable measurements were not replaced. In the primary analysis of solicited symptoms, missing daily recordings were replaced by the maximum value recorded for that participant. For participants reporting fever as present in the absence of temperature measurement, missing daily recordings were replaced by grade 1. If the percentage of children reporting a symptom without a single daily recording was above 1%, a sensitivity analysis of the impact of missing data on the endpoints was to be conducted, however 0.1% of participants in both the PRIORIX and M-M-R II groups reported fever with no accompanying temperature measurement. For the analyses of unsolicited AEs, SAEs, and concomitant medication, all vaccinated participants were considered. Those not reporting an event were considered as participants without an event.

Protocol Amendments

Protocol Amendment 1 (May 14, 2014) included the following changes:

- Vaccination with inactivated influenza vaccine and *Haemophilus influenzae* b vaccine could be given at any time before, during, or after the study.
- All medically attended events from Day 0 to Day 180 were to be recorded in the eCRF, but routine well child visits would not be recorded in the eCRF.

Protocol Amendment 2 (February 26, 2015) included the following changes:

- The (b) (4) would not be used, so the secondary endpoint related to the assessment of the percentage of participants with *S. pneumoniae* antibody concentrations ≥0.05, 0.2, 0.5, and 1.0 µg/mL with the (b) (4) was removed.
- Assessment of a validated pneumococcal assay was 'ongoing' at the time of the protocol amendment (see Reviewer Comment below).
- Serological assays for antibodies against measles, rubella, and varicella viruses would be performed by GSK's laboratory in (b) (4).
- The immunogenicity data analysis for the concomitantly administered vaccines would be included in the final analysis performed at the end of the study.

  Reviewer Comment: The (b) (4) assay used by the Applicant is a multiplexed immune assay that uses two different kinds of pneumococcal cell wall polysaccharides to reduce cross-reactivity with serum antibodies and which simplifies the coating process (as compared to (b) (4). Under Amendment 14 to the BLA, the Applicant responded to CBER's request for information regarding the status of the pneumococcal (b) (4) assay used in study MMR-160. This was reviewed by the FDA assay reviewer, who confirmed that it was validated for assessing the immune responses to the pneumococcal antigens in the concomitant administration studies.

Changes in the Conduct of the Study and Planned Analyses

Issues related to study conduct included the following:

- The decommissioning of the local vaccine depot (b) (4) located in (b) (4) revealed that appropriate documentation of cold chain management of (b) (4) stand-alone freezer units was lacking between December 2012 and June 2015. This could have potentially led to temperature deviations in the storage conditions for the vaccines stored in these freezer units, (Varivax vaccine used in studies MMR-158 and MMR-160). Since more than 5% of participants in each study were administered Varivax that was potentially affected, an additional sensitivity analysis that excluded affected participants was performed if there was any potential impact on study conclusions. The study conclusions were considered unchanged if the new point estimates of GMC or SRRs were in similar ranges compared to that of the original analyses. The additional sensitivity analyses did not alter the relevant study conclusions.

- Two technical problems were identified in the Electronic Data Capture system. One was related to the incorrect display of the investigator's signature on the electronic screens in the system, and the second was that the reasons for change of the data noted in the audit trail were overwritten, although the original entry and data changes were not affected. Both issues were corrected and were determined to have neither changed the validity of the data collected nor had any impact on the data reported.

All analyses were performed as planned in the protocol.

Please see the statistical review for further discussion.

6.1.10 Study Population and Disposition

A total of 5,016 participants were enrolled in the study. The first participant was enrolled in the study on November 9, 2012, and the last study visit was on April 16, 2015.

6.1.10.1 Populations Enrolled/Analyzed

The *Total Vaccinated Cohort (TVC)* included all vaccinated participants.

- The *TVC for Safety Analysis* included all vaccinated participants with at least one documented vaccine administration of either PRIORIX or M-M-R II.
- The *TVC for Immunogenicity Analysis* included all vaccinated participants for whom immunogenicity data were available.

According-to-Protocol (ATP) Cohort for Safety Analysis included eligible participants:

- who had received at least one MMR study vaccine/comparator as per protocol
- who had not received a vaccine leading to exclusion from the ATP cohort in the protocol up to Visit 2[3]
- for whom the randomization code had not been broken
- for whom the route of administration of study vaccine(s) was known and correct

ATP Cohort for Immunogenicity Analysis included all eligible participants from the ATP Cohort for Safety:

- with pre-vaccination and post-dose serology results available for at least one antigen of measles, mumps, or rubella
- who were below the assay cut-off for at least one vaccine antigen for MMR at pre-vaccination
- who did not meet any elimination criteria up to the Visit 2 blood sample as described below
- who complied with the post-vaccination blood sample schedule between vaccination at Visit 1 and the blood draw at Visit 2

  Reviewer Comment: The Applicant clarified with Amendment submissions to this application (Amendments 14 and 16) that the percentage of participants eliminated from each TVC analysis for immunogenicity was dependent upon the relevant assay and available (i.e., pre- and/or post-vaccination) immunogenicity results. Accordingly, for the primary immunogenicity analyses, the ATP Cohort for Immunogenicity was determined separately for each antigen to decide whether secondary immunogenicity analyses using the TVC population would be needed (i.e., if the percentage of enrolled participants with serological results excluded from the ATP Cohort for Immunogenicity was higher than 5%) to confirm the primary analyses.

3 For an explanation of the vaccines leading to exclusion from the ATP Cohort for Analysis of Safety, see *Protocol Deviations* below.

Protocol Deviations
Exclusion from the *ATP Cohort for Immunogenicity Analyses* occurred if participants were confirmed to have an immunodeficiency condition or if they developed measles, mumps, or rubella in the interval between vaccination and the collection of the blood specimen for immunogenicity at Visit 2.

Any of the following resulted in elimination from the ATP analyses:

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) during the study period.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs during the period starting at vaccination and ending at Visit 2. For corticosteroids, this meant prednisone >0.5 mg/kg/day, or equivalent. Inhaled and topical steroids were allowed.
- Planned administration/ administration of a vaccine not foreseen by the study protocol during the study period starting at vaccination and ending at Visit 2.
- Inactivated Influenza and Hib vaccines could be given at any time, including the day of study vaccination (Influenza and Hib vaccines were to be administered at a different location than the study vaccine).
- Any other age-appropriate vaccine could be given starting at Visit 2 and any time thereafter.
- Administration of immunoglobulins and/or any blood products starting at vaccination and ending at Visit 2.

6.1.10.1.1 Demographics

Table 5. Demographic Characteristics, TVC, Study MMR-160

Characteristic	PRIORIX Lot 1 N=1,239	PRIORIX Lot 2 N=1,232	PRIORIX Lot 3 N=1,243	M-M-R II N=1,289
Sex	--	--	--	--
Ratio male:female	632:607	638:594	628:615	671:618
% male:% female	51.0%:49.0%	51.8%:48.2%	50.5%:49.5%	52.1%:47.9%
Age, months	--	--	--	--
Mean age (SD)	12.3 (0.7)	12.3 (0.7)	12.3 (0.7)	12.3 (0.7)
Median age	12.0	12.0	12.0	12.0
Age range	12, 16	12, 15	12, 16	11, 15
Ethnicity, n (%)	--	--	--	--
Hispanic/Latino	219 (17.7%)	239 (19.4%)	234 (18.8%)	240 (18.6%)
Not Hispanic/Latino	1020 (82.3%)	993 (80.6%)	1009 (81.2%)	1049 (81.4%)
Racial Origin (Geographic Ancestry), n (%)	--	--	--	--
Am. Indian/A.N.	25 (2.0%)	37 (3.0%)	33 (2.7%)	31 (2.4%)
All Asian	44 (3.6%)	43 (3.5%)	40 (3.2%)	46 (3.6%)
Central/South Asian	14 (1.1%)	6 (0.5%)	7 (0.6%)	9 (0.7%)
East Asian	8 (0.6%)	10 (0.8%)	10 (0.8%)	10 (0.8%)
Japanese	1 (0.1%)	2 (0.2%)	2 (0.2%)	1 (0.1%)
Southeast Asian	21 (1.7%)	25 (2.0%)	21 (1.7%)	26 (2.0%)
African/A.A.	60 (4.8%)	52 (4.2%)	57 (4.6%)	70 (5.4%)
All White	937 (75.6%)	944 (76.6%)	946 (76.1%)	977 (75.8%)
Arabic/North African	5 (0.4%)	6 (0.5%)	2 (0.2%)	7 (0.5%)
Caucasian/European	932 (75.2%)	938 (76.1%)	944 (75.9%)	970 (75.3%)
N. Hawaiian/P.I.	3 (0.2%)	1 (0.1%)	5 (0.4%)	2 (0.2%)
Other	170 (13.7%)	155 (12.6%)	162 (13.0%)	163 (12.6%)

Characteristic	PRIORIX Lot 1 N=1,239	PRIORIX Lot 2 N=1,232	PRIORIX Lot 3 N=1,243	M-M-R II N=1,289
Country, n (%)	--	--	--	--
Estonia	124 (10.0%)	125 (10.1%)	125 (10.1%)	127 (9.9%)
Spain	61 (4.9%)	62 (5.0%)	64 (5.1%)	69 (5.4%)
Finland	338 (27.3%)	335 (27.2%)	337 (27.1%)	340 (26.4%)
Mexico	98 (7.9%)	98 (8.0%)	99 (8.0%)	99 (7.7%)
United States	618 (49.9%)	612 (49.7%)	618 (49.7%)	654 (50.7%)

Source: Adapted from STN 125748/0, MMR-160 Clinical Study Report Amendment 2, Table 6.5
Abbreviations: A.A.=African American; Am. Indian/A.N=American Indian/Alaskan Native; N: total number of participants for the TVC Safety Analysis Set (participants with at least 1 vaccination of either PRIORIX or M-M-R II); n=number of participants fulfilling the item; N. Hawaiian/P.I.: Native Hawaiian/Pacific Islander; Other=mixed race or not otherwise specified; SD=standard deviation; TVC=total vaccinated cohort
Note: Two different lots of M-M-R II were used during this study. Data from both lots were pooled for this summary.

The median age of participants in the TVC was 12.0 months, with a range of 11 to 16 months, at the time of the first study vaccination. Overall, the majority of participants were White/Caucasian (75.6%) and male (51.3%), which was observed in each study group as well. In general, demographic and baseline characteristics were similar across study groups. Approximately 50% of study participants in all study groups were enrolled at US sites. The demographic characteristics observed for participants in the TVC were comparable to those observed in the ATP Cohort for Immunogenicity; however, the median age was 12.3 months with a range of 12 to 15 months.

> Reviewer Comment: Median age and age range varied slightly between the TVC and the ATP Cohort for Immunogenicity with the age range in the TVC extending beyond the pre-defined protocol specifications. However, according to the study design, protocol deviations related to participant age outside of the study inclusion criteria did not lead to elimination from ATP analyses and were similar across study groups.

6.1.10.1.2 Participant Disposition

Table 6. Participant Disposition and Data Analyses, All Randomized Participants, Study MMR-160

Population, n (%)	PRIORIX Lot 1 N=1239	PRIORIX Lot 2 N=1234	PRIORIX Lot 3 N=1246	M-M-R II N=1291
Enrolled	1239 (100%)	1234 (100%)	1246 (100%)	1291 (100%)
TVC	1239 (100%)	1232 (99.8%)	1243 (99.8%)	1289 (99.8%)
Completed study	1175 (94.8%)	1162 (94.2%)	1190 (95.5%)	1232 (95.4%)
TVC-Safety	1239 (100%)	1232 (99.8%)	1243 (99.8%)	1289 (99.8%)
TVC-Imm.	1230 (99.3%)	1228 (99.5%)	1238 (99.4%)	1279 (99.1%)
ATP-Safety	1226 (99.0%)	1222 (99.0%)	1233 (99.0%)	1277 (98.9%)

Population, n (%)	PRIORIX Lot 1 N=1239	PRIORIX Lot 2 N=1234	PRIORIX Lot 3 N=1246	M-M-R II N=1291
ATP-Imm.	1108 (89.4%)	1098 (89.0%)	1130 (90.7%)	1162 (90.0%)
≥1 Important protocol deviation[a]	131 (10.6%)	136 (11.0%)	116 (9.3%)	129 (10.0%)
Maximum percentage of participants eliminated for ATP-Imm analyses[b]	3.58%[c]	3.58%[c]	3.58%[c]	3.23%

Source: Adapted from STN 125748/0, MMR-160 Clinical Study Report Amendment 2, Table 23, Table 24; MMR (RIT) Analysis #16 Table 5
Abbreviations: ATP=According-to-protocol; N=total number of participants enrolled; n=number of participants fulfilling the item followed by (%); TVC=Total vaccinated cohort, included all vaccinated participants; ≥1 Prot. Deviation: participants with one or more protocol deviations
Note: Two different lots of M-M-R II were used during this study. Data from both lots were pooled for this summary.
a. Includes participants with important protocol violations that resulted in exclusion from the ATP-Imm. analysis population.
b. For each antigen and each objective, the percentage of participants who had the necessary immunogenicity results to contribute to the TVC analysis but were eliminated for the ATP analysis was computed. This value represents the maximum over all objectives and antigens. If this percentage was ≥5%, then a secondary analysis based on the TVC would have been performed.
c. This is the maximum value for the non-inferiority objectives using the pooled PRIORIX lots. For the lot consistency objectives using the individual lots, the maximum value was 1.84%
TVC-Safety: included all vaccinated participants with at least one vaccine administration of either PRIORIX or M-M-R II documented.
TVC-Imm.: included all vaccinated participants for whom immunogenicity data were available.
ATP-Safety: Safety analyses using the ATP cohort included eligible participants who received at least one MMR study vaccine/comparator as per protocol; did not receive a vaccine leading to exclusion from the ATP cohort; for whom the randomization code had not been broken; and the administration route of study vaccine(s) was known and correct.
ATP-Imm.: Immunogenicity analyses using the ATP cohort included all eligible participants. from the ATP cohort for safety with pre-vaccination and post-dose serology results available for at least one antigen of measles, mumps, or rubella; below the assay cut-off for at least one MMR vaccine antigen pre-vaccination; did not meet any elimination criteria up to the Visit 2 blood sample; and complied with the post-vaccination blood sample schedule.

A total of 5,016 participants were enrolled in the study and 5,003 participants received a study vaccination. Of those vaccinated, 4,759 (95.1%) completed the study. The most common reasons for withdrawal were loss to follow-up with complete vaccination (133 participants) and consent withdrawal not due to an adverse event (68 participants). Two participants were withdrawn due to experiencing a non-serious AE, both in the PRIORIX Lot 1 group. Four participants were withdrawn due to protocol violations which the Applicant stated were due to non-compliance with protocol and study visits, three in the PRIORIX Lot 1 group and one in the PRIORIX Lot 3 group.[4]

A total of 4,958 participants (99.1%) were included in the ATP Cohort for Safety, the most common reasons for exclusion from this cohort included administration of vaccines forbidden in the protocol (22 participants) and vaccine temperature deviation (12 participants). A total of 4,498 participants (89.9%) were included in the ATP Cohort for Immunogenicity, the primary reason for exclusion from this cohort was "essential serological data missing" (276 participants) and included 17 participants whose blood samples were collected using expired "Vacutainer tubes." An additional 139 participants were excluded due to the presence of detectable baseline antibody levels or unknown baseline antibody status, and 39 were excluded for non-compliance with the blood sampling schedule.

Protocol deviations from specifications for participant age and intervals between study visits were similar across study groups and did not lead to elimination from ATP analyses. Additional protocol deviations not leading to elimination from ATP analyses included five participants who were administered Varivax vaccine that was stored at a temperature colder than advised, and two participants who were entered and/or randomized without a signed Informed Consent Form (ICF). No other study procedure was performed until the signed ICF was obtained.

> Reviewer Comment: The proportion of reported protocol deviations was comparable across study groups. The observed protocol deviations do not raise concerns about study conduct.

4 Submitted under Amendment 16 to the BLA

6.1.11 Immunogenicity Analyses

The study design did not include clinical efficacy endpoints. Serologic immune endpoints were used to assess the response to vaccination. Except for anti-pneumococcal antibodies, the criteria were specific to children seronegative for the assay at pre-vaccination. Missing or non-evaluable immunogenicity measurements were not replaced.

The primary analysis of immunogenicity was performed on the ATP Cohort for Immunogenicity. A secondary analysis based on the TVC was not performed because less than 5% of participants were eliminated from each group in the ATP Cohort for Immunogenicity. A sensitivity analysis was performed on the ATP Cohort for Immunogenicity to assess if there was any potential impact on study conclusions due to data from participants impacted by a potential Varivax storage temperature deviation (see Section 6.1.9), and it was concluded that excluding these participants from the analysis had no impact on study conclusions.

> Reviewer Comment: The TVC for Immunogenicity listed in Table 6 includes all vaccinated participants for whom immunogenicity data were available at any time point, including pre-vaccination. Subsets of the TVC for Immunogenicity were created for each assay in each confirmatory objective to be used as the basis for determining the need for a secondary analysis to complement the primary analysis in the ATP Cohort for Immunogenicity since the success criteria for these objectives were based on post-vaccination immunogenicity data. The maximum percentage of participants excluded was less than 5% across all endpoints, and thus no secondary analyses were done.

6.1.11.1 Analyses of Primary Endpoint(s)

Co-Primary Objectives 1 and 2: Lot-to Lot Consistency

Lot-to-lot consistency was demonstrated if, for each pairwise comparison, the two-sided 95% CI for the differences in SRRs were within the [-5%, 5%] margin and for the adjusted GMC ratio (adjusted by country) were within the [0.67, 1.5] margin for anti-measles, anti-mumps, and anti-rubella antibodies. Co-primary objectives 1 and 2 were ***met*** as shown in Table 7 and Table 8.

Table 7. Seroresponse Rate Differences at Day 42, ATP Cohort for Immunogenicity, Study MMR-160

Antibody	Lot 1 to Lot 2 SRR Difference (95% CI)	Lot 2 to Lot 3 SRR Difference (95% CI)	Lot 1 to Lot 3 SRR Difference (95% CI)
Anti-Measles	-0.54 (-1.69, 0.58)	0.79 (-0.35, 1.98)	0.25 (-0.98, 1.50)
Anti-Mump	0.02 (-1.05, 1.09)	0.61 (-0.53, 1.79)	0.63 (-0.50, 1.81)
Anti-Rubella	0.14 (-1.30, 1.58)	-0.62 (-2.02, 0.74)	-0.49 (-1.86, 0.86)

Source: Adapted from STN 125748/0, MMR-160 Clinical Study Report Amendment 2, Table 26
Abbreviations: ATP=according to protocol; CI=confidence interval; ELISA=enzyme-linked immunosorbent assay; EU=ELISA unit; IU=international unit; SRR=Seroresponse Rate: percentage of initially seronegative participants with concentration above seroresponse threshold
Assays: Anti-Measles, (b) (4) ELISA; Anti-Mumps, (b) (4) ELISA; Anti-Rubella, (b) (4) ELISA (For each assay - seroresponse thresholds are 200 mIU/mL, 10 EU/mL, and 10 IU/mL for anti-measles, anti-mumps, and anti-rubella antibodies respectively).
95% CI numbers indicate the interval margin for which statistical testing was performed for the respective test.
Success criteria to demonstrate consistency of the 3 lots: for each pairwise comparison, the 2-sided 95% CI of the SRR difference must be within the [−5%, 5%] margin.

Table 8. GMC Ratios at Day 42, ATP Cohort for Immunogenicity, Study MMR-160

Antibody	Lot 1 to Lot 2 GMC Ratio (95% CI)	Lot 2 to Lot 3 GMC Ratio (95% CI)	Lot 1 to Lot 3 GMC Ratio (95% CI)
Anti-Measles	0.99 (0.91, 1.06)	0.99 (0.91, 1.06)	0.97 (0.90, 1.05)
Anti-Mumps	0.93 (0.87, 1.00)	1.11 (1.04, 1.19)	1.04 (0.97, 1.11)
Anti-Rubella	1.08 (1.01, 1.15)	0.93 (0.87, 0.99)	1.00 (0.94, 1.07)

Source: Adapted from STN 125748/0, MMR-160 Clinical Study Report Amendment 2, Table 27
Abbreviations: ANOVA=analysis of variance; ATP=according to protocol; CI=confidence interval; ELISA=enzyme-linked immunosorbent assay; GMC=geometric mean antibody concentration adjusted for country (ANOVA model: adjustment for country - pooled variance with more than 2 groups)
Assays: Anti-Measles, (b) (4) ELISA; Anti-Mumps, (b) (4) ELISA; Anti-Rubella, (b) (4) ELISA
95% CI numbers indicate the interval margin for which statistical testing was performed for the respective test.
Success criteria to demonstrate consistency of the 3 lots: for each pair-wise comparison, the 2-sided 95% CI for the GMC ratio must be within the [0.67, 1.5] margin.

Co-Primary Objectives 3 and 4: Non-Inferiority

The success criteria to demonstrate non-inferiority were met if the LL of the two-sided 95% CI for the group difference in SRR (PRIORIX minus M-M-R II) was ≥-5%, and for the adjusted GMC ratio (PRIORIX over M-M-R II) was ≥0.67 for anti-measles, anti-mumps, and anti-rubella antibodies. Co-primary objectives 3 and 4 were ***met***, as shown in Table 9 and Table 10.

Table 9. Proportion of Participants With Seroresponse and Difference Across Groups at 42 Days Post-Vaccination, ATP Cohort for Immunogenicity, Study MMR-160

Antibody	PRIORIX N=3,187 to 3,248 SRR	M-M-R II N=1,107 to 1,137 SRR	PRIORIX - M-M-R II SRR Difference (95% CI)
% anti-Measles ≥200 mIU/mL	98.2%	98.0%	0.18 (-0.68, 1.25)
% anti-Mumps ≥10 EU/mL	98.4%	97.6%	0.81 (-0.10, 1.96)
% anti-Rubella ≥10 IU/mL	97.3%	98.5%	-1.15 (-2.00, -0.15)

Source: Adapted from STN 125748/0, MMR-160 Clinical Study Report Amendment 2, Table 28, Table 7.27, Table 7.37, Table 7.47
Abbreviations: ATP=According to Protocol cohort; ELISA=enzyme-linked immunosorbent assay; EU=ELISA unit; IU=international unit; N=number of participants in ATP Cohort for Immunogenicity; SRR=Seroresponse Rate: percentage of initially seronegative participants with concentration above seroresponse threshold for each assay; Assays: Anti-Measles, (b) (4) ELISA; Anti-Mumps, (b) (4) ELISA; Anti-Rubella, (b) (4) ELISA (For each assay - seroresponse thresholds are 200 mIU/mL, 10 EU/mL, and 10 IU/mL for anti-measles, anti-mumps, and anti-rubella antibodies respectively).
Note: Two different lots of M-M-R II were used during this study. Data from both lots were pooled for this summary.
Note: Data from the three PRIORIX lots were pooled for this summary.
Lower 95% CI numbers indicate lower limits of 95% CI for which statistical testing was performed for the respective test.
Success criteria: the lower limit of the 2-sided 95% CI for the group difference in SRR (PRIORIX minus M-M-R II) must be ≥−5% for anti-measles, anti-mumps, and anti-rubella antibodies.

Table 10. GMCs and GMC Ratio at 42 Days Post-Vaccination, ATP Cohort for Immunogenicity, Study MMR-160

Antibody	PRIORIX N=3,187 to 3,248 GMC	M-M-R II N=1,107 to 1,137 GMC	PRIORIX/M-M-R II GMC Ratio (95% CI)
Anti-Measles (mIU/mL)	3165.2	3215.4	0.98 (0.93, 1.05)
Anti-Mumps (EU/mL)	76.4	73.0	1.05 (0.99, 1.11)
Anti-Rubella (IU/mL)	52.5	60.0	0.87 (0.83, 0.92)

Source: Adapted from STN 125748/0, MMR-160 Clinical Study Report Amendment 2, Table 29, Table 7.28, Table 7.38, Table 7.48
Abbreviations: ANOVA=analysis of variance; ATP=According to Protocol cohort; CI=confidence interval; ELISA=enzyme-linked immunosorbent assay; EU=ELISA unit; GMC: geometric mean antibody concentration adjusted for country (ANOVA model: adjustment for country – pooled variance); IU=international unit; N=number of participants in ATP Cohort for Immunogenicity;
Assays: Anti-Measles, (b) (4) ELISA; Anti-Mumps, (b) (4) ELISA; Anti-Rubella, (b) (4) ELISA
Note: Two different lots of M-M-R II were used during this study. Data from both lots were pooled for this summary.
Note: Data from the three PRIORIX lots were pooled for this summary.
Lower 95% CI numbers indicate lower limits of 95% CI for which statistical testing was performed for the respective test.
Success criteria: the lower limit of the 2-sided 95% CI for the adjusted GMC ratio (PRIORIX over M-M-R II) must be ≥0.67 for anti-measles, anti-mumps, and anti-rubella antibodies.

Co-Primary Objective 5: Immune Response

The success criterion was met if the LL of the two-sided 95% CI for the SRR for the PRIORIX lots was ≥90% for each of the vaccine virus antigens. Co-primary objective 5 was ***met***: anti-measles (PRIORIX 98.2% vs M-M-R II 98.0%), anti-mumps (PRIORIX 98.4% vs M-M-R II 97.6%), and anti-rubella (PRIORIX 97.3% vs M-M-R II 98.5%). See Table 11.

Table 11. Seroresponse Rate and GMC at 42 Days Post-Vaccination, ATP Cohort for Immunogenicity, Study MMR-160

Antibody	PRIORIX (N=3187 to 3248)	M-M-R II (N=1107 to 1137)
Anti-Measles	--	--
% ≥200 mIU/mL (95% CI)	98.2% (97.6, 98.6)	98.0% (97.0, 98.7)
GMC (95% CI)	3017.4 (2923.9, 3113.8)	3074.4 (2911.0, 3246.9)
Anti-Mumps	--	--
% ≥10 EU/mL (95% CI)	98.4% (97.9, 98.8)	97.6% (96.5, 98.4)
GMC (95% CI)	72.4 (70.4, 74.5)	69.1 (65.7, 72.7)
Anti-Rubella antibody	--	--
% ≥10 IU/mL (95% CI)	97.3% (96.7, 97.9)	98.5% (97.6, 99.1)
GMC (95% CI)	55.7 (54.2, 57.3)	64.0 (61.1, 67.0)

Source: Adapted from STN 125748/0, MMR-160 Clinical Study Report Amendment 2, Table 30, Table 31, Table 32
Abbreviations: ATP=According to Protocol; CI=confidence interval; ELISA=enzyme-linked immunosorbent assay; EU=ELISA unit; GMC=geometric mean concentration calculated on all participants (performed by taking the anti-log of the mean of the log concentration transformations. Antibody concentrations below the cut-off of the assay were given an arbitrary value of half the cut-off for the purpose of GMC calculation.); IU=international unit; N=number of participants with available results; Seroresponse Rate: percentage of initially seronegative participants with concentration above seroresponse threshold for each assay; Assays: Anti-Measles, (b) (4) ELISA; Anti-Mumps, (b) (4)

ELISA; Anti-Rubella, (b) (4) ELISA (For each assay - seroresponse thresholds are 200 mIU/mL, 10 EU/mL, and 10 IU/mL for anti-measles, anti-mumps, and anti-rubella antibodies respectively).
Note: Two different lots of M-M-R II were used during this study. Data from both lots were pooled for this summary.
Note: Data from the three PRIORIX lots were pooled for this summary.
Success criteria: the lower limit of the 2-sided 95% CI for the SRR for the PRIORIX lots must be ≥90% for anti-measles, anti-mumps, and anti-rubella antibodies.

The SRRs and GMCs for participants enrolled at US study sites who had received PCV13 concomitant vaccination, as well as other protocol-specified concomitant vaccinations are provided below in Table 12. Overall, these descriptive results from US sites were similar to those of the primary analyses.

Table 12. Seroresponse Rate and GMC at 42 Days Post-Vaccination, ATP Cohort for Immunogenicity, US participants only, Study MMR-160

	PRIORIX	M-M-R II
Antibody		
Anti-Measles	N=1549	N=554
% ≥200 mIU/mL (95% CI)	98.2 (97.4, 98.8)	98.4% (96.9, 99.3)
GMC, mIU/mL (95% CI)	3273.3 (3129.6, 3423.6)	3404.1 (3159.7, 3667.5)
Anti-Mumps	N=1573	N=559
% ≥10 EU/mL (95% CI)	98.9 (98.2, 99.3)	98.0 (96.5, 99.0)
GMC, EU/mL (95% CI)	76.7 (73.7, 79.9)	70.3 (65.5, 75.6)
Anti-Rubella	N=1549	N=553
% ≥10 IU/mL (95% CI)	98.5 (97.8, 99.1)	99.1 (97.9, 99.7)
GMC, IU/mL (95% CI)	66.5 (64.0, 69.1)	75.8 (71.3, 80.5)

Source: STN 125748/0, MMR-160 Clinical Study Report Amendment 1, Table 7.33, Table 7.43, and Table 7.53
Abbreviations: ATP=According to Protocol; ELISA=enzyme-linked immunosorbent assay; EU=ELISA unit; GMC=geometric mean concentration calculated on all participants (performed by taking the anti-log of the mean of the log concentration transformations. Antibody concentrations below the cut-off of the assay were given an arbitrary value of half the cut-off for the purpose of GMC calculation.); IU=international unit; N=number of participants with available results; Seroresponse Rate: percentage of initially seronegative participants with concentration above seroresponse threshold for each assay; Assays: Anti-Measles, (b) (4) ELISA; Anti-Mumps, (b) (4) ELISA; Anti-Rubella, (b) (4) ELISA (For each assay - seroresponse thresholds are 200 mIU/mL, 10 EU/mL, and 10 IU/mL for anti-measles, anti-mumps, and anti-rubella antibodies respectively).
Note: Two different lots of M-M-R II were used during this study. Data from both lots were pooled for this summary.
Note: Data from the three PRIORIX lots were pooled for this summary.

> Reviewer Comment: Primary analyses of anti-measles, anti-mumps, and anti-rubella antibody responses at Day 42 showed that all five co-primary objectives were met. The consistency of the three manufacturing lots of PRIORIX was demonstrated, as was non-inferiority of PRIORIX compared to US-licensed M-M-R II. SRRs to the measles, mumps, and rubella antigenic components in PRIORIX all met the pre-defined success criteria. Descriptive data from US participants who received concomitant administration of PCV13 in addition to HAV and VV was comparable to the primary analysis.

6.1.11.2 Analyses of Secondary Endpoints

Since co-primary objectives 1 to 5 were met, this allowed for the hierarchical analyses to evaluate the subsequent secondary objectives, to assess non-inferiority of the humoral immune response to the concomitantly administered vaccines, each in a subset of participants enrolled in the US where the subsets are defined as follows: Subset A=the 1st 1,250 children enrolled in the US; Subset B=the 2nd 1,250 children enrolled in the US; and Subset C=the remaining 2,500 children enrolled.

Secondary Objective 1: Varicella Zoster Virus (VZV)
The success criteria were met if the LL of the two-sided 95% CI for the group difference (PRIORIX minus M-M-R II) in SRRs for anti-VZV antibodies was ≥-10%, and for the GMC ratio (PRIORIX over

M-M-R II) was ≥0.67 for anti-VZV antibodies in a subset of children enrolled in the US (subsets A and B). The objective was ***met,*** as shown in Table 13.

Table 13. Difference in Proportion of Participants with Anti-VZV Antibody Seroresponse and GMC Ratio at 42 Days Post-Vaccination, ATP Cohort for Immunogenicity, VZV Subset, Study MMR-160

Anti-VZV Antibody	PRIORIX N=1492	M-M-R II N=540	PRIORIX – M-M-R II SRR Difference (95% CI)	PRIORIX/M-M-R II GMC Ratio (95% CI)
% ≥75 mIU/mL	92.2%	90.9%	1.30 (-1.31, 4.29)	--
GMC	169.6	167.2	--	1.01 (0.95, 1.08)

Source: Adapted from STN 125748/0, MMR-160 Clinical Study Report Amendment 2, Table 34, Table 35
Abbreviations: ANOVA=analysis of variance; ATP=according to protocol; CI=confidence interval; IU=international unit; N=number of participants with available results; GMC=geometric mean antibody concentration (one-way ANOVA without adjustment for country); n=number of participants with concentration ≥ specified value; SRR=Seroresponse Rate: percentage of initially seronegative participants [defined as VZV antibody concentration <25mIU/mL] with VZV antibody concentration ≥75 mIU/mL); VZV: varicella zoster virus
Note: Two different lots of M-M-R II were used during this study. Data from both lots were pooled for this summary.
Note: Data from the three PRIORIX lots were pooled for this summary.
Lower 95% CI numbers indicate lower limits of 95% CI for which statistical testing was performed for the respective test.
Success criteria to demonstrate non-inferiority: the lower limit of the 2-sided 95% CI for the group difference (PRIORIX minus M-M-R II) in SRR for anti-VZV antibodies must be ≥-10% and the lower limit of the 2-sided 95% CI on the GMC ratio (PRIORIX over M-M-R II) must be ≥0.67 for anti-VZV antibodies.

Secondary Objective 2: Hepatitis A Virus The success criterion was met if the LL of the two-sided 95% CI for the GMC ratio (PRIORIX over M-M-R II) was ≥0.5 for antibodies to hepatitis A virus in a subset of children enrolled in the US (subset A). The objective was *met* as shown in Table 14.

Table 14. Anti-Hepatitis A Virus GMC Ratio at 42 Days Post-Vaccination in Initially Seronegative Participants Only, ATP Cohort for Immunogenicity, HAV Subset, Study MMR-160

Anti-Hepatitis A Virus Antibody	PRIORIX N=748	M-M-R II N=271	PRIORIX/M-M-R II GMC Ratio (95% CI)
GMC	41.8	42.8	0.98 (0.86, 1.11)

Source: Adapted from STN 125748/0, MMR-160 Clinical Study Report Amendment 2, Table 37
Abbreviations: ANOVA=analysis of variance; ATP=according to protocol; CI=confidence interval; GMC=geometric mean antibody concentration (ANOVA model - pooled variance); HAV=Havrix; N=number of participants with available results.
Note: Two different lots of M-M-R II were used during this study. Data from both lots were pooled for this summary.
Note: Data from the three PRIORIX lots were pooled for this summary.
Lower 95% CI number indicates lower limit of 95% CI for which statistical testing was performed.
Success criteria to demonstrate non-inferiority: the lower limit of the 2-sided 95% CI for the GMC ratio (PRIORIX over M-M-R II) must be ≥0.5 for antibodies to hepatitis A virus.

Secondary Objective 3: *S. pneumoniae*, 13 serotypes
The success criterion was met if the LL of the two-sided 95% CI for the GMC ratio (PRIORIX over M-M-R II) was ≥0.5 for each of the 13 *S. pneumoniae* serotypes in a subset of children administered Prevnar 13 in the US (subset B). The objective was ***met*** for each serotype**,** as shown in Table 15.

Table 15. Anti-PS GMC Ratios at 42 Days Post-Vaccination, ATP Cohort for Immunogenicity, PCV Subset, Study MMR-160

Anti-PS Antibody Serotypes (b) (4) (µg/mL)	PRIORIX N=701 to 740 GMC	M-M-R II N=240 to 256 GMC	PRIORIX/M-M-R II GMC Ratio (95% CI)
Anti-PS 1 antibody	2.258	2.392	0.94 (0.85, 1.05)
Anti-PS 3 antibody	0.499	0.503	0.99 (0.91, 1.08)
Anti-PS 4 antibody	1.620	1.844	0.88 (0.79, 0.98)
Anti-PS 5 antibody	2.092	2.280	0.92 (0.83, 1.01)
Anti-PS 6A antibody	5.815	5.761	1.01 (0.92, 1.11)
Anti-PS 6B antibody	5.812	5.924	0.98 (0.89, 1.09)
Anti-PS 7F antibody	3.658	3.887	0.94 (0.86, 1.03)
Anti-PS 9V antibody	2.295	2.324	0.99 (0.90, 1.08)
Anti-PS 14 antibody	6.512	7.151	0.91 (0.81, 1.02)
Anti-PS 18C antibody	2.082	2.255	0.92 (0.84, 1.02)
Anti-PS 19A antibody	4.708	4.876	0.97 (0.87, 1.07)
Anti-PS 19F antibody	4.186	4.367	0.96 (0.87, 1.06)
Anti-PS 23F antibody	2.178	2.301	0.95 (0.85, 1.06)

Source: Adapted from STN 125748/0, MMR-160 Clinical Study Report Amendment 2, Table 38
Abbreviations: ANCOVA=analysis of covariance; Anti-PS=anti-*Streptococcus pneumoniae*; ATP=according to protocol; CI=confidence interval; (b) (4) ; GMC=geometric mean concentration (ANCOVA model: adjustment for baseline concentration – pooled variance); N=number of participants with available pre- and post- vaccination results; PCV=Pneumococcal Conjugate Vaccine (Prevnar 13)
Note: Two different lots of M-M-R II were used during this study. Data from both lots were pooled for this summary.
Note: Data from the three PRIORIX lots were pooled for this summary.
Lower 95% CI numbers indicate lower limit of 95% CI for which statistical testing was performed.
Success criteria to demonstrate non-inferiority: the lower limit of the 2-sided 95% CI for the group GMC ratio (PRIORIX over M-M-R II) must be ≥0.5 for each of the 13 PS serotypes.

Secondary Objective 4 (Descriptive): Havrix

Secondary objective 4 was to assess the immunogenicity of Havrix with respect to the SRRs for antibodies to hepatitis A virus in the PRIORIX groups compared to the M-M-R II vaccine groups in a subset of children enrolled in the US (subset A). The results show that the percentages of participants with antibodies to hepatitis A virus 15 mIU/mL were 86.5% and 84.9% of participants in the PRIORIX and M-M-R II groups, respectively.

> Reviewer Comment: All secondary objectives related to the non-inferiority of PRIORIX compared to M-M-R II in terms of the concomitantly administered vaccines Varivax, Havrix, and Prevnar 13 were met. The descriptive assessment of the immunogenicity of Havrix demonstrated comparable SRRs to Havrix when concomitantly administered with PRIORIX and M-M-R II.

6.1.11.3 Subpopulation Analyses

Subpopulation analyses were descriptive and done for participants by country, gender, and race if there were at least 50 participants per treatment group. All countries represented in the study were included in the subpopulation analyses: Estonia, Spain, Finland, Mexico, and the United States.
When evaluating the primary endpoints for US participants only, who received PCV13 concomitant vaccine administration, the results supported the findings of the primary analyses for all participants for each antigen. These data are provided above in Section 6.1.11.

Race was analyzed by three groups which had at least 50 participants per treatment group: White Caucasian/European heritage, American Hispanic or Latino, and African/African American heritage. PRIORIX was comparable to M-M-R II in terms of SRRs for each of the antigenic components. In the PRIORIX group, numerically higher measles antibody GMCs were observed in African and Hispanic/Latino participants (4211.8 to 4401.4 mIU/mL) compared with White participants (2784.9 mIU/mL). This was also observed in the M-M-R II group (African and Hispanic/Latino: 4559.5 to 4653.4

mIU/mL and White: 2831.4 mIU/mL). Otherwise, the immune responses by country, gender, and race were similar to those reported in the primary immunogenicity analyses.

6.1.11.4 Dropouts and/or Discontinuations

Approximately 95% of enrolled participants completed the study. Missing or non-evaluable immunogenicity measurements were not replaced. Immunogenicity analyses therefore excluded participants with missing or non-evaluable measurements. See Section 6.1.10.1.2.

6.1.11.5 Exploratory and Post Hoc Analyses

Not applicable.

6.1.12 Safety Analyses

6.1.12.1 Methods

Safety data surveillance is described in Section 6.1.7 above and shown in Table 16. Participant compliance with returning symptom sheets for collection of local and systemic solicited AEs following administered vaccines was ≥95.4%.

6.1.12.2 Overview of Adverse Events

Safety Overview
Safety data were collected for PRIORIX groups (by lot and pooled) and the M-M-R II group (pooled lots). Safety data were overall similar between individual lots and pooled lots for PRIORIX groups. Table 16 provides an overview of the rates of adverse events in the pooled PRIORIX lots compared to the pooled M-M-R II lots during the study period.

Table 16. Proportion of Participants Reporting at Least One Adverse Event Following MMR Vaccination, TVC, Study MMR-160

AE Type: Monitoring Period[a]	PRIORIX % (n/N)	M-M-R II % (n/N)
Immediate AE: 30 minutes	0.1% (3/3714)	0.2% (3/1289)
Solicited local at injection site[b]: 0-3 days	39.8% (1416/3555)	41.5% (515/1242)
Solicited systemic[c]: 0-14 days	71.8% (2560/3566)	74.7% (929/1243)
Fever (temperature ≥38.0 ºC): 0-42 days	34.7% (1239/3566)	33.1% (411/1243)
Rash: 0-42 days	29.2% (1043/3566)	30.4% (378/1243)
varicella-like rash	7.0% (250/3566)	6.8% (85/1243)
Measles/rubella-like rash	6.6% (235/3566)	6.2% (77/1243)
Other rash	19.0% (679/3566)	20.8% (259/1243)
Parotid/salivary gland swelling: 0-42 days	0	0
Meningism[d]: 0-42 days	0.3% (10/3566)	0.2% (3/1243)
Unsolicited: 0-42 days	50.0% (1857/3714)	47.9% (618/1289)
AEs leading to study w/d: Entire study period	<0.01% (2/3714)	0
SAEs: Entire study period	2.1% (77/3714)	1.9% (25/1289)

AE Type: Monitoring Period[a]	PRIORIX % (n/N)	M-M-R II % (n/N)
AEs of specific interest[e]: Entire study period	12.9% (478/3714)	13.1% (169/1289)
Deaths: Entire study period	0	0

Source: Adapted from STN 125748/0, MMR-160 Clinical Study Report Amendment 2, Section 8.2.1, Table 23, Table 24, Tables 47-50, Table 8.44, and MMR (RIT) Analysis #16 Table 6
Abbreviations: AE=adverse event; N=number of participants in population; n=number of participants who experienced the event; SAE=serious adverse event; TVC=Total Vaccinated Cohort was used as the analyses set for safety; w/d=withdrawal
Temperature 38.0 C =100.4 F
Note: For unsolicited events, the N is the number of participants in the TVC; For solicited local events, the N is the number of participants from the TVC with documented local events; For solicited systemic events, the N is the number of participants from the TVC with documented systemic events.
Two different lots of M-M-R II were used during this study. Data from both lots were pooled for this summary.
Data from the three PRIORIX lots were pooled for this summary.
a. Monitoring Period: time interval that the relevant type of AE was monitored for post-vaccination
b. Solicited local included pain, redness, and swelling at injection site
c. Solicited systemic included any systemic symptom including drowsiness, loss of appetite, or irritability
d. Signs or symptoms indicative of meningism (i.e., neck stiffness with or without light intolerance [photophobia] and headache; or convulsion/seizure) and included febrile convulsions
e. AEs of specific interest included new onset chronic disease (NOCD, e.g., autoimmune disorders, asthma, type I diabetes, vasculitis, celiac disease, conditions associated with sub-acute or chronic thrombocytopenia and allergies) and AEs prompting emergency room (ER) visit

The rates for any reported AE, including local and systemic solicited reactions, unsolicited AEs, and SAEs, were similar between the PRIORIX and M-M-R II pooled groups. Overall, 87.1% and 88.3% of participants, respectively, reported at least one solicited or unsolicited symptom during the 43-day post-vaccination period. There were two AEs in the PRIORIX group that led to study withdrawal and no deaths throughout the entire study period for either group.

Subpopulation Analyses

Descriptive summary safety data were reported by country, gender, and race if there were at least 50 participants per treatment group. In general, findings were similar to those reported in the safety analyses for the overall group. No clinically meaningful differences between vaccine groups in incidence of solicited local or systemic symptoms were observed in females and males or in any race group.

Solicited Adverse Reactions

Table 17 includes the percentages of PRIORIX and M-M-R II participants who reported any solicited adverse reactions, which are stratified by grade.

Table 17. Proportion of Participants With Solicited Reactions Post-Vaccination, TVC, Study MMR-160

Solicited Adverse Reaction	PRIORIX N=3555-3566	M-M-R II N=1242-1243
Local (injection site)	--	--
Pain[a], % (n/N)	--	--
Any	25.9% (919/3555)	28.1% (349/1242)
Grade 0	0.1% (2/3555)	0.0% (0/1242)
Grade 1	19.6% (697/3555)	20.9% (260/1242)
Grade 2	5.5% (196/3555)	6.2% (77/1242)
Grade 3	0.7% (24/3555)	1% (12/1242)
Erythema, % (n/N)	--	--
Any	24.5% (870/3555)	25.2% (313/1242)
Grade 0 (none)	0.1% (2/3555)	0.0% (0/1242)
Grade 1 (>0 to ≤5 mm)	20.5% (728/3555)	21.9% (272/1242)
Grade 2 (>5 to ≤20 mm)	3.5% (126/3555)	2.7% (33/1242)
Grade 3 (>20 mm)	0.4% (14/3555)	0.6% (8/1242)

Solicited Adverse Reaction	PRIORIX N=3555-3566	M-M-R II N=1242-1243
Swelling, % (n/N)	--	--
Any	8.9% (318/3555)	10.7% (133/1242)
Grade 0 (none)	0.1% (2/3555)	0.0% (0/1242)
Grade 1 (>0 to ≤5 mm)	7.4% (262/3555)	8.7% (108/1242)
Grade 2 (>5 to ≤20 mm)	1.2% (42/3555)	1.6% (20/1242)
Grade 3 (>20 mm)	0.3% (12/3555)	0.4% (5/1242)
Systemic Events	--	--
Measles/Rubella-like rash, % (n/N)	--	--
Any	6.6% (235/3566)	6.2% (77/1243)
Grade 0	0.0% (1/3566)	0.0% (0/1243)
Grade 1 (1-50 lesions)	2.6% (94/3566)	2.9% (36/1243)
Grade 2 (51-150 lesions)	2% (73/3566)	2.1% (26/1243)
Grade 3 (>150 lesions)	1.9% (67/3566)	1.2% (15/1243)
varicella-like rash, % (n/N)	--	--
Any	7% (250/3566)	6.8% (85/1243)
Grade 1 (1-50 lesions)	6.4% (228/3566)	6.1% (76/1243)
Grade 2 (51-150 lesions)	0.4% (16/3566)	0.6% (7/1243)
Grade 3 (>150 lesions)	0.2% (6/3566)	0.2% (2/1243)
Parotid/salivary gland swelling, % (n/N)	0.0% (0/3566)	0.0% (0/1243)
Irritability/fussiness[b], % (n/N)	--	--
Any	63.3% (2258/3566)	65.9% (819/1243)
Grade 1	35.5% (1267/3566)	36% (448/1243)
Grade 2	22.8% (812/3566)	25.2% (313/1243)
Grade 3	4.9% (176/3566)	4.7% (58/1243)
Drowsiness[b], % (n/N)	--	--
Any	44.9% (1601/3566)	47.1% (586/1243)
Grade 1	30.5% (1088/3566)	33.1% (411/1243)
Grade 2	11.9% (426/3566)	12.3% (153/1243)
Grade 3	2.4% (85/3566)	1.8% (22/1243)
Loss of appetite[b]	--	--
Any	45.1% (1608/3566)	44.1% (548/1243)
Grade 1	31.6% (1127/3566)	30.9% (384/1243)
Grade 2	11.4% (406/3566)	10.7% (133/1243)
Grade 3	2% (72/3566)	2.5% (31/1243)
Fever (temperature ≥38ºC), % (n/N)	--	--
Any Fever	34.9% (1244/3566)	33.1% (412/1243)
Fever with unknown temperature[c]	0.1% (5/3566)	0.1% (1/1243)
38.00-38.50°C	15.5% (554/3566)	15.7% (195/1243)
38.51-39.00°C	10.9% (387/3566)	9.7% (121/1243)
39.01-39.50°C	5.4% (193/3566)	5.1% (63/1243)
39.51-40.00°C	2.2% (77/3566)	1.9% (24/1243)
≥40.01°C	0.8% (28/3566)	0.6% (8/1243)

Solicited Adverse Reaction	PRIORIX N=3555-3566	M-M-R II N=1242-1243
Signs of meningism/seizure (including febrile convulsions)[b], % (n/N)	--	--
Any	0.3% (10/3566)	0.2% (3/1243)
Grade 1	0.1% (3/3566)	0.2% (2/1243)
Grade 2	0.1% (3/3566)	0.1% (1/1243)
Grade 3	0.1% (4/3566)	0.0% (0/1243)

Source: Adapted from STN 125748/0, MMR-160 Clinical Study Report Amendment 2, Table 12, Table 24, MMR (RIT) Analysis #16 Table 16.
Abbreviations: AE=adverse event; LAR=legally acceptable representative; N=number of participants in population; n=number of participants who experienced the event TVC=Total Vaccinated Cohort was used as the analyses set for safety
Note: For solicited local events, the N is the number of participants from the TVC with documented local events (i.e., they have documented the presence or absence of at least one local event).
Note: For solicited systemic events, the N is the number of participants from the TVC with documented systemic events (i.e., they have documented the presence or absence of at least one systemic event).
Note: Two different lots of M-M-R II were used during this study. Data from both lots were pooled for this summary.
Note: Data from the three PRIORIX lots were pooled for this summary.
a. Pain: Grade 0: none, Grade 1: Minor reaction to touch (digital pressure), Grade 2: Cried/protested on touch (digital pressure), Grade 3: Cried when limb was moved/spontaneously painful
b. Other rash/Irritability/Fussiness/Drowsiness/Loss of appetite/Meningism: Grade 1: caused minimal discomfort/easily tolerated and not interfering with everyday activities, Grade 2: sufficiently discomforting to interfere with normal everyday activities, Grade 3: prevented normal, everyday activities (in a young child, such an AE would, for example, prevent attendance at school/day care and would cause the parent(s)/LAR(s) to seek medical advice)
c. Reported fever without associated daily temperature measurement resulting in fever with unknown temperature

The incidences of solicited local symptoms were comparable across the groups. For both pooled groups, injection site pain was the most frequently reported local reaction (pooled PRIORIX 25.9% vs. pooled M-M-R II 28.1%). The median duration for pain was 1 day in both groups, and the median duration for erythema and swelling were the same in both groups as well (2 days and 1 day, respectively). The percentage of participants reporting severe (grade 3) injection site pain was low (pooled PRIORIX 0.7% vs pooled M-M-R II 1.0%).

Overall, the incidences of solicited systemic symptoms within 15 days post-vaccination were similar between the groups: irritability or fussiness was the most frequently reported (pooled PRIORIX 63.3% vs. pooled M-M-R II 65.9%) followed by drowsiness (44.9% vs. 47.1%, respectively) and loss of appetite (45.1% vs. 44.1%, respectively). The percentage of participants reporting severe (grade 3) irritability or fussiness was 4.9% in the PRIORIX group compared to 4.7% in the M-M-R II group. The median duration of each solicited systemic symptom was also similar between groups, ranging from 2 to 5 days.

Fever (temperature ≥38ºC/100.4ºF) from Day 5 to Day 12 post-vaccination occurred in 24.3% of participants in the PRIORIX group compared to 22.8% in the M-M-R II group. Incidences of grade 3 fever (temperature >39.5ºC) considered related to the study vaccination were 1.0% and 0.7% of participants in the PRIORIX and M-M-R II groups, respectively. The peak prevalence of fever was observed from approximately Day 5 to Day 12 after vaccination with a median duration of 2 days in both groups.

Solicited Systemic Symptoms Specific to MMR Vaccination
Solicited systemic symptoms specific to MMR vaccination (signs of meningism [including febrile convulsions], parotid/salivary gland swelling, and rash) were collected from Day 0 to Day 42 post-vaccination. Seven participants (0.2%) in the PRIORIX group and 3 (0.2%) in the M-M-R II group reported febrile convulsions. Four of the 7 events in the PRIORIX group and 2 of the 3 events in the M-M-R II group were considered related to vaccination by the investigator. There were no reports of parotid gland swelling. The percentages of participants with any incidence of rash post-vaccination were similar among the groups with 29.2% in the PRIORIX group and 30.4% in the M-M-R II group. Measles/rubella-like rash was seen in 6.6% of the PRIORIX and 6.2% of the M-M-R II groups. 13.7% and 13.0% of

participants in the PRIORIX and M-M-R II groups, respectively, were considered to have a rash related to the study vaccination. A severe (grade 3) rash was reported in 3.0% and 2.0% of the PRIORIX and M-M-R II groups, respectively. The median duration of each symptom was the same for each group (0 days for parotid/salivary gland swelling, 1 day for meningism/febrile convulsion, and 6 days for rash).

Reviewer Comment:

1. Overall, the rates of solicited reactions were comparable across groups. The most frequently reported solicited local reactions were injection site pain and redness, and the most frequently reported solicited systemic symptom was irritability/fussiness. The proportion of PRIORIX recipients who reported Grade 3 or higher severity events was <1% for each local solicited reaction and <5% for any solicited reaction. Overall, the reviewer agrees with the assessment of the causality of the study vaccinations in association with the febrile convulsions, described above.
2. In an Information Request (IR) response (STN 125748/Am 28), the Applicant provided the proportion of participants with meningism (without febrile convulsions) and the proportion of participants with febrile convulsions separately for all studies included in this application. For all studies except MMR-157, the investigator indicated in the case report form (CRF) whether a sign of meningism could be considered a febrile convulsion. The Applicant determined that for events where the verbatim description as reported in the safety database was clear (i.e., febrile seizure/convulsion), the event was categorized as reported. Events with ambiguous verbatim descriptions in terms of febrile convulsion categorization were considered febrile convulsions in certain situations. Descriptions containing seizure, but not fever, where the investigator considered the event to fulfill the criteria for febrile convulsion, qualified as febrile convulsions. Descriptions not considered febrile seizures by the investigator, but with an overlap in time between fever and signs of meningism, also qualified as febrile convulsions. For study MMR-160, the proportion with each event were provided as follows:
    - Meningism excluding febrile convulsions:
        - PRIORIX: 0.08% (3/3,566 participants)
        - M-M-R II: 0% (0/1,243 participants)
    - Febrile convulsions:
        - PRIORIX: 0.20% (7/3,566 participants)
        - M-M-R II: 0.24% (3/1,243 participants)

Ongoing Adverse Reactions and Adverse Reactions with Onset After Reporting Period
Overall, the proportion of participants with solicited reactions with onset during the solicited reporting period that were ongoing after the last day of the reporting period was similar across groups, low, and predominantly grade 1 to 2. The highest percentages for ongoing solicited ARs were for irritability/fussiness (PRIORIX 3.53% and M-M-R II 3.30%) and rash (PRIORIX 3.03% and M-M-R II 3.78%).

The proportion of any local solicited reaction with onset after the reporting period (Day 0 to Day 3) ranged from 0-0.22% in the PRIORIX group and 0-0.47% in the M-M-R II group. The proportion of solicited systemic symptoms with onset after the reporting period (Day 0 to Day 14) and symptoms specific to MMR vaccination with onset after the reporting period (Day 0 to Day 42) ranged from 0.03-1.86% in the PRIORIX group and 0-1.55% in the M-M-R II group. Fever was the most common solicited symptom with onset after the reporting period (Day 0 to Day 42) being reported in 4.63% of PRIORIX vaccinees and 4.81% of M-M-R II vaccinees.

Reviewer Comment: In an IR response (STN 125748/Am 25), the Applicant provided information on the duration of solicited adverse reactions, including information on solicited

reactions ongoing after the reporting period and with onset after the reporting period. The duration of solicited adverse reactions was calculated as the difference between the first and last day of the event plus 1 regardless of whether the event was experienced on all days between. For partial dates with only the month and year, the first day of the month was used for the start date unless that date was before vaccination, in which case the vaccination date was used as the start date. The last day of the month was used for partial end dates. If the end date was missing, the last study contact date was used to ensure that durations were not underestimated. Solicited adverse reactions that started after the end of the solicited reporting period were selected from the corresponding reported unsolicited adverse events.

Immediate AEs: within 30 minutes

The incidence of adverse events within 30 minutes of vaccination were similar between groups (pooled PRIORIX 0.1% vs. pooled M-M-R II 0.2%). In each group, there were four immediate adverse events reported by three participants. By MedDRA preferred term (PT), 7 of the events were injection site reactions, and one in the M-M-R II group was reported as erythema.

Reviewer Comment: In an IR response, the Applicant explained that based on the reporting of these immediate AEs as unsolicited (rather than as solicited local symptoms at the MMR injection body site), the events were associated with the concomitantly administered vaccines rather than with either of the MMR vaccines.

Unsolicited AEs (Non-Serious): 0-42 days

The rates of unsolicited, non-serious AEs during the 43-day post-vaccination period were similar in both groups (PRIORIX 50.0%, M-M-R II 47.9%). Unsolicited AEs were most frequently classified in MedDRA System Organ Class (SOC) *Infections and infestations* (PRIORIX 43.6%, M-M-R II 44.9%), followed by SOC *Gastrointestinal disorders* (PRIORIX 15.8%, M-M-R II 19%). By MedDRA PT, the most common AE was URI (9.5% in both groups). Most unsolicited non-serious AEs in both groups were Grade 1 or 2, with 6.1% of the PRIORIX group and 6.6% of the M-M-R II group reporting at least one Grade 3 symptom. Causal relationship to vaccination was attributed to 3.9% of unsolicited AEs in the PRIORIX group and 4.9% in the M-M-R II group.

Adverse Events of Specific Interest

AEs of specific interest include NOCDs (e.g., autoimmune disorders, asthma, type I diabetes, vasculitis, celiac disease, conditions associated with sub-acute or chronic thrombocytopenia, and allergies) and AEs prompting ER visit.

New Onset Chronic Disease (NOCD)

At least one NOCD was reported in 3.4% of participants in the PRIORIX group and 3.7% in the M-M-R II group. The most frequent NOCD reported was atopic dermatitis in 0.7% of participants in the PRIORIX group and 0.5% in the M-M-R II group, followed by allergic rhinitis (0.5% in both groups).

AEs prompting Emergency Room Visit

Overall, 10.1% in the PRIORIX and 10.4% in M-M-R II groups experienced an AE that required an ER visit. The most frequent AEs that required an ER visit were otitis media reported in 80 participants (PRIORIX 1.6%, M-M-R II 1.5%); URI reported in 60 participants (PRIORIX 1.1%, M-M-R II 4%); and pyrexia reported in 45 participants (PRIORIX 0.8%, M-M-R II 1.3%).

Medically Attended AEs

A total of 59.4% of participants in the PRIORIX group and 60.4% in the M-M-R II group had at least one symptom that required medical attention during the study period. The most commonly reported were the same in the PRIORIX and M-M-R II groups as follows: otitis media (17.0% and 19.2%, respectively),

URI (13.4% and 13.5%, respectively), nasopharyngitis (8.4% and 7.6%, respectively), and conjunctivitis (6.6% and 7.2%, respectively).

> Reviewer Comment: The reported rates and types of unsolicited adverse events were comparable across groups and represent common medical conditions in the general population for the evaluated age cohort (children 12 through 15 months of age).

6.1.12.3 Deaths

There were no deaths reported in this study.

6.1.12.4 Nonfatal Serious Adverse Events

A total of 98 SAEs were reported in 77 participants (2.1%) in the PRIORIX group and 40 SAEs were reported in 25 participants (1.9%) in the M-M-R II group during the entire study post-vaccination period. The most frequently reported SAE was bronchitis (PRIORIX: 0.2% [8 participants]; M-M-R II: 0.2% [2 participants]).

Within 42 days of study vaccination, there were 32 SAEs reported in 25 participants (0.67%) in the PRIORIX group compared to 7 SAEs reported in 5 participants (0.39%) in the M-M-R II group. The majority of these events were of the SOC *Infections and infestations,* and the 3 most frequently reported PTs were bronchiolitis, dehydration, and asthma.

> Reviewer Comment: While the proportion of participants reporting SAEs within 42 days of study vaccination was higher in the PRIORIX group compared to the M-M-R II group, the rate was low overall (less than 1%) with no clustering of events. The clinical reviewer agrees with the study investigator assessment that the events, other than the two described below, were unlikely related to study vaccinations.

Two SAEs in the PRIORIX groups were considered by the investigator to have a reasonable possibility of being related to the study vaccination:

- A 12-month-old white female in the PRIORIX Lot 2 group developed gastroenteritis on Day 0 (day of vaccination with PRIORIX, Havrix, and Varivax). She was hospitalized and treated with intravenous fluids and was discharged after 3 days. The event resolved after 14 days.

- A 13-month-old white female in the PRIORIX Lot 3 group with past medical history significant for ‘temper tantrum cramps’ that previously involved loss of consciousness experienced a febrile convulsion during an episode of crying on Day 9 post-vaccination with PRIORIX, Havrix, and Varivax. The event lasted approximately 1 to 1.5 minutes. The child was taken to the emergency room by ambulance and was found to be afebrile and recovered.

  > Reviewer Comment: The clinical reviewer agrees with the study investigator assessment that the above two events had reasonable possibility of being related to study vaccinations due to the temporal relationship of events.

6.1.12.5 Dropouts and/or Discontinuations

The most common reasons for study discontinuation were lost to follow-up with complete vaccination course followed by consent withdrawal. The rate of those lost to follow-up with complete vaccination course was comparable across groups (2.6% PRIORIX and 2.9% M-M-R II), while the rate of participants

lost due to consent withdrawal was greater for PRIORIX compared to M-M-R II (1.6% and 0.8%, respectively). Two non-serious adverse events (gastroesophageal reflux and gastroenteritis) occurred in two participants that led to premature discontinuation from the study. Neither AE was considered related to study vaccination by the investigator, and the outcome of both events was recovered/resolved. There were no SAEs leading to discontinuation from the study or deaths (Table 18).

Table 18. Discontinuations, All Randomized Participants, Study MMR-160

Population	PRIORIX Lot 1 N=1239 % (n/N)	PRIORIX Lot 2 N=1234 % (n/N)	PRIORIX Lot 3 N=1246 % (n/N)	M-M-R II N=1,291 % (n/N)
Enrolled[a]	100% (1239/1239)	100% (1234/1234)	100% (1246/1246)	100% (1291/1291)
Vaccinated	100% (1239/1239)	99.8% (1232/1234)	99.8% (1243/1246)	99.8% (1289/1291)
Completed study	94.8% (1175/1239)	94.3% (1162/1232)	95.7% (1190/1243)	95.6% (1232/1289)
Withdrawal due to	--	--	--	--
Consent withdrawal	1.7% (21/1239)	1.9% (23/1232)	1.1% (14/1243)	0.8% (10/1289)
Lost to follow-up	--	--	--	--
Migrated/moved from study area	0.6% (7/1239)	0.2% (3/1232)	0.5% (6/1243)	0.5% (6/1289)
Lost to follow-up (participants with incomplete vaccination course)	0	0	0	0
Lost to follow-up (participants with complete vaccination course)	2.1% (26/1239)	3.1% (38/1232)	2.5% (31/1243)	2.9% (38/1289)
Protocol deviation	0.2% (3/1239)	0	0.1% (1/1243)	0
Non-serious AE	0.2% (2/1239)	0	0	0
Serious AE	0	0	0	0
Death	0	0	0	0
Other[b]	0.4% (5/1239)	0.5% (6/1232)	0.1% (1/1243)	0.2% (3/1289)

Source: Adapted from STN 1257480, MMR-160 Clinical Study Report Amendment 2, Table 23, Table 24
Abbreviations: AE=adverse event; N=number of participants in population; n=number of participants who met given criteria
Note: Two different lots of M-M-R II were used during this study. Data from both lots were pooled for this summary
a. A total of 5,016 participants were enrolled in this study. Six participants were enrolled but not randomized to a treatment group.
b. Other reasons included: lost health plan (n=3), by job and personal reasons the parents cannot assist to the site (n=1) and parents too busy (n=1) in PRIORIX Lot 1 group; lost health plan (n=5) and mother transferred care and did not want to come (n=1) in PRIORIX Lot 2 group; by lack of time the mother cannot assist with the participant to the site (n=1) in PRIORIX Lot 3 group; and lost health plan/coverage (n=3) in the M-M-R II group.

6.1.13 Study Summary and Conclusions

Study MMR-160 was designed as a lot-to-lot consistency, immunogenicity, and safety study in children 12 through 15 months of age. Participants received a first dose of either investigational PRIORIX vaccine or US-licensed M-M-R II vaccine, along with concomitant vaccines Varivax, Havrix, and Prevnar 13 at US study sites and Varivax and Havrix at study sites outside the US. The co-primary objectives to demonstrate PRIORIX lot-to-lot consistency and immunological non-inferiority of PRIORIX to M-M-R II, were met. When concomitantly administered with routine pediatric vaccines, non-inferiority of PRIORIX to M-M-R II was demonstrated. The immune responses to concomitant vaccine antigens were also similar across groups, demonstrating the lack of immune interference when PRIORIX was concomitantly administered with routine pediatric vaccines (Varivax, Havrix, and Prevnar 13) compared to when M-M-R II was concomitantly administered with these vaccines. Immunogenicity results of the US population, which received Prevnar 13, was overall comparable to the results of the entire cohort. The safety profile of PRIORIX was comparable to the safety profile of the US-licensed vaccine control group, M-M-R II, when concomitantly administered with Varivax and Havrix (to all children) and Prevenar 13 (to children enrolled in the US). Overall, the results of study MMR-160 support the effectiveness of

PRIORIX due to demonstration of non-inferiority of the antibody responses to measles, mumps and rubella virus as compared to a licensed US vaccine, and an acceptable (>90%) seroresponse rate for each vaccine virus antigen.

6.2 Trial #2 (Study MMR-158)

NCT01621802
"A Phase 3a, observer-blind, randomized study to evaluate non-inferiority of a second dose of GSK's MMR vaccine (PRIORIX) vs. a second dose of Merck's MMR vaccine (M-M-R II) when administered with and without DTaP-IPV vaccine and varicella vaccine to healthy children four to six years of age."

Study Overview: This study was designed to evaluate the safety and immunogenicity of PRIORIX compared to M-M-R II for use in individuals 4 through 6 years of age as a second dose when administered with and without concomitant Kinrix (DTaP-IPV) and VV.

6.2.1 Design Overview

Study MMR-158 was an observer-blind, randomized, controlled, multi-center, multi-country study with nine parallel groups. Participants were randomized 3:1 to receive GSK's MMR vaccine (PRIORIX) or Merck's MMR vaccine (M-M-R II). The study design included three sub-cohorts in which participants were randomized 6:1:1 to receive PRIORIX or one of two M-M-R II lots, respectively. Sub-cohort 1 (US participants only) was a safety and immunogenicity cohort in which participants received US-licensed concomitantly administered vaccines DTaP-IPV and VV. Sub-cohort 2 was also a safety and immunogenicity cohort, but participants did not receive any concomitantly administered vaccines. Sub-cohort 3 was a safety cohort in which participants did not receive any concomitantly administered vaccines. The two commercial lots of Merck's M-M-R II used in the study were analyzed as pooled lots.

Each group participated in two study visits (Day 0 and Day 42) and a concluding phone contact at Day 180. All participants received vaccination/s at Visit 1 (Day 0). Participants in sub-cohorts 1 and 2 had blood samples taken at both study visits. Safety follow-up was done with all groups at Visit 2 (Day 42) and at the telephone contact on Day 180. The study duration was approximately six months starting at Visit 1 (Day 0) and ending with a phone contact at Day 180.

6.2.2 Objectives

Co-Primary Objectives

1. To demonstrate the non-inferiority of PRIORIX vaccine to M-M-R II vaccine, when administered with VV and DTaP-IPV vaccines in terms of SRRs to measles, mumps, and rubella viruses at Day 42.
   Endpoint: Seroresponse (as defined in Section 6.1.1) to measles, mumps, and rubella viruses when given with VV and DTaP-IPV
   Criterion for determination of non-inferiority for measles, mumps, rubella viruses: LL of the two-sided 97.5% CI for group difference (PRIORIX with concomitantly administered vaccines group minus pooled M-M-R II with concomitantly administered vaccines group) in SRRs to measles, mumps and rubella viruses is ≥-5%.

2. To demonstrate the non-inferiority of PRIORIX vaccine to M-M-R II vaccine, when administered with VV and DTaP-IPV vaccines in terms of antibody concentrations to measles, mumps, and rubella viruses at Day 42.
   Endpoint: Measles, mumps, and rubella virus antibody concentrations when given with VV and DTaP-IPV
   Criterion for determination of non-inferiority for measles, mumps, rubella viruses: LL of the two-sided 97.5% CI for the adjusted GMC ratio (PRIORIX with concomitantly administered vaccines

group divided by pooled M-M-R II with concomitantly administered vaccines group) is ≥0.67 for antibodies to measles, mumps, and rubella viruses.

3. To demonstrate the non-inferiority of PRIORIX vaccine to M-M-R II vaccine, when administered without VV and DTaP-IPV vaccines in terms of SRRs to measles, mumps, and rubella viruses at Day 42.
   Endpoint: Seroresponse to measles, mumps, and rubella viruses when given without VV and DTaP-IPV
   Criterion for determination of non-inferiority for measles, mumps, rubella viruses: LL of the two-sided 97.5% CI for group difference (PRIORIX immunogenicity group minus pooled M-M-R II immunogenicity group) in SRRs to measles, mumps, and rubella viruses is ≥-5%.

4. To demonstrate the non-inferiority of PRIORIX vaccine to M-M-R II vaccine, when administered without VV and DTaP-IPV vaccines in terms of antibody concentrations to measles, mumps, and rubella viruses at Day 42.
   Endpoint: Measles, mumps, and rubella virus antibody concentrations when given without VV and DTaP-IPV
   Criterion for determination of non-inferiority for measles, mumps, rubella viruses: LL of the two-sided 97.5% CI for the adjusted GMC ratio (PRIORIX immunogenicity group divided by pooled M-M-R II immunogenicity group) is ≥0.67 for antibodies to measles, mumps, and rubella viruses.

Secondary Objectives

1. To demonstrate the non-inferiority in terms of SRRs and antibody concentrations to VZV at Day 42 when VV is administered with PRIORIX and DTaP-IPV vaccines as compared to when administered with M-M-R II and DTaP-IPV vaccines.
   Endpoints: Immunogenicity of VV in terms of seroresponse to VZV (defined as post-vaccination concentration ≥75 mIU/mL) and VZV antibody concentrations
   Criteria for the determination of non-inferiority for VV:
   - The LL of the two-sided standardized asymptotic 97.5% CI for the group difference (PRIORIX with concomitantly administered vaccines group minus pooled M-M-R II with concomitantly administered vaccines group) in SRRs to anti-VZV antibody is ≥-5%.
   - The LL of the two-sided 97.5% CI for group adjusted GMC ratio (PRIORIX with concomitantly administered vaccines group divided by pooled M-M-R II with concomitantly administered vaccines group) is ≥0.67 for anti-VZV antibody.

2. To demonstrate the non-inferiority in terms of antibody booster response to diphtheria (D), tetanus (T), pertussis toxoid (PTx), filamentous hemagglutinin (FHA), and pertactin (PRN) when DTaP-IPV is administered with PRIORIX and VV as compared to when administered with M-M-R II and VV.
   Endpoint: Immunogenicity of DTaP-IPV vaccine in terms of booster responses to the DTaP components
   Booster response definitions defined as follows:
   - For D and T antigens:
     - For participants with pre-vaccination concentration <0.1 IU/mL (i.e., below the seroprotection cut-off), antibody concentrations at least ≥0.4 IU/mL one month after vaccination.
     - For participants with pre-vaccination concentration ≥0.1 IU/mL (i.e., equal to or above the seroprotection cut-off), an increase in antibody concentrations of at least four times the pre-vaccination concentration one month after vaccination.
   - For pertussis antigens (PTx, FHA, and PRN):

- For participants with pre-vaccination antibody concentration below the assay cut-off, post-vaccination antibody concentration ≥4 times the assay cut-off.
- For participants with pre-vaccination antibody concentration between the assay cut-off and four times the assay cut-off, post-vaccination antibody concentration ≥4 times the pre-vaccination antibody concentration.
- For participants with pre-vaccination antibody concentration ≥4 times the assay cut-off, post-vaccination antibody concentration ≥4 times the pre-vaccination antibody concentration
  Criteria for the determination of non-inferiority for DTaP: For D, T, PTx, FHA, and PRN, the LL of the two-sided 97.5% CI for the difference (PRIORIX with concomitantly administered vaccines group minus pooled M-M-R II with concomitantly administered vaccines group) in the percentage of participants with a booster response is ≥-10%.

3. To demonstrate the non-inferiority in terms of antibody titers to poliovirus types 1, 2, and 3 when DTaP-IPV is administered with PRIORIX vaccine and VV as compared to when administered with M-M-R II and VV.
   Endpoint: Immunogenicity of DTaP-IPV vaccine in terms of anti-polio types 1, 2, and 3 antibody titers
   Criteria for the determination of non-inferiority for IPV: For antibodies to polio viruses, the LL of the two-sided 97.5% CI for the geometric mean titer (GMT) ratio (PRIORIX with concomitantly administered vaccines group divided by pooled M-M-R II with concomitantly administered vaccines group) is ≥0.67.

4. To demonstrate the non-inferiority in terms of anti-PTx, anti-FHA, and anti-PRN antibody concentrations when DTaP-IPV is administered with PRIORIX vaccine and VV as compared to when administered with M-M-R II and VV.
   Endpoint: Immunogenicity of DTaP-IPV vaccine in terms of pertussis antibody concentrations
   Criteria for the determination of non-inferiority of pertussis antigens: For PTx, FHA, and PRN, the LL of the two-sided 97.5% CI for group adjusted GMC ratio (PRIORIX with concomitantly administered vaccines group divided by pooled M-M-R II with concomitantly administered vaccines group) is ≥0.67 for each antibody.

5. To assess safety and reactogenicity of PRIORIX and M-M-R II vaccines in each sub-cohort separately.
   Endpoints (Descriptive): see Section 6.1.1 for a description of the safety endpoints.

6.2.3 Study Treatments or Agents Mandated by the Protocol

PRIORIX: investigational measles, mumps, and rubella vaccine

- Dose/RoA/Formulation/Presentation: see Section 6.1.4.
- Lots:
  - Taiwan: DMJRA013A, DMJRA020A
  - Korea: DMJRA013A, DMJRA020A
  - US: DMJRA013A, DMJRA020A

M-M-R II: comparator measles, mumps, and rubella vaccine

- Dose/RoA/Formulation/Presentation: see Section 6.1.4.
- Lots:
  - Lot 1:
    - Taiwan: G019547, H014762, H017980
    - Korea: G009391, G015673, H014762, H020866
    - US: 0351AA, 0258AE, H011906, J003002, J015488, K002527

- Lot 2:
  - Taiwan: G017523, G018240, H020866
  - Korea: G007769, G017523, G018240, H017980
  - US: 0599AA, 0184AE, H011907, H018945, J015222, K001997

DTaP-IPV:

- Dose/RoA: 0.5 mL IM
- Formulation: D 30 IU (25 flocculating units); T 40 IU (10 flocculating units); PTx 25 µg; FHA 25 µg; PRN 8 µg; poliovirus (PV) type 1, 40 d-antigen units; PV type 2, 8 d-antigen units; PV type 3, 32 d-antigen units; Aluminum as salts 0.5 mg/mL
- Presentation: PFS containing a turbid white suspension
- Lots: AC20B171DA, AC20B213AA, JP2HP, AC20VB292A

VV:

- Dose/RoA/Formulation/Presentation: see Section 6.1.4.
- US Lots: 1060AA, 0693AE, J003543, J004158

6.2.4 Population

Eligibility Criteria

Inclusion criteria were described previously (see Section 6.1.3) with the following differences: participants must be males or females 4 through 6 years of age at the time of vaccination and must have received either a single dose of M-M-R II, M-M-R VaxPro,[5] or ProQuad in the second year of life.

For individuals enrolled in sub-cohort 1 receiving concomitantly administered DTaP-IPV and VV, participants must have received previous DTaP vaccine doses with Infanrix (diphtheria and tetanus toxoids and acellular pertussis vaccine, adsorbed) and/or Pediarix (diphtheria and tetanus toxoids and acellular pertussis vaccine, adsorbed, hepatitis B [recombinant], inactivated poliovirus vaccine) for the first three doses and Infanrix for the fourth dose of the DTaP-containing vaccine, as well as received a first dose of VV (given as Varivax or ProQuad) in the second year of life.

Exclusion criteria were described previously (see Section 6.1.3), with the following differences:

- Previous vaccination with a second dose of measles, mumps, rubella containing vaccine/s.
- History of measles, mumps, and/or rubella disease.
- Known exposure to measles, mumps and/or rubella during the period starting 30 days prior to enrollment.

For participants enrolled in the sub-cohort 1 receiving concomitantly administered DTaP-IPV and VV:

- Previous vaccination with a second dose of varicella-containing vaccine.
- Receipt of any varicella-containing vaccine during the period starting 90 days before the day of study vaccination.
- History of varicella/zoster disease.
- Known exposure to varicella/zoster during the period starting 30 days prior to enrollment.
- History of diphtheria, tetanus, pertussis, and/or poliomyelitis disease.
- Vaccination against diphtheria, tetanus, pertussis, or polio given after the second year of life (i.e., after 24-month birthday).
- Occurrence of transient thrombocytopenia or neurological complications following an earlier immunization against diphtheria and/or tetanus toxoids.

[5] In the European Union, M-M-R II is licensed under the tradename M-M-R VaxPro™.

- Occurrence of any of the following events after a previous administration of diphtheria, tetanus, pertussis (DTP) vaccine:
- A temperature (≥40.6ºC (≥105ºF) during the period starting 48 hours after vaccination not due to another identifiable cause.
- A collapse or shock-like state (hypotonic-hypo-responsive episode) during the period starting 48 hours after vaccination.
- Persistent, inconsolable crying lasting three hours or more within 48 hours after vaccination.
- Seizures with or without fever occurring during the period starting three days after vaccination.
- Encephalopathy of unknown etiology occurring during the period starting within 7 days of vaccination of a previous administration of DTP vaccine.
- Hypersensitivity reaction to any component of the DTaP-IPV and/or varicella vaccines (e.g., latex).

6.2.5 Directions for Use

See Section 6.1.5.

6.2.6 Sites and Centers

There were 70 sites in the United States, Republic of Korea, and Taiwan with a total vaccinated cohort of 4,007 participants. There were 52 US sites with a total vaccinated cohort of 2,681 participants.

6.2.7 Surveillance/Monitoring

Surveillance
See Section 6.1.7. For this study, CROs were involved with study sites in all countries.

Safety Monitoring
Solicited local AEs (pain, redness, or swelling at injection site) were recorded from Day 0 to Day 3. Solicited systemic AEs collected for all sub-cohorts (fever, measles/rubella-like rash, other rash, parotid/salivary gland swelling, and meningism [including febrile convulsion]) were collected from Day 0 to Day 42. For sub-cohort 1 only, solicited systemic adverse events of varicella-like rash, drowsiness, and loss of appetite were collected from Day 0 to Day 3. All AEs occurring from Day 0 through 42 days after vaccination were recorded. Diary cards and remote data entry were used. Safety monitoring of AEs, including AEs of specific interest, MAEs, and SAEs, are as previously described (see Section 6.1.7).

Immunogenicity monitoring
Serological assays for the determination of measles, mumps, rubella and VZV IgG antibodies, were the same assays used in study MMR-160 (see Section 6.1.7). Serological assays for the determination of immune responses for the components of the DTaP-IPV concomitantly administered vaccine are presented in Table 19.

Table 19. Summary of Serological Assays for DTaP-IPV Immune Responses, Study MMR-158

Component	Method	Unit	Cut-Off	Threshold	Kit/ Manufacturer	Location
Corynebacterium diphtheriae diphtheria toxoid antibody IgG	(b) (4)	IU/mL	0.057	0.1	In-house	GSK Biologicals
Clostridium tetani tetanus toxoid antibody IgG	(b) (4)	IU/mL	0.043	0.1	In-house	GSK Biologicals
Bordetella pertussis pertussis toxoid antibody IgG	(b) (4)	IU/mL	2.693	--	In-house	GSK Biologicals
Bordetella pertussis filamentous hemagglutinin antibody IgG	(b) (4)	IU/mL	2.046	--	In-house	GSK Biologicals
Bordetella pertussis pertactin antibody IgG	(b) (4)	IU/mL	2.187	--	In-house	GSK Biologicals
Poliovirus Sabin Types 1, 2 and 3	(b) (4)	ED_{50}	1:8	--	In-house	GSK Biologicals

Source: Adapted from STN 125748/0, Clinical Overview, Table 4
Abbreviations: DTaP-IPV=diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine; ED_{50}=endpoint dilution 50%; (b) (4); IgG=immunoglobin G; IU=international unit

6.2.8 Endpoints and Criteria for Study Success

See Section 6.2.1.

6.2.9 Statistical Considerations and Statistical Analysis Plan

Sample Size

The target enrollment was approximately 4,000 children. With an assumed 20% non-evaluable rate in the ATP Cohort for Immunogenicity, the planned enrollment would result in 876 evaluable children in sub-cohort 1 (657 in the PRIORIX group and 219 in the pooled M-M-R II groups) and 876 evaluable children in sub-cohort 2 (657 in the PRIORIX group and 219 in the pooled M-M-R II groups).

Methods

The co-primary objectives were assessed in parallel, making it possible to conclude independently between them. Secondary objectives were assessed hierarchically; therefore at least one primary objective had to be reached to conclude on secondary objectives. To control the type I error below 2.5%, a Bonferroni adjustment was used for comparing PRIORIX and M-M-R II independently in either sub-cohort 1 or 2. In addition, a hierarchical procedure was used for the secondary objectives.

The global power to reach all non-inferiority objectives of PRIORIX versus M-M-R II in sub-cohort 1 was at least 94.04%. The global power to reach all non-inferiority objectives of PRIORIX vs. M-M-R II in sub-cohort 2 was at least 98.88%. The global power to reach all non-inferiority objectives for both cohorts was at least 93%.

The analysis was performed in two steps which were combined in the final clinical report. Subpopulation analysis methods, as well as safety analysis methods, are as previously described (see Section 6.1.9).

Protocol Amendments

Issued before study initiation (June 21, 2012):

Protocol Amendment 1 (May 28, 2012) included the following changes:

- All endpoints related to evaluation of antibody responses to MMR to be reflected in the primary objectives/endpoints
- Safety analyses to be separated among sub-cohorts and by country, not pooled
- Modifications to diphtheria and tetanus analyses
- Plan implemented for suboptimal responders
- Inclusion criterion added for specific childhood vaccinations required for US participants
- Adjustments to intensity of solicited fever and injection site swelling and redness, and to priority ranking for mumps

Protocol Amendment 2 (June 7, 2012) included the following changes:

- Prior vaccination history only needed for MMR and concomitantly administered vaccines, and for concomitantly administered vaccines, only required for sub-cohort 1

Issued during the study period:

Protocol Amendment 3 (June 11, 2013) included the following changes:

- Increased flexibility in sub-cohort enrollment
- Clarifications regarding allowed timing of influenza vaccine and site staff roles
- Clarification that only conditions prompting ER visits need to be recorded from Visit 2 to EOS, not all medically attended visits

Protocol Amendment 4 (September 4, 2013) included the following changes:

- All conditions leading to non-routine medically attended visits to be recorded for the entire study

Protocol Amendment 5 (May 11, 2015) included the following changes:

- Serological assays for the determination of antibodies against measles, rubella, and varicella to be performed by a new third party CRO, (b) (4) (formerly (b) (4)). The assays and facilities are the same.

Changes in the Conduct of the Study and Planned Analyses

The assays (b) (4) used to measure the anti-D, anti-T, anti-PTx, anti-FHA, and anti-PRN IgG antibody concentrations were re-developed and revalidated, and both the assay units and assay cut-offs were adapted. For the pertussis antigens, the new (b) (4) was calibrated against the (b) (4) to allow expression of concentrations in IU/mL rather than (b) (4) units (EU)/mL. The new DTaP (b) (4) has a lower assay cut-off. The following endpoints are used in GSK's clinical primary and/or booster studies for inferential evaluation: seroprotection rates (percentage of participants with concentration ≥0.1 IU/mL), booster response rates (percentage of participants with concentration ≥1.0 IU/mL or by evaluation of the four-fold increase pre-vaccination to post-vaccination), and/or GMCs. An agreement was demonstrated between the old and new (b) (4) with regards to the two thresholds of clinical relevance for the diphtheria toxoid and tetanus toxoid response (0.1 IU/mL and 1.0 IU/mL).

See Section 6.1.9 regarding two technical problems identified in the Electronic Data Capture system and possible temperature deviations in vaccine storage that potentially affected participants who were administered Varivax. The technical problems were corrected and determined to have no impact on the reported data, and the additional sensitivity analysis done for the potential vaccine temperature deviations did not alter the relevant study conclusions.

Please see the statistical review for further discussion.

6.2.10 Study Population and Disposition

A total of 4,011 participants were enrolled in the study. The first participant was enrolled in the study on June 21, 2012, and the last study visit was on November 9, 2015.

6.2.10.1 Populations Enrolled/Analyzed

Total Vaccinated Cohort (TVC): see Section 6.1.10.1.

ATP Cohort for Safety Analysis: see Section 6.1.10.1.

ATP Cohort for Immunogenicity Analysis included all eligible participants from the ATP Cohort for Safety:

- with post-vaccination serology results for at least one antigen of measles, mumps, or rubella as appropriate for the sub-cohort.
- who did not meet any elimination criteria up to the Visit 2 blood sample as described below.
- who complied with the procedures and intervals defined in the protocol.

Protocol Deviations
Exclusion from the ATP Cohort for Immunogenicity Analyses occurred for the same reasons as described in Section 6.1.10.1. In addition, participants in sub-cohort 1 would be eliminated from the ATP Cohort for Immunogenicity if they developed varicella, diphtheria, tetanus, pertussis, or polio in the same interval between vaccination and the collection of the blood specimen for immunogenicity at Visit 2.

6.2.10.1.1 Demographics

Table 20. Demographic Characteristics, TVC, Study MMR-158

Characteristic	PRIORIX Sub-cohort 1 N=802	M-M-R II Sub-cohort 1 N=298	PRIORIX Sub-cohort 2 N=796	M-M-R II Sub-cohort 2 N=303	PRIORIX Sub-cohort 3 N=1,319	M-M-R II Sub-cohort 3 N=489
Sex	--	--	--	--	--	--
Ratio male:female	404:398	164:134	435:361	150:153	687:632	264:225
% male:% female	50.4%:49.6%	55.0%:45.0%	54.6%:45.4%	49.5%:50.5%	52.1%:47.9%	54.0%:46.0%
Age, months	--	--	--	--	--	--
Mean (SD)	4.1 (0.3)	4.1 (0.3)	4.4 (0.6)	4.3 (0.6)	4.4 (0.6)	4.4 (0.6)
Median	4.0	4.0	4.0	4.0	4.0	4.0
Range	4, 6	4, 6	3, 6	4, 6	4, 6	4, 6
Ethnicity, n (%)	--	--	--	--	--	--
Hispanic/Latino	205 (25.6%)	76 (25.5%)	131 (16.5%)	43 (14.2%)	166 (12.6%)	70 (14.3%)
Not Hispanic/Latino	597 (74.4%)	222 (74.5%)	665 (83.5%)	260 (85.8%)	1153 (87.4%)	419 (85.7%)
Racial Origin (Geographic Ancestry), n (%)	--	--	--	--	--	--
Am. Indian/A.N.	130 (16.2%)	38 (12.8%)	15 (1.9%)	3 (1.0%)	4 (0.3%)	0 (0)
All Asian	92 (11.5%)	36 (12.1%)	402 (50.5%)	152 (50.2%)	590 (44.7%)	217 (44.4%)
Central/South Asian	12 (1.5%)	5 (1.7%)	7 (0.9%)	1 (0.3%)	8 (0.6%)	0 (0)
East Asian	28 (3.5%)	6 (2.0%)	384 (48.2%)	146 (48.2%)	565 (42.8%)	209 (42.7%)
Japanese	3 (0.4%)	0 (0)	0 (0)	1 (0.3%)	1 (0.1%)	0 (0)
Southeast Asian	49 (6.1%)	25 (8.4%)	11 (1.4%)	4 (1.3%)	16 (1.2%)	8 (1.6%)
African/A.A.	96 (12.0%)	39 (13.1%)	48 (6.0%)	19 (6.3%)	94 (7.1%)	32 (6.5%)
All White	368 (45.9%)	138 (46.3%)	294 (36.9%)	120 (39.6%)	576 (43.7%)	218 (44.6%)
Arabic/North African	5 (0.6%)	3 (1.0%)	3 (0.4%)	3 (1.0%)	1 (0.1%)	0 (0)
Caucasian/European	363 (45.3%)	135 (45.3%)	291 (36.6%)	117 (38.6%)	575 (43.6%)	218 (44.6%)
N. Hawaiian/ P.I.	4 (0.5%)	2 (0.7%)	2 (0.3%)	0 (0)	3 (0.2%)	0 (0)
Other	112 (14.0%)	45 (15.1%)	35 (4.4%)	9 (3.0%)	52 (3.9%)	22 (4.5%)

Characteristic	PRIORIX Sub-cohort 1 N=802	M-M-R II Sub-cohort 1 N=298	PRIORIX Sub-cohort 2 N=796	M-M-R II Sub-cohort 2 N=303	PRIORIX Sub-cohort 3 N=1,319	M-M-R II Sub-cohort 3 N=489
Country, n (%)	--	--	--	--	--	--
Republic of Korea	0 (0)	0 (0)	158 (19.8%)	66 (21.8%)	91 (6.9%)	43 (8.8%)
Taiwan	0 (0)	0 (0)	226 (28.4%)	80 (26.4%)	492 (37.3%)	170 (34.8%)
United States	698 (100%)	250 (100%)	412 (51.8%)	157 (51.8%)	736 (55.8%)	276 (56.4%)

Source: Adapted from STN 125748/0, MMR-158 Clinical Study Report Amendment 2, Section 6.4, Table 6.12, Table 6.13, Table 34
Abbreviations: A.A.=African American; Am. Indian/A.N=American Indian/Alaskan Native; DTaP-IPV=diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine; N. Hawaiian/P.I.=Native Hawaiian/Pacific Islander; N=total number of participants for the TVC Safety Analysis Set (participants with at least 1 vaccination of either PRIORIX or M-M-R II); n=number of participants with indicated characteristic; Other=mixed race or not otherwise specified; TVC: total vaccinated cohort; SD: standard deviation
Sub-cohort 1: safety and immunogenicity, MMR vaccines concomitantly administered with varicella vaccine and DTaP-IPV in United States participants only.
Sub-cohort 2: safety and immunogenicity, MMR vaccines alone.
Sub-cohort 3: safety, MMR vaccines alone
Note: Two different lots of M-M-R II were used in each sub-cohort in this study. Data from both lots were pooled in each sub-cohort for this summary.

The median age of participants in the TVC was 4 years with a range of 3 to 6 years. Overall, 52.5% of the participants were male, and this distribution was similar across sub-cohorts. Overall, 42.4% of participants were White (Caucasian) and 33.4% were East Asian. Since the percentage of participants excluded from the ATP Cohort for Safety was less than 5% for all treatment groups, and no safety analysis on the ATP Cohort for Safety was required, there was no demographic summary on this cohort.

6.2.10.1.2 Participant Disposition

Table 21. Participant Disposition and Data Analyses Sets, All Randomized Participants, Study MMR-158

Population	PRIORIX Sub-cohort 1 (N=802)	M-M-R II Sub-cohort 1 (N=299)	PRIORIX Sub-cohort 2 (N=796)	M-M-R II Sub-cohort 2 (N=303)	PRIORIX Sub-cohort 3 (N=1,320)	M-M-R II Sub-cohort 3 (N=489)
Enrolled, n (%)	802 (100%)[a]	299 (100%)†	796 (100%)	303 (100%)	1320 (100%)	489 (100%)
TVC, n (%)	802 (100%)	298 (99.7%)	796 (100%)	303 (100%)	1319 (99.9%)	489 (100%)
Completed study, n (%)	755 (94.1%)	275 (92.0%)	763 (95.9%)	292 (96.4%)	1284 (97.3%)	477 (97.5%)
TVC-Safety, n (%)	802 (100%)	298 (99.7%)	796 (100%)	303 (100%)	1319 (99.9%)	489 (100%)
TVC-Imm., n (%)	800 (99.8%)	297 (99.3%)	790 (99.2%)	301 (99.3%)	NA	NA
ATP-Safety, n (%)	779 (97.1%)	288 (96.3%)	782 (98.2%)	294 (97.0%)	1297 (98.3%)	481 (98.4%)
ATP-Imm., n (%)	698 (87.0%)	250 (83.6%)	742 (93.2%)	283 (93.4%)	NA	NA
≥1 Important prot. deviation, n (%)	104 (13.0%)[b]	49 (16.4%)[b]	54 (6.8%)[b]	20 (6.6%)[b]	23 (1.7%)[c]	8 (1.6%)[c]
Maximum percentage of participants eliminated for ATP-Imm analyses[d]	4.32%	4.35%	2.41%	2.44%	NA	NA

Source: Adapted from STN 125748/0, MMR-158 Clinical Study Report Amendment 2, Table 24, Table 25, Table 26, Table 27, Table 28, Table 29; MMR (RIT) Analysis #16 Table 1 and Table 2
Abbreviations: ATP=according to protocol; N=total number of participants enrolled; n=number of participants fulfilling the item; NA: not applicable; TVC: Total Vaccinated Cohort, included all vaccinated participants; ≥1 Prot. Deviation: participants with one or more protocol deviations
Sub-cohort 1: safety and immunogenicity, MMR vaccines concomitantly administered with varicella vaccine and DTaP-IPV in United States participants only; Sub-cohort 2: safety and immunogenicity, MMR vaccines alone; Sub-cohort 3: safety, MMR vaccines alone
Note: Two different lots of M-M-R II were used in this study. Data from both lots were pooled in each sub-cohort for this summary.
a. A total of 1,103 participants were enrolled in sub-cohort 1. Two participants were enrolled but not randomized to any treatment group.
b. Includes participants with important protocol violations that resulted in exclusion from the ATP-Imm. analysis population.
c. Includes participants with important protocol violations that resulted in exclusion from the ATP-Safety analysis population.
d. For each antigen and each confirmatory objective, the percentage of participants who had the necessary immunogenicity results to contribute to the TVC analysis but were eliminated for the ATP analysis was computed. This value represents the maximum over all confirmatory objectives and antigens.
TVC-Safety: included all vaccinated participants with at least one vaccine administration of either PRIORIX or M-M-R II documented.
TVC-Imm.: included all vaccinated participants for whom immunogenicity data were available.
ATP-Safety: Safety analyses using the ATP Cohort included eligible participants who received the study vaccine(s) as per protocol; had not received a vaccine leading to exclusion from the ATP Cohort up to Visit 2; for whom the administration route of study vaccine(s) was known and correct; and for whom the randomization code had not been broken.
ATP-Imm.: Immunogenicity analyses using the ATP Cohort included all evaluable participants. from the ATP Cohort for safety with post-vaccination serology results for at least one antigen of measles, mumps, or rubella; who complied with the procedures and intervals in the protocol; and did not meet any elimination criteria up to the Visit 2 blood sample.

A total of 4,011 participants were enrolled in the study with 4,009 randomized to a treatment group. Of those randomized, 4,007 received a study vaccination and 3,846 (96%) vaccinated participants completed the study. The most common reason for premature withdrawal in each sub-group was lost to follow-up with complete vaccination course. Seventy participants in sub-cohort 1 were prematurely withdrawn, 52 of whom were lost to follow-up with complete vaccination course. Twelve participants were withdrawn due to consent withdrawal not due to an AE. Forty-four participants in sub-cohort 2 were withdrawn prior to completion with 31 participants lost to follow-up with complete vaccination course and 6 participants being withdrawn due to consent withdrawal not due to an AE. Forty-seven participants were prematurely withdrawn in sub-cohort 3 with 42 of them being lost to follow-up with complete vaccination course.

Ninety-seven percent of participants in sub-cohort 1, 97.9% of participants in sub-cohort 2, and 98.3% of participants in sub-cohort 3 were included in the ATP Cohort for Safety. In sub-cohorts 1 and 3, the most common reason for exclusion from the ATP Cohort for Safety was for non-eligibility criteria due to protocol violation owing to inclusion/exclusion criteria including age (27 participants in each). There were 11 participants in sub-cohort 2 who were excluded for that reason as well. The most common reason for exclusion in sub-cohort 2 was due to administration of a vaccine forbidden in the protocol (12 participants). In sub-cohort 1, 6 participants were excluded due to vaccine temperature deviation.

Eighty-six percent of participants in sub-cohort 1 and 93.3% of participants in sub-cohort 2 were included in the ATP Cohort for Immunogenicity, with the most common reason for exclusion being that serological results were not available for antigens following vaccination (108 participants and 45 participants, respectively).

> Reviewer Comment: Sub-cohort 3 was a safety cohort, therefore those participants were not included in the ATP Cohort for Immunogenicity. The observed protocol deviations do not raise concerns about study conduct.

6.2.11 Immunogenicity Analyses

The study design did not include clinical efficacy endpoints. Serologic immune endpoints were used to assess the response to vaccination. Over 95% of all participants had baseline antibody levels above the seroresponse thresholds for each vaccine antigen. Seroresponses for MMR and VZV did not consider pre-vaccination concentrations. Endpoints for the two lots of comparator M-M-R II vaccine were analyzed as pooled lots throughout.

The primary analysis of immunogenicity was performed on the ATP Cohort for Immunogenicity. A second analysis based on the TVC was not performed because less than 5% of participants with serological results were eliminated from each group in sub-cohorts 1 and 2 in the ATP Cohort. As in study MMR-160, a sensitivity analysis was performed on the ATP Cohort for Immunogenicity to assess if there was any potential impact on study conclusions due to data from participants impacted by a potential Varivax storage temperature deviation (see Section 6.1.9), and it was concluded that excluding these participants from the analysis had no impact on study conclusions.

Participants in immunogenicity sub-cohorts 1 and 2 with a Day 42 sub-optimal immune response to measles, mumps, or rubella virus components, as confirmed by blood sample results, were offered re-vaccination with M-M-R II (or PRIORIX in settings outside the US where PRIORIX is currently licensed). Those in sub-cohort 1 with a sub-optimal response to varicella virus were offered re-vaccination with Varivax.

6.2.11.1 Analyses of Primary Endpoint(s)

The primary analysis was performed on the ATP Cohort for Immunogenicity separately for sub-cohort 1, with concomitantly administered varicella and DTaP-IPV vaccines, and sub-cohort 2, without concomitantly administered vaccines.

Primary Objectives 1 and 2: Non-Inferiority when Concomitantly administered With VV and DTaP-IPV (Sub-cohort 1)

The success criteria to demonstrate non-inferiority were met if the LL of the two-sided 97.5% CI for the difference in SRR (PRIORIX minus M-M-R II) was ≥-5%, and for the adjusted GMC (adjusted for pre-vaccination/baseline antibody concentration) ratio (PRIORIX over M-M-R II) was ≥0.67 for anti-Measles, anti-Mumps, and anti-Rubella antibodies. Co-primary objectives 1 and 2 were ***met***. See Table 22 and Table 23.

Table 22. Proportion of Participants With Seroresponse and Difference Across Groups at 42 Days Post-Vaccination When Concomitantly administered With Varicella and DTaP-IPV Vaccines, ATP Cohort for Immunogenicity, Sub-cohort 1, Study MMR-158

Antibody	PRIORIX N=696 to 698 SRR	M-M-R II N=249 to 250 SRR	PRIORIX - M-M-R II SRR Difference (97.5% CI)
% anti-Measles ≥200 mIU/mL	100%	100%	0.00 (-0.72, 1.98)
% anti-Mumps ≥10 EU/mL	100%	100%	0.00 (-0.72, 1.97)
% anti-Rubella ≥10 IU/mL	99.9%	100%	-0.14 (-0.98, 1.84)

Source: Adapted from STN 125748/0, MMR-158 Clinical Study Report Amendment 2, Table 36, Table 38, Table 39, Table 40
Abbreviations: ATP=According to Protocol cohort; CI=confidence interval; DTaP-IPV=diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine; ELISA=enzyme-linked immunosorbent assay; EU=ELISA unit; IU=international unit; N=number of participants in ATP Cohort for Immunogenicity; SRR=Seroresponse Rate (percentage of initially seronegative participants with concentration above seroresponse threshold for each assay; Assays: Anti-Measles, (b) (4) ELISA; Anti-Mumps, (b) (4) ELISA; Anti-Rubella, (b) (4) ELISA (For each assay - seroresponse thresholds are 200 mIU/mL, 10 EU/mL, and 10 IU/mL for anti-measles, anti-mumps, and anti-rubella antibodies respectively).
Note: Two different lots of M-M-R II were used in this study. Data from both lots were pooled for this summary.
Lower 97.5% CI numbers indicate lower limits of 97 5% CI for which statistical testing was performed for the respective test.
Success criteria: the lower limit of the 2-sided 97.5% CI for the difference in SRR between the PRIORIX group and the M-M-R II group must be ≥ −5% for anti-measles, anti-mumps, and anti-rubella antibodies.

Table 23. GMCs and GMC Ratio at 42 Days Post-Vaccination When Concomitantly administered With Varicella and DTaP-IPV Vaccines, ATP Cohort for Immunogenicity, Sub-cohort 1, Study MMR-158

Antibody	PRIORIX (N=690 to 691) GMC	M-M-R II (N=245 to 248) GMC	PRIORIX/M-M-R II GMC Ratio (97.5% CI)
Anti-Measles(mIU/mL)	4285.0	4333.5	0.99 (0.92, 1.06)
Anti-Mumps (EU/mL)	171.3	188.5	0.91 (0.83, 1.00)
Anti-Rubella (IU/mL)	97.1	94.5	1.03 (0.97, 1.09)

Source: Adapted from STN 125748/0, MMR-158 Clinical Study Report Amendment 2, Table 37, Table 7.2
Abbreviations: ANCOVA=analysis of covariance; ATP=according to protocol; CI=confidence interval; DTaP-IPV=diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine; ELISA=enzyme-linked immunosorbent assay; EU=ELISA unit; GMC=geometric mean antibody concentration adjusted for pre-vaccination concentration (ANCOVA model: adjustment for baseline concentration – pooled variance); IU=international unit; N=number of participants in ATP Cohort for Immunogenicity
Assays: Anti-Measles, (b) (4) ELISA; Anti-Mumps, (b) (4) ELISA; Anti-Rubella, (b) (4) ELISA
Note: Two different lots of M-M-R II were used in this study. Data from both lots were pooled for this summary.
Lower 97.5% CI numbers indicate lower limits of 97 5% CI for which statistical testing was performed for the respective test.
Success criteria: the lower limit of the 2-sided 97.5% CI for the adjusted GMC ratio between the PRIORIX group and the M-M-R II group must be ≥0.67 for anti-measles, anti-mumps, and anti-rubella antibodies.

Primary Objectives 3 and 4: Non-Inferiority When Administered Alone (Sub-cohort 2)

The success criteria to demonstrate non-inferiority were met if the LL of the two-sided 97.5% CI for the difference in SRR (PRIORIX minus M-M-R II) was ≥-5%, and for the adjusted GMC (adjusted for country and baseline antibody concentration) ratio (PRIORIX over M-M-R II) was ≥0.67 for anti-

Measles, anti-Mumps, and anti-Rubella antibodies. Co-primary objectives 3 and 4 were ***met***. See Table 24 and Table 25.

Table 24. Proportion of Participants With Seroresponse and Difference Across Groups at 42 Days Post-Vaccination When Administered Alone, ATP Cohort for Immunogenicity, Sub-cohort 2, Study MMR-158

Antibody	PRIORIX N=736 SRR	M-M-R II N=283 SRR	PRIORIX - M-M-R II SRR Difference (97.5% CI)
% anti-Measles ≥200 mIU/mL	100%	99.3%	0.71 (0.02, 2.97)
% anti-Mumps ≥10 EU/mL	100%	100%	0.00 (-0.68, 1.75)
% anti-Rubella ≥10 IU/mL	100%	100%	0.00 (-0.68, 1.75)

Source: Adapted from STN 125748/0, MMR-158 Clinical Study Report Amendment 2, Table 52, Table 7.39
Abbreviations: ATP=according to protocol cohort; CI=confidence interval; ELISA=enzyme-linked immunosorbent assay; EU=ELISA unit; IU=international unit; N=number of participants in ATP Cohort for Immunogenicity; SRR=Seroresponse Rate: percentage of initially seronegative participants with concentration above seroresponse threshold for each assay; Assays: Anti-Measles, (b) (4) ELISA; Anti-Mumps, (b) (4) ELISA; Anti-Rubella, (b) (4) ELISA (For each assay - seroresponse thresholds are 200 mIU/mL, 10 EU/mL, and 10 IU/mL for anti-measles, anti-mumps, and anti-rubella antibodies respectively).
Note: Two different lots of M-M-R II were used in this study. Data from both lots were pooled for this summary.
Lower 95% CI numbers indicate lower limits of 97.5% CI for which statistical testing was performed for the respective test.
Success criteria: the lower limit of the 2-sided 97.5% CI for the difference in SRR between the PRIORIX group and the M-M-R II group must be ≥-5% for anti-measles, anti-mumps, and anti-rubella antibodies.

Table 25. GMCs and GMC Ratio at 42 Days Post-Vaccination When Administered Alone, ATP Cohort for Immunogenicity, Sub-cohort 2, Study MMR-158

Antibody	PRIORIX N=729 to 732 GMC	M-M-R II N=280 to 282 GMC	PRIORIX/M-M-R II GMC Ratio (97.5% CI)
Anti-Measles (mIU/mL)	3600.3	3504.3	1.03 (0.96, 1.10)
Anti-Mumps (EU/mL)	167.7	174.6	0.96 (0.87, 1.06)
Anti-Rubella (IU/mL)	99.3	98.6	1.01 (0.95, 1.07)

Source: Adapted from STN 125748/0, MMR-158 Clinical Study Report Amendment 2, Table 53, Table 7.40
Abbreviations: ANCOVA=analysis of covariance; ATP=According to Protocol cohort; CI=confidence interval; ELISA=enzyme-linked immunosorbent assay; EU=ELISA unit; GMC=geometric mean antibody concentration adjusted for country and pre-vaccination concentration country (ANCOVA model: adjustment for country-pooled variance); IU=international unit; N=number of participants in ATP Cohort for Immunogenicity
Assays: Anti-Measles, (b) (4) ELISA; Anti-Mumps, (b) (4) ELISA; Anti-Rubella, (b) (4) ELISA
Note: Two different lots of M-M-R II were used in this study. Data from both lots were pooled for this summary.
Lower 95% CI numbers indicate lower limits of 97.5% CI for which statistical testing was performed for the respective test.
Success criteria: the lower limit of the 2-sided 97.5% CI for the adjusted GMC ratios between the PRIORIX group and the M-M-R II group must be ≥0.67 for anti-measles, anti-mumps, and anti-rubella antibodies.

Descriptive Analysis of Immune Responses

Immune responses to PRIORIX as compared to M-M-R II in terms of antibody concentrations to measles, mumps, and rubella are shown in Table 26.

Table 26. Seroresponse Rate and GMC at 42 Days Post-Vaccination, ATP Cohort for Immunogenicity, Sub-cohorts 1 and 2, Study MMR-158

Antibody	PRIORIX Sub-cohort 1 N=697 to 698	M-M-R II Sub-cohort 1 N=249 to 250	PRIORIX Sub-cohort 2 N=736	M-M-R II Sub-cohort 2 N=283
Anti-Measles	--	--	--	--
% ≥200 mIU/mL (95% CI)	100% (99.5, 100)	100% (98.5, 100%)	100% (99.5, 100)	99.3% (97.5, 99.9)
GMC (95% CI)	4335.0 (4089.7, 4594.9)	4215.6 (3806.7, 4668.4)	3646.6 (3453.5, 3850.4)	3503.9 (3174.6, 3867.4)
Anti-Mumps	--	--	--	--
% ≥10 EU/mL (95% CI)	100% (99.5, 100)	100% (98.5, 100)	100% (99.5, 100)	100% (98.7, 100)
GMC (95% CI)	170.5 (161.6, 179.9)	190.1 (174.7, 206.8)	167.2 (158.6, 176.3)	176.2 (161.5, 192.2)
Anti-Rubella	--	--	--	--
% ≥10 IU/mL (95% CI)	99.9% (99.2, 100%)	100% (98.5, 100)	100% (99.5, 100)	100% (98.7, 100)
GMC (95% CI)	96.4 (92.6, 100.4)	96.0 (89.5, 103.0)	98.9 (95.3, 102.8)	98.7 (93.2, 104.5)

Source: Adapted from STN 125748/0, MMR-158 Clinical Study Report Amendment 2, Table 38, Table 39, Table 40, Table 54, Table 55, Table 56

Abbreviations: ATP=according to protocol; CI=confidence interval; ELISA=enzyme-linked immunosorbent assay; EU=ELISA unit; IU=international unit; N=number of participants with available results; GMC=geometric mean concentration calculated on all participants (performed by taking the anti-log of the mean of the log concentration/titer transformations. Antibody concentrations/titers below the cut-off of the assay would be given an arbitrary value of half the cut-off for the purpose of GMC calculation.); Seroresponse Rate: percentage of initially seronegative participants with concentration above seroresponse threshold for each assay; Assays: Anti-Measles, (b) (4) ELISA; Anti-Mumps, (b) (4) ELISA; Anti-Rubella, (b) (4) ELISA (For each assay - seroresponse thresholds are 200 mIU/mL, 10 EU/mL, and 10 IU/mL for anti-measles, anti-mumps, and anti-rubella antibodies respectively).

Sub-cohort 1: safety and immunogenicity, MMR vaccines concomitantly administered with varicella vaccine and DTaP-IPV in United States participants only.

Sub-cohort 2: safety and immunogenicity, MMR vaccines alone

Note: Two different lots of M-M-R II were used in this study. Data from both lots were pooled in each sub-cohort for this summary.

Reviewer Comment: Primary analyses of anti-Measles, anti-Mumps, and anti-Rubella antibody responses at Day 42 showed that all 4 co-primary objectives to demonstrate non-inferiority of PRIORIX compared to US-licensed M-M-R II, with and without concomitantly administered VV and DTaP-IPV vaccine, were met. Additionally, the LL of the two-sided 95% CI for the SRR for PRIORIX was ≥90% for each vaccine virus antigen when descriptively evaluated.

6.2.11.2 Analyses of Secondary Endpoints

Secondary Objective 1: Non-Inferiority for varicella Vaccine
The success criteria were met if the LL of the two-sided standardized asymptotic 97.5% CI for the group difference (PRIORIX minus M-M-R II) in to anti-VZV antibody was ≥-5%, and the LL of the two-sided 97.5% CI for group adjusted GMC ratio (PRIORIX over M-M-R II) was ≥0.67 for anti-VZV antibody. The objective was ***met***. See Table 27 and Table 28.

Secondary Objective 2: Non-Inferiority for DTaP
The success criteria were met if the LL of the two-sided 97.5% CI for the difference (PRIORIX minus M-M-R II) in the percentage of participants with a booster response to diphtheria (D), tetanus (T), pertussis toxoid (PTx), filamentous hemagglutinin (FHA), and Pertactin (PRN) was ≥-10%. The objective was ***met***. See Table 27.

Table 27. Difference in Proportion of Participants With Seroresponse (VZV) and Booster Response (Diphtheria, Tetanus, Pertussis) at 42 Days Post-Vaccination, ATP Cohort for Immunogenicity, Sub-cohort 1, Study MMR-158

Antibody, % Participants SRR or BRR	PRIORIX N=659 to 695	M-M-R II N=233 to 247	PRIORIX – M-M-R II SRR or BRR Difference (97.5% CI)
anti-VZV	99.7%	100%	-0.29 (-1.22, 1.71)
anti-D	99.7%	100%	-0.30 (-1.29, 1.81)
anti-T	93.9%	95.7%	-1.78 (-5.08, 2.60)
anti-PTx	97.6%	96.6%	1.01 (-1.54, 4.95)
anti-FHA	94.1%	94.4%	-0.36 (-3.90, 4.34)
anti-PRN	99.5%	99.6%	-0.03 (-1.17, 2.44)

Source: Adapted from STN 125748/0, MMR-158 Clinical Study Report Amendment 2, Table 41, Table 7.15, Table 7.17
Abbreviations: ATP=according to protocol; CI=confidence interval; D=diphtheria toxoid; FHA=filamentous hemagglutinin; N=number of participants with available results; PRN=pertactin; PTx=pertussis toxoid; SRR/BRR=seroresponse/booster response rate (percentage of participants with concentration above seroresponse threshold for anti-VZV antibodies or with a booster response to anti-D, anti-T, anti-PTx, anti-FHA, or anti-PRN antibodies); T=tetanus toxoid; VZV=varicella zoster virus.
Sub-cohort 1: safety and immunogenicity, MMR vaccines concomitantly administered with varicella vaccine and DTaP-IPV in United States participants only
Note: Two different lots of M-M-R II were used in this study. Data from both lots were pooled for this summary.
Lower 97.5% CI numbers indicate lower limits of 97.5% CI for which statistical testing was performed for the respective test.
Success criteria: the lower limit of the 2-sided 97.5% CI for the difference in SRR between the PRIORIX group and M-M-R II group must be ≥−5% for anti-VZV antibody and the lower limit of the 2-sided 97.5% CI for the difference in booster response between the PRIORIX group and the M-M-R II group must be ≥-10% for anti-D, anti-T, anti-PTx, anti-FHA, and anti-PRN antibodies.

Secondary Objective 3: Non-Inferiority for IPV
The success criteria were met if the LL of the two-sided 97.5% CI for the GMT ratios to poliovirus types 1, 2, and 3 (PRIORIX over M-M-R II) was ≥0.67. The objective was ***met***. See Table 28.

Secondary Objective 4: Non-Inferiority for Pertussis Antigens
The success criteria were met if the LL of the two-sided 97.5% CI for the group adjusted GMC ratio in terms of anti-PTx, anti-FHA and anti-PRN (PRIORIX over M-M-R II) was ≥0.67 for each antibody. The objective was ***met***. See Table 28.

Table 28. GMC/GMT Ratios of Antibodies (VZV, Poliovirus 1, 2, and 3, and Pertussis) at 42 Days Post-Vaccination, ATP Cohort for Immunogenicity, Sub-cohort 1, Study MMR-158

Antibody	PRIORIX N=554 to 687 GMC/GMT	M-M-R II N=199 to 242 GMC/GMT	PRIORIX/M-M-R II GMC/T Ratio (97.5% CI)
anti-VZV (mIU/mL)	879.7	830.1	1.06 (0.95, 1.18)
Polio 1 (ED_{50})	1636.5	1558.4	1.05 (0.88, 1.25)
Polio 2 (ED_{50})	2032.7	2197.0	0.93 (0.78, 1.09)
Polio 3 (ED_{50})	2794.4	2978.8	0.94 (0.77, 1.14)
anti-PTx (IU/mL)	76.1	73.0	1.04 (0.92, 1.18)
anti-FHA (IU/mL)	313.7	323.3	0.97 (0.88, 1.07)
anti-PRN (IU/mL)	399.9	417.6	0.96 (0.84, 1.09)

Source: Adapted from STN 125748/0, MMR-158 Clinical Study Report Amendment 2, Table 42, Table 7.16, Table 7.18, Table 7.19
Abbreviations: ANCOVA=analysis of covariance; ATP=according to protocol; CI=confidence interval; DTaP-IPV=diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine; ED_{50}=endpoint dilution 50%; FHA=filamentous hemagglutinin; GMC=geometric mean concentration; GMC/GMT = geometric mean antibody concentration/titer adjusted for pre-vaccination concentration (ANCOVA model-adjustment for baseline concentration – pooled variance); IU=international unit; N=number of participants with available results; PRN=pertactin; PTx=pertussis toxoid; VZV=varicella zoster virus.
Sub-cohort 1: safety and immunogenicity, MMR vaccines concomitantly administered with varicella vaccine and DTaP-IPV in United States participants only
Note: Two different lots of M-M-R II were used in this study. Data from both lots were pooled for this summary.
Lower 97.5% CI numbers indicate lower limit of 97.5% CI for which statistical testing was performed.
Success criteria: the lower limit of the 2-sided 97.5% CI for the adjusted GMC/GMT ratios between the PRIORIX group and the M-M-R II group must be ≥0.67 for anti-VZV, anti-PTx, anti-FHA, and anti-PRN antibodies and antibodies against polio.

6.2.11.3 Subpopulation Analyses

Analyses of immunogenicity were conducted by country for sub-cohort 2 for all countries represented in the study (US, Republic of Korea, and Taiwan) and were generally similar to the findings among all participants in the primary analysis.

Sub-group analyses by gender were conducted separately for sub-cohorts 1 and 2. Humoral immune responses by gender were similar to those reported in the primary immunogenicity analyses.

Sub-group analyses by race were conducted if there were at least 50 participants per treatment group. Only White race was analyzed for sub-cohort 1, with results demonstrating comparable immune responses to those reported in the primary immunogenicity analyses. For sub-cohort 2, analyses included White and East Asian races. Overall, results were comparable across groups and similar to the findings reported in the primary analysis.

Sub-group analyses by age in this 4 through 6-year-old age cohort were not provided.

> Reviewer Comment: Sub-group analyses by age were not provided; however, given the narrow age cohort and intended indication, it is not anticipated that there would be any significant difference in immunogenicity for this age group.

6.2.11.4 Dropouts and/or Discontinuations

Approximately 96% of enrolled participants completed the study. Missing or non-evaluable immunogenicity measurements were not replaced. See Section 6.2.10.1.2.

6.2.11.5 Exploratory and Post Hoc Analyses

Not applicable.

6.2.12 Safety Analyses

6.2.12.1 Methods

Safety data surveillance is described in Section 6.2.7 and shown in Table 29. Participant compliance with returning symptom sheets for collection of local and systemic solicited AEs following administered vaccines ranged from 89.6% to 98.4%, with the highest compliance rates in sub-cohort 3 and the lowest in sub-cohort 1.

6.2.12.2 Overview of Adverse Events

Safety Overview
Safety data were presented by sub-cohort. Table 29 provides an overview of the rates of adverse events in each sub-cohort for both PRIORIX and M-M-R II during the study period.

Table 29. Proportion of Participants Reporting at Least One Adverse Event Following MMR Vaccination, TVC, Study MMR-158

AE Type: Monitoring Period[a], % (n/N)	PRIORIX Sub-cohort 1	M-M-R II Sub-cohort 1	PRIORIX Sub-cohort 2	M-M-R II Sub-cohort 2	PRIORIX Sub-cohort 3	M-M-R II Sub-cohort 3
Immediate AE: 30 minutes	0	0	0	0	0	0
Solicited local at injection site[b]: 0-3 days	48.3% (351/727)	48.7% (130/267)	29.8% (228/766)	30.4% (88/289)	33.0% (426/1289)	36.9% (177/480)
Solicited systemic[c]: 0-3 days	33.5% (245/731)	33.2% (89/268)	NA	NA	NA	NA
Fever (Any): 0-42 days	24.2% (177/731)	25.0% (67/268)	19.0% (146/767)	19.9% (58/291)	19.9% (257/1291)	20.0% (96/481)
Rash: 0-42 days	--	--	--	--	--	--
Any rash	8.3% (61/731)	10.4% (28/268)	4.8% (37/767)	4.1% (12/291)	4.3% (56/1291)	4.8% (23/481)
varicella-like rash[d]	0.5% (4/731)	1.1% (3/268)	NA	NA	NA	NA
Measles/rubella-like rash	1.9% (14/731)	1.9% (5/268)	0.4% (3/767)	0.7% (2/291)	0.3% (4/1291)	0.4% (2/481)
Other rash (not measles/rubella-like)	6.2% (45/731)	7.5% (20/268)	4.4% (34/767)	3.4% (10/291)	4.0% (52/1291)	4.4% (21/481)
Parotid/salivary gland swelling: 0-42 days	0	0	0	0.3% (1/291)	0.1% (1/1291)	0.2% (1/481)
Meningism[e]: 0-42 days	0	0.7% (2/268)	0.1% (1/767)	0	0	0
Unsolicited: 0-42 days	34.4% (276/802)	30.2% (90/298)	39.4% (314/796)	37.0% (112/303)	38.5% (508/1319)	38.0% (186/489)
AEs leading to study w/d: Entire study period	0	0	0	0	0	0
SAEs: Entire study period	0.5% (4/802)	0	1.8% (14/796)	0.3% (1/303)	1.9% (25/1319)	1.8% (9/489)

AE Type: Monitoring Period[a], % (n/N)	PRIORIX Sub-cohort 1	M-M-R II Sub-cohort 1	PRIORIX Sub-cohort 2	M-M-R II Sub-cohort 2	PRIORIX Sub-cohort 3	M-M-R II Sub-cohort 3
AEs of specific interest[f]: Entire study period	8.5% (68/802)	10.7% (32/298)	8.5% (68/796)	7.3% (22/303)	8.4% (111/1319)	7.8% (38/489)
Deaths: Entire study period	0	0	0	0	0	0

Source: Adapted from STN 125748/0, MMR-158 Clinical Study Report Amendment 2 Section 8.2.1 and Tables 24, 25, 26, 27, 28, 29, 69, 70, 71, 72, 73, 74, 75, 85, 8.67, 8.71, 8.72, 8.73, 8.77, 8.78, and 8.79; MMR (RIT) Analysis #16 Tables 1, 2, and 3.
Abbreviations: AE=adverse event; N=number of participants in cohort; n=number of participants who experienced the event; SAE=serious adverse event; TVC=Total Vaccinated Cohort was used as the analyses set for safety; w/d=withdrawal
Temperature 38.0 C =100.4 F
Note: For unsolicited events, the N is the number of participants in the TVC; For solicited local events, the N is the number of participants from the TVC with documented local events; For solicited systemic events, the N is the number of participants from the TVC with documented systemic events.
Note: Sub-cohort 1 (co-administration) = GSK PRIORIX or Merck M-M-R II concomitantly administered with varicella vaccine and DTaP-IPV and analyzed for immunogenicity and safety.
Sub-cohort 2 (immunogenicity) = GSK PRIORIX or Merck M-M-R II alone and analyzed for immunogenicity and safety.
Sub-cohort 3 (safety) = GSK PRIORIX or Merck M-M-R II alone and analyzed for safety only.
a. Monitoring Period: time interval that the relevant type of AE was monitored for post-vaccination
b. Solicited local includes pain, redness, and swelling at injection site
c. Drowsiness and loss of appetite are standard solicited symptoms in clinical trials evaluating DTaP-IPV vaccine recipients
d. Only collected for participants who received varicella vaccine
e. Signs or symptoms indicative of meningism (i.e., neck stiffness with or without light intolerance [photophobia] and headache; or convulsion/seizure) and includes febrile convulsions
f. AEs of specific interest includes new onset chronic disease (NOCD, e.g., autoimmune disorders, asthma, type I diabetes, vasculitis, celiac disease, conditions associated with sub-acute or chronic thrombocytopenia and allergies) and AEs prompting emergency room (ER) visit

Overall, for any solicited or unsolicited AE, the rates were similar between the PRIORIX and M-M-R II groups within each sub-cohort (PRIORIX vs. M-M-R II):

- Sub-cohort 1: 72.2% vs. 68.1%
- Sub-cohort 2: 59.7% vs. 58.4%
- Sub-cohort 3: 60.5% vs. 64.6%

There were no AEs leading to study withdrawal and no deaths throughout the entire study period.

Subpopulation Analyses

In general, findings were similar to those reported in the safety analyses for the overall group. No clinically meaningful differences between vaccine groups in incidence of solicited local or systemic symptoms were observed in females and males or in any race group.

Solicited Adverse Reactions

The following table includes the percentages of PRIORIX and M-M-R II participants who reported any solicited adverse reactions, which are stratified by grade.

Table 30. Proportion of Participants With Solicited Reactions Post-Vaccination, TVC, Study MMR-158

Solicited Adverse Reaction, % (n/N)	PRIORIX Sub-cohort 1 N=727-731	M-M-R II Sub-cohort 1 N=267-268	PRIORIX Sub-cohort 2 N=766-767	M-M-R II Sub-cohort 2 N=289-291	PRIORIX Sub-cohort 3 N=1289-1291	M-M-R II Sub-cohort 3 N=480-481
Local (injection site)	--	--	--	--	--	--
Pain[a]	--	--	--	--	--	--
Any	40.6% (295/727)	40.8% (109/267)	19.8% (152/766)	22.1% (64/289)	21.6% (278/1289)	25.6% (123/480)
Grade 0	0.0% (0/727)	0.0% (0/267)	0.1% (1/766)	0.0% (0/289)	0.1% (1/1289)	0.2% (1/480)
Grade 1	28.3% (206/727)	24.7% (66/267)	16.7% (128/766)	18.7% (54/289)	19.2% (248/1289)	21.9% (105/480)
Grade 2	9.2% (67/727)	14.6% (39/267)	2.2% (17/766)	2.8% (8/289)	1.9% (24/1289)	3.1% (15/480)
Grade 3	3% (22/727)	1.5% (4/267)	0.8% (6/766)	0.7% (2/289)	0.4% (5/1289)	0.4% (2/480)
Erythema	--	--	--	--	--	--
Any	21.6% (157/727)	25.8% (69/267)	19.1% (146/766)	18.3% (53/289)	18.8% (242/1289)	18.8% (90/480)
Grade 0 (none)	0.1% (1/727)	0.0% (0/267)	0.1% (1/766)	0.0% (0/289)	0.1% (1/1289)	0.2% (1/480)
Grade 1 (>0 to ≤20 mm)	18.6% (135/727)	22.5% (60/267)	18.8% (144/766)	16.3% (47/289)	18.6% (240/1289)	18.5% (89/480)
Grade 2 (>20 to ≤50 mm)	1.7% (12/727)	1.9% (5/267)	0.1% (1/766)	2.1% (6/289)	0.1% (1/1289)	0.0% (0/480)
Grade 3 (>50 mm)	1.2% (9/727)	1.5% (4/267)	0.0% (0/766)	0.0% (0/289)	0.0% (0/1289)	0.0% (0/480)
Swelling	--	--	--	--	--	--
Any	11.3% (82/727)	10.5% (28/267)	8.4% (64/766)	8% (23/289)	8.4% (108/1289)	8.8% (42/480)
Grade 0 (none)	0.3% (2/727)	0.0% (0/267)	0.1% (1/766)	0.0% (0/289)	0.2% (2/1289)	0.2% (1/480)
Grade 1 (>0 to ≤20 mm)	9.5% (69/727)	8.6% (23/267)	8% (61/766)	7.3% (21/289)	8.1% (104/1289)	7.7% (37/480)
Grade 2 (>20 to ≤50 mm)	1.1% (8/727)	0.7% (2/267)	0.3% (2/766)	0.7% (2/289)	0.2% (2/1289)	0.8% (4/480)
Grade 3 (>50 mm)	0.4% (3/727)	1.1% (3/267)	0.0% (0/766)	0.0% (0/289)	0.0% (0/1289)	0.0% (0/480)
Systemic	--	--	--	--	--	--
Measles/Rubella-like rash	--	--	--	--	--	--
Any	1.9% (14/731)	1.9% (5/268)	0.4% (3/767)	0.7% (2/291)	0.3% (4/1291)	0.4% (2/481)
Grade 1 (1-50 lesions)	1.6% (12/731)	1.5% (4/268)	0.4% (3/767)	0.7% (2/291)	0.3% (4/1291)	0.2% (1/481)
Grade 2 (51-150 lesions)	0.3% (2/731)	0.4% (1/268)	0.0% (0/767)	0.0% (0/291)	0.0% (0/1291)	0.2% (1/481)
varicella-like rash[b]	--	--	--	--	--	--
Any	0.5% (4/731)	1.1% (3/268)	NA	NA	NA	NA
Grade 1 (1-50 lesions)	0.5% (4/731)	0.4% (1/268)	NA	NA	NA	NA
Grade 2 (51-150 lesions)	0.0% (0/731)	0.7% (2/268)	NA	NA	NA	NA
Other rash[d]	--	--	--	--	--	--
Any	6.2% (45/731)	7.5% (20/268)	4.4% (34/767)	3.4% (10/291)	4% (52/1291)	4.4% (21/481)
Grade 1	4.4% (32/731)	6.3% (17/268)	3.9% (30/767)	3.1% (9/291)	3.6% (47/1291)	4.2% (20/481)
Grade 2	1.4% (10/731)	1.1% (3/268)	0.4% (3/767)	0.3% (1/291)	0.2% (2/1291)	0.2% (1/481)
Grade 3	0.4% (3/731)	0.0% (0/268)	0.1% (1/767)	0.0% (0/291)	0.2% (3/1291)	0.0% (0/481)

Solicited Adverse Reaction, % (n/N)	PRIORIX Sub-cohort 1 N=727-731	M-M-R II Sub-cohort 1 N=267-268	PRIORIX Sub-cohort 2 N=766-767	M-M-R II Sub-cohort 2 N=289-291	PRIORIX Sub-cohort 3 N=1289-1291	M-M-R II Sub-cohort 3 N=480-481
Parotid/salivary gland swelling[e]	--	--	--	--	--	--
Any	0.0% (0/731)	0.0% (0/268)	0.0% (0/767)	0.3% (1/291)	0.1% (1/1291)	0.2% (1/481)
Grade 1	0.0% (0/731)	0.0% (0/268)	0.0% (0/767)	0.3% (1/291)	0.1% (1/1291)	0.2% (1/481)
Drowsiness[b, d]	--	--	--	--	--	--
Any	27.2% (199/731)	26.9% (72/268)	NA	NA	NA	NA
Grade 1	20.5% (150/731)	19.4% (52/268)	NA	NA	NA	NA
Grade 2	5.3% (39/731)	6.3% (17/268)	NA	NA	NA	NA
Grade 3	1.4% (10/731)	1.1% (3/268)	NA	NA	NA	NA
Loss of appetite[b, d]	--	--	--	--	--	--
Any	21.1% (154/731)	22% (59/268)	NA	NA	NA	NA
Grade 1	16.1% (118/731)	18.3% (49/268)	NA	NA	NA	NA
Grade 2	4.7% (34/731)	3% (8/268)	NA	NA	NA	NA
Grade 3	0.3% (2/731)	0.7% (2/268)	NA	NA	NA	NA
Fever (temperature ≥38ºC)	--	--	--	--	--	--
Any fever	24.2% (177/731)	25% (67/268)	19% (146/767)	19.9% (58/291)	19.9% (257/1291)	20% (96/481)
Fever with unknown temperature[c]	0.1% (1/731)	0.4% (1/268)	0.0% (0/767)	0.0% (0/291)	0.0% (0/1291)	0.0% (0/481)
38.00-38.50°C	11.2% (82/731)	10.1% (27/268)	7.3% (56/767)	9.6% (28/291)	8.4% (109/1291)	7.7% (37/481)
38.51-39.00°C	7.4% (54/731)	10.1% (27/268)	6.5% (50/767)	5.5% (16/291)	6% (77/1291)	7.5% (36/481)
39.01-39.50°C	4.5% (33/731)	2.2% (6/268)	3.4% (26/767)	1.7% (5/291)	3.9% (50/1291)	3.1% (15/481)
39.51-40.00°C	0.5% (4/731)	2.2% (6/268)	1.3% (10/767)	2.1% (6/291)	0.9% (11/1291)	1.5% (7/481)
≥40.01°C	0.4% (3/731)	0.0% (0/268)	0.5% (4/767)	1% (3/291)	0.8% (10/1291)	0.2% (1/481)

Solicited Adverse Reaction, % (n/N)	PRIORIX Sub-cohort 1 N=727-731	M-M-R II Sub-cohort 1 N=267-268	PRIORIX Sub-cohort 2 N=766-767	M-M-R II Sub-cohort 2 N=289-291	PRIORIX Sub-cohort 3 N=1289-1291	M-M-R II Sub-cohort 3 N=480-481
Signs of meningism/seizure (including febrile convulsions) #	--	--	--	--	--	--
Any	0.0% (0/731)	0.7% (2/268)	0.1% (1/767)	0.0% (0/291)	0.0% (0/1291)	0.0% (0/481)
Grade 1	0.0% (0/731)	0.4% (1/268)	0.0% (0/767)	0.0% (0/291)	0.0% (0/1291)	0.0% (0/481)
Grade 2	0.0% (0/731)	0.4% (1/268)	0.1% (1/767)	0.0% (0/291)	0.0% (0/1291)	0.0% (0/481)

Source: Adapted from STN 125748/0, MMR-158 Clinical Study Report, Table 14, Table 27, Table 28, Table 29, and MMR (RIT) Analysis #16 Table 14
Abbreviations: AE=adverse event; LAR=legally acceptable representative; N=number of participants in cohort; n=number of participants who experienced the solicited event; NA=not applicable (varicella-like rash, drowsiness, and loss of appetite were only collected for sub-cohort 1); TVC=Total Vaccinated Cohort was used as the analyses set for safety
Note: For solicited local events, the N is the number of participants from the TVC with documented local events
Note: For solicited systemic events, the N is the number of participants from the TVC with documented systemic events
a. Pain: Grade 0: none, Grade 1: Minor reaction to touch (digital pressure), Grade 2: Cried/protested on touch (digital pressure), Grade 3: Cried when limb was moved/spontaneously painful
b. Varicella-like rash, drowsiness, and loss of appetite were only collected for sub-cohort 1
c. Reported fever without associated daily temperature measurement resulting in fever with unknown temperature
d. Other rash/Drowsiness/Loss of appetite/Meningism: Grade 1: caused minimal discomfort and did not interfere with everyday activities, Grade 2: sufficiently discomforting to interfere with normal everyday activities, Grade 3: prevented normal, everyday activities (in a young child, such an AE would, for example, prevent attendance at school/day care and would cause the parent(s)/LAR(s) to seek medical advice)
e. Parotid/salivary gland swelling: Grade 1: Swelling without difficulty moving the jaw, Grade 2: Swelling with difficulty moving the jaw, Grade 3: Swelling with accompanying general symptoms

Injection site pain was the most frequently reported solicited local adverse reaction for both groups (PRIORIX and M-M-R II) in all three sub-cohorts as follows, respectively:

- Sub-cohort 1: 40.6% vs. 40.8%
- Sub-cohort 2: 19.8% vs. 22.1%
- Sub-cohort 3: 21.6% vs. 25.6%

Across sub-cohorts and vaccine groups, the median duration for solicited local reactions ranged from 1 to 2 days for pain and swelling and was 2 days for erythema. Overall, most reported solicited local reactions (i.e., injection site pain, erythema, and swelling) were grade 1.

The solicited systemic adverse reactions of drowsiness and loss of appetite were only collected from participants in sub-cohort 1 since these reactions relate to participants receiving DTaP and VV vaccines. Drowsiness was the most common solicited systemic reaction in sub-cohort 1 (PRIORIX 27.2% and M-M-R II 26.9%) with a median duration of 1 day in both groups. The percentage of participants reporting grade 3 drowsiness was 1.4% in the PRIORIX group compared to 1.1% in the M-M-R II group.

Fever (temperature ≥38ºC/100.4ºF) from Day 5 to Day 12 post-vaccination occurred in 11.8% and 13.4% of participants in the sub-cohort 1 PRIORIX and M-M-R II groups, in 7.3% and 7.6% of participants in the sub-cohort 2 PRIORIX and M-M-R II groups, and in 9.1% and 7.3% of participants in the sub-cohort 3 PRIORIX and M-M-R II groups, respectively. Median duration was 1 day across groups in sub-cohorts 1 and 2. In sub-cohort 3, the median duration was 2 days for the PRIORIX group and 1.5 days for the M-M-R II group. Incidences of grade 3 fever (temperature >39.5ºC) considered related to the study vaccination were 0.1% for the PRIORIX groups in each sub-cohort and up to 0.4% for the M-M-R II groups.

Solicited Systemic Symptoms Specific to MMR Vaccination
Solicited systemic symptoms specific to MMR vaccination were collected from Day 0 to Day 42 post-vaccination. There were three reports of signs of meningism overall: two participants (0.7%) in the M-M-R II group in sub-cohort 1 and one participant (0.1%) in the PRIORIX group in sub-cohort 2. Both events in the M-M-R II group were reported as headache, with a median duration of 1.5 days, and were considered related to vaccination. The event in the PRIORIX group was a febrile convulsion, with a reported duration of 1 day, considered not related to the study vaccine.

Overall, there were three reports of parotid/salivary gland swelling and all were considered related. One participant (0.3%) in the M-M-R II group of sub-cohort 2 reported fever with slight swelling of the submandibular area lasting 2 days, one participant (0.1%) in the PRIORIX group of sub-cohort 3 reported post-auricular lesion swelling lasting 6 days, and one participant (0.2%) in the M-M-R II group of sub-cohort 3 reported swelling inside the sides of the mouth lasting 6 days.

Incidences of rash considered related to the study vaccines were as follows for each sub-cohort (PRIORIX vs. M-M-R II):

- Sub-cohort 1: 3.4% vs. 4.1%
- Sub-cohort 2: 0.3% vs. 0.7%
- Sub-cohort 3: 0.6% vs. 0.6%

Measles/rubella-like rash was reported as follows for each sub-cohort (PRIORIX vs. M-M-R II):

- Sub-cohort 1: 1.9% vs. 1.9%
- Sub-cohort 2: 0.4% vs. 0.7%
- Sub-cohort 3: 0.3% vs. 0.4%

Severe (grade 3) rashes were reported in a small number of participants in the PRIORIX group of each sub-cohort: 3 (0.4%) in sub-cohort 1, 1 (0.1%) in sub-cohort 2, and 3 (0.2%) in sub-cohort 3. The median duration for rashes was comparable across sub-cohorts and vaccine groups ranging between 4 to 5 days.

Reviewer Comment:

1. Overall, the rates of solicited reactions were comparable across groups. The most frequently reported solicited local reaction was injection site pain. Solicited systemic adverse reactions were only collected in sub-cohort 1, and drowsiness was the most commonly reported. Most solicited adverse reactions were Grade 1.
2. In an IR response (STN 125748/Am 28), the Applicant provided the proportion of participants with meningism (without febrile convulsions) and the proportion of participants with febrile convulsions separately for all studies included in this application. See Reviewer Comment 2 in Section 6.1.12.2 under the subsection *Solicited Systemic Symptoms Specific to MMR Vaccination* for an explanation of which events qualified as febrile convulsions. For study MMR-158, the proportion with each event were provided as follows:
    - Meningism excluding febrile convulsions:
        - PRIORIX (Sub-cohorts 1, 2, and 3): 0%
        - M-M-R II:
            - Sub-cohort 1: 0.75% (2/268 participants)
            - Sub-cohorts 2 and 3: 0%
    - Febrile convulsions:
        - PRIORIX:
            - Sub-cohort 1 and 3: 0%
            - Sub-cohort 2: 0.13% (1/767 participants)
        - M-M-R II (Sub-cohorts 1, 2, and 3): 0%

Ongoing Adverse Reactions and Adverse Reactions with Onset After Reporting Period
The proportion of participants with solicited adverse reactions with onset during the solicited reporting period that were ongoing after the last day of the reporting period across sub-cohorts were as follows:
Solicited local reactions (reporting period Day 0 to Day 3):

- PRIORIX: 0-1.24%
- M-M-R II: 0-1.87%

Solicited systemic reactions (reporting period Day 0 to Day 3; sub-cohort 1 only):

- PRIORIX: 0.68-0.82%
- M-M-R II: 0-0.75%

Solicited systemic symptoms specific to MMR vaccination (reporting period Day 0 to Day 42):

- PRIORIX: 0-0.78%
- M-M-R II: 0-0.62%

Fever (reporting period Day 0 to Day 42):

- PRIORIX: 0.39-0.70%
- M-M-R II: 0-0.83%

Ongoing events were predominantly grade 1 and 2. There were no ongoing events of parotid/salivary gland swelling or signs of meningism (including febrile convulsions).

In general, the proportion of participants with solicited symptoms with onset after the reporting period was low. For local solicited reactions, injection site pain with onset after the reporting period (Day 0 to Day 3) was reported in 0.25% of PRIORIX vaccinees (n=2) and in 0.34% of M-M-R II vaccinees (n=1) in sub-cohort 1 only, all of mild severity. There were no events of erythema or swelling. The proportion of solicited systemic symptoms with onset after the reporting period (Day 0 to Day 14) and symptoms

specific to MMR vaccination with onset after the reporting period (Day 0 to Day 42) ranged from 0-0.76% across sub-cohorts in both vaccine groups. Fever was the most common solicited symptom with onset after the reporting period (Day 0 to Day 42) being reported in 0.63-2.24% of PRIORIX vaccinees across sub-cohorts and 0.61-3.36% of M-M-R II vaccinees across sub-cohorts.

See Reviewer Comment in Section 6.1.12.2 under the subsection *Ongoing Adverse Reactions and Adverse Reactions with Onset After Reporting Period* for an explanation of how duration was calculated.

Immediate AEs: within 30 minutes
There were no reported adverse events within 30 minutes of vaccination.

Unsolicited AEs (Non-Serious): 0-42 days
At least one unsolicited AE was reported in the PRIORIX and M-M-R II groups, respectively, as follows:

- Sub-cohort 1: 34.4% and 30.2%
- Sub-cohort 2: 39.4% and 37.0%
- Sub-cohort 3: 38.5% and 38.0%

Unsolicited AEs were most frequently classified in MedDRA SOC *Infections and infestations*. The most common reported AEs by MedDRA PT by sub-cohort were cough in sub-cohort 1 (4.7% PRIORIX and 5.4% M-M-R II) and viral upper respiratory tract infection in sub-cohorts 2 and 3 (8.5% PRIORIX and 8.9% M-M-R II in sub-cohort 2; 8.3% PRIORIX and 8.4% M-M-R II in sub-cohort 3).

At least one Grade 3 unsolicited symptom was reported in the PRIORIX and M-M-R II groups, respectively, as follows:

- Sub-cohort 1: 3.0% and 3.7%
- Sub-cohort 2: 2.4% and 3.3%
- Sub-cohort 3: 2.2% and 2.2%

Causal relationship to vaccination was attributed as follows (PRIORIX and M-M-R II):

- Sub-cohort 1: 5.4% and 2.7%
- Sub-cohort 2: 0.9% and 2.0%
- Sub-cohort 3: 1.5% and 1.2%

Adverse Events of Specific Interest
New Onset Chronic Disease
At least one NOCD was reported in the PRIORIX and M-M-R II groups, respectively, as follows:

- Sub-cohort 1: 1.0% and 1.3%
- Sub-cohort 2: 0.8% and 0.0%
- Sub-cohort 3: 0.8% and 0.6%

In sub-cohorts 1 and 3, allergic rhinitis was the most common NOCD and was reported in 3 participants in the PRIORIX group and 2 in the M-M-R II group of sub-cohort 1 and in 6 participants in the PRIORIX group and 2 in the M-M-R II group of sub-cohort 3.

AEs prompting Emergency Room Visit
At least one AE prompting an ER visit was reported as follows (PRIORIX vs. M-M-R II, respectively):

- Sub-cohort 1: 7.6% vs. 9.7%
- Sub-cohort 2: 8.0% vs. 7.3%
- Sub-cohort 3: 7.7% vs. 7.4%

The most commonly reported events were as follows (# participants):

- Sub-cohort 1:
  - PRIORIX: laceration (9), URI (5), and constipation (5)
  - M-M-R II: laceration (5) and vomiting (3)
- Sub-cohort 2:
  - PRIORIX: laceration (7), gastroenteritis (6), abdominal pain (5), pharyngitis (5), and URI (5)
  - M-M-R II: urticaria (4), pharyngotonsillitis (2), pneumonia (2), urinary tract infection (2), and asthma (2)
- Sub-cohort 3:
  - PRIORIX: vomiting (10), URI (10), contusion (9), and croup infection (7)
  - M-M-R II: bronchitis (4), gastroenteritis (4), URI (4), and laceration (4)

Medically Attended AEs

At least one AE leading to a medically attended visit was reported as follows (PRIORIX vs. M-M-R II, respectively):

- Sub-cohort 1: 34.7% vs. 33.6%
- Sub-cohort 2: 45.1% vs. 41.6%
- Sub-cohort 3: 48.8% vs. 47.2%

The most commonly reported events were as follows:

Sub-cohort 1:

- PRIORIX vs. M-M-R II: otitis media (6.7% vs. 4.4%), URI (6.2% vs. 5.7%), pharyngitis (3.2% vs. 1.0%), cough (3.0% vs. 2.7%), pyrexia (2.1% vs. 3.4%), viral infection (1.1% vs. 3.0%), and conjunctivitis (1.9% vs. 2.0%)

Sub-cohort 2:

- PRIORIX vs. M-M-R II: URI (10.2% vs. 11.9%), viral URI (10.1% vs. 9.6%), otitis media (3.3% vs. 2.0%), pharyngitis (3.0% vs. 2.0%), bronchitis (2.8% vs. 2.3%), gastroenteritis (2.6% vs. 0.7%), cough (2.6% vs. 1.7%), conjunctivitis (1.6% vs. 2.6%), and pneumonia (1.3% vs. 2.0%)

Sub-cohort 3:

- PRIORIX vs. M-M-R II: URI (10.7% vs. 10.4%), viral URI (10.5% vs. 11.5%), otitis media (4.9% vs. 3.9%), bronchitis (4.3% vs. 5.1%), pharyngitis (3.6% vs. 3.9%), and allergic rhinitis (3.0% vs. 3.1%)

  Reviewer Comment: The reported rates and types of unsolicited adverse events were comparable across groups and represent common medical conditions in the general population for the evaluated age cohort (children 4 through 6 years of age).

6.2.12.3 Deaths

There were no deaths reported in this study.

6.2.12.4 Nonfatal Serious Adverse Events

During the course of the study, at least one SAE was reported in 1.47% of participants in pooled PRIORIX sub-cohorts and 0.92% of participants in M-M-R II pooled sub-cohorts. By sub-cohort, at least one SAE was reported in the PRIORIX and M-M-R II groups, respectively, as follows:

- Sub-cohort 1: 5 in 4 participants (0.5%) and 0
- Sub-cohort 2: 21 in 14 participants (1.8%) and 1 in 1 participant (0.3%)
- Sub-cohort 3: 37 in 25 participants (1.9%) and 16 in 9 participants (1.8%)

The most frequently reported SAEs overall were gastroenteritis (PRIORIX: 0.24% [7 participants]; M-M-R II: 0.09% [1 participant]) and asthma (PRIORIX: 0.21% [6 participants]; M-M-R II: 0.18% [2 participants]).

Within 42 days of study vaccination, at least one SAE was reported for 0.34% of participants in PRIORIX pooled sub-cohorts and 0.37% of participants in M-M-R II pooled sub-cohorts. The majority of these events were of the SOC *Infections and infestations*, and the most frequently reported PTs were tonsilitis, gastritis, and asthma.

None of the SAEs in sub-cohorts 1 or 2 were considered related to the study vaccination. In sub-cohort 3, one 5-year-old Asian female participant in the PRIORIX group had an SAE of generalized skin rash that started 24 days following study vaccination for which she was hospitalized. The rash lasted 51 days and was considered by the investigator to have a reasonable possibility of being related to the study vaccination. All SAEs were resolved before the study end.

> Reviewer Comment: Overall, the percentage of participants reporting SAEs within 42 days of study vaccination was less than 0.5% and was similar in the PRIORIX group compared to the M-M-R II group. The clinical reviewer agrees with the study investigator assessment that the events, other than the one described above, were unlikely related to study vaccinations. Due to the temporal relationship of the SAE described above, the reviewer agrees with the study investigator assessment that the event had a reasonable possibility of being related to study vaccination.

6.2.12.5 Dropouts and/or Discontinuations

The most common reasons for study discontinuation were lost to follow-up with complete vaccination course followed by consent withdrawal, as shown in Table 31. The rates of discontinuation were similar across groups within each sub-cohort. There were no AEs leading to discontinuation from the study or deaths.

Table 31. Discontinuations, All Randomized Participants, Study MMR-158

Population	PRIORIX Sub-cohort 1 N=802 % (n/N)	M-M-R II Sub-cohort 1 N=299 % (n/N)	PRIORIX Sub-cohort 2 N=796 % (n/N)	M-M-R II Sub-cohort 2 N=303 % (n/N)	PRIORIX Sub-cohort 3 N=1,320 % (n/N)	M-M-R II Sub-cohort 3 N=489 % (n/N)
Enrolled	100% (802/802)[a]	100% (299/299)[a]	100% (796/796)	100% (303/303)	100% (1320/1320)	100% (489/489)
Vaccinated	100% (802/802)	99.7% (298/299)	100% (796/796)	100% (303/303)	99.9% (1319/1320)	100% (489/489)
Completed study	94.1% (755/802)	92.0% (275/299)	95.9% (763/796)	96.4% (292/303)	97.3% (1284/1319)	97.5% (477/489)
Withdrawal due to	--	--	--	--	--	--
Consent withdrawal	1.0% (8/802)	1.3% (4/298)	0.5% (4/796)	0.7% (2/303)	0.2% (2/1319)	0
Lost to follow-up	--	--	--	--	--	--
Migrated/moved from study area	0	0	0.3% (2/796)	0	0.1% (1/1319)	0
Lost to follow-up (participants with incomplete vaccination course)	0	0	0	0	0	0
Lost to follow-up (participants with complete vaccination course)	4.5% (36/802)	5.4% (16/298)	3.0% (24/796)	2.3% (7/303)	2.4% (31/1319)	2.2% (11/489)
Protocol deviation	0	0	0	0	0	0.2% (1/489)
Non-serious AE	0	0	0	0	0	0
Serious AE	0	0	0	0	0	0
Death	0	0	0	0	0	0
Other	0.4% (3/802)	1.0% (3/298)	0.4% (3/796)	0.7% (2/303)	0.1% (1/1319)	0

Source: Adapted from STN 125748/0, MMR-158 Clinical Study Report Amendment 2, Table 24, Table 25, Table 26, Table 27, Table 28, Table 29
Abbreviations: AE=adverse event; N=number of participants in cohort; n=number of participants falling within indicated population
Sub-cohort 1: safety and immunogenicity, MMR vaccines concomitantly administered with varicella vaccine and DTaP-IPV in United States participants only.
Sub-cohort 2: safety and immunogenicity, MMR vaccines alone
Sub-cohort 3: safety, MMR vaccines alone
Note: Two different lots of M-M-R II were used in this study. Data from both lots were pooled in each sub-cohort for this summary.
a. A total of 1,103 participants were enrolled in Sub-cohort 1. Two participants were enrolled but not randomized to a treatment group.

6.2.13 Study Summary and Conclusions

Study MMR-158 was designed to evaluate the non-inferiority of PRIORIX as compared to M-M-R II as a second dose when administered with and without concomitant DTaP-IPV and varicella vaccines in children 4 through 6 years of age. The primary objectives to demonstrate non-inferiority of PRIORIX to M-M-R II, when administered either with DTaP-IPV and Varivax or alone, were met. The secondary immunogenicity objectives, to demonstrate non-inferiority of PRIORIX versus M-M-R II in terms of immune responses to the concomitantly administered vaccines, DTaP-IPV and Varivax, were met. The safety profile of PRIORIX was acceptable as compared to the safety profile of the US-licensed vaccine control group, M-M-R II, when administered both alone and with concomitant vaccines DTaP-IPV and Varivax. The data from study MMR-158 support the safety and effectiveness of PRIORIX as a second dose in children 4 through 6 years of age when concomitantly administered with ACIP-recommended vaccines.

6.3 Trial #3 (Study MMR-161)

NCT01681992
"A Phase 3a, randomized, observer-blind, controlled, multinational study to evaluate the immunogenicity and safety of GSK's MMR vaccine (PRIORIX) at an EOSL potency compared to Merck's MMR vaccine (M-M-R II), when both are concomitantly administered with Varivax, Havrix, and Prevnar 13 (subset of children), and given on a two-dose schedule to healthy children in their second year of life."

Study Overview: This study was designed to establish the EOSL potency of PRIORIX by giving the first dose at 12 through 15 months of age as one of two lots: a minimum potency lot and a medium potency lot, and to evaluate the immunogenicity of PRIORIX compared to M-M-R II. In the US, the study also evaluated the safety and immunogenicity of both PRIORIX and M-M-R II vaccines with concomitantly administered Varivax (VV), Havrix (HAV), and Prevnar 13 (PCV13) vaccines. At sites outside the US, concomitant vaccines were VV and HAV. Six weeks following the first dose, participants received a second dose of PRIORIX (at a potency within release range of the marketed vaccine) or M-M-R II, and immune responses were evaluated in a sub-cohort of children enrolled in the US.

6.3.1 Objectives

Primary Objectives
To control for the risk of erroneous conclusions, a hierarchical procedure was used for the multiple study objectives with the possibility to conclude on objectives 6-10, associated with medium potency PRIORIX, even if one or more of objectives 1-5, associated with minimum potency PRIORIX, were not met.

All primary immunogenicity objectives were evaluated with an ELISA unless otherwise specified.

Minimum potency (min potency) PRIORIX vaccine:

1. To demonstrate non-inferiority of min potency PRIORIX vaccine compared to pooled M-M-R II vaccine in terms of SRRs to measles, mumps, and rubella viruses at Day 42.
   Endpoint: Seroresponse to measles, mumps, and rubella viruses, as defined above in Section 6.1.1.
   Statistical Criterion for Success: The lower limit of the two-sided 97.5% CI on the group difference (min potency PRIORIX minus pooled M-M-R II) in SRR is ≥-5% for antibodies to measles, mumps, and rubella viruses.

2. To demonstrate non-inferiority of min potency PRIORIX vaccine compared to pooled M-M-R II vaccine in terms of GMCs for antibodies to measles, mumps, and rubella viruses at Day 42.
   Endpoint: Measles, mumps, and rubella virus antibody concentrations

Statistical Criterion for Success: The lower limit of the two-sided 97.5% CI on the group ratio of GMCs (min potency PRIORIX over pooled M-M-R II) is ≥0.67 for antibodies to measles, mumps and rubella viruses.

3. To demonstrate an acceptable immune response of min potency PRIORIX vaccine in terms of SRRs for measles, mumps, and rubella viruses at Day 42.
   Endpoint: Seroresponse to measles, mumps, and rubella viruses
   Statistical Criterion for Success: The lower limit of the two-sided 97.5% CI for the SRR of min potency PRIORIX is ≥90% for antibodies to measles, mumps, and rubella viruses.

4. To demonstrate non-inferiority of the min potency PRIORIX vaccine compared to pooled M-M-R II vaccine in terms of SRRs for mumps virus (by (b) (4) at Day 42.
   Endpoint: Seroresponse to mumps virus by (b) (4) using the following seroresponse definition:
   For mumps virus as measured by (b) (4), a post-vaccination anti-mumps virus antibody concentration ≥4 endpoint dilution 50% (ED_{50}) among children who were seronegative (antibody concentration <2.5 ED_{50}) before Dose 1.
   Statistical Criterion for Success: The lower limit of the two-sided 97.5% CI on the group difference (min potency PRIORIX minus pooled M-M-R II) in SRR is ≥-10% for antibodies to mumps virus.

5. To demonstrate non-inferiority of the min potency PRIORIX vaccine compared to pooled M-M-R II vaccine in terms of geometric mean titer (GMT) for antibodies to mumps virus (by (b) (4) at Day 42.
   Endpoint: Mumps virus antibody titers by (b) (4)
   Statistical Criterion for Success: The lower limit of the two-sided 97.5% CI on the GMT ratio (min potency PRIORIX over pooled M-M-R II) is ≥0.67 for antibodies to mumps virus.

Medium potency (med potency) PRIORIX vaccine:

6. To demonstrate non-inferiority of med potency PRIORIX vaccine compared to pooled M-M-R II vaccine in terms of SRRs to measles, mumps, and rubella viruses at Day 42.
   Endpoint: Seroresponse to measles, mumps, and rubella viruses, as defined above in Section 6.1.1.
   Statistical Criterion for Success: The lower limit of the two-sided 97.5% CI on the group difference (med potency PRIORIX minus pooled M-M-R II) in SRR is ≥–5% for antibodies to measles, mumps, and rubella viruses.

7. To demonstrate non-inferiority of med potency PRIORIX vaccine compared to pooled M-M-R II vaccine in terms of GMCs for antibodies to measles, mumps, and rubella viruses at Day 42.
   Endpoint: Measles, mumps, and rubella virus antibody concentrations
   Statistical Criterion for Success: The lower limit of the two-sided 97.5% CI on the group ratio of GMCs (med potency PRIORIX over pooled M-M-R II) is ≥0.67 for antibodies to measles, mumps, and rubella viruses.

8. To demonstrate an acceptable immune response of medium potency PRIORIX vaccine in terms of SRRs for measles, mumps, and rubella viruses at Day 42.
   Endpoint: Seroresponse to measles, mumps, and rubella viruses
   Statistical Criterion for Success: The lower limit of the two-sided 97.5% CI for the SRR of med potency PRIORIX is ≥90% for antibodies to measles, mumps, and rubella viruses.

9. To demonstrate non-inferiority of the med potency PRIORIX vaccine compared to pooled M-M-R II vaccine in terms of SRRs for mumps virus (by (b) (4) at Day 42.
   Endpoint: Seroresponse to mumps virus by (b) (4) using the above seroresponse definition
   Statistical Criterion for Success: The lower limit of the two-sided 97.5% CI on the group difference (med potency PRIORIX minus pooled M-M-R II) in SRR is ≥-10% for antibodies to mumps virus.

10. To demonstrate non-inferiority of the med potency PRIORIX vaccine compared to pooled M-M-R II vaccine in terms of GMT for antibodies to mumps virus (by (b) (4) at Day 42.
    Endpoint: Mumps virus antibody titers by (b) (4)
    Statistical Criterion for Success: The lower limit of the two-sided 97.5% CI on the GMT ratio (med potency PRIORIX over pooled M-M-R II) is ≥0.67 for antibodies to mumps virus.

Secondary Objectives

1. To assess the immunogenicity of min potency PRIORIX followed by release potency PRIORIX and pooled M-M-R II vaccine in terms of SRRs and GMCs for antibodies to measles, mumps, and rubella viruses at Day 84 (post Dose 2) (in a sub-cohort of children enrolled in the US).
   Endpoints (Descriptive):
   - Seroresponse to measles, mumps, and rubella viruses
   - Measles, mumps, and rubella virus antibody concentrations

2. To assess the immunogenicity of med potency PRIORIX followed by release potency PRIORIX and pooled M-M-R II vaccine in terms of SRR and GMCs for antibodies to measles, mumps, and rubella viruses at Day 84 (post Dose 2) (in a sub-cohort of children enrolled in the US).
   Endpoints (Descriptive):
   - Seroresponse to measles, mumps, and rubella viruses
   - Measles, mumps, and rubella virus antibody concentrations

3. To assess the safety and reactogenicity of min potency PRIORIX, med potency PRIORIX, and M-M-R II when concomitantly administered with Varivax and Havrix (to all children), and Prevnar 13 (only to children enrolled in the US).
   Endpoints (Descriptive): see Section 6.1.1 for a description of the safety endpoints.

6.3.2 Design Overview

Study MMR-161 was an observer-blind, randomized, controlled, multi-center, multi-country, EOSL study with four parallel groups. Overall, participants were randomized into 4 treatment groups in a 2:2:1:1 ratio to receive a first dose of minimum potency PRIORIX, medium potency PRIORIX, or one of the two M-M-R II lots, respectively. For the second dose, participants who received either minimum or medium potency PRIORIX for the first dose received targeted release potency PRIORIX, and participants who received M-M-R II received M-M-R II again. The study was conducted in a double-blind fashion with regard to the two PRIORIX vaccine lots (min potency and med potency) and in an observer-blind fashion for the lots of PRIORIX vaccine versus the pooled M-M-R II vaccine lots.

Children in each group participated in four study visits (Days 0, 42, 84, and 222). Vaccinations occurred on Day 0 and Day 42. Blood samples were collected from each child at Day 0 and Day 42. A third blood sample was collected from all US children at Day 84 (42 days post-dose 2). The study duration was approximately 7.5 months starting at Visit 1 (Day 0) and ending at Visit 4 (Day 222).

6.3.3 Population

Eligibility Criteria

Individuals were eligible for inclusion if they met the criteria previously described (see Section 6.1.3) with the additional exclusion criterion of administration of immunoglobulins and/or any blood products through the immunogenicity evaluation at Visit 3 for the US sub-cohort.

6.3.4 Study Treatments or Agents Mandated by the Protocol

PRIORIX: investigational measles, mumps, and rubella vaccine

- Dose/RoA/Presentation: see Section 6.1.4.
  - Minimum potency
    - Formulation: Measles virus (Schwarz strain) $\leq 10^{3.1}$ $CCID_{50}$; Mumps virus (RIT4385 strain) $\leq 10^{4.1}$ $CCID_{50}$; Rubella virus (Wistar RA 27/3 strain) $\leq 10^{2.9}$ $CCID_{50}$; anhydrous lactose; sorbitol; mannitol; amino acids; neomycin
      Note: Actual potency at release of the mumps component was $10^{3.9}$ $CCID_{50}$ and actual potency at release of the rubella component was $10^{3.0}$ $CCID_{50}$
    - Lot: DMJRA019A
  - Medium potency
    - Formulation: Measles virus (Schwarz strain) $\leq 10^{3.4}$ $CCID_{50}$; Mumps virus (RIT4385 strain) $\leq 10^{4.3}$ $CCID_{50}$; Rubella virus (Wistar RA 27/3 strain) $\leq 10^{3.2}$ $CCID_{50}$; anhydrous lactose; sorbitol; mannitol; amino acids; neomycin
    - Lot: DMJRA018A
  - Targeted release potency
    - Formulation: see Section 6.1.4.
    - Lots: DMJRA014A, DMJRA020

M-M-R II: comparator measles, mumps, and rubella vaccine

- Dose/RoA/Formulation/Presentation: see Section 6.1.4.
- Lots:
  - Lot 1: G004486, H000662, H004594, H014762, H020866, H021002, J003177, J008276, J008405, J015956, K008227, K008461
  - Lot 2: 1556AA, G019547, H000663, H021708, H014763, H017980, J002990, J014066, J007624, J008276, J008405, K010570

Varivax

- Dose/RoA/Formulation/Presentation: see Section 6.1.4.
- Lots: 0016AE, H006221, H004550, H019070, H014477, H012465, J007624, J0037478, J012375

Havrix

- Dose/RoA/Formulation/Presentation: see Section 6.1.4.
- Lots: AHAVB549BA, AHAVB667CB, AHAVB605BA, AHAVVB738B, AHAVB666C, AHAVB573F, AHAVB573C, AHAVB675A, AHAVB731A

Prevnar 13

- Dose/RoA/Formulation/Presentation: see Section 6.1.4.
- Lots: F75398, F94001, F92473, G94059

6.3.5 Directions for Use

See Section 6.1.5.

6.3.6 Sites and Centers

There were 83 sites in the United States (including Puerto Rico), Czech Republic, Finland, Malaysia, Spain, and Thailand with a total vaccinated cohort of 4,516 participants. There were 45 US sites with a total vaccinated cohort of 1,000 participants.

6.3.7 Surveillance/Monitoring

Surveillance
See Section 6.1.7. For this study, CROs were employed for monitoring at sites in Finland.

Safety Monitoring
Safety monitoring of adverse events was as previously described (see Section 6.1.7.) with the following differences ascribed to the 2-dose study design. Solicited local adverse events (pain, redness, or swelling at injection site) were recorded from Day 0 to Day 3 after each vaccination. Solicited systemic adverse events of drowsiness, loss of appetite, and irritability were collected from Day 0 to Day 14 after dose 1. The solicited systemic adverse event of varicella-like rash was followed up from Day 0 to Day 42 after dose 1, and the solicited systemic adverse events of measles/rubella-like rash, other rash (not measles/rubella-like nor varicella-like), fever (defined as temperature ≥38ºC/100.4ºF), parotid gland/salivary gland swelling, and meningism (including febrile convulsions) were collected from Day 0 to Day 42 after each vaccination.

Immunogenicity Monitoring
Serological assays for the determination of measles, mumps, and rubella IgG antibodies by ELISA were the same assays used in previous studies (see Section 6.1.7). The serological assay for the determination of mumps by (b) (4) is presented in Table 32.

Table 32. Summary of Serological Assays, Study MMR-161

Component	Method	Unit	Cut-Off	Threshold	Kit/Manufacturer	Location
Mumps Virus Strain Mu90 Ab	(b) (4)	ED_{50}	2.5	4	GSK In-house	GSK Biologicals

Source: Adapted from STN 125748/0, Clinical Overview, Table 4
Abbreviations: Ab=antibody; ED_{50}=endpoint dilution 50%; (b) (4) test

6.3.8 Endpoints and Criteria for Study Success

See Section 6.3.1.

6.3.9 Statistical Considerations and Statistical Analysis Plan

Sample Size
The target to enroll approximately 4,500 children assumed a 20% non-evaluable rate which would result in an evaluable population of 3,600 children with 1,200 in each PRIORIX lot group (minimum and medium potency) and 600 in each M-M-R II lot group.

Methods
To control the global type I error below 2.5%, a hierarchical procedure with adjustment of the nominal type I error used at the level of a study objective was required. To conclude on objectives 6-10 (pertaining to medium potency PRIORIX) if one or more of objectives 1-5 (pertaining to minimum potency PRIORIX) were not met, a Bonferroni adjustment was used for the set of objectives 1-5 and for the set of objectives 6-10. To control the type I error within each set of objectives, 1-5 and 6-10 respectively, a hierarchical procedure was used. Namely, the primary objective 5 could only be reached if all the associated criteria were met and the previous primary objectives 1, 2, 3 and 4 had been reached. Likewise, the primary objective 10 could only be reached if all the associated criteria were met and the previous primary objectives 6, 7, 8 and 9 were reached.

The analysis was performed in two steps:

1. A summary of post-dose 1 (Day 42) and post-dose 2 (Day 84) GMCs and SRRs for measles, mumps, and rubella (by ELISA) was generated by independent statisticians once all CRF study data were available and cleaned, and measles, mumps, and rubella ELISA testing was fully completed.
2. A final analysis, including full immunogenicity analysis for post-dose 1 (Day 42) and post-dose 2 (Day 84), including mumps (b) (4) results post-dose 1 and all safety data (including all immunogenicity and safety analyses), was performed once the final serology data were available.

These two analyses were combined in the final clinical report.

For the first analysis step, access to group attribution and individual laboratory results was limited to statisticians at an independent data analysis center. Members of the GSK study team were only able to view summary tables (GMCs and SRRs per group, and GMC ratios and differences in SRRs between groups), thereby ensuring that they remained blinded to the treatment group attribution until all data were available and the final analysis was carried out.

Subpopulation analysis methods, as well as safety analysis methods, were the same as for the previous studies: see Section 6.1.9.

> Reviewer Comment: Subpopulation analyses of study data based on age were not presented, as the age range of study participants in this study was limited to 12 through 15 months of age. Additional evaluation of data stratified within this age cohort are considered unnecessary by the reviewer.

Protocol Amendments

Protocol Amendment 1 (February 17, 2014) included the following changes:

- A sub-cohort of US children enrolled after the target enrollment was removed per request by CBER, and the serologic response after each dose of MMR vaccine (PRIORIX and M-M-R II) was evaluated in all US participants, rather than in only the first 1,000 participants. For those in whom the pre-specified criteria for seroresponse were not met, vaccination with M-M-R II was offered.
- Vaccination with inactivated influenza vaccine and Hib vaccine would be allowed at any time before, during, or after the study.
- All medically attended events from Day 0 to Day 222 were to be recorded in the eCRF, but routine well child visits will not be recorded in the eCRF.

Protocol Amendment 2 (May 19, 2015) included the following changes:

- GSK's laboratory in (b) (4) became part of (b) (4). The assays (for antibodies against measles, rubella, and varicella viruses) and facility were the same but would be performed by a new 3rd party CRO named (b) (4).
- Due to a delay in serologic data availability for the mumps (b) (4) data, analyses were separated into two parts as described above.

Changes in the Conduct of the Study and Planned Analyses

See Section 6.1.9 regarding two technical problems identified in the Electronic Data Capture system. The technical problems were corrected and determined to have no impact on the reported data.

Two study conduct issues related to collection of informed consent were identified through site monitoring/study oversight.

- For three participants in Thailand, the ICF was signed by a parent under the age of 20, the legal adult age in Thailand. As a result, those participants were excluded from all statistical analyses.

- Nineteen participants across seven sites in Thailand and Czech Republic were entered and/or randomized before the ICF was signed by their parent/LAR. No other study procedure was performed before the ICF was signed, and data from these participants was used for the study analyses.

This study was conducted according to the protocol and all analyses were performed as planned in the protocol and the statistical analysis plan.

Please see the statistical review for further discussion.

6.3.10 Study Population and Disposition

A total of 4,538 participants were enrolled in the study. The first participant was enrolled in the study on October 10, 2012, and the last study visit was on August 18, 2015.

6.3.10.1 Populations Enrolled/Analyzed

Total Vaccinated Cohort (TVC): see Section 6.1.10.1.

The *ATP Cohort for Safety Analysis* was as previously described (see Section 6.1.10.1) with the additional criteria to include all eligible participants who had received all planned study vaccines/comparators as per protocol and, for US participants, those who had not received a vaccine leading to exclusion from the ATP Cohort up to Visit 3.

The *ATP Cohort for Immunogenicity Analysis* post-dose 1 was as previously described (see Section 6.1.10.1).

The *ATP Cohort for Immunogenicity Analysis* post-dose 2 included all eligible participants in the ATP Cohort for Safety:

- who were US participants
- who had received two doses of MMR study vaccine/comparator as per protocol with pre-vaccination and post-dose 2 serology results available for at least one antigen of measles, mumps, or rubella
- who did not meet any elimination criteria up to the Visit 3 blood collection
- who complied with the post-dose 2 blood sample schedule

The *Adapted ATP Cohort* was used for summaries that included the ATP Cohort for Immunogenicity post-dose 1 for the Day 42 time point and the ATP Cohort for Immunogenicity post-dose 2 for the Day 84 time point.

Protocol Deviations
Exclusion from the ATP Cohort for Immunogenicity Analyses occurred for the same reasons as described in Section 6.1.10.1. For US participants, the elimination criteria which applied through Visit 2 (i.e., chronic administration of immunosuppressants or other immune-modifying drugs, administration of immunoglobulins and/or any blood products, and any immunodeficiency conditions or the development of measles, mumps, or rubella) extended to Visit 3.

6.3.10.1.1 Demographics

Table 33. Demographic Characteristics, TVC, Study MMR-161

Characteristic	Minimum Potency PRIORIX N=1,493	Medium Potency PRIORIX N=1,497	M-M-R II N=1,526
Sex	--	--	--
Ratio male:female	789:704	779:718	768:758
% male:% female	52.8%:47.2%	52.0%:48.0%	50.3%:49.7%
Age, months	--	--	--
Mean (SD)	12.6 (0.9)	12.6 (0.9)	12.6 (0.9)
Median	12.0	12.0	12.0
Range	11, 15	12, 16	11, 15
Ethnicity, n (%)	--	--	--
Hispanic/Latino	84 (5.6%)	77 (5.1%)	90 (5.9%)
Not Hispanic/Latino	1409 (94.4%)	1420 (94.9%)	1436 (94.1%)
Racial Origin (Geographic Ancestry), n (%)	--	--	--
Am. Indian/A.N.	2 (0.1%)	1 (0.1%)	1 (0.1%)
All Asian	366 (24.5%)	366 (24.4%)	370 (24.2%)
Central/South Asian	1 (0.1%)	0 (0)	2 (0.1%)
East Asian	3 (0.2%)	0 (0)	1 (0.1%)
Japanese	0 (0)	0 (0)	0 (0)
South East Asian	362 (24.2%)	366 (24.4%)	367 (24.0%)
African/A.A.	45 (3.0%)	53 (3.5%)	46 (3.0%)
All White	1025 (68.7%)	1030 (68.8%)	1060 (69.5%)
Arabic/North African	8 (0.5%)	8 (0.5%)	8 (0.5%)
Caucasian/European	1017 (68.1%)	1022 (68.3%)	1052 (68.9%)
N. Hawaiian/P.I.	0 (0)	1 (0.1%)	0 (0)
Other	55 (3.7%)	46 (3.1%)	49 (3.2%)
Country, n (%)	--	--	--
Czech Republic	232 (15.5%)	231 (15.4%)	237 (15.5%
Spain	430 (28.8%)	433 (28.9%)	437 (28.6%)
Finland	141 (9.4%)	141 (9.4%)	138 (9.0%)
Malaysia	43 (2.9%)	45 (3.0%)	46 (3.0%)
Thailand	319 (21.4%)	321 (21.4%)	322 (21.1%)
United States	328 (22.0%)	326 (21.8%)	346 (22.7%)

Source: Adapted from STN 125748/0, MMR-161 Clinical Study Report Amendment 2, Table 6.5
Abbreviations: A.A.=African American; Am. Indian/A.N=American Indian/Alaskan Native; N. Hawaiian/P.I.=Native Hawaiian/Pacific Islander; N=total number of participants for the TVC Safety Analysis Set (participants with at least 1 vaccination of either PRIORIX or M-M-R II); n=number of participants with indicated characteristic; Other=mixed race or not otherwise specified; SD=standard deviation; TVC=Total Vaccinated Cohort
Note: Two different lots of M-M-R II were used during this study. Data from both lots were pooled for this summary.

The median age of participants in the TVC was 12 months at the time of the first study vaccination. Overall, the majority of the participants were White/Caucasian (68.4%) and male (51.7%); this distribution was reflected across the study groups as shown in the table above. The demographic characteristics of the ATP Cohort for Immunogenicity reflected what was observed for the TVC.

6.3.10.1.2 Participant Disposition

Table 34. Participant Disposition and Data Analyses Sets, All Randomized Participants, Study MMR-161

Population	Minimum Potency PRIORIX N=1,497	Medium Potency PRIORIX N=1,501	M-M-R II N=1,530
Enrolled[a], n (%)	1,497 (100%)	1,501 (100%)	1,530 (100%)
TVC, n (%)	1,493 (99.7%)	1,497 (99.7%)	1,526 (99.7%)
Completed study, n (%)	1,427 (95.3%)	1,427 (95.1%)	1,443 (94.3%)
TVC-Safety, n (%)	1,493 (99.7%)	1,497 (99.7%)	1,526 (99.7%)
TVC-Imm., n (%)	1,489 (99.5%)	1,493 (99.5%)	1,522 (99.5%)
ATP-Safety, post-dose 1, n (%)	1,470 (98.2%)	1,470 (97.9%)	1,498 (97.9%)
ATP-Safety, post-dose 2, n (%)	1,459 (97.5%)	1,463 (97.5%)	1,486 (97.1%)
ATP-Imm., post-dose 1, n (%)	1,363 (91.0%)	1,373 (91.5%)	1,381 (90.3%)
ATP-Imm., post-dose 2, n (%)	245 (16.4%)	261 (17.4%)	258 (16.9%)
≥1 Important prot. deviation, post-dose 1[b], n (%)	134 (9.0%)	128 (8.5%)	149 (9.7%)
≥1 Important prot. deviation, post-dose 2[c], n (%)	120 (8.0%)		135 (8.8%)
Maximum percentage of participants eliminated for ATP-Imm analyses[d]	2.42%	2.75%	3.03%

Source: Adapted from STN 125748/0, MMR-161 Clinical Study Report Amendment 2, Table 22, Table 23, Table 24; MMR (RIT) Analysis #16 Table 7, Table 8, Table 9
Abbreviations: ATP=According-to-protocol; N=total number of participants enrolled; n=number of participants fulfilling the item followed by (%); TVC=Total vaccinated cohort, included all vaccinated participants; ≥1 Prot. Deviation: participants with one or more protocol deviations
Note: Two different lots of M-M-R II were used during this study. Data from both lots were pooled for this summary.
a. A total of 4,538 participants were enrolled in the study. Ten participants were enrolled but not randomized to any treatment group.
b. Includes participants with important protocol violations that resulted in exclusion from the ATP-Imm. analysis population post-dose 1.
c. Includes participants with important protocol violations that resulted in exclusion from the ATP-Imm. analysis population post-dose 2 (does not include participants for whom a blood draw was not planned for analysis post-dose 2).
d. For each antigen and each confirmatory objective, the percentage of participants who had the necessary immunogenicity results to contribute to the TVC analysis but were eliminated for the ATP analysis was computed. This value represents the maximum over all confirmatory objectives and antigens.
TVC-Safety: included all vaccinated participants with at least one vaccine administration of either PRIORIX or M-M-R II documented.
TVC-Imm.: included all vaccinated participants for whom immunogenicity data were available.
ATP-Safety: cohort for analysis of safety, included eligible participants who received all planned study vaccines/comparator as per protocol; had not received a vaccine leading to exclusion from the ATP Cohort up to Visit 2 for the non-US participants and up to Visit 3 for the US participants; for whom the randomization code had not been broken; and the administration route of study vaccine(s) was known and correct.
ATP-Imm. cohort for analysis of immunogenicity post-dose 1: Included all eligible participants. from the ATP Cohort for Safety with pre-vaccination and post-dose 1 serology results available for at least one antigen of measles, mumps, or rubella; below the assay cut-off for at least one MMR vaccine antigen pre-vaccination; and complied with the post-dose 1 blood sample schedule.
ATP-Imm. cohort for analysis of immunogenicity post-dose 2: Included all eligible participants. from the ATP Cohort for Safety who were US participants; received two doses of MMR study/comparator as per protocol; with pre-vaccination and post-dose 2 serology results available for at least one antigen of measles, mumps, or rubella; did not meet any elimination criteria up to the Visit 3 blood sample; and complied with the post-dose 2 blood sample schedule.

Of the total 4,538 enrolled participants, 10 were not randomized to any treatment group. Of the remaining 4,528 randomized participants, 4,516 received a study vaccination. Of those vaccinated, 4,297 (95.2%) completed the study.

The most common reasons for withdrawal were lost to follow-up (109 participants), either after receiving an incomplete (35 participants) or complete (74 participants) vaccination course, and consent withdrawal (82 participants). Four participants were withdrawn due to experiencing an SAE: one in each PRIORIX group and two in the M-M-R II group. Four participants were withdrawn due to experiencing a non-serious AE: two in the minimum potency and one in the medium potency PRIORIX groups, and one in the M-M-R II group.

A total of 4,438 participants (98.3%) were included in the ATP Cohort for Safety post-dose 1 with the most common reasons for exclusion being vaccine temperature deviations (28 participants) and

administration of prohibited vaccines (24 participants). There were 4,408 participants (97.6%) included in the ATP Cohort for Safety post-dose 2 with the most common reasons for exclusion being administration of prohibited vaccines (41 participants) and vaccine temperature deviations (24 participants).

A total of 4,117 participants (91.2%) were included in the ATP Cohort for Immunogenicity post-dose 1 with the primary reason for exclusion being due to serological results not available for vaccine virus antigens following vaccination for 199 participants. The next most common reasons were the presence of detectable baseline antibody levels or unknown baseline antibody status for 59 participants, followed by non-compliance with blood sampling schedules for 51 participants.

A total of 764 participants (all from US sites) were included in the ATP Cohort for Immunogenicity post-dose 2. The major reason for exclusion was that blood collection was not planned post-dose 2 for children at non-US study sites (3,401 participants). The next most common reasons were essential serological data missing for 114 participants, due to the presence of detectable baseline antibody levels or unknown baseline antibody status for 57 participants, and non-compliance with vaccination schedule for 51 participants.

Additional protocol deviations not leading to elimination from ATP analyses included 24 participants for whom the unblinded pharmacist did not change the syringe or apply a masking label, 4 participants for whom an unblinded nurse did not change the syringe, 1 participant for whom an unblinded nurse did not apply a masking label, and 1 participant who was vaccinated with diluent alone. For all instances, site staff were retrained on procedures to follow, and the participant who did not receive active substance was revaccinated on the same study day.

> Reviewer Comment: The distribution of protocol deviations was similar across study groups. The observed protocol deviations do not raise concerns about study conduct.

6.3.11 Immunogenicity Analyses

The study design did not include clinical efficacy endpoints. Serological endpoints were used to assess the response to vaccination. The analysis of immunogenicity was based on the ATP Cohort for Immunogenicity. A second analysis based on the TVC was not performed because less than 5% of participants were eliminated from each group in the ATP Cohort. Analyses post-dose 1 and 2 were based on participants who were seronegative for that assay prior to the first vaccination.

6.3.11.1 Analyses of Primary Endpoint(s)

To control the risk of erroneous conclusions, a hierarchical procedure was used for the multiple primary objectives with the possibility to conclude on objectives 6-10, associated with medium potency PRIORIX, even if one or more of objectives 1-5, associated with minimum potency PRIORIX, were not met. The primary analysis of immunogenicity was performed on the ATP Cohort for Immunogenicity post-dose 1. All primary immunogenicity objectives were evaluated by an enzyme-linked immunosorbent assay (ELISA), unless otherwise specified.

Primary Objectives 1-5: Minimum Potency PRIORIX

Primary Objective 1: Non-Inferiority in Terms of Seroresponse Rates
The success criterion to demonstrate non-inferiority was met if the LL of the two-sided 97.5% CI for the difference in SRR (minimum potency PRIORIX minus M-M-R II) was ≥-5% for antibodies to measles, mumps, and rubella viruses tested with ELISA. Primary objective 1 was ***not met*** since the LL for anti-measles antibodies was -7.65%. See Table 35.

Table 35. Proportion of Participants With Seroresponse and Difference Across Groups at 42 Days Post-Vaccination, ATP Cohort for Immunogenicity Post-Dose 1, Study MMR-161

Antibody	Minimum Potency PRIORIX N=1,161 to 1,361 SRR	M-M-R II N=1,155 to 1,378 SRR	PRIORIX - M-M-R II SRR Difference (97.5% CI)
% anti-measles ≥200 mIU/mL	90.8%	96.3%	-5.48 (-7.65, -3.43)
% anti-mumps (ELISA) ≥10 EU/mL	97.4%	97.8%	-0.42 (-1.91, 1.04)
% anti-mumps (b) (4) ≥4 ED_{50}	71.2%	80.6%	-9.41 (-13.20, -5.62)
% anti-rubella ≥10 IU/mL	96.8%	98.5%	-1.71 (-3.11, -0.42)

Source: Adapted from STN 125748/0, MMR-161 Clinical Study Report Amendment 2, Table 27, Table 31, Table 32, Table 33, Table 34
Abbreviations: ATP=According to Protocol cohort; CI=confidence interval; ED_{50}=endpoint dilution 50%; ELISA=enzyme-linked immunosorbent assay; EU=ELISA unit; IU-international unit; N=number of participants in ATP Cohort for Immunogenicity; (b) (4) test; SRR=Seroresponse Rate: percentage of initially seronegative participants with concentration above seroresponse threshold for each assay; Assays: Anti-Measles, (b) (4) ELISA; Anti-Mumps, (b) (4) ELISA and (b) (4); Anti-Rubella, (b) (4) ELISA
(For each assay - seroresponse thresholds are 200 mIU/mL, 10 EU/mL, 10 IU/mL, and 4 ED_{50} for anti-measles, anti-mumps (b) (4), anti-rubella, and anti-mumps (b) (4) antibodies respectively)
Note: Two different lots of M-M-R II were used during this study. Data from both lots were pooled for this summary.
Lower 97.5% CI numbers indicate lower limits of 97.5% CI for which statistical testing was performed for the respective test.
Success criteria: the lower limit of the 2-sided 97.5% CI for the difference in SRR (Minimum Potency PRIORIX minus M-M-R II) must be ≥-5% for anti-measles, anti-mumps, and anti-rubella antibodies.

Reviewer Comment: The purpose of primary objectives 1-5 was to assess the non-inferiority of minimum potency PRIORIX compared to licensed M-M-R II and to determine if the SRR to each antigenic component in minimum potency PRIORIX met the pre-defined success criteria. Since objective 1 did not demonstrate non-inferiority of the measles component of minimum potency PRIORIX, objectives 2-5 were not assessed.

Primary Objectives 6-10: Medium Potency PRIORIX

Primary Objective 6: Non-Inferiority in Terms of Seroresponse Rates

The success criterion to demonstrate non-inferiority was met if the LL of the two-sided 97.5% CI for the difference in SRR (medium potency PRIORIX minus M-M-R II) was ≥-5% for antibodies to measles, mumps, and rubella viruses tested with ELISA. Primary objective 6 was ***met***. See Table 36.

Table 36. Proportion of Participants With Seroresponse and Difference Across Groups at 42 Days Post-Vaccination, ATP Cohort for Immunogenicity Post-Dose 1, Study MMR-161

Antibody	Medium Potency PRIORIX N=1,131 to 1,366 SRR	M-M-R II N=1,155 to 1,378 SRR	PRIORIX - M-M-R II SRR Difference (97.5% CI)
% anti-measles ≥200 mIU/mL	94.2%	96.3%	-2.08 (-3.96, -0.27)
% anti-mumps (ELISA) ≥10 EU/mL	97.3%	97.8%	-0.58 (-2.11, 0.91)
% anti-mumps (b) (4) ≥4 ED_{50}	73.4%	80.6%	-7.22 (-10.94, -3.49)
% anti-rubella ≥10 IU/mL	97.3%	98.5%	-1.18 (-2.50, 0.05)

Source: Adapted from STN 125748/0, MMR-161 Clinical Study Report Amendment 2, Table 29, Table 31, Table 32, Table 33, Table 34
Abbreviations: ATP=According to protocol; CI=confidence interval; ED_{50}=endpoint dilution 50%; ELISA=enzyme-linked immunosorbent assay; EU=ELISA unit; IU=international unit; N=number of participants in ATP Cohort for Immunogenicity; (b) (4) test; SRR=Seroresponse Rate: percentage of initially seronegative participants with concentration above seroresponse threshold for each assay; Assays: Anti-Measles, (b) (4) ELISA; Anti-Mumps, (b) (4) ELISA and (b) (4); Anti-Rubella, (b) (4) ELISA
(For each assay - seroresponse thresholds are 200 mIU/mL, 10 EU/mL, 10 IU/mL, and 4 ED_{50} for anti-measles, anti-mumps (b) (4), anti-rubella, and anti-mumps (b) (4) antibodies respectively)
Note: Two different lots of M-M-R II were used during this study. Data from both lots were pooled for this summary.
Lower 97.5% CI numbers indicate lower limits of 97.5% CI for which statistical testing was performed for the respective test.
Success criteria: the lower limit of the 2-sided 97.5% CI interval for the difference in SRR (Medium Potency PRIORIX minus M-M-R II) must be ≥−5% for anti-measles, anti-mumps, and anti-rubella antibodies. The lower limit of the two-sided 97.5% CI on the group difference in SRR (Medium Potency PRIORIX minus M-M-R II) must be ≥-10% for antibodies to mumps virus by (b) (4).

Primary Objective 7: Non-Inferiority in Terms of GMCs

The success criterion to demonstrate non-inferiority was met if the LL of the two-sided 97.5% CI for the adjusted GMC (adjusted by country) ratio (medium potency PRIORIX over M-M-R II) was ≥0.67 for antibodies to measles, mumps, and rubella viruses tested with ELISA. Primary objective 7 was ***met***. See Table 37.

Table 37. GMC and GMC Ratio at 42 Days Post-Vaccination, ATP Cohort for Immunogenicity Post-Dose 1, Study MMR-161

Antibody	Medium Potency PRIORIX N=1,131 to 1,366 GMC	M-M-R II N=1,155 to 1,378 GMC	PRIORIX/M-M-R II GMC Ratio (97.5% CI)
Anti-Measles (mIU/mL)	2,553.8	2,798.9	0.91 (0.83, 1.01)
Anti-Mumps (ELISA) (EU/mL)	59.4	70.6	0.84 (0.78, 0.91)
Anti-Rubella (IU/mL)	55.6	63.0	0.88 (0.83, 0.95)

Source: Adapted from STN 125748/0, MMR-161 Clinical Study Report Amendment 2, Table 30
Abbreviations: ANOVA=analysis of variance; ATP=According to Protocol Cohort; CI=confidence interval; ED_{50}=endpoint dilution 50%; ELISA=enzyme-linked immunosorbent assay; EU=ELISA unit; GMC=geometric mean antibody concentration adjusted for country (ANOVA model: adjustment for country – pooled variance with more than 2 groups); IU=international unit; N=number of participants in ATP Cohort for Immunogenicity; (b) (4) test
Assays: Anti-Measles, (b) (4) ELISA; Anti-Mumps, (b) (4) ELISA and (b) (4); Anti-Rubella, (b) (4) ELISA
Note: Two different lots of M-M-R II were used during this study. Data from both lots were pooled for this summary.
Lower 97.5% CI numbers indicate lower limits of 97.5% CI for which statistical testing was performed for the respective test.
Success criteria: the lower limit of the 2-sided 97.5% CI interval for the adjusted GMC ratio (Medium Potency PRIORIX over M-M-R II) must be ≥0.67 for anti-measles, anti-mumps, and anti-rubella antibodies.

Primary Objective 8: Immune Response in Terms of Seroresponse Rates

The success criterion was met if the LL of the two-sided 97.5% CI for the SRR of medium potency PRIORIX was ≥90% for each of the vaccine virus antigens. Primary objective 8 was ***met***. See Table 38.

Table 38. Seroresponse Rate and GMC at 42 Days, Post-Vaccination Dose 1, ATP Cohort for Immunogenicity, Study MMR-161

Antibody	Minimum Potency PRIORIX N=1,161 to1,361	Medium Potency PRIORIX N=1,131 to 1,366	M-M-R II N=1,155 to 1,378
Anti-Measles	--	--	--
% ≥200 mIU/mL, (97.5% CI)	90.8% (88.9, 92.5)	94.2% (92.6, 95.5)	96.3% (95.0, 97.3)
GMC (97.5% CI)	2209 (2041.3, 2392.4)	2540.9 (2368.8, 2725.5)	2787.7 (2619.5, 2966.7)
Anti-Mumps	--	--	--
% ≥10 EU/mL, (97.5% CI)	97.4% (96.2, 98.3)	97.3% (96.0, 98.2)	97.8% (96.7, 98.7)
GMC (97.5% CI)	58.7 (55.5, 62.1)	60.2 (56.8, 63.7)	71.6 (67.7, 75.8)
Anti-Rubella	--	--	--
% ≥10 IU/mL, (97.5% CI)	96.8% (95.5, 97.7)	97.3% (96.1, 98.2)	98.5% (97.6, 99.1
GMC (97.5% CI)	57.0 (54.1, 60.0)	56.9 (54.2, 59.8)	64.4 (61.4, 67.5)

Source: Adapted from STN 125748/0, MMR-161 Clinical Study Report, Table 31, Table 32, Table 34
Abbreviations: ATP=According to protocol; CI=confidence interval; ED_{50}=endpoint dilution 50%; ELISA=enzyme-linked immunosorbent assay; EU=ELISA unit; GMC=geometric mean concentration; IU=international unit; N=number of participants with available results; n=number of participants with concentration ≥ specified value
Assays: Anti-Measles, (b) (4) ELISA; Anti-Mumps, (b) (4) ELISA and (b) (4); Anti-Rubella, (b) (4) ELISA
Note: Two different lots of M-M-R II were used during this study. Data from both lots were pooled for this summary.

Primary Objectives 9 and 10: Non-Inferiority in Terms of Seroresponse Rate and GMT for Mumps by (b) (4)

The success criterion to demonstrate non-inferiority in terms of SRR was met if the LL of the two-sided 97.5% CI for the difference in SRR (medium potency PRIORIX minus M-M-R II) was ≥-10% for antibodies to mumps virus (by (b) (4)). Primary objective 9 was ***not met*** (see Table 35).

> Reviewer Comment: The mumps (b) (4) allows for measurement of the neutralization antibodies and was performed in this study "to identify suboptimal responders." Objective 9 (SRR) was not met by a marginal difference. The success criterion was for the lower bound to be ≥-10%, and the results show the lower bound was -10.94.
>
> Although the LL success criterion was not met for SRR by (b) (4), the SRR response rate by (b) (4) was measured in Phase 2 MMR-157 after administration of PRIORIX lot with a mumps potency lower than the medium potency lot used in MMR-161 ($10^{4.1}$ $CCID_{50}$ in lot 2 group in MMR-157 and $\leq 10^{4.3}$ $CCID_{50}$ in medium potency lot in MMR-161). In study MMR-157, the results demonstrate that at Day 42, the PRIORIX lot 2 group in MMR-157 (N=89) had a comparable proportion of participants with (b) (4) antibody responses above the seroresponse threshold as compared to those in the M-M-R II comparator group (N=102)(see Section 6.6.11.1). An exploratory analysis was also performed for the immunogenicity results at year 1 and year 2 post-vaccination, showing the seroresponses between the PRIORIX lot 2 group and the M-M-R II group were comparable. Taken together, these (b) (4) data from these two studies do not indicate a reason for concern about the neutralizing antibody responses to the mumps component of PRIORIX.

6.3.11.2 Analyses of Secondary Endpoints

The descriptive secondary objectives, to assess the immune response of minimum potency PRIORIX followed by targeted release potency PRIORIX, medium potency PRIORIX followed by release potency PRIORIX, and M-M-R II vaccine in terms of SRRs and GMCs for antibodies to measles, mumps, and rubella viruses at Day 84 (6 weeks post Dose 2), were evaluated in a sub-cohort of children enrolled in the US. The results are shown in Table 39.

Table 39. Seroresponse Rate and GMC at 42 Days Post-Vaccination Dose 2 (Day 84), ATP Cohort for Immunogenicity, Study MMR-161

Antibody	Minimum Potency PRIORIX N=216 to 245	Medium Potency PRIORIX N=199 to 259	M-M-R II N=212 to 257
Anti-Measles	--	--	--
≥200 mIU/mL, % (95% CI)	99.6% (97.7, 100)	98.4% (96.1,99.6)	98.4% (96.1, 99.6)
GMC (95% CI)	4803.5 (4290.4, 5378.0)	4557.7 (4061.5, 5114.4)	4453.9 (3951.9, 5019.8)
Anti-Mumps	--	--	--
≥10 EU/mL, % (95% CI)	99.1% (96.7, 99.9)	100% (98.2, 100)	98.6% (95.9, 99.7)
GMC (95% CI)	88.9 (80.4, 98.3)	94.1 (85.3, 103.8)	86.4 (77.4, 96.5)

Antibody	Minimum Potency PRIORIX N=216 to 245	Medium Potency PRIORIX N=199 to 259	M-M-R II N=212 to 257
Anti-Rubella	--	--	--
≥10 IU/mL, % (95% CI)	99.6% (97.7, 100)	99.6% (97.9, 100)	99.6% (97.8, 100)
GMC (95% CI)	112.7 (104.1, 122.0)	110.7 (102.9, 119.1)	110.9 (101.8, 120.8)

Source: Adapted from STN 125748/0, MMR-161 Clinical Study Report Amendment 2, Table 35, Table 36, Table 37
Abbreviations: ATP=According to protocol; CI=confidence interval; ELISA=enzyme-linked immunosorbent assay; EU=ELISA unit; GMC =geometric mean concentration; IU=international unit; N=number of participants with available results; n=number of participants with concentration ≥ specified value
Assays: Anti-Measles, (b) (4) ELISA; Anti-Mumps, (b) (4) ELISA and (b) (4); Anti-Rubella, (b) (4) ELISA
Note: Two different lots of M-M-R II were used during this study. Data from both lots were pooled for this summary

Reviewer Comment: The percentages of participants with anti-measles, anti-mumps, and anti-rubella antibody concentrations above the respective seroresponse thresholds were comparable across the 3 groups, as were the GMCs.

6.3.11.3 Subpopulation Analyses

As in the previous studies, subpopulation analyses were descriptive and conducted for participants by country, gender, and race if there were at least 50 participants per treatment group. Sub-group analyses by age in this 12 through 15-month-old cohort were not provided.

Immunogenicity analyses of the first dose were conducted by country for all countries represented in the study (Spain, United States, Thailand, Czech Republic, Finland, and Malaysia) and were generally similar to the findings among all participants in the primary analysis. The immunogenicity evaluation of the second dose only included US participants, and these results were also similar to those in the overall study population. Sub-group analyses by race following the first dose included White and SE Asian races, while only White race was analyzed post-dose 2. In the gender and race sub-group analyses, group differences in immune responses were in general similar to the findings in the primary analysis.

6.3.11.4 Dropouts and/or Discontinuations

Approximately 95% of enrolled participants completed the study. Missing or non-evaluable immunogenicity measurements were not replaced, therefore immunogenicity analyses excluded participants with missing or non-evaluable measurements: see Section 6.3.10.1.2.

6.3.11.5 Exploratory and Post Hoc Analyses

Not applicable.

6.3.12 Safety Analyses

6.3.12.1 Methods

Safety data surveillance is described in Section 6.3.7 and shown in Table 40. Participant compliance with returning symptoms sheets for collection of local and systemic solicited AEs following administered vaccines was >97.0% in all groups.

6.3.12.2 Overview of Adverse Events

Safety Overview
Table 40 provides an overview of the rates of adverse events in each group following both dose 1 and dose 2 during the study period for minimum potency PRIORIX and medium potency PRIORIX, respectively. Since the minimum potency PRIORIX lot was below the defined end-of-shelf-life potency

for use in the US, the minimum potency PRIORIX group safety data was not included in the post-dose 1 safety analyses.

Table 40. Proportion of Participants Reporting at Least One Adverse Event Following MMR Vaccination, TVC, Study MMR-161

AE Type: Monitoring Period[a], % (n/N)	Medium Potency PRIORIX Post-Dose 1	M-M-R II Post-Dose 1	Medium Potency PRIORIX Post-Dose 2	M-M-R II Post-Dose 2
Immediate AE: 30 minutes	0.1% (1/1497)	0	0	0
Solicited local at injection site[b]: 0-3 days after each dose	28.6% (419/1464)	31.2% (462/1482)	21.1% (304/1440)	22.7% (330/1456)
Solicited systemic[c]: 0-14 days after dose 1	64.7% (948/1466)	62.4% (927/1486)	NA	NA
Fever (temperature ≥38.0 ºC): 0-42 days after each dose	42.0% (616/1466)	41.5% (616/1486)	32.5% (469/1443)	34.3% (499/1455)
Rash: 0-42 days after each dose	22.0% (322/1466)	22.4% (333/1486)	10.4% (150/1443)	9.7% (141/1455)
Varicella-like rash	3.6% (53/1466)	3.0% (45/1486)	0	0.1% (1/1455)
Measles/rubella-like rash	4.2% (61/1466)	4.6% (68/1486)	1.0% (14/1443)	1.0% (14/1455)
Other rash	15.7% (230/1466)	16.6% (247/1486)	9.6% (138/1443)	8.7% (127/1455)
Parotid/salivary gland swelling: 0-42 days after each dose	0.1% (2/1466)	0.2% (3/1486)	0.1% (2/1443)	0
Meningism[d]: 0-42 days after each dose	0.3% (4/1466)	0.2% (3/1486)	0.4% (6/1443)	0.3% (4/1455)
Unsolicited: 0-42 days	53.0% (794/1497)	50.9% (777/1526)	48.0% (703/1464)	46.5% (690/1483)
AEs leading to study w/d: Entire study period	NA	NA	0.1% (2/1497)	0.2% (3/1526)
SAEs: Entire study period	NA	NA	6.8% (102/1497)	6.0% (92/1526)
AEs of specific interest[e]: Entire study period	NA	NA	25.7% (384/1497)	24.2% (370/1526)
Deaths: Entire study period	NA	NA	0.06% (1/1497)	0.06% (1/1526)

Source: Adapted from STN 125748/0, MMR-161 Clinical Study Report Amendment 2, Section 8.2.1, Table 22, Tables 44-46, Table 8.2, and MMR (RIT) Analysis #16 Tables 7-12
Abbreviations: AE=adverse event; N=number of participants in cohort; n=number of participants who experienced the event; SAE=serious adverse event; TVC=Total Vaccinated Cohort was used as the analyses set for safety; w/d=withdrawal
Temperature 38.0 C =100.4 F
Note: For unsolicited events, the N is the number of participants in the TVC
Note: For solicited local events, the N is the number of participants from the TVC with documented local events
Note: For solicited systemic events, the N is the number of participants from the TVC with documented systemic events
a. Monitoring Period: time interval that the relevant type of AE was monitored for post-vaccination
b. Solicited local includes pain, redness, and swelling at injection site
c. Solicited systemic includes any systemic symptom including drowsiness, loss of appetite, or irritability
d. Signs or symptoms indicative of meningism (i.e., neck stiffness with or without light intolerance [photophobia] and headache; or convulsion/seizure) and includes febrile convulsions
e. AEs of specific interest includes new onset chronic disease (NOCD, e.g., autoimmune disorders, asthma, type I diabetes, vasculitis, celiac disease, conditions associated with sub-acute or chronic thrombocytopenia and allergies) and AEs prompting emergency room (ER) visit

Overall, for any solicited or unsolicited symptom, the rates were similar across groups. Post-dose 1, the rate was 85.1% in the minimum potency PRIORIX group, 86.3% in the medium potency PRIORIX group, and 84.8% in the M-M-R II group. Rates were also similar across groups post-dose 2, and lower than following the first dose, at 63.9%, 67.4%, and 67.0%, respectively. There were 4 AEs (2 in the min potency PRIORIX group and 1 each in the med potency PRIORIX and M-M-R II groups), 1 nonfatal SAE (M-M-R II group), and 3 fatal events (1 each in the min potency PRIORIX group, med potency PRIORIX group, and M-M-R II group) that led to premature discontinuation from the study. None of these events were considered by the investigator to be related to the study vaccination.

Subpopulation Analyses

In general, findings were similar to those reported in the safety analyses for the overall group. No clinically meaningful differences between vaccine groups in incidence of solicited local or systemic symptoms were observed in females and males or in any race group.

Solicited Adverse Reactions

The following two tables include the percentages of participants in each group who reported any solicited adverse reactions, by grade, post-dose 1 and post-dose 2, for the minimum potency PRIORIX group and medium potency PRIORIX group, respectively.

Table 41. Proportion of Participants With Solicited Reactions Post-Vaccination, TVC, Study MMR-161

Solicited Adverse Reaction	Medium Potency PRIORIX Post-Dose 1 N=1464-1466	M-M-R II Post-Dose 1 N=1482-1486	Medium Potency PRIORIX Post-Dose 2 N=1440-1443	M-M-R II Post-Dose 2 N=1455-1456
Local (injection site), % (n participants/N)	--	--	--	--
Pain[a]	--	--	--	--
Any	17.9% (262/1464)	20.3% 301/1482)	12.7% (183/1440)	13.5% (196/1456)
Grade 0	0.0% (0/1464)	0.1% (1/1482)	0.0% (0/1440)	0.1% (1/1456)
Grade 1	15.1% (221/1464)	16.5% (244/1482)	10.8% (156/1440)	11.6% (169/1456)
Grade 2	2.7% (40/1464)	3.4% (51/1482)	1.6% (23/1440)	1.6% (23/1456)
Grade 3	0.1% (1/1464)	0.3% (5/1482)	0.3% (4/1440)	0.2% (3/1456)
Erythema	--	--	--	--
Any	17.5% (256/1464)	19.3% (286/1482)	13.6% 196/1440)	14.9% (217/1456)
Grade 0 (none)	0.0% (0/1464)	0.1% (1/1482)	0.0% (0/1440)	0.1% (1/1456)
Grade 1 (>0 to ≤5 mm)	15.2% (223/1464)	15.5% (230/1482)	11.7% (168/1440)	11.8% (172/1456)
Grade 2 (>5 to ≤20 mm)	2% (30/1464)	2.6% (38/1482)	1.7% (25/1440)	2.1% (31/1456)
Grade 3 (>20 mm)	0.2% (3/1464)	1.1% (17/1482)	0.2% (3/1440)	0.9% (13/1456)
Swelling	--	--	--	--
Any	6.6% (97/1464)	8.2% (122/1482)	6.3% (91/1440)	6.6% (96/1456)
Grade 0 (none)	0.0% (0/1464)	0.1% (1/1482)	0.0% (0/1440)	0.1% (1/1456)
Grade 1 (>0 to ≤5 mm)	5.5% (80/1464)	6.5% (96/1482)	5.6% (81/1440)	4.9% (71/1456)
Grade 2 (>5 to ≤20 mm)	1% (14/1464)	1.3% (19/1482)	0.7% (10/1440)	1.2% (17/1456)
Grade 3 (>20 mm)	0.2% (3/1464)	0.4% (6/1482)	0.0% (0/1440)	0.5% (7/1456)

Solicited Adverse Reaction	Medium Potency PRIORIX Post-Dose 1 N=1464-1466	M-M-R II Post-Dose 1 N=1482-1486	Medium Potency PRIORIX Post-Dose 2 N=1440-1443	M-M-R II Post-Dose 2 N=1455-1456
Systemic	--	--	--	--
Measles/Rubella-like rash	--	--	--	--
Any	4.2% (61/1466)	4.6% (68/1486)	1% (14/1443)	1% (14/1455)
Grade 0	0.1% (1/1466)	0.0% (0/1486)	--	--
Grade 1 (1-50 lesions)	1.4% (20/1466)	2.1% (31/1486)	0.6% (8/1443)	0.2% (3/1455)
Grade 2 (51-150 lesions)	1.6% (24/1466)	1.3% (20/1486)	0.1% (2/1443)	0.5% (7/1455)
Grade 3 (>150 lesions)	1.1% (16/1466)	1.1% (17/1486)	0.3% (4/1443)	0.3% (4/1455)
varicella-like rash	--	--	--	--
Any	3.6% (53/1466)	3% (45/1486)	0.0% (0/1443)	0.1% (1/1455)
Grade 1 (1-50 lesions)	3.4% (50/1466)	2.8% (41/1486)	0.0% (0/1443)	0.1% (1/1455)
Grade 2 (51-150 lesions)	0.1% (1/1466)	0.2% (3/1486)	--	--
Grade 3 (>150 lesions)	0.1% (2/1466)	0.1% (1/1486)	--	--
Other rash[b]	--	--	--	--
Any	15.7% (230/1466)	16.6% (247/1486)	9.6% (138/1443)	8.7% (127/1455)
Grade 1	12.9% (189/1466)	14% (208/1486)	8.3% (120/1443)	6.7% (97/1455)
Grade 2	2.6% (38/1466)	2.2% (33/1486)	0.9% (13/1443)	1.6% (23/1455)
Grade 3	0.2% (3/1466)	0.4% (6/1486)	0.3% (5/1443)	0.5% (7/1455)
Parotid/salivary gland swelling[c]	--	--	--	--
Any	0.1% (2/1466)	0.2% (3/1486)	0.1% (2/1443)	0.0% (0/1455)
Grade 1	0.1% (2/1466)	0.2% (3/1486)	0.1% (2/1443)	0.0% (0/1455)
Irritability/fussiness[b]	--	--	--	--
Any	54% (792/1466)	53% (788/1486)	NA	NA
Grade 1	35.4% (519/1466)	33.6% (499/1486)	NA	NA
Grade 2	15.1% (221/1466)	16% (238/1486)	NA	NA
Grade 3	3.5% (52/1466)	3.4% (51/1486)	NA	NA
Drowsiness[b]	--	--	--	--
Any	38.5% (565/1466)	39.2% (582/1486)	NA	NA
Grade 1	28.7% (421/1466)	28.3% (421/1486)	NA	NA
Grade 2	8.1% (119/1466)	9.2% (137/1486)	NA	NA
Grade 3	1.7% (25/1466)	1.6% (24/1486)	NA	NA
Loss of appetite[b]	--	--	--	--
Any	40.2% 589/1466)	39.8% (591/1486)	NA	NA
Grade 1	28.9% (423/1466)	28.1% (417/1486)	NA	NA
Grade 2	10% (146/1466)	9.6% (142/1486)	NA	NA
Grade 3	1.4% (20/1466)	2.1% (31/1486)	NA	NA

Solicited Adverse Reaction	Medium Potency PRIORIX Post-Dose 1 N=1464-1466	M-M-R II Post-Dose 1 N=1482-1486	Medium Potency PRIORIX Post-Dose 2 N=1440-1443	M-M-R II Post-Dose 2 N=1455-1456
Fever (temperature ≥38ºC)	--	--	--	--
Any fever	42.1% (617/1466)	41.6% (618/1486)	32.6% (471/1443)	34.3% (499/1455)
Fever with unknown temperature[d]	0.1% (1/1466)	0.1% (2/1486)	0.1% (2/1443)	0.0% (0/1455)
38.00-38.50°C	18.3% 269/1466)	19.3% (287/1486)	14.1% (203/1443)	15.5% (226/1455)
38.51-39.00°C	11.9% (175/1466)	12% (179/1486)	8.9% (128/1443)	10.1% (147/1455)
39.01-39.50°C	7.4% (109/1466)	6% (89/1486)	6.1% (88/1443)	5.5% (80/1455)
39.51-40.00°C	3.5% (51/1466)	3% (44/1486)	2.6% (38/1443)	2.3% (33/1455)
≥40.01°C	0.8% (12/1466)	1.1% (17/1486)	0.8% (12/1443)	0.9% (13/1455)
Signs of meningism/seizure (including febrile convulsions)[b]	--	--	--	--
Any	0.3% (4/1466)	0.2% (3/1486)	0.4% (6/1443)	0.3% (4/1455)
Grade 1	0.1% (1/1466)	0.0% (0/1486)	0.1% (2/1443)	0.1% (1/1455)
Grade 2	0.0% (0/1466)	0.1% (2/1486)	0.1% (2/1443)	0.1% (2/1455)
Grade 3	0.2% (3/1466)	0.1% (1/1486)	0.1% (2/1443)	0.1% (1/1455)

Source: STN 125748/0, MMR-161, MMR (RIT) Analysis #16 Table 18
Abbreviations: AE=adverse event; LAR=legally acceptable representative; N=number of participants in cohort; n=number of participants who experienced the event; TVC=Total Vaccinated Cohort was used as the analyses set for safety
Note: Data in the PRIORIX Minimum Potency Post-Dose 1 column (first column) were not included in the overall presentation of safety in the Summary of Clinical Safety of the Biologics Licensing Application (BLA) submission.
Note: For solicited local events, the N is the number of participants from the TVC with documented local events
Note: For solicited systemic events, the N is the number of participants from the TVC with documented systemic events
a. Pain: Grade 0: none, Grade 1: Minor reaction to touch (digital pressure), Grade 2: Cried/protested on touch (digital pressure), Grade 3: Cried when limb was moved/spontaneously painful
b. Other rash/Irritability/Fussiness/Drowsiness/Loss of appetite/Meningism: Grade 1: caused minimal discomfort/easily tolerated and did not interfere with everyday activities, Grade 2: sufficiently discomforting to interfere with normal everyday activities, Grade 3: prevented normal, everyday activities (in a young child, such an AE would, for example, prevent attendance at school/day care and would cause the parent(s)/LAR(s) to seek medical advice)
c. Parotid/salivary gland swelling: Grade 1: Swelling without difficulty moving the jaw, Grade 2: Swelling with difficulty moving the jaw, Grade 3: Swelling with accompanying general symptoms
d. Reported fever without associated daily temperature measurement resulting in fever with unknown temperature.

The incidences of solicited local symptoms were comparable across the groups. The most frequently reported local reactions following dose 1 in the medium potency PRIORIX and M-M-R II groups were injection site pain (17.9% and 20.3%) and erythema (17.5% and 19.3%), respectively, as shown in the table above. Injection site pain (12.7% and 13.5%) and erythema (13.6% and 14.9%), respectively, were also the most frequently reported local reactions following dose 2 (see table above), although at a lower rate than post-dose 1. The median duration for solicited local reactions ranged from 1-2 days across groups and was the same following dose 1 and dose 2 in the medium potency PRIORIX group. Overall, the percentage of participants reporting grade 3 solicited local symptoms was low, ranging from 0.0% to 0.3% in the medium potency PRIORIX group and 0.2% to 1.1% in the M-M-R II group.

In general, the incidences of solicited systemic symptoms within 15 days post-dose 1 were similar across the groups with irritability/fussiness being the most commonly reported (medium potency PRIORIX 54.0% and M-M-R II 53.0%). The median duration for irritability/fussiness was 4 days across groups. The percentage of participants reporting grade 3 irritability/fussiness was 3.5% and 3.4%, respectively.

Fever (temperature ≥38ºC/100.4ºF) from Day 5 to Day 12 post-vaccination occurred in 26.9% of participants in the medium potency PRIORIX group and 28.2% in the M-M-R II group following dose 1, and in 15.4% and 14.8%, respectively, following dose 2. The median duration for fever was 2 days across groups and was the same following dose 1 and dose 2. Incidences of grade 3 fever (temperature >39.5ºC) considered related to the study vaccination were 1.0% and 1.1%, respectively, post-dose 1, and 0.1% and 0.0%, respectively, post-dose 2.

Solicited Systemic Symptoms Specific to MMR Vaccination
Solicited systemic symptoms specific to MMR vaccination (signs of meningism [including febrile convulsions], parotid/salivary gland swelling, and rash) were collected from Day 0 to Day 42 post-vaccination. 4 participants (0.3%) in the medium potency PRIORIX group and 3 (0.2%) in the M-M-R II group reported febrile convulsions post-dose 1. The median duration of these events was 2 days and 1 day, respectively. Two of these events were considered related to vaccination, both in the M-M-R II group. Following dose 2, febrile convulsions were reported in 6 participants (0.4%) in the medium potency PRIORIX group and 4 (0.3%) in the M-M-R II group. The median duration of these events was 1.5 days in both M-M-R II groups. None of these events was considered related to vaccination.

There were five reports of salivary/parotid gland swelling following the first dose, all were grade 1, and four were considered related to vaccination (medium potency PRIORIX 1 and M-M-R II 3). The median duration of these events was 9.5 days in the medium potency PRIORIX group (ranging from 3 to 16 days) and 4 days in the M-M-R II group (ranging from 3 to 45 days). Following dose 2, there were 2 reports of salivary/parotid gland swelling in the medium potency PRIORIX group. Both were grade 1 and both were considered related to vaccination. One event lasted 5 days and the other lasted 73 days.

The percentages of participants with any incidence of rash post-dose 1 were similar across the groups with 22.0% in medium potency PRIORIX and 22.4% in M-M-R II. Post-dose 2, 10.4% and 9.7% reported rash, respectively. See Table 40 for rates and severity of measles/rubella-like rash post-dose 1 and post-dose 2. The median duration for rashes was comparable across groups following both dose 1 and dose 2, ranging from 5 to 6 days. Post-dose 1, 7.0% and 6.4% of participants in the medium potency PRIORIX group and M-M-R II group, respectively, were considered to have a rash related to the study vaccination, while post-dose 2, 1.7% and 2.0%, respectively, were considered to have a rash related to study vaccination. A severe (grade 3) rash was reported in 1.4% and 1.6% of each group, respectively, following dose 1, and in 0.6% and 0.8% of each group, respectively, following dose 2.

Reviewer Comment:

1. Overall, the rates of solicited reactions were comparable across groups. The most frequently reported solicited local reactions were injection site pain and erythema, and the most frequently reported solicited systemic symptom was irritability/fussiness. The proportion of PRIORIX recipients who reported Grade 3 or higher severity events was <0.5% for each local solicited reaction and <4% for any solicited reaction.
2. See Reviewer Comment 2 in Section 6.1.12.2 under the subsection *Solicited Systemic Symptoms Specific to MMR Vaccination* for an explanation of which events qualified as febrile convulsions. For study MMR-161, the proportion with each event were provided as follows:
    - Meningism excluding febrile convulsions:
        - Post-dose 1:
            - Medium potency PRIORIX: 0.07 (1/1,466 participants)
            - M-M-R II: 0% (0/1,486 participants)
        - Post-dose 2:
            - Medium potency PRIORIX: 0.07% (1/1,443 participants)
            - M-M-R II: 0% (0/1,455 participants)
    - Febrile convulsions:
        - Post-dose 1:
            - Medium potency PRIORIX: 0.20% (3/1,466 participants)
            - M-M-R II: 0.20% (3/1,486 participants)
        - Post-dose 2:
            - Medium potency PRIORIX: 0.35% (5/1,443 participants)
            - M-M-R II: 0.27% (4/1,455 participants)

Ongoing Adverse Reactions and Adverse Reactions with Onset After Reporting Period
The proportion of participants with solicited adverse reactions with onset during the solicited reporting period that were ongoing after the last day of the reporting period for each dose were as follows:

- Solicited local reactions (reporting period Day 0 to Day 3):
    - Post-dose 1:
        - Medium potency PRIORIX: 0.75-1.84%
        - M-M-R II: 0.20-0.81%
    - Post-dose 2:
        - Medium potency PRIORIX: 0.14-0.97%
        - M-M-R II: 0.07-0.27%
- Solicited systemic symptoms (reporting period Day 0 to Day 14):
    - Post-dose 1:
        - Medium potency PRIORIX: 0.95-2.32%
        - M-M-R II: 1.28-2.76%
- Solicited systemic symptoms specific to MMR vaccination (reporting period Day 0 to Day 42):
    - Post-dose 1:
        - Medium potency PRIORIX: 0-1.98%
        - M-M-R II: 0-1.68%
    - Post-dose 2:
        - Medium potency PRIORIX: 0-1.11%
        - M-M-R II: 0-1.37%
- Fever (reporting period Day 0 to Day 42):
    - Post-dose 1:
        - Medium potency PRIORIX: 1.71%
        - M-M-R II: 1.28%

    - Post-dose 2:
        - Medium potency PRIORIX: 1.04%
        - M-M-R II: 0.89%

The majority of ongoing events post-dose 1 and dose 2 were grade 1. There were no ongoing events of signs of meningism (including febrile convulsions) after either dose in any group. Solicited systemic reactions of drowsiness, loss of appetite, and irritability/fussiness were solicited systemic events post-dose 1 only.

The proportion of participants with solicited adverse reactions with onset after the reporting period for each dose were as follows:

- Solicited local reactions (reporting period Day 0 to Day 3):
    - Post-dose 1:
        - Medium potency PRIORIX: 0-0.13%
        - M-M-R II: 0
    - Post-dose 2:
        - Medium potency PRIORIX: 0-0.07% (n=1)
        - M-M-R II: 0
- Solicited systemic symptoms (reporting period Day 0 to Day 14):
    - Post-dose 1:
        - Medium potency PRIORIX: 0.13-0.60%
        - M-M-R II: 0-0.59%
- Solicited systemic symptoms specific to MMR vaccination (reporting period Day 0 to Day 42):
    - Post-dose 1:
        - Medium potency PRIORIX: 0-0.27%
        - M-M-R II: 0-0.26%
    - Post-dose 2:
        - Medium potency PRIORIX: 0-1.5%
        - M-M-R II: 0-2.16%
- Fever (reporting period Day 0 to Day 42):
    - Post-dose 1:
        - Medium potency PRIORIX: 0.80%
        - M-M-R II: 0.66%
    - Post-dose 2:
        - Medium potency PRIORIX: 7.45%
        - M-M-R II: 7.01%

For local solicited reactions with onset after the reporting period (Day 1 to 3), there were no events of pain after dose 1 or 2 in any vaccine group. Solicited systemic reactions of drowsiness, loss of appetite, and irritability/fussiness were collected only after dose 1. Irritability/fussiness was the most common systemic event with onset after the reporting period (Day 0 to Day 14) reported in 0.60% of participants in the medium potency PRIORIX group and 0.59% in the M-M-R II group. Rash was the most common solicited symptom specific to MMR vaccination with onset after the reporting period (Day 0 to Day 42) following both dose 1 and dose 2. There were no events of parotid/salivary gland swelling after either dose in any group. Fever was the most common symptom with onset after the reporting period (Day 0 to Day 42) after either dose. The majority of solicited events with onset after the reporting period post-dose 1 and dose 2 were of mild severity with the exception of signs of meningism (including febrile convulsions) for which most were of moderate severity.

See Reviewer Comment in Section 6.1.12.2 under the subsection *Ongoing Adverse Reactions and Adverse Reactions with Onset After Reporting Period* for an explanation of how duration was calculated.

Immediate AEs: within 30 minutes
Post-dose 1, there were 2 immediate AEs reported by one participant in the medium potency PRIORIX group. By MedDRA PT, both events were injection site reactions (erythema and swelling). There were no immediate AEs in the M-M-R II group. There were no immediate AEs post-dose 2.

Unsolicited AEs (Non-Serious): 0-42 days
The rates of unsolicited, non-serious AEs were similar across groups. At least one unsolicited AE was reported in the medium potency PRIORIX and M-M-R II groups, respectively, as follows:

- Post-dose 1: 53.0% and 50.9%
- Post-dose 2: 48.0% and 46.5%

Post-dose 1 and 2, unsolicited AEs were most frequently classified in MedDRA SOC *Infections and infestations*, followed by SOC *Gastrointestinal disorders*. The most commonly reported AE by MedDRA PT in the medium potency PRIORIX and M-M-R II groups, respectively, following each dose was URI, as follows:

- Post-dose 1: 14.6% and 15.0%
- Post-dose 2: 13.0% and 13.1%

At least one Grade 3 unsolicited symptom was reported in the medium potency PRIORIX and M-M-R II groups, respectively, as follows:

- Post-dose 1: 3.5% and 4.0%
- Post-dose 2: 5.2% and 3.8%

Causal relationship to vaccination was attributed as follows (medium potency PRIORIX and M-M-R II groups, respectively), with no unsolicited AE considered by the investigator to be causally related occurring with a frequency >0.6%:

- Post-dose 1: 2.9% and 1.8%
- Post-dose 2: 1.6% and 1.4%

Adverse Events of Specific Interest
New Onset Chronic Disease
At least one NOCD was reported in 2.6% of participants in the medium potency PRIORIX group and 2.2% of the M-M-R II group. The most frequent NOCD reported was atopic dermatitis in 24 participants (0.7% and 0.9% in the respective groups). None of the reported NOCDs were considered to be related to the study vaccination.

AEs prompting Emergency Room Visit
Overall, 24.1% of participants in the medium potency PRIORIX group and 22.7% in the M-M-R II group experienced an AE that required an ER visit. The most frequent AEs that required an ER visit were URI reported in 206 participants (7.0% and 6.6% in the 2 groups, respectively); gastroenteritis in 91 participants (3.0% in each group); acute otitis media in 97 participants (3.1% and 3.3%, respectively); and bronchitis in 99 participants (3.5% and 3.1%, respectively).

Medically Attended AEs
At least one symptom that required medical attention during the study period was reported in 76.0% of participants in the medium potency PRIORIX group and 73.7% of the M-M-R II group. The most

commonly reported symptoms were URI (28.9% and 27.8% in the 2 groups, respectively); otitis media (13.0% and 14.0%, respectively); and gastroenteritis (12.8% and 11.3%, respectively).

> Reviewer Comment: The reported rates and types of unsolicited adverse events are comparable across groups and represent common medical conditions in the general population for the evaluated age cohort (children 12 through 15 months of age).

6.3.12.3 Deaths

Three fatal events were reported during the study period. None were considered by the investigator to be related to the study vaccination.

- A 19-month-old Asian male in the minimum potency PRIORIX group died due to drowning 171 days post-dose 2.
- A 12-month-old White female had pyelonephritis reported as starting 5 days prior to study vaccination, along with a febrile convulsion, obstipation, otitis media, suspected autosomal recessive polycystic kidney disease, and urinary tract infection. The child was treated with standard of care medical therapy that included antibiotics. Her death occurred 14 days after vaccination with the first dose of medium potency PRIORIX, Varivax, and Havrix vaccines. Post-mortem histologic specimens did not show any signs consistent with measles, mumps, rubella, or varicella infection. The immediate cause of death was ruled by the coroner to be acute pyelonephritis due to cystic renal dysplasia. According to the neuropathologist's findings, an epileptic attack was the likely cause of death.
- A 21-month-old White male in the M-M-R II group was hospitalized due to drowning and multiple injuries 153 days post-dose 2. He died 6 days later. The reported cause of death was polytrauma and drowning.

> Reviewer Comment: The enrollment of the child with pyelonephritis was determined to be a protocol violation of the exclusion criterion since she had an acute disease at the time of enrollment (i.e., the ongoing pyelonephritis). In addition, her history of a febrile convulsion and acute otitis media 5 days prior to vaccination was not known at the time of enrollment. The clinical reviewer agrees with the study investigator assessment that there was no reasonable possibility that these three fatal events were related to study vaccination.

6.3.12.4 Nonfatal Serious Adverse Events

A total of 464 SAEs were reported in 285 participants during the entire study post-vaccination period as follows:
Minimum potency PRIORIX: 143 SAEs in 91 participants (6.1%)
Medium potency PRIORIX: 174 SAEs in 102 participants (6.8%)
M-M-R II: 147 SAEs in 92 participants (6.0%)

The most frequently occurring SAEs were as follows:

- gastroenteritis in 45 participants (1.1% [16 participants] in the minimum potency PRIORIX group, 1.3% [19 participants] in the medium potency PRIORIX group, and 0.7% [10 participants] in the M-M-R II group)
- pneumonia in 31 participants (0.5% [7], 0.9% [14], and 0.7% [10], respectively)
- febrile convulsion in 28 participants (0.5% [7], 0.9% [13], and 0.5% [8], respectively)
- bronchitis in 22 participants (0.3% [4], 0.7% [10], and 0.5% [8], respectively)

Within 42 days of the dose 1 vaccination, 21 participants (1.4%) in the medium potency PRIORIX group and 23 participants (1.51%) in the M-M-R II group had at least 1 SAE. The majority of these events were of the SOC *Infections and infestations,* and the 3 most frequently reported PTs were gastroenteritis, pneumonia, and pyrexia. Two of the post-dose 1 SAEs were considered to have a reasonable possibility of being related to study vaccination by the investigator:

- A 12-month-old White male had onset of pyrexia (maximum temperature 39.5ºC) 5 days following dose 1 of medium potency PRIORIX, Havrix, and Varivax, and lasting six days. The participant was hospitalized and treated with antibiotics. The event was considered resolved 6 days later.
- A 15-month-old White female developed a toxic skin eruption (toxoallergic exanthema) 14 days following dose 1 of M-M-R II, Havrix, and Varivax. The participant was hospitalized and treated with anti-histamines and prednisone, and the event was considered resolved five days later with no sequelae.

Within 42 days of the dose 2 vaccination, 44 participants (1.51%) in the PRIORIX group (pooled minimum and medium potency) and 26 participants (1.75%) in the M-M-R II group had at least 1 SAE. The majority of these events were of the SOC *Infections and infestations,* and the 3 most frequently reported PTs were gastroenteritis, febrile convulsion, and dehydration. None of the SAEs reported post-dose 2 were considered related to either vaccine by the investigator.

> Reviewer Comment: As previously noted, the minimum potency PRIORIX group was not included in the post-dose 1 safety analysis. Overall, the proportion of participants reporting SAEs within 42 days of study vaccination was low (less than 2%) and was similar in the PRIORIX group compared to the M-M-R II group. The clinical reviewer agrees with the study investigator assessment that due to the temporal relationship of the SAEs described above, the events had a reasonable possibility of being related to study vaccination.

6.3.12.5 Dropouts and/or Discontinuations

The most common reasons for study discontinuation were consent withdrawal and lost to follow-up with complete vaccination course, as shown in Table 42. Overall, the rates of discontinuation were similar across groups.

There were 4 AEs and 4 SAEs that led to premature discontinuation from the study. All were reported as not related to study vaccination by the investigator. Three of the SAEs were fatal (see Section 6.3.12.3). The non-fatal SAE was a serious event of Henoch-Schönlein purpura in a 12-month-old White male that occurred on day 21 post-dose 1 of M-M-R II and continued for 110 days. Two of the AEs leading to premature discontinuation occurred in the minimum potency PRIORIX group (mild URI and moderate diarrhea with mild gastroenteritis), one AE of vomiting occurred in the medium potency PRIORIX group, and one AE of simple febrile seizure occurred in a participant in the M-M-R II group.

Table 42. Discontinuations, All Randomized Participants, Study MMR-161

Population	Minimum Potency PRIORIX N=1,497 % (n/N)	Medium Potency PRIORIX N=1,501 % (n/N)	M-M-R II N=1,530 % (n/N)
Enrolled[a]	100% (1497/1497)	100% (1501/1501)	100% (1530/1530)
Vaccinated	99.7% (1493/1497)	99.7% (1497/1501)	99.7% (1526/1530)
Completed study	95.6% (1427/1493)	95.3% (1427/1497)	94.6% (1443/1526)
Withdrawal due to	--	--	--

Population	Minimum Potency PRIORIX N=1,497 % (n/N)	Medium Potency PRIORIX N=1,501 % (n/N)	M-M-R II N=1,530 % (n/N)
Consent withdrawal	1.8% (27/1493)	2.0% (30/1497)	1.6% (25/1526)
Lost to follow up	--	--	--
Migrated/moved from study area	0.4% (6/1493)	0.3% (5/1497)	0.5% (7/1526)
Lost to follow-up (participants with incomplete vaccination course)	0.8% (13/1493)	0.4% (6/1497)	1.0% (16/1526)
Lost to follow-up (participants with complete vaccination course)	1.1% (17/1493)	1.8% (27/1497)	2.0% (30/1526)
Protocol deviation	0	0	0.1% (1/1526)
Non-serious AE	0.1% (2/1493)	0.1% (1/1497)	0.1% (1/1526)
Serious AE (including death)[b]	0.1% (1/1493)	0.1% (1/1497)	0.1% (2/1526)
Death	0.1% (1/1493)	0.1% (1/1497)	0.1% (1/1526)
Other[c]	0	0	0.1% (1/1526)

Source: Adapted from STN 125748/0, MMR-161 Clinical Study Report Amendment 2, Table 22, Table 8.14
Abbreviations: AE=adverse event; N=number of participants in population; n=number of participants who met given criteria
Note: Two different lots of M-M-R II were used during this study. Data from both lots were pooled for this summary.
a. A total of 4,538 participants were enrolled in the study. Ten participants, including 3 participants who did not have valid informed consent forms, were enrolled but not randomized to a treatment group.
b. SAEs included fatal AE of drowning in Minimum Potency PRIORIX group, fatal AE of pyelonephritis in Medium Potency PRIORIX group, and moderate Henoch-Schoenlein purpura and fatal AE of polytrauma/drowning in the M-M-R II group.
c. Other reason included: Participant was withdrawn due to sponsor decision.

6.3.13 Study Summary and Conclusions

Study MMR-161 was designed to establish the EOSL potency of PRIORIX and to evaluate the immunogenicity of PRIORIX compared to M-M-R II, as 2 doses given 6 weeks apart in children 12 through 15 months of age. Participants received a first dose of either minimum potency PRIORIX, medium potency PRIORIX, or M-M-R II, and a second dose of PRIORIX (at a targeted release potency) or a second dose of M-M-R II. In the US, concomitantly administered vaccines were VV, HAV, and PCV13 vaccines. At sites outside the US, concomitantly administered vaccines were VV and HAV. The primary objectives to demonstrate non-inferiority of minimum potency PRIORIX to M-M-R II were not met. The primary objectives to demonstrate non-inferiority of medium potency PRIORIX to M-M-R II as measured by ELISA were met; however, the immune response against mumps virus as measured by (b) (4) did not meet the non-inferiority criteria. The secondary immunogenicity objectives demonstrated comparable immune responses following the second dose across all three groups (minimum potency PRIORIX, medium potency PRIORIX, or M-M-R II) in a sub-cohort of children enrolled in the US. The safety profile of PRIORIX was comparable to the safety profile of M-M-R II when concomitantly administered with VV and HAV (to all children) and PCV13 (only to children in the US). This study supports the safety and immunogenicity of PRIORIX when administered at an EOSL potency.

6.4 Trial #4 (Study MMR-162)

NCT02184572
"A Phase 3a, randomized, observer-blind, controlled, multinational study to evaluate the safety and immunogenicity of GSK's MMR vaccine (PRIORIX) compared to Merck's MMR vaccine (M-M-R II), as a first dose, both concomitantly administered with Varivax, Havrix (all participants), and Prevnar 13 (US subset) in healthy children 12 through 15 months of age."

Study Overview: This study was designed to descriptively evaluate the immunogenicity and safety of PRIORIX compared to M-M-R II when both are used as a first dose in healthy children 12 through 15

months of age and to define the maximum release limits of PRIORIX when given with recommended concomitant vaccinations. In the US, concomitant vaccines were Varivax (VV), Havrix (HAV), and Prevnar 13 (PCV13) and for sites outside the US, concomitant vaccines were VV and HAV.

6.4.1 Objectives

Primary Objectives

The co-primary objectives were assessed in a hierarchical manner according to the order presented below. A co-primary objective can only be met if the statistical criterion for that objective is met as well as the statistical criteria for all previous co-primary objectives.

1. To demonstrate the safety profile (fever >39.0°C [>102.2°F]) of PRIORIX compared to M-M-R II (pooled lots) when concomitantly administered with VV and HAV (to all participants) and PCV13 (participants enrolled in the US).
   Endpoint: Occurrence of fever >39.0°C (>102.2°F) from Day 5 through Day 12
   Statistical Criterion for Success: The upper limit of the two-sided 95% CI for the group difference (PRIORIX minus M-M-R II) in incidence of fever >39.0°C within 5-12 days post-vaccination is equal to or below 5%.

2. To demonstrate the safety profile (fever ≥38.0°C [≥100.4°F]) of PRIORIX compared to M-M-R II (pooled lots) when concomitantly administered with VV and HAV (to all children) and PCV13 (children enrolled in the US).
   Endpoint: Occurrence of fever ≥38.0°C (≥100.4°F) from Day 5 through Day 12
   Statistical Criterion for Success: The upper limit of the two-sided 95% CI for the group difference (PRIORIX minus M-M-R II) in incidence of fever ≥38.0°C within 5-12 days post-vaccination is equal to or below 10%.

   Reviewer Comments: The peak prevalence of fever following vaccination with measles-containing vaccines coincides with the timing of peak measles viral replication, approximately 5 to 12 days after vaccination. The study objectives assessed the rates of fever between groups during this time period, in addition to through 42 days post-vaccination.

Secondary Objectives

1. To assess the immunogenicity of PRIORIX and M-M-R II in terms of seroresponse and GMCs for anti-measles, anti-mumps, and anti-rubella virus antibodies at Day 42.
   Endpoints (Descriptive):
   - Seroresponse to measles virus by ELISA: see Section 6.1.1.
   - Seroresponse to mumps virus by ELISA/(b) (4)
     - A post-vaccination anti-mumps virus antibody concentration ≥10 EU/mL (ELISA, (b) (4) and ≥4 ED_{50} (b) (4) among children who were seronegative (antibody concentration <5 EU/mL) before vaccination.
   - Seroresponse to rubella virus: see Section 6.1.1.

2. To assess safety and reactogenicity of PRIORIX and M-M-R II when concomitantly administered with VV and HAV (to all children) and PCV13 (only to children enrolled in the US).
   Endpoints (Descriptive): see Section 6.1.1 for a description of the safety endpoints.

3. To assess any measles-like illness (MLI) occurring within 5 to 12 days after vaccination
   Endpoint:
   - Occurrence of any MLIs from Day 5 through Day 12 post-vaccination.

- MLI was defined as the occurrence of the following signs/symptoms in the absence of another confirmed diagnosis (e.g., laboratory confirmed scarlet fever):
  - temperature ≥38°C/100.4°F
  - maculopapular rash (includes measles/rubella-like rash)
  - at least one of the following signs/symptoms: cough, coryza (runny nose), conjunctivitis or diarrhea with fever or rash occurring during the period of Day 5 through Day 12 post-vaccination.

6.4.2 Design Overview

Study MMR-162 was an observer-blind, randomized, controlled, multicenter, multi-country study, with 3 parallel groups. Overall, participants were randomized 2:1 to receive PRIORIX or M-M-R II. Within each group, participants were randomized 4:1:1 to receive either a single dose of PRIORIX or one of the two M-M-R II lots (sub-groups identified as M-M-R II Lot 1 and M-M-R II Lot 2, respectively).

All study participants had three study visits (Days 0, 42, and 180) that had the following study activities:

- Day 0-Visit 1 at 12 through 15months of age: Blood samplings; single vaccination with either PRIORIX or one of two M-M-R II active control lots, along with the concomitantly administered vaccines Varivax and Havrix (to all children) and Prevnar 13 (only to children enrolled in the US).
- Day 42-Visit 2 at 13 through 17 months of age: Blood sampling and diary card transcriptions
- Day180-Visit 3 at 18 through 22 months of age: Safety follow-up.

The study duration was approximately six months starting at Visit 1 (Day 0) and ending with Visit 3 (Day 180).

6.4.3 Population

Eligibility Criteria
Individuals were eligible for inclusion if they met all the following criteria: healthy male or female between 12 through 15 months of age, whose parent(s)/legally acceptable representative(s) could and would comply with protocol requirements and for whom a written informed consent was provided. For US participants only, participants had to have received all routine vaccinations as per ACIP recommendations prior to study entry.

Exclusion criteria were described previously (Section 6.1.3).

6.4.4 Study Treatments or Agents Mandated by the Protocol

PRIORIX: investigational measles, mumps, and rubella vaccine

- Dose/RoA/Presentation: see Section 6.1.4.
- Formulation: Measles virus (Schwarz strain) $10^{4.5}$ $CCID_{50}$ Schwarz measles strain; Mumps virus (RIT 4385 strain) $10^{5.7}$ $CCID_{50}$; Rubella virus (Wistar RA 27/3 strain)$10^{4.1}$ $CCID_{50}$.
- Lot: DMJRA029A

  Reviewer Comment: The dose of PRIORIX was at a potency used to define maximum targeted release limits. This included the following for each antigenic component:
  Measles virus: $10^{4.5}$ $CCID_{50}$
  Mumps virus: $10^{5.7}$ $CCID_{50}$
  Rubella virus: $10^{4.4}$ $CCID_{50}$

M-M-R II: comparator measles, mumps, and rubella vaccine

- Dose/RoA/Presentation/Formulation: see Section 6.1.4.
- Lots:
  - Lot 1: J004429, J008405, K001106, K024606, J015488, J014872
  - Lot 2: J008276, K001548, K005790, K024605, J015222, J016232

Varivax
- Dose/RoA/Presentation/Formulation: see Section 6.1.4.
- Lots: K005537, K006583, K026626, J012252, K001388

Havrix
- Dose/RoA/Presentation/Formulation: see Section 6.1.4.
- Lots: AHAVB761A, AHAVB767A, AHAVB788B, AHAVB799C, AHAVB738B

Prevnar 13
- Dose/RoA/Presentation/Formulation: see Section 6.1.4.
- Lot: H86640

6.4.5 Directions for Use

See Section 6.1.5.

6.4.6 Sites and Centers

There were 104 sites in the United States (including Puerto Rico), Estonia, Finland, and Taiwan with a Total Vaccinated Cohort of 1,736 participants. There were 88 US sites with a Total Vaccinated Cohort of 734.

6.4.7 Surveillance/Monitoring

Surveillance
See Section 6.1.7. For this study, CROs were involved with study sites in Taiwan and Finland.

Safety Monitoring:
See Section 6.1.7.

Fever and Measles-like illness (MLI)
Fever post-vaccination (Day 0 to Day 42) were cause for the parent(s)/LAR(s) to contact the study site. Fever between Day 5-12 would prompt the investigator to inquire about rash. If rash was present, the investigator would inquire for additional signs/symptoms (above) to assess for MLI. A visit would be arranged as soon as possible (ideally within 48 hours) for evaluation. Investigators would follow up within 48 hours after the initial call and would document any MLI in the eCRF.

Independent Data Monitoring Committee (IDMC)
Given the higher viral potencies of the PRIORIX lot being tested in this study compared to a typically targeted released lot, an IDMC monitored and followed-up on the (unblinded) safety and tolerability of the candidate MMR vaccine during the entire study period. The IDMC was composed of clinical experts and an independent statistician, external to GSK. The role of the IDMC was to review the data and make recommendations regarding study continuation.

Immunogenicity monitoring
See Table 4 and Table 32 for a summary of serological assays for Study MMR-162.

6.4.8 Endpoints and Criteria for Study Success

See Section 6.4.1.

6.4.9 Statistical Considerations and Statistical Analysis Plan

Sample size
The target to enroll approximately 1,734 children assumed a 5% non-evaluable rate which would result in an evaluable population of 1,647 children, with an estimated 1,098 children in the PRIORIX group and 275 children in each M-M-R II lot group.

Methods
To control the type I error below 2.5%, a hierarchical procedure was used for the primary objectives. The objective on fever ≥38.0°C (≥100.4°F) could only be reached if the associated criterion and the first primary objective on fever >39.0°C (>102.2°F) were met. The global power for fever objectives were 90.37%. For the secondary objectives, descriptive analyses were performed for each treatment group at each blood sampling time point for which a serological result was available and only in children who were seronegative for that assay prior to first vaccination.

The analysis was performed in two steps which were combined in the final clinical report:

- A final analysis of the immunogenicity data, solicited symptoms, and MLI up to Day 42 was performed as soon as all immunogenicity data and reactogenicity data (i.e., solicited symptoms and MLI cases) up to Visit 2 were available and cleaned.
- A final analysis of unsolicited AEs from Day 0 to Day 42 following vaccination, and of SAEs and specific AEs covering the period from Day 0 to study end (including the 6-months safety follow-up) was performed at the end of the study.

Following unblinding for the analysis up to Day 42, accessibility to group attribution was limited to the statisticians until all study procedures pertaining to the active Phase and the 6-months safety follow-up were completed for all children. An additional reanalysis was conducted due to the correction of the database for one participant.

Descriptive immunogenicity analyses and safety analyses were repeated by county, gender and race (geographic ancestry).

Only participants with a completed solicited AE section of the eCRF were considered for analysis of solicited symptoms. Missing or non-evaluable measurements were not replaced. In the primary analysis of solicited symptoms, missing daily recordings were replaced by the maximum value recorded for the participant. In the primary analysis of solicited symptoms, missing daily recordings were replaced by the maximum value recorded for that participant. For participants reporting fever as present in the absence of temperature measurement, missing daily recordings were replaced by grade 1. For the analyses of unsolicited AEs, SAEs, and concomitant medication, all vaccinated participants were considered. Those not reporting an event were considered as participants without an event.

Temperature deviation
A local vaccine depot which stored vaccines for MMR-162 was decommissioned between December 2012 and June 2015, potentially leading to temperature deviations in the stored vaccines. Some study participants were immunized with PRIORIX or M-M-R II doses that may have been affected, so an impact assessment was performed. Since the percentage of participants administered with potentially affected PRIORIX doses was more than 5% of total participants, an additional sensitivity analysis

(recalculation of fever rate in both groups) was performed excluding those impacted. This was performed in line with the current ICH guidelines on statistical principles for clinical trials. The analysis concluded that the exclusion of participants due to potential temperature deviations did not impact the safety conclusions for the study.

Protocol Amendments
Original Protocol, dated August 25, 2014
Protocol Amendment 1 (April 30, 2015) included the following changes:

- The serological assays to detect measles, rubella, and varicella viruses were changed to be performed by (b) (4) (CRO), instead of GSK (Rixensart, Belgium) as GSK's laboratory (b) (4) became part of (b) (4). The only change in the laboratory was the name, while the assays and facilities remained the same.
- The anti-mumps ELISA was originally to be performed by (b) (4)) which had acquired (b) (4) vaccine assay development laboratory in (b) (4) had acquired the lab back from (b) (4) in (b) (4) , after which (b) (4) could no longer perform the anti-mumps ELISA on GSK samples. Because some samples were not transferred to (b) (4) in time for testing, they were tested using GSK's (b) (4) assay. A line listing of the 26 participants who had evaluable post-vaccination (b) (4) titers was provided by the Applicant.
- Enrollment target numbers per country could be adjusted based on feasibility as enrollment progressed with recruitment rate being monitored by a study-specific central randomization system.

Changes in the Conduct of the Study and Planned Analyses
There were no changes in the planned analyses
All analyses were performed as planned in the protocol.

6.4.10 Study Population and Disposition

A total of 1,742 participants were enrolled in the study. The first participant was enrolled in the study on August 25, 2014, and the last study visit was on December 22, 2015

6.4.10.1 Populations Enrolled/Analyzed

The *Total Vaccinated Cohort (TVC): see* Section 6.1.10.1.

According to Protocol (ATP) Cohort for Analysis of Safety: see Section 6.1.10.1.

According to Protocol (ATP) Cohort for Analysis of Immunogenicity: see Section 6.1.10.1.

Exclusion from the ATP Cohort for Immunogenicity Analyses occurred for the same reasons as described in Section 6.1.10.1. An exception to development of measles as a reason for elimination was development of a measles-like illness between Day 5 and Day 12.

If, for any vaccine group, the percentage of enrolled participants with serological results excluded from the ATP Cohort for Immunogenicity was higher than 5%, a second analysis based on the TVC was performed to complement the ATP analysis.

6.4.10.1.1 Demographics

Table 43. Demographic Characteristics, Total Vaccinated Cohort, Study MMR-162

Characteristic	PRIORIX N=1,164	M-M-R II N=572
Sex	--	--
Ratio male:female	613:551	302:270
% male:% female	52.7%:47.3%	52.8%:47.2%
Age, months	--	--
Mean (SD)	12.3 (0.7)	12.3 (0.7)
Median	12.0	12.0
Range	12, 16	12, 16
Ethnicity, n (%)	--	--
Hispanic/Latino	125 (10.7%)	65 (11.4%)
Not Hispanic/Latino	1039 (89.3%)	507 (88.6%)
Racial Origin (Geographic Ancestry), n (%)	--	--
Am. Indian/A.N.	29 (2.5%)	16 (2.8%)
All Asian	234 (20.1%)	119 (20.8%)
Central/South Asian	9 (0.8%)	4 (0.7%)
East Asian	131 (11.3%)	65 (11.4%)
Japanese	2 (0.2%)	0 (0)
South East Asian	28 (2.4%)	12 (2.1%)
African/A.A.	64 (5.5%)	38 (6.6%)
All White	811 (69.7%)	388 (67.8%)
Arabic/North African	3 (0.3%)	3 (0.5%)
Caucasian/European	808 (69.4%)	385 (67.3%)
N. Hawaiian/P.I.	1 (0.1%)	2 (0.3%)
Other	89 (7.6%)	47 (8.2%)
Country, n (%)	--	--
Estonia	160 (13.7%)	80 (14.0%)
Taiwan	123 (10.6%)	62 (10.8%)
Finland	147 (12.6%)	73 (12.8%)
United States	734 (63.1%)	357 (62.4%)

Source: Adapted from STN 125748/0, Study MMR-162, Clinical Study Report Amendment 2, Table 20
Abbreviations: A.A.=African American; Am. Indian/A.N=American Indian/Alaskan Native; N. Hawaiian/P.I.=Native Hawaiian/Pacific Islander; N=total number of participants for the TVC Safety Analysis Set (participants with at least 1 vaccination of either PRIORIX or M-M-R II); n=number of participants with indicated characteristic; Other=mixed race or not otherwise specified; SD=standard deviation; TVC=Total vaccinated cohort
Note: Two different lots of M-M-R II were used during this study. Data from both lots were pooled for this summary.

The median age of participants in the TVC was 12.3 months with a range of 12 to 16 months at the time of the first study vaccination. Overall, the majority of the participants were White/Caucasian (69.0%), and male (52.7%) which was observed within in each study group as well. In general, the demographic and baseline characteristics were similar across the study groups. The demographic characteristics observed for participants were comparable to those observed in the ATP Cohort for Immunogenicity.

> Reviewer Comment: One participant in PRIORIX group (0.1%) and 1 participant in M-M-R II group (0.2%) had a protocol deviation due to age. Deviations in age were not criteria for elimination (see Reviewer Comment in Section 6.1.10.1.2).

6.4.10.1.2 Participant Disposition

Table 44. Participant Disposition and Data Analyses Sets, All Randomized Participants, Study MMR-162

Population, n (%)	PRIORIX N=1,165	M-M-R II N=575
Enrolled	1165 (100%)	575 (100%)
TVC	1164 (99.9%)	572 (99.5%)
Completed study	1117 (95.9%)	542 (94.3%)
TVC-Safety	1164 (99.9%)	572 (99.5%)
TVC-Immunogenicity	1150 (98.7%)	569 (99.0%)
ATP-Safety	1142 (98.0%)	565 (98.3%)
ATP-Immunogenicity	1045 (89.7%)	523 (91.0%)
≥1 Important protocol deviation[a]	120 (10.3%)	52 (9.0%)
Maximum percentage of participants eliminated for ATP-Immunogenicity analyses[b]	2.16%	2.23%

Source: Adapted from STN 125748/0, Study MMR-162, Clinical Study Report Amendment 2, Table 17, Table 18; MMR (RIT) Analysis #16 Table 13
Abbreviations: ATP=According-to-protocol; N=number of participants in cohort;; n=number of participants fulfilling the item followed by (%); TVC=Total vaccinated cohort (included all vaccinated participants)
Note: Two different lots of M-M-R II were used during this study. Data from both lots were pooled for this summary.
a. Includes participants with important protocol violations that resulted in exclusion from the ATP-Imm. analysis population.
b. For each antigen and each confirmatory objective, the percentage of participants who had the necessary immunogenicity results to contribute to the TVC analysis but were eliminated for the ATP analysis was computed. This value represents the maximum over all confirmatory objectives and antigens.
TVC-Safety: included all vaccinated participants with at least one vaccine administration of either PRIORIX or M-M-R II documented.
TVC-Imm.: included all vaccinated participants for whom immunogenicity data were available.
ATP-Safety: Safety analyses using the ATP cohort included eligible participants who received at least one MMR study vaccine/comparator as per protocol; were not excluded from the ATP cohort; for whom the randomization code had not been broken; and the administration route of study vaccine(s) was known and correct.
ATP-Immunogenicity: Immunogenicity analyses using the ATP cohort included all eligible participants from the ATP cohort for safety with pre-vaccination and post-dose serology results available for at least one antigen of measles, mumps, or rubella; below the assay cut-off for at least one MMR vaccine antigen pre-vaccination; did not meet any elimination criteria up to the Visit 2 blood sample; and complied with the post-vaccination blood sample schedule.

A total of 1742 participants were enrolled in the study. Two participants were not assigned a group and of the remaining 1740 participants, 1736 received a study vaccination. Of those vaccinated 1,659 (95.6%) completed the study. The most common reasons for withdrawal were: lost to follow up, with complete vaccination course (42 participants) and consent withdrawal, due to an adverse event (23 participants).

A total of 1,707 participants (98.3%) were included in the ATP Cohort for Safety. The most common reasons for exclusion from this cohort included: violation of inclusion/exclusion criteria, including those specifying participant age, history of allergic reactions, or previous vaccination history (16 participants), administration of prohibited vaccines (8 participants) or study vaccines not being administered according to the protocol (4 participants). The randomization code was prematurely broken for a single participant in a US study site, as the participant experienced an unexpected serious adverse event of pneumonia and respiratory syncytial viral infection. A total of 1,568 participants (90.3%) were included in the ATP cohort for immunogenicity. The primary reason for exclusion from this cohort was due to serological results not available for antigens following vaccination (74 participants). An additional 53 participants were excluded due to the presence of detectable baseline antibody levels or initially unknown baseline antibody status. Other reasons for exclusion included non-compliance with blood sampling schedules (10 participants) and administration of prohibited medications (2 participants).

Protocol deviations from specifications for participant age and intervals between study visits were similar across study groups and did not lead to elimination from ATP analyses. Other protocol deviations that did

not lead to elimination from any analysis cohort included (# participants): Informed consent process (1), Study vaccine (3), Reporting of safety events (6), Study visits (7), Diary cards (19), Biological specimens (31), Study blind/unblind procedures (1), Assessment procedures (23), Other (missed assessment) (3).

6.4.11 Immunogenicity Analyses

The study design did not include clinical efficacy endpoints. Serologic immune measurements were used to assess the response to vaccination. The criteria were specific to children seronegative for the assay at pre-vaccination. Missing or non-evaluable immunogenicity measurements were not replaced.

The primary analysis of immunogenicity was performed on the ATP Cohort for Immunogenicity. A secondary analysis based on the TVC was not performed because less than 5% of participants were eliminated from each group in the ATP Cohort for Immunogenicity.

6.4.11.1 Analyses of Primary Endpoints

The study design did not include primary immunogenicity endpoints.

6.4.11.2 Analyses of Secondary Endpoints

The secondary immunogenicity endpoints descriptively evaluated the immune responses at 42 days post-vaccination to the measles, mumps and rubella virus in PRIORIX compared to M-M-R II based on the percentage of participants with antibody concentrations above seroresponse thresholds and GMCs.

Secondary objective 1 (Descriptive): Seroresponse and GMCs

Anti-Measles antibody response
The results (Table 45) show that the participants with antibodies to measles ≥200 mIU/mL were 99.0% and 96.5% of participants in the PRIORIX and M-M-R II groups, respectively. The anti-measles antibody GMCs were 2751.9 mIU/mL and 3133.3 mIU/mL in the PRIORIX and M-M-R II groups, respectively, and the 95% CIs for GMCs did overlap.

Anti-Mumps antibody response
The results (Table 45) show that the participants with antibodies to mumps ≥10 EU/mL were 99.4% and 97.9% of participants in the PRIORIX and M-M-R II groups, respectively. The anti-mumps antibody GMCs were 86.0 EU/mL and 82.6 EU/mL in the PRIORIX and M-M-R II groups, respectively, with overlapping 95% CIs. As less than 30 participants had evaluable (b) (4) titers (26 total), a descriptive statistical analysis was not performed.

Anti-Rubella antibody response
The results (Table 45) show that the participants with antibodies to rubella ≥10 IU/mL were 95.7% and 98.3% of participants in the PRIORIX and M-M-R II groups, respectively. The anti-rubella antibody GMCs were 45 IU/mL in the PRIORIX group and 66.8 IU/mL, in the M-M-R II groups, though 95% CIs did not overlap.

Table 45. Seroresponse Rate and GMC at 42 Days Post-Vaccination, ATP Cohort for Immunogenicity, Study MMR-162

Antibody	PRIORIX N=964 to 1043	M-M-R II N=483 to 521
Anti-Measles antibody	--	--
% ≥200 mIU/mL (95% CI)	99.0% (98.2, 99.5)	96.5% (94.6, 97.9)
GMC (95% CI)	2751.9 (2618.3, 2892.2)	3133.3 (2878.6, 3410.6)

Antibody	PRIORIX N=964 to 1043	M-M-R II N=483 to 521
Anti-Mumps antibody	--	--
% ≥10 EU/mL (95% CI)	99.4% (98.7, 99.8)	97.9% (96.2, 99.0)
GMC (95% CI)	86.0 (82.0, 90.3)	82.6 (76.5, 89.2)
Anti-Rubella antibody	--	--
% ≥10 IU/mL (95% CI)	95.7% (94.3, 96.8)	98.3% (96.7, 99.2)
GMC (95% CI)	45.0 (42.8, 47.2)	66.8 (62.3, 71.7)

Source: Adapted from STN 125748/0, Study MMR-162, Clinical Study Report Amendment 2, Table 34, Table 35, Table 36
Abbreviations: ATP=According to protocol; CI=confidence interval; ELISA=enzyme-linked immunosorbent assay; EU=ELISA unit; GMC=geometric mean concentrations (performed by taking the anti-log of the mean of the log concentration transformations); IU=international unit; N=number of participants in ATP; Seroresponse Rate (percentage of initially seronegative participants with concentration above seroresponse threshold for each assay; Assays: Anti-Measles, (b) (4) ELISA; Anti-Mumps, (b) (4) ELISA; Anti-Rubella, (b) (4) ELISA (For each assay - seroresponse thresholds are 200 mIU/mL, 10 EU/mL, and 10 IU/mL for anti-measles, anti-mumps, and anti-rubella antibodies respectively).
Note: Two different lots of M-M-R II were used during this study. Data from both lots were pooled for this summary.

Reviewer Comment: Although the descriptive immunogenicity results found in this study were overall similar between the PRIORIX and M-M-R II groups, the 95% CIs for the proportion of participants with antibody levels above the seroresponse threshold at Day 42 for measles and the Day 42 GMCs for rubella did not overlap. Despite this, the totality of evidence in this BLA, including data summarized in studies MMR-160 and MMR-161, demonstrate that the immune response generated by PRIORIX against measles and rubella viruses is non-inferior to that of M-M-R II.

6.4.11.3 Subpopulation Analyses

Subpopulation analyses were descriptive and done for participants by country, gender, and race (geographic ancestry). All countries represented in the study were included in the subpopulation analyses: United States (including Puerto Rico), Estonia, Finland, and Taiwan. Racial origin (geographic ancestry) was analyzed in two groups: White Caucasian/European heritage and East Asian heritage. PRIORIX was comparable to M-M-R II in terms of SRRs and GMCs for each antigenic component. Immune responses were overall similar to those reported in the secondary immunogenicity analyses for the overall group.

6.4.11.4 Dropouts and/or Discontinuations

Approximately 95% of participants completed the study. Missing or non-evaluable immunogenicity measurements were not replaced. Immunogenicity analyses therefore excluded participants with missing or non-evaluable measurements.

6.4.11.5 Exploratory and Post Hoc Analyses

Not applicable.

6.4.12 Safety Analyses

The analysis of safety was based on the Total Vaccinated Cohort.

6.4.12.1 Methods

Safety data surveillance is described in Sections 6.4.2 and 6.4.7 and shown in Table 47. Participant compliance with returning symptom sheets for collection of local and general solicited AEs following administered vaccines was greater than 96%.

6.4.12.2 Overview of Adverse Events

Co-Primary objectives: Rates of Fever

The comparability of observed rates of fever between groups was determined if the upper limit of the 95% CI for the difference [PRIORIX minus M-M-R II] in fever rates was <5% when fever was defined as >39.0°C (Primary Objective #1) and was <10% when fever was defined as ≥38.0°C (Primary Objective 2). The co-primary objectives of Fever >39.0°C and Fever ≥38.0°C were ***met*** as shown in Table 46.

Table 46. Percentage Difference in Participants Reporting Fever, Days 5 Through 12 Post-Vaccination, TVC, Study MMR-162

Axillary Temperature	PRIORIX N=1,126 n (%)	M-M-R II N=555 n (%)	PRIORIX-M-M-R II Difference Percentage (95% CI)
All	250 (22.2%)	123 (22.2%)	0.04% (-4.28, 4.17)
≥38.0°C	205 (18.2%)	95 (17.1%)	1.09% (-2.89, 4.85)
>39.0°C	47 (4.2%)	17 (3.1%)	1.11% (-0.93, 2.89)

Source: Adapted from STN 125748/0, Study MMR-162 Amendment 2, Table 22
Abbreviations: CI=confidence interval; N=number of participants in TVC; n=number of participants fulfilling the item followed by (%); TVC=Total Vaccinated Cohort was used as the analyses set for safety
Note: Two different lots of M-M-R II were used during this study. Data from both lots were pooled for this summary.

Safety Overview

Safety data were presented for the PRIORIX group and the M-M-R II groups (pooled lots). Table 47 provides an overview of the rates of adverse events in the PRIORIX lot compared to the pooled M-M-R II lots during the study period.

Table 47. Proportion of Participants Reporting at Least One Adverse Event Following MMR Vaccination, TVC, Study MMR-162

AE Type: Monitoring Period[a]	PRIORIX % (n/N)	M-M-R II % (n/N)
Immediate AE: 30 minutes	0.1% (1/1164)	0
Solicited local at injection site[b]: 0-3 days	40.2% (451/1123)	38.5% (213/553)
Solicited systemic[c]: 0-14 days	71.3% (803/1126)	70.1% (389/555)
Measles-like illness[d]: 5-12 days	1.5% (18/1164)	0.9% (5/572)
Temperature ≥38.0ºC: 0-42 days	31.1% (350/11260)	32.3% (179/555)
Rash: 0-42 days	24.4% (275/1126)	27.4% (152/555)
Parotid gland swelling: 0-42 days	0	0
Meningism[e]: 0-42 days	0.2% (2/1126)	0
Unsolicited AE: 0-42 days	51.4% (598/1164)	48.4% (277/572)
AEs leading to study withdrawal: Entire study period	0	0
SAEs: Entire study period	2.1% (24/1164)	1.6% (9/572)

AE Type: Monitoring Period[a]	PRIORIX % (n/N)	M-M-R II % (n/N)
AEs of specific interest[f]: Entire study period	16.4% (191/1164)	11.0% (63/572)
Deaths: Entire study period	0	0

Source: Adapted from STN 125748/0, Study MMR-162, Clinical Study Report Amendment 2, Section 7.2.1, Table 17, Table 18, Tables 26-29, Table 33, and MMR (RIT) Analysis #16 Table 13
TVC: Total Vaccinated Cohort was used as the analyses set for safety. n: #participants who experienced the event; C: degrees Celsius. AE: adverse event; AEs leading to w/d: adverse events leading to study withdrawal; SAEs: serious adverse events.
Temperature 38.0 C =100.4 F
Note: For unsolicited events, the N is the number of participants in the TVC (see Table B); For solicited local events, the N is the number of participants from the TVC with documented local events; For solicited systemic events, the N is the number of participants from the TVC with documented systemic events.
a. Monitoring Period: time interval that the relevant type of AE was monitored for post-vaccination
b. Solicited local includes pain, redness, and swelling at injection site
c. Solicited systemic includes any systemic symptom including drowsiness, loss of appetite, or irritability
d. Measles-like illness is defined as the occurrence of the following signs and symptoms in the absence of another confirmed diagnosis: maculopapular rash and fever (≥38 C), and at least one symptom of cough, coryza, conjunctivitis, or diarrhea, with fever or rash occurring between Day 5 and Day 12 inclusive.
e. Signs or symptoms indicative of meningism (i e., neck stiffness with or without light intolerance [photophobia] and headache; or convulsion/seizure) and included febrile convulsions
f. AEs of specific interest included new onset chronic disease (NOCD, e.g., autoimmune disorders, asthma, type I diabetes, vasculitis, celiac disease, conditions associated with sub-acute or chronic thrombocytopenia and allergies) and AEs prompting emergency room (ER) visit

The rates for any reported AE including local and systemic solicited reactions, unsolicited AEs and SAEs were comparable between groups. Overall, 51.4% and 48.8% of participants in the PRIORIX and M-M-R II groups, respectively, reported at least one solicited or unsolicited symptom during the 43-day post-vaccination period. There were no AEs that lead to study withdrawal and no deaths throughout the entire study period for either group.

Subpopulation Analyses

Descriptive summary safety data were reported by country, gender, and race (geographic ancestry). In general, findings were similar to those reported in the safety analyses for the overall group. Number and percentages of those compliant in returning symptom information and incidence and nature of symptoms reported (local and systemic reactions) were similar when evaluated as sub-groups. No clinically meaningful differences between vaccine groups in incidence of solicited local or general symptoms were observed in females and males or in any race group.

Solicited Adverse Reactions

Table 48 includes the percentages of PRIORIX and M-M-R II participants who reported any solicited adverse reactions, which are stratified by grade.

Table 48. Proportion of Participants With Solicited Reactions Post-Vaccination, TVC, Study MMR-162

Solicited Adverse Reaction	PRIORIX N=1123-1126	M-M-R II N=553-555
Local (injection site)	--	--
Pain[a], % (n/N)	--	--
Any	27.8% (312/1123)	23.7% (131/553)
Grade 1	21.5% (242/1123)	18.6% (103/553)
Grade 2	5.7% (64/1123)	4.7% (26/553)
Grade 3	0.5% (6/1123)	0.4% (2/553)
Erythema, % (n/N)	--	--
Any	23.2% (260/1123)	24.8% (137/553)
Grade 1 (>0 to ≤5 mm)	18.1% (203/1123)	19.9% (110/553)
Grade 2 (>5 to ≤20 mm)	4.4% (49/1123)	3.6% (20/553)
Grade 3 (>20 mm)	0.7% (8/1123)	1.3% (7/553)

Solicited Adverse Reaction	PRIORIX N=1123-1126	M-M-R II N=553-555
Swelling, % (n/N)	--	--
Any	8.5% (96/1123)	10.5% (58/553)
Grade 1 (>0 to ≤5 mm)	7.1% (80/1123)	8.5% (47/553)
Grade 2 (>5 to ≤20 mm)	1.2% (13/1123)	1.6% (9/553)
Grade 3 (>20 mm)	0.3% (3/1123)	0.4% (2/553)
Systemic Events	--	--
Measles/Rubella-like rash, % (n/N)	--	--
Any	5.8% (65/1126)	4.7% (26/555)
Grade 1 (1-50 lesions)	2.3% (26/1126)	1.4% (8/555)
Grade 2 (51-150 lesions)	1.9% (21/1126)	2.5% (14/555)
Grade 3 (>150 lesions)	1.6% (18/1126)	0.7% (4/555)
Varicella-like rash, % (n/N)	--	--
Any	3.6% (40/1126)	4% (22/555)
Grade 1 (1-50 lesions)	3.5% (39/1126)	3.6% (20/555)
Grade 2 (51-150 lesions)	0.1% (1/1126)	0.2% (1/555)
Grade 3 (>150 lesions)	0.0% (0/1126)	0.2% (1/555)
Other Rash[b], % (n/N)	--	--
Any	17% (191/1126)	21.1% (117/555)
Grade 1	14.8% (167/1126)	16.9% (94/555)
Grade 2	1.8% (20/1126)	3.6% (20/555)
Grade 3	0.4% (4/1126)	0.5% (3/555)
Parotid Gland Swelling, % (n/N)	0.0% (0/1126)	0.0% (0/555)
Irritability/Fussiness[b], % (n/N)	--	--
Any	64.1% (722/1126)	62.2% (345/555)
Grade 1	36% (405/1126)	36.9% (205/555)
Grade 2	24.4% (275/1126)	21.8% (121/555)
Grade 3	3.7% (42/1126)	3.4% (19/555)
Drowsiness[b], % (n/N)	--	--
Any	46.8% (527/1126)	43.2% (240/555)
Grade 1	32.1% (361/1126)	28.6% (159/555)
Grade 2	12% (135/1126)	11.9% (66/555)
Grade 3	2.8% (31/1126)	2.3% (13/555)
Loss of Appetite[b], % (n/N)	--	--
Any	43.8% (493/1126)	41.8% (232/555)
Grade 1	31.3% (352/1126)	29.7% (165/555)
Grade 2	10.7% (121/1126)	10.3% (57/555)
Grade 3	1.8% (20/1126)	1.8% (10/555)
Signs of Meningism/Seizure (including febrile convulsions)[b], % (n/N)	--	--
Any	0.2% (2/1126)	0.0% (0/555)
Grade 2	0.1% (1/1126)	0.0% (0/555)
Grade 3	0.1% (1/1126)	0.0% (0/555)

Solicited Adverse Reaction	PRIORIX N=1123-1126	M-M-R II N=553-555
Fever (temperature ≥38ºC), % (n/N)	--	--
Any grade	31.1% (350/1126)	32.4% (180/555)
Fever with unknown temperature[c]	0.0% (0/1126)	0.2% (1/555)
38-38.5°C	12% (135/1126)	15.1% (84/555)
38.51-39°C	9.6% (108/1126)	9.7% (54/555)
39.01-39.5°C	5.5% (62/1126)	4.7% (26/555)
39.51-40°C	3.2% (36/1126)	1.4% (8/555)
≥40.01°C	0.8% (9/1126)	1.3% (7/555)

Source: Adapted from STN 125748/0, Study MMR-162, Clinical Study Report Amendment 2, Table 12, Table 18, MMR (RIT) Analysis #16 Table 19
Abbreviations: AE=adverse event; LAR: legally acceptable representative; N=number of participants in cohort; n=number of participants who experienced event; TVC=Total Vaccinated Cohort was used as the analyses set for safety
Note: For solicited local events, the N is the number of participants from the TVC with documented local events; For solicited systemic events, the N is the number of participants from the TVC with documented systemic events
a. Pain: Grade 0: none, Grade 1: Minor reaction to touch (digital pressure), Grade 2: Cried/protested on touch (digital pressure), Grade 3: Cried when limb was moved/spontaneously painful.
b. Other rash/Irritability/Fussiness/Drowsiness/Loss of appetite/Meningism: Grade 1: caused minimal discomfort/easily tolerated and did not interfere with everyday activities, Grade 2: sufficiently discomforting to interfere with normal everyday activities, Grade 3: prevented normal, everyday activities (in a young child, such an AE would, for example, prevent attendance at school/day care and would cause the parent(s)/LAR(s) to seek medical advice)
c. Reported fever without associated daily temperature measurement resulting in fever with unknown temperature.

The incidences of solicited local symptoms were comparable across the groups. For both groups, injection site pain was the most frequently reported local reaction, (PRIORIX 27.8% vs. pooled M-M-R II 23.7%). The percentage of participants reporting severe (grade 3) injection site pain was low (PRIORIX 0.5% vs pooled M-M-R II 0.4%). The second most frequently reported local reaction was redness, which was reported in 23.2% and 24.8% of the PRIORIX and M-M-R II recipients, respectively.

Overall, the incidences of solicited general symptoms within 15 days post-vaccination were similar between the groups: irritability or fussiness was the most frequently reported (PRIORIX 64.1% vs. M-M-R II 62.2%, followed by drowsiness (46.8% vs. 43.2%, respectively) and loss of appetite (43.8% vs. 41.8%, respectively). The percentage of participants reporting severe (grade 3) irritability or fussiness was 3.7% in the PRIORIX group compared to 3.4% in the M-M-R II group.

Fever (temperature ≥38.0/100.4°C) from Day 5 to Day 12 post-vaccination occurred in 18.2% of participants in the PRIORIX group compared to 17.1% in the M-M-R II group. Incidence of grade 3 fever (temperature and >39.5°C) considered related to the study vaccination were 3.2% and 1.4% of participants in the PRIORIX and M-M-R II groups respectively. The peak prevalence of fever was observed approximately Day 5 to Day 12 after vaccination.

Measles-like Illness (MLI), as defined in Section 6.4.1, during the 5-to-12-day post-vaccination period, in the absence of another confirmed diagnosis was reported in 1.5% of participants in the PRIORIX group compared to 0.9% in the M-M-R II group, with overlapping confidence intervals.

Solicited Systemic Symptoms Specific to MMR Vaccination
Solicited general symptoms specific to MMR vaccination (signs of meningism [including febrile convulsions], parotid/salivary gland swelling, and rash) were collected from Day 0 to Day 42 post-vaccination. Two participants (0.2%) in the PRIORIX group reported signs of meningism compared to none in the M-M-R II group. One participant reported a simple febrile convulsion 7 days post-vaccination, and another reported a simple febrile convulsion 36 days post-vaccination. While the first case was considered by the investigator as related to the study vaccination, the second was accompanied by diarrhea and URI symptoms and was not considered by the investigator to be causally related to the

study vaccination. There were no reports of parotid gland swelling. The percentages of participants with any incidence of rash post-vaccination were similar among groups with 24.4% in the PRIORIX group and 27.4% in the M-M-R II group. Measles/rubella -like rash was seen in 5.8% of the PRIORIX group and 4.7% of the M-M-R II group. There were 6.2% and 6.7% of participants in the PRIORIX and M-M-R II groups, respectively, that were considered to have a rash related to the study vaccination. A severe (grade 3) rash was reported in 2% and 1.4% of the PRIORIX and M-M-R II groups, respectively.

Reviewer Comment:

1. Overall, the occurrence of solicited reactions were similar between the two groups (release potency PRIORIX vs. M-M-R II). The most frequently reported solicited local reactions were injection site pain and redness and the most frequently reported solicited general symptoms were irritability or fussiness followed by drowsiness. The proportion of PRIORIX recipients who reported a Grade 3 or higher severity symptom was <0.5% for each local solicited reaction and <4% for each general solicited reaction. The reviewer agrees with the assessment of the investigator regarding the relation to study vaccination with the above-described convulsions.
2. See Reviewer Comment 2 in Section 6.1.12.2 under the subsection Solicited Systemic Symptoms Specific to MMR Vaccination for an explanation of which events qualified as febrile convulsions. For study MMR-162, the proportion with each event were provided as follows:
    - Meningism excluding febrile convulsions:
        - PRIORIX: 0% (0/1126 participants)
        - M-M-R II: 0% (0/555 participants)
    - Febrile convulsions:
        - PRIORIX: 0.18% (2/1126 participants)
        - M-M-R II 0% (0/555 participants)

Ongoing Adverse Reactions and Adverse Reactions with Onset After Reporting Period
Overall, the proportion of participants with solicited reactions with onset during the solicited reporting period that were ongoing after the last day of the reporting period was similar across groups, low, and predominantly grade 1 to 2. The highest percentages for ongoing solicited ARs were for rash (PRIORIX 1.95% and M-M-R II 2.16%). irritability/fussiness (PRIORIX 1.78% and M-M-R II 1.80%)

In general, the proportion of participants with solicited symptoms with onset after the reporting period was low. The proportion of any local solicited reaction with onset after the reporting period (Day 0 to Day 3) ranged from 0-0.69% in the PRIORIX group and 0-0.17% in the M-M-R II group. The proportion of solicited systemic symptoms with onset after the reporting period (Day 0 to Day 14) and symptoms specific to MMR vaccination with onset after the reporting period (Day 0 to Day 42) ranged from 0-7.73% in the PRIORIX group and 0-6.12% in the M-M-R II group, with fever being reported most frequently.

See Section 6.1.12.2 under the subsection Ongoing Adverse Reactions and Adverse Reactions with Onset After Reporting Period for an explanation of how duration was calculated.

Immediate AEs: within 30 minutes
The incidence of adverse events within 30 minutes of vaccination were similar between groups (PRIORIX 0.1% vs. pooled M-M-R II 0%). In the PRIORIX group, there was 1 immediate adverse event reported by 1 participant. By MedDRA PT, this event was vaccination site erythema (redness).

Unsolicited AEs (Non-Serious): 0-42 days
The rates of unsolicited, non-serious AEs during the 43-day post-vaccination period were similar in both groups (PRIORIX 51.4% and M-M-R II 48.4%). Unsolicited AEs were most frequently classified in MedDRA SOC *Infections and infestations* (PRIORIX 43.9% vs. M-M-R II 46.9%), followed by SOC *Gastrointestinal disorders* (PRIORIX 20.2%, M-M-R II 17.3%). By MedDRA PT, the most common AE was URI (9.5% PRIORIX vs. 12.8% M-M-R II). Causal relationship to vaccination was attributed to 4.6% of unsolicited AEs in the PRIORIX group and 4.0% in the M-M-R II group. Diarrhea was the most commonly reported causally related AE in both groups (1.1% and 1%, respectively).

Adverse Events of Specific Interest
AEs considered AEs of specific interest are described in Section 6.1.12.2.

New Onset Chronic Disease (NOCD)
At least one NOCD was reported in 2.5% of participants in the PRIORIX group and 1.9% of participants in M-M-R II group. The most frequently reported NOCD was atopic dermatitis in PRIORIX (0.8% of participants), and allergic dermatitis allergic in M-M-R II (0.5%). No reported NOCDs were considered to be related to the study vaccination.

AEs prompting ER Visit
Overall, 14.3% of participants in the PRIORIX group and 9.6% in M-M-R II experienced an AE that required an ER visit. The most frequent AEs that required an ER visit were URI reported in 1.8% and 0.9% of PRIORIX and M-M-R II recipients, respectively; otitis media reported in 1.6% and 1.0% of PRIORIX and M-M-R II recipients, respectively; and pyrexia reported in 1.2% of both PRIORIX and M-M-R II recipients.

Medically Attended AEs
A total of 61.7% and 55.6% participants in the PRIORIX and M-M-R II groups, respectively, had at least one symptom that required medical attention during the study period. The most commonly reported symptoms requiring a medically attended visit in the PRIORIX group and M-M-R II group were as follows: URI (17.4% and 18.5%, respectively) and otitis media (16.6% and 14.9%, respectively). After Day 42, the 9 reported febrile convulsions (PRIORIX, 6 participants; M-M-R II, 3 participants), were not considered to be causally related to the study vaccination and were not included in analysis of MMR vaccine-associated solicited general symptoms. In one participant in the PRIORIX group, the convulsion led to hospitalization, and it was considered a SAE.

> Reviewer Comment: Overall, the unsolicited AEs occurring immediately and up to 42 days post-vaccination, were similar between the PRIORIX groups and M-M-R II groups. Diarrhea was found to be the most commonly reported unsolicited adverse event that was likely related to vaccination and occurred at equal frequency in the PRIORIX group as compared to the M-M-R II group. Less than 5% of those in the PRIORIX group reported at least one Grade 3 unsolicited symptoms. When compared to M-M-R-II, PRIORIX the rates and nature of observed unsolicited AEs were similar.

6.4.12.3 Deaths

There were no deaths reported in this study.

6.4.12.4 Nonfatal Serious Adverse Events

A total of 39 SAEs were reported by 24 participants (2.1%) in the PRIORIX group and 12 SAEs were reported by 9 participants (1.6%) in the M-M-R II group during the entire study post-vaccination period.

The most frequently reported SAE across both groups was pneumonia (PRIORIX 0.3% [4 participants]; M-M-R II 0.2% [1 participant]).

Within 42 days post-vaccination, there were 14 SAEs reported in 6 participants (0.52%) in the PRIORIX group and 5 participants (0.87%) in the M-M-R II group. The majority of these events were of the SOC *Metabolism and nutrition disorders,* and the most frequently reported PTs was dehydration reported in 2 participants (0.17%) in the PRIORIX group.

One participant in the PRIORIX group reported an SAE of febrile convulsion 94 days post-vaccination and was not included in the analysis of MMR vaccine-associated solicited general symptoms because it was outside of the pre-defined reporting period for meningism and febrile convulsions (which was 0 to 42 days post-vaccination). It was accompanied by an SAE of otitis media.

All reported SAEs were resolved prior to the end of the study with the exception of the following: A 13-month-old female participant in the M-M-R II group in the US was diagnosed with grade 3 immune thrombocytopenic purpura 2 days post-vaccination. This SAE was considered by the investigator as being probably related to the study vaccination and was ongoing at study end as she was lost to follow up due to moving from the study site. There were no SAEs considered to be related to the vaccine in the PRIORIX group.

> Reviewer Comment: The frequency of SAEs occurring in those receiving PRIORIX was less than 1%, similar to those receiving M-M-R II. None of the reported SAEs in the PRIORIX groups were considered to be related to study vaccination by the investigators. After reviewing the reported SAEs, the clinical reviewer agrees with these assessments of causality.

6.4.12.5 Dropouts and/or Discontinuations

The most common reasons for study discontinuation (Table 49) were lost to follow up (participants with complete vaccination course) followed by consent withdrawal. The rate of those lost to follow up, with complete vaccination course was similar in the PRIORIX group as compared to the M-M-R II (2.1% vs. 3.0%, respectively). The rates of those with consent withdrawal were also similar (PRIORIX 1.2%; M-M-R II 1.6%). There were no SAEs leading to discontinuation from the study or deaths.

Table 49. Discontinuations, All Randomized Participants, Study MMR-162

Population	PRIORIX N=1,165 % (n/N)	M-M-R II N=575 % (n/N)
Enrolled[a]	100% (1165/1165)	100% (575/575)
Vaccinated	99.9% (1164/1165)	99.5% (572/575)
Completed study	96.0% (1117/1164)	94.8% (542/572)
Withdrawal due to	--	--

Population	PRIORIX N=1,165 % (n/N)	M-M-R II N=575 % (n/N)
Consent withdrawal	1.2% (14/1164)	1.6% (9/572)
Lost to follow-up	--	--
Migrated/moved from study area	0.3% (4/1164)	0.7% (4/572)
Lost to follow-up (participants with incomplete vaccination course)	0	0
Lost to follow-up (participants with complete vaccination course)	2.1% (25/1164)	3.0% (17/572)
Protocol deviation	0	0
Non-serious AE	0	0
Serious AE	0	0
Death	0	0
Other[b]	0.3% (4/1164)	0

Source: Adapted from STN 125748/0, Study MMR-162, Clinical Study Report Amendment 2, Table 17, Table 18
Abbreviations: AE=adverse event; N=number of participants in population; n=number of participants who met given criteria
Note: Two different lots of M-M-R II were used during this study. Data from both lots were pooled for this summary.
a. A total of 1,742 participants were enrolled in this study. Two participants were enrolled but not randomized to a treatment group.
b. Other reasons included: travelling outside of country (n=2), loss of insurance (n=1), and refused 2nd blood draw/diary card not completed (n=1).

6.4.13 Study Summary and Conclusions

Study MMR-162 was designed to demonstrate the safety and immunogenicity of PRIORIX when administered as the 1st dose in children 12 through 15 months of age at maximum release limits. Participants received a first dose of either investigational PRIORIX or US standard of care, vaccine M-M-R II, along with concomitantly administered vaccines Varivax, Havrix, and Prevnar 13 (US sites only). The co-primary safety objectives, to demonstrate that the two-sided 95% UL of the difference in fever rates (PRIORIX minus M-M-R II) did not exceed 5% for fever >39.0°C and 10% for fever ≥38.0°C, were met. The secondary immunogenicity analyses described comparable SRRs to the measles, mumps, and rubella vaccine antigenic components, with >96% SRR in both groups and similar GMCs for measles and mumps viruses. The GMCs to rubella were notably lower than observed for M-M-R II in this descriptive analysis. There were no notable differences observed in other safety outcomes of PRIORIX when administered at maximum release limit concomitantly with routinely administered age-recommended vaccines Varivax, Havrix, and Prevnar 13, when compared to M-M-R II. This data supports the safety of PRIORIX when administered at potencies to define maximum release limits.

6.5 Trial #5 (Study MMR-159)

NCT02058563
"A Phase 3a, observer-blind, randomized study to evaluate non-inferiority of a second dose of GSK's MMR vaccine (PRIORIX) compared to Merck's MMR vaccine (M-M-R II) when administered to healthy participants seven years of age and older."

Study Overview: This study was designed to evaluate immunogenicity of PRIORIX compared to M-M-R II when both are used as a second dose in healthy children over 7 years of age who had previously received a first dose on or after the 1st birthday and for adults≥ 18 years had received at least 1 dose prior to study entry.

6.5.1 Objectives

Primary objective

1. To demonstrate the non-inferiority of PRIORIX to M-M-R II in terms of geometric mean concentrations (GMCs) for anti-measles, anti-mumps, and anti-rubella antibodies at Day 42.
   Endpoint: Immunogenicity of the study vaccines at Day 42 in terms of GMCs

Statistical Criterion: The lower limit of the two-sided 95% CI on GMC ratio (PRIORIX/M-M-R II) was equal to or above 0.67 for antibodies to measles, mumps, and rubella viruses.

Secondary objectives

1. To demonstrate the non-inferiority of PRIORIX to M-M-R II in terms of SRRs to measles, mumps, and rubella viruses at Day 42.
   Endpoint: Immunogenicity of the study vaccines at Day 42 in terms of seroresponse: see Section 6.1.1.
   Statistical Criterion: The lower limit of the two-sided standardized asymptotic 95% CI for the group difference (PRIORIX minus M-M-R II) in SRRs to measles, mumps, and rubella viruses was equal to or above −5%.

2. To assess the percentage of participants who achieve a minimum 4-fold rise in anti-measles, anti-mumps, or anti-rubella virus antibody concentrations at Day 42.
   Endpoint (Descriptive): 4-fold or greater rise in anti-measles, anti-mumps, and anti-rubella virus antibody concentration at Day 42.

3. To assess safety and reactogenicity of PRIORIX and M-M-R II
   Endpoints (Descriptive): see Section 6.1.1 for a description of the safety endpoints. Additionally, the solicited general adverse event of Joint pain (arthralgia/arthritis) was collected from Day 0 to Day 42.

6.5.2 Design Overview

Study MMR-159 was an observer-blind, randomized, controlled, multi-center, multi-country, non-inferiority study with three parallel groups. Overall, participants were randomized 1:1 to receive PRIORIX or M-M-R II. Within each group, participants were randomized 2:1:1 to receive PRIORIX or one of the two M-M-R II lots. The two lots of M-M-R II were analyzed as pooled lots.

All study participants had two study visits (Day 0 and Day 42) that had the following major study activities:

- Day 0-Visit 1: Blood samplings; single vaccination with either PRIORIX lots or one of two M-M-R II active control lots
- Day 42-Visit 2: Blood sampling and diary card transcriptions

The study duration was approximately six months starting at Visit 1 (Day 0) and ending with Day 180.

6.5.3 Population

Eligibility Criteria

Individuals were eligible to be included if they were healthy male or female, children or adults, 7 years of age or older, born after December 31, 1956 (except health care workers born before 1957 without other evidence of immunity to mumps), who had previously received one dose of any MMR vaccine administered on or after the first birthday (for all children 7-17 years of age) or had previously received at least one dose of MMR vaccine (for adults over 18 years of age). The individual or their parent(s)/legally acceptable representative(s) could and would comply with protocol requirements and for whom a written informed consent was provided.

Exclusion criteria were described previously (Section 6.1.3) with the addition of the following exclusion criteria:

- an adult, 18 years of age and older, born outside the US.

- used any measles, mumps, or rubella-containing vaccine during the period starting 42 days before Day 0.
- active alcohol or drug abuse or history of any substance abuse.
- pregnant or lactating female or planning pregnancy during entire study period.

6.5.4 Study Treatments or Agents Mandated by the Protocol

PRIORIX: investigational measles, mumps, and rubella vaccine
- Dose/RoA/Presentation/Formulation: see Section 6.1.4.
- Lot #: DMJRA020A, DMJRA020AZ

M-M-R II: comparator measles, mumps, and rubella vaccine
- Dose/RoA/Presentation/Formulation: Section 6.1.4.
- Lots:
  - Lot 1: DLOCA078AZ, J015488
  - Lot 2: DLOCA078AY, J015222

6.5.5 Directions for Use

See Section 6.1.5.

6.5.6 Sites and Centers

There were 17 sites in the United States, Slovakia, and Estonia with a Total Vaccinated Cohort of 911 participants. There were 10 US sites with a total vaccinated cohort of 586 participants.

6.5.7 Surveillance/Monitoring

Surveillance
See Section 6.1.7. For this study, CROs were involved with study sites in all countries.

Safety Monitoring
See Section 6.1.7. Additional safety monitoring that occurred in this study included:
- Solicited general adverse event of Joint pain (arthralgia/arthritis) was collected from Day 0 to Day 42.
- For two US sites that were found to have significant GCP violations, (described further in Section 6.5.9), the following were also monitored during additional contacts for safety follow-up: any symptoms (within the 6 months after entry into the study) that they perceived as serious or were concerned about; any AEs prompting medically attended visits; any NOCDs or any SAEs or pregnancies within the 6 months after the entry into the study.

Pregnancy: Investigators were not obligated to actively seek information regarding pregnancy from the participants, however once an investigator became knowledgeable of a pregnancy, they were required to report all information of the pregnancy in a Pregnancy Report Form. Participants who became pregnant/began lactation subsequent to enrollment were not to receive additional doses of study vaccine(s) but could continue study procedures at the discretion of the investigator. While pregnancy was not considered AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons was to be considered an AE/SAE. Pregnant participants were to be followed to determine the outcome of the pregnancy. At the end of the pregnancy, information on the status of the mother and child was to be reported. Any SAE occurring as a result of a post-study pregnancy AND considered by

the investigator to be reasonably related in time to the receipt of the investigational product(s) was to be reported.

Immunogenicity monitoring[6]
See Table 4 for a summary of serological assays for Study MMR-159. The following assays were performed at the below listed locations for this study:

- Measles virus IgG – Laboratory: GSK (b) (4)
- Rubella virus IgG – Laboratory: GSK (b) (4)

6.5.8 Endpoints and Criteria for Study Success

See Section 6.5.1.

6.5.9 Statistical Considerations and Statistical Analysis Plan

Sample size
The target to enroll approximately 1,000 children assumed a 20% non-evaluable rate which would result in an evaluable population of 800 children, with an estimated 400 children in the PRIORIX group and 400 children in each M-M-R II lot group.

To ensure sufficient sample size for sub-group analyses, the enrollment was constrained to at least:

- 334 participants under 18 years of age with a target to enroll 28 of these participants in the US
- 334 participants 18 years of age and older from the US
- 334 females
- 334 males

Methods
The power to meet the primary objective of non-inferiority for the measles, mumps, and rubella virus GMCs and the secondary objective of non-inferiority for the measles, mumps, and rubella virus seroresponses simultaneously was at least 92.7% (100% minus sum of Type II error for each antigen component regarding GMCs and SRR).

All analyses were performed when all study data were available and cleaned (after Day 42 for immunogenicity data and solicited and unsolicited symptom data, and after Day 180 for AE and SAE data). A final analysis of immunogenicity and safety data was combined in a final clinical report.

Immunogenicity analyses and safety analyses were repeated by country, gender, and age.

Only participants with a completed solicited AE section of the eCRF were considered for analysis of solicited symptoms. Missing or non-evaluable measurements were not replaced. In the primary analysis of solicited symptoms, missing daily recordings were replaced by either grade 1 or the maximum value recorded for the participant (whichever was greater). For participants reporting fever as present in the absence of temperature measurement, missing daily recordings were replaced by grade 1. For the analyses of unsolicited AEs, SAEs, and concomitant medication, all vaccinated participants were considered. Those not reporting an event were considered as participants without an event.

The randomization algorithm used a minimization procedure accounting for gender, age, and country strata. All minimization factors had equal weight in the minimization algorithm. Additional sub-group analyses were provided for each minimization factor used for the randomization (gender, age, country).

6 The central laboratory changed its name from (b) (4) and it was decided not to update the protocol.

Analysis specific to US sites (#102914 and 102915)- see Section 6.5.10.1.2:
Descriptive summaries of demography, primary and secondary immunogenicity and safety endpoints were provided for the participants vaccinated in sites 102914 and 102915.

Protocol Amendments
Original Protocol, dated January 30, 2012
Protocol Amendment 1 (November 12, 2013) included the following changes:

- The study was simplified to evaluate the administration of 1 dose of MMR vaccine only due to the heterogenous nature of the study population in terms of prior vaccination with a measles-containing vaccine
- Prior receipt of at least 1 dose of MMR was added as a study inclusion criterion. Whereas children 7-17 years of age were excluded if they had received more than 1 dose of MMR vaccine, adults 18 years of age and older was able to enroll with a verbal or written history of 1 or more doses of MMR vaccine.
- Increase in samples size to maintain statistical power
- Definitions and categories of solicited local and general AEs were refined. Addition of a rescue plan for participants that failed to meet the seroresponse threshold for antibodies to measles, mumps or rubella virus components.

Protocol Amendment 2 (September 29, 2014) had no major changes.
Protocol Amendment 3 (March 8, 2015) had no major changes.
Protocol Amendment 4 (April 16, 2016) had no major changes.

Changes in the Conduct of the Study and Planned Analyses:

- Due to the significant GCP concerns where credible evidence had emerged pointing to data fabrication, 83 participants from two US sites (102914 and 102915) were excluded from safety/immunogenicity analyses based on TVC and ATP cohorts. Sensitivity analyses of selected safety/immunogenicity endpoints for these two sites were conducted.

All analyses were performed as planned in the protocol.
Please see statistical review for further discussion.

6.5.10 Study Population and Disposition

A total of 996 participants were enrolled in the study. The first participant was enrolled in the study on July 18, 2014, and the last study visit was September 17, 2015.

6.5.10.1 Populations Enrolled/Analyzed

The *Total Vaccinated Cohort (TVC): see* Section 6.1.10.1.

According to Protocol (ATP) Cohort for Analysis of Safety: see Section 6.1.10.1.

According to Protocol (ATP) Cohort for Analysis of Immunogenicity included all eligible participants from the *ATP Cohort for Safety*:

- with post-vaccination serology results available for at least one of the three vaccine antigen components (measles, mumps, or rubella).
- who complied with the procedures and intervals defined in the protocol.
- who did not meet any elimination criteria up to the Visit 2 blood sample (as described below)

Exclusion from the ATP Cohort for Immunogenicity Analyses occurred for the same reasons as described in Section 6.1.10.1.

6.5.10.1.1 Demographics

Table 50. Demographic Characteristics, Total Vaccinated Cohort, Study MMR-159

Characteristic	PRIORIX N=454	M-M-R II N=457
Sex		
Ratio male:female	204:250	205:252
% male:% female	44.9%:55.1%	44.9%:55.1%
Age, years	--	--
Mean (SD)	25.9 (13.9)	25.6 (13.8)
Median	27.0	27.0
Range	7, 59	7, 59
Ethnicity	--	--
Hispanic/Latino	63 (13.9%)	59 (12.9%)
Not Hispanic/Latino	391 (86.1%)	398 (87.1%)
Racial origin (geographic ancestry), n (%)	--	--
Am. Indian/A.N.	2 (0.4%)	4 (0.9%)
All Asian	2 (0.4%)	1 (0.2%)
Central/South Asian	1 (0.2%)	0 (0)
East Asian	1 (0.2%)	0 (0)
Japanese	0 (0)	1 (0.2%)
South East Asian	0 (0)	0 (0)
African/A.A.	108 (23.8%)	103 (22.5%)
All white	334 (73.6%)	345 (75.5%)
Arabic/North African	0 (0)	1 (0.2%)
Caucasian/European	334 (73.6%)	344 (75.3%)
N. Hawaiian/P.I.	1 (0.2%)	0 (0)
Other	7 (1.5%)	4 (0.9%)
Country, n (%)	--	--
Estonia	54 (11.9%)	55 (12.0%)
Slovakia	107 (23.6%)	109 (23.9%)
United States	293 (64.5%)	293 (64.1%)

Source: Adapted from STN 125748/0, MMR-159, Clinical Study Report, Table 14.1.2.1
Abbreviations: A.A.=African American; Am. Indian/A.N=American Indian/Alaskan Native; N. Hawaiian/P.I.=Native Hawaiian/Pacific Islander; N=total number of participants for the TVC Safety Analysis Set (participants with at least 1 vaccination of either PRIORIX or M-M-R II); n=number of participants with indicated characteristic; Other=mixed race or not otherwise specified; SD=standard deviation; TVC=total vaccinated cohort
Note: Two different lots of M-M-R II were used during this study. Data from both lots were pooled for this summary.

The median age of participants in the TVC was 27 years, with a range of 7 to 59 years at the time of the study vaccination. Overall, in the study, the majority of participants were White/Caucasian (74.5%) and female (55.1%), which was observed in each study group as well. In general, demographic and baseline characteristics were similar across study groups. The demographics characteristics observed for participants were comparable to those observed in the ATP Cohort for Immunogenicity.

6.5.10.1.2 Participant Disposition

Table 51. Participant Disposition and Data Analyses Sets, All Randomized Participants, Study MMR-159

Population	PRIORIX (N=497)	M-M-R II (N=497)
Enrolled, n (%)	497 (100%)	497 (100%)
TVC, n (%)	454 (91.3%)	457 (92.0%)

Population	PRIORIX (N=497)	M-M-R II (N=497)
Completed study, n (%)	426 (93.8%)	433 (94.7%)
TVC-Safety, n (%)	454 (91.3%)	457 (92.0%)
TVC-Immunogenicity, n (%)	454 (91.3%)	457 (92.0%)
ATP-Safety, n (%)	451 (90.7%)	454 (91.3%)
ATP-Immunogenicity, n (%)	433 (87.1%)	436 (87.7%)
≥1 Important protocol deviation[a], n (%)	64 (12.9%)	61 (12.3%)
Maximum percentage of participants eliminated for ATP-Immunogenicity analyses[b], n (%)	0.23%	0.91%

Source: Adapted from STN 125748/0, Study MMR-159, Clinical Study Report Amendment 1, Table 14, Table 15; MMR (RIT) Analysis #16 Table 4
Abbreviations: ATP=According-to-protocol; N=total number of participants enrolled; n=number of participants fulfilling the item; TVC=Total vaccinated cohort, included all vaccinated participants; ≥1 Prot. Deviation: participants with one or more protocol deviations
Note: Two different lots of M-M-R II were used during this study. Data from both lots were pooled for this summary.
a. Includes participants with important protocol violations that resulted in exclusion from the ATP-Imm. analysis population.
b. For each antigen and each objective, the percentage of participants who had the necessary immunogenicity results to contribute to the TVC analysis but were eliminated for the ATP analysis was computed. This value represents the maximum overall confirmatory objectives and antigens.
TVC-Safety: included all vaccinated participants with at least one vaccine administration of either PRIORIX or M-M-R II documented.
TVC-Imm.: included all vaccinated participants for whom immunogenicity data were available.
ATP-Safety: Safety analyses using the ATP cohort included eligible participants who received at least one MMR study vaccine/comparator as per protocol; were not excluded from the ATP cohort; for whom the randomization code had not been broken; and the administration route of study vaccine(s) was known and correct.
ATP-Immunogenicity: Immunogenicity analyses using the ATP cohort included all eligible participants from the ATP cohort for safety with pre-vaccination and post-dose serology results available for at least one antigen of measles, mumps, or rubella; below the assay cut-off for at least one MMR vaccine antigen pre-vaccination; did not meet any elimination criteria up to the Visit 2 blood sample; and complied with the post-vaccination blood sample schedule.

A total of 996 participants were enrolled in the study and 994 received a study vaccination. Of the 994 vaccinated participants, 83 participants from sites 102914 and 102915 were excluded (due to significant GCP concerns, see below), resulting in 911 participants in the Total Vaccinated Cohort. Of those vaccinated and not excluded, 859 (94%) completed the study. The most common reasons for withdrawal were: lost to follow up (48 participants) and consent withdrawal (2 participants).

A total of 905 participants (99.3%) were included in the ATP Cohort for Safety. The most common reasons for exclusion from this cohort was protocol violation (6 participants). A total of 869 participants (95.4%) were included in the ATP Cohort for Immunogenicity. The primary reason for exclusion from this cohort were essential serological data missing (33 participants), non-compliance with the blood sampling schedule, including wrong and unknown dates (2 participants), and administration of a medication forbidden to the protocol (1 participant).

US sites 102914 and 102915
During the study, issues in study conduct were identified via site monitoring activities where credible evidence had emerged pointing to data fabrication and all participants (83 participants) from 2 out of 10 sites in the US were excluded from the TVC and ATP cohorts. GSK Global Regulatory Affairs contacted FDA Center for Biologics Evaluation and Research (CBER) on October 23, 2015 to inform FDA that all the MMR-159 participants (including 7 pediatric participants) at US sites 102914 and 102915 would be excluded from analysis due to the GCP violations. This resulted in the total number of evaluable children in the study dropping from 334 to 327. Despite the loss of participants, based on data provided by (b) (4) (a Contract Research Organization or CRO facilitating study site monitoring/management and data management, based in (b) (4) GSK determined that the study had adequate evaluable participants to meet the protocol analysis criteria, and that additional participant enrollment was not necessary.

Sensitivity analyses of selected safety/immunogenicity endpoints for these two sites as of the data lock point (Apr 21, 2016) were conducted. These analyses included primary and secondary immunogenicity objectives, solicited and unsolicited AEs through 42 days post-vaccination, NOCDs, AEs prompting medically attended visits and ER visits, and SAEs through 6 months post-vaccination.

6.5.11 Immunogenicity Analyses

The study design did not include clinical efficacy endpoints. Serologic immune endpoints were used to assess the response to vaccination. Over 80% of participants had baseline antibody levels above each of the seroresponse thresholds for each vaccine antigen. Missing or non-evaluable immunogenicity measurements were not replaced.

The primary analysis of immunogenicity was performed on the ATP Cohort for Immunogenicity.

6.5.11.1 Analyses of Primary Endpoint(s)

Primary Objective: Non-inferiority in terms of GMCs

Non-inferiority was demonstrated if the lower limit of the two-sided 95% CI on adjusted GMC (adjusted for pre-vaccination/baseline antibody concentration) ratio (PRIORIX/M-M-R II) was >0.67 for each vaccine antigen. The objective was ***met*** as shown in Table 52.

Table 52. GMCs and GMC Ratio at 42 Days Post-Vaccination, ATP Cohort for Immunogenicity, Study MMR-159

Antibody	PRIORIX N=432 GMC (95% CI)	M-M-R II N=435 GMC (95% CI)	PRIORIX/M-M-R II GMC Ratio (95% CI)
Anti-Measles (mIU/mL)	1790.2 (1669.6, 1919.5)	1781.5 (1661.8, 1909.7)	1.00 (0.91, 1.11)
Anti-Mumps (EU/mL)	113.5 (106.0, 121.6)	107.8 (100.7, 115.4)	1.05 (0.96, 1.16)
Anti-Rubella (IU/mL)	76.1 (71.5, 81.0)	74.6 (70.2, 79.4)	1.02 (0.93, 1.11)

Source: Adapted from STN 125748/0, MMR-159, Clinical Study Report Amendment 1, Table 17
Abbreviations: ANCOVA=analysis of covariance; ATP=according to protocol; CI=confidence interval; ELISA=enzyme-linked immunosorbent assay; EU=ELISA unit; GMC=geometric mean concentrations (ANCOVA model on the logarithm-transformed concentrations including the vaccine group [for adjusted GMC ratio] as fixed effect, gender, age and country groups as continuous effects and the pre-vaccination log-transformed concentration as regressor); IU=international unit; N=number of participants in ATP;
Assays: Anti-Measles, (b) (4) ELISA; Anti-Mumps, (b) (4) ELISA; Anti-Rubella, (b) (4) ELISA
Note: Two different lots of M-M-R II were used during this study. Data from both lots were pooled for this summary.
Lower 95% CI numbers indicate the interval margin for which statistical testing was performed for the respective test.
Success criteria: the lower limit of the 2-sided 95%CI for the adjusted GMC ratio must be ≥0.67 for anti-measles, anti-mumps, and anti-rubella antibodies.

Table 53 characterizes the proportion of participants with the that achieved the predefined threshold for seroresponse by group.

Table 53. Seroresponse Rate and GMC at 42 Days Post-Vaccination, ATP Cohort for Immunogenicity, Study MMR-159

Antibody	PRIORIX N=433	M-M-R II N=436
Anti-Measles	--	--
% ≥200 mIU/mL (95% CI)	98.8% (97.3, 99.6)	99.1% (97.7, 99.7)
GMC (95% CI)	1795.6 (1641.1, 1964.7)	1783.3 (1624.6, 1957.4)
Anti-Mumps	--	--
% ≥10 EU/mL (95% CI)	98.4% (96.7, 99.3)	99.5% (98.4, 99.9)

Antibody	PRIORIX N=433	M-M-R II N=436
GMC (95% CI)	110.6 (102.1, 119.8)	110.2 (101.9, 119.2)
Anti-Rubella	--	
% ≥10 IU/mL (95% CI)	99.5% (98.3, 99.9)	99.8% (98.7, 100.0)
GMC (95% CI)	75.3 (70.3, 80.6)	75.6 (70.8, 80.7)

Source: Adapted from STN 125748/0, MMR-159, Clinical Study Report Amendment 1, Table 20, Table 21, Table 22
Abbreviations: ATP=according to protocol cohort; CI: confidence interval; ELISA=enzyme-linked immunosorbent assay; EU=ELISA unit; GMC=geometric mean concentration (performed by taking the anti-log of the mean of the log concentration transformations. Antibody concentrations below the cut-off of the assay were to be given an arbitrary value of half the cut-off for the purpose of GMC calculation); IU=international unit; N=number of participants in ATP; Seroresponse Rate (percentage of initially seronegative participants with concentration above seroresponse threshold for each assay; Assays: Anti-Measles, (b) (4) ELISA; Anti-Mumps, (b) (4) ELISA; Anti-Rubella, (b) (4) ELISA (For each assay - seroresponse thresholds are 200 mIU/mL, 10 EU/mL, and 10 IU/mL for anti-measles, anti-mumps, and anti-rubella antibodies respectively).
Note: Two different lots of M-M-R II were used during this study. Data from both lots were pooled for this summary.

6.5.11.2 Analyses of Secondary Endpoints

Secondary endpoint 1: Seroresponse rates

Non-inferiority was demonstrated if the lower limit of the two-sided standardized asymptotic 95% CI for the group difference in SRRs to measles, mumps, and rubella viruses was ≥ −5%. As shown in Table 54, the objective was ***met***.

Table 54. Seroresponse Rate Differences at Day 42, ATP Cohort for Immunogenicity, Study MMR-159

Antibody	PRIORIX N=433 SRR	M-M-R II N=436 SRR	PRIORIX-M-M-R II SRR Difference (95% CI)
Anti-Measles antibody ≥200 mIU/mL	98.8%	99.1%	-0.24 (-1.87, 1.32)
Anti-Mumps antibody ≥10 IU/mL	98.4%	99.5%	-1.16 (-2.90, 0.23)
Anti-Rubella antibody ≥10 EU/mL	99.5%	99.8%	-0.23 (-1.46, 0.86)

Source: Adapted from STN 125748/0, MMR-159, Clinical Study Report Amendment 1, Table 18
Abbreviations: ATP=according to protocol; N=number of participants in ATP; CI=confidence interval; EU=ELISA unit; ELISA=enzyme-linked immunosorbent assay; IU=international unit;; SRR=Seroresponse Rate (percentage of initially seronegative participants with concentration above seroresponse threshold for each assay; Assays: Anti-Measles, (b) (4) ELISA; Anti-Mumps, (b) (4) ELISA; Anti-Rubella, (b) (4) ELISA (For each assay - seroresponse thresholds are 200 mIU/mL, 10 EU/mL, and 10 IU/mL for anti-measles, anti-mumps, and anti-rubella antibodies respectively).
Note: Two different lots of M-M-R II were used during this study. Data from both lots were pooled for this summary.
Success criteria: the lower limit of the 2-sided standardized asymptotic 95%CI for the group difference (PRIORIX minus M-M-R II) in SRR to measles, mumps, and rubella viruses must be ≥ −5%.

Secondary endpoint 2 (Descriptive): Four-fold rise of antibody concentrations

The second secondary objective was to descriptively assess the percentage of participants who achieved a minimum 4-fold rise in anti-measles, anti-mumps, or anti-rubella virus antibody concentrations in each group. The percentages of participants who achieved a minimum 4-fold rise in anti-measles, anti-mumps, and anti-rubella virus antibody concentrations at Day 42 were similar between the PRIORIX and M-M-R II groups, respectively (9.7% vs 11.0% for anti-measles, 35.2% vs 29.4% for anti-mumps, and 41.4% vs 37.0% for anti-rubella).

6.5.11.3 Subpopulation Analyses

Subpopulation analyses were descriptive and done for participants by country, gender, and age. All countries represented in the study were included in the subpopulation analyses: United States, Slovakia, and Estonia. Age was analyzed in two groups: <18 years and ≥18 years. Humoral immune responses in the sub-groups were generally similar to those reported in the primary and secondary immunogenicity analyses for the overall group. GMCs were lower in the Estonia sub-group (1441.7 mIU/mL, 133.6

EU/mL, 68.2 IU/mL) as compared to GMCs in the US sub-group (1809.3 mIU/mL, 103.1 EU/mL, 68.2 IU/mL) and the Slovakia sub-group (1922.7 mIU/mL, 133.8 EU/mL, 74.1 IU/mL) for anti-measles, -mumps, and -rubella antibody concentrations, respectively. However, sub-group analyses by age, sex and country determined that criteria for non-inferiority of PRIORIX was met for GMCs within each sub-group. For SRR, criteria for non-inferiority of PRIORIX as compared to M-M-R II were met within sub-group analyses for age and sex, and SRRs were nominally similar across the three countries (>97%) for all three vaccine virus antigens.

> Reviewer Comment: In a response to an IR submitted by the Applicant (STN 125748/Am 44), reports of first MMR-containing vaccine doses received by the participants in the study are as follows:
>
> - PRIORIX group:
> - US – 90.1% (n=264) received 1 dose of MMR, 9.6% (n=28) received 2 doses of MMR
> - Slovakia – 99.1% (n=106) received PRIORIX
> - Estonia – 100% (n=54) received PRIORIX
> - M-M-R II group
> - US – 91.1% (n=267) received 1 dose of MMR, 7.8% (n=23) received 2 doses of MMR
> - Slovakia – 100% (n=109) received PRIORIX
> - Estonia – 100% (n=55) received PRIORIX
>
> The Applicant also notes that almost all of the participants in the US were >18 years of age while those in Slovakia and Estonia predominantly <18 years of age. Data provided descriptively for the age sub-groups, shows comparable SRRs in both age sub-groups (>98.1%) for all three vaccine antigens, and comparable GMCs at Day 42 for anti-measles (1726.5 mIU/mL vs. 1838.3 mIU/mL) and anti-rubella (72.4 IU/mL vs. 77.1 IU/mL), and anti-mumps antibody (132.6 EU/mL vs. 99.3 EU/mL).

6.5.11.4 Dropouts and/or Discontinuations

Approximately 94% of enrolled participants completed the study. Missing or non-evaluable immunogenicity measurements were not replaced. Immunogenicity analyses therefore excluded participants with missing or non-evaluable measurements.

6.5.11.5 Exploratory and Post Hoc Analyses

Not applicable.

6.5.12 Safety Analyses

The analysis of safety was based on the Total Vaccinated cohort.

6.5.12.1 Methods

Safety data surveillance is described in Section 6.5.2 and Section 6.5.7 and shown Table 55. Participant compliance with returning symptom sheets for collection of local and general solicited AEs following administered vaccines was greater than 94%.

6.5.12.2 Overview of Adverse Events

Safety Overview

Safety data were presented for PRIORIX and M-M-R II groups. Table 55 provides an overview of the rates of adverse events in the PRIORIX compared to the M-M-R II groups during the study period.

Table 55. Proportion of Participants Reporting at Least One Adverse Event Following MMR Vaccination, TVC, Study MMR-159

AE Type: Monitoring Period[a]	PRIORIX % (n/N)	M-M-R II % (n/N)
Immediate AE: 30 minutes	0.4% (2/454)	1.1% (5/457)
Solicited local at vaccine site[b]: 0-3 days	19.4% (84/433)	19.3% (86/445)
Solicited systemic[c]:	NA	NA
Temperature ≥38.0 ºC: 0-42 days	3.0% (13/431)	5.2% (23/445)
Rash: 0-42 days	2.1% (9/431)	1.1% (5/445)
Parotid gland swelling: 0-42 days	0.2% (1/431)	0.2% (1/445)
Arthralgia/Joint pain	1.9% (8/431)	0.9% (4/445)
Meningism[d]: 0-42 days	0.2% (1/431)	0.2% (1/445)
Unsolicited AE: 0-42 days	20.9% (95/454)	17.9% (82/457)
AEs leading to study withdrawal: Entire study period	0	0
SAEs: Entire study period	0	0
AEs of specific interest[e]: Entire study period	3.5% (16/454)	2.2% (10/457)
Deaths: Entire study period	0	0

Source: Adapted from STN 125748/0, MMR-159, Clinical Study Report Amendment 1, Table 14, Table 15, Tables 24-30, and MMR (RIT) Analysis #16 Table 4
Abbreviations: AE=adverse event; N=number of participants in cohort; n=number of participants who experienced the solicited event; SAE=serious adverse event; TVC=Total Vaccinated Cohort was used as the analyses set for safety
Temperature 38.0 C=100.4 F
Note: For unsolicited events, the N is the number of participants in the TVC; For solicited local events, the N is the number of participants from the TVC with documented local events; For solicited systemic events, the N is the number of participants from the TVC with documented systemic events
a. Monitoring Period: time interval that the relevant type of AE was monitored for post-vaccination.
b. Solicited local includes pain, redness, and swelling at injection site.
c. Due to ages of the participants, the following solicited systemic reactions were not collected in this study: drowsiness, loss of appetite, or irritability/fussiness.
d. Signs or symptoms indicative of meningism (i.e., neck stiffness with or without light intolerance [photophobia] and headache; or convulsion/seizure) and included febrile convulsions.
e. AEs of specific interest included new onset chronic disease (NOCD, e.g., autoimmune disorders, asthma, type I diabetes, vasculitis, celiac disease, conditions associated with sub-acute or chronic thrombocytopenia and allergies) and AEs prompting emergency room (ER) visit

Within 43 days post-vaccination, the rates for any reported AE, including local and systemic, solicited reactions, unsolicited AEs, and SAEs were generally similar between the PRIORIX and M-M-R II groups. Overall, 35.7% and 33.9% of participants, respectively reported at least one solicited or unsolicited symptom during the 43-day post-vaccination period. There were no AEs in the PRIORIX group that let to study withdrawal and no deaths throughout the entire study period for either group.

Subpopulation Analyses

Descriptive summary safety data were reported by country, gender, and age. In general, findings were similar to those reported in the safety analyses for the overall group. No clinically meaningful differences between vaccine groups in incidence of solicited local or general symptoms were observed in females and males or in any age group.

Solicited Adverse Reactions

Table 56 includes the percentages of PRIORIX and M-M-R II participants who reported any solicited adverse reactions, which are stratified by grade.

Table 56. Proportion of Participants With Solicited Reactions Post-Vaccination, TVC, Study MMR-159

Solicited Adverse Reaction	PRIORIX N=431-433	M-M-R II N=445
Local (injection site)	--	--
Pain[a], % (n/N)	--	--
Any	11.8% (51/433)	11.5% (51/445)
Grade 0	0.2% (1/433)	0.0% (0/445)
Grade 1	10.4% (45/433)	9.7% (43/445)
Grade 2	0.9% (4/433)	1.8% (8/445)
Grade 3	0.2% (1/433)	0.0% (0/445)
Erythema, % (n/N)	--	--
Any	12.2% (53/433)	11.7% (52/445)
Grade 0 (none)	0.5% (2/433)	0.2% (1/445)
Grade 1 (>0 to ≤20 mm)	10.2% (44/433)	10.6% (47/445)
Grade 2 (>20 to ≤50 mm)	1.6% (7/433)	0.9% (4/445)
Swelling, % (n/N)	--	--
Any	5.3% (23/433)	6.5% (29/445)
Grade 1 (>0 to ≤20 mm)	4.4% (10/433)	5.8% (26/445)
Grade 2 (>20 to ≤50 mm)	0.9% (4/433)	0.7% (3/445)
Systemic Events	--	--
Measles/Rubella-like rash, % (n/N)	--	--
Any	0.0% (0/431)	0.4% (2/445)
Grade 1 (1-50 lesions)	0.0% (0/431)	0.4% (2/445)
Other rash[b], % (n/N)	--	--
Any	2.1% (9/431)	0.7% (3/445)
Grade 1	1.9% (8/431)	0.2% (1/445)
Grade 2	0.2% (1/431)	0.4% (2/445)
Parotid/salivary gland swelling[c], % (n/N)	--	--
Any	0.2% (1/431)	0.2% (1/445)
Grade 2	0.0% (0/431)	0.2% (1/445)
Grade 3	0.2% (1/431)	0.0% (0/445)
Arthralgia/Joint pain[b], % (n/N)	--	--
Any	1.9% (8/431)	0.9% (4/445)
Grade 1	1.4% (6/431)	0.4% (2/445)
Grade 2	0.5% (2/431)	0.4% (2/445)
Signs of meningism/seizure (including febrile convulsions)[b], % (n/N)	--	--
Any	0.2% (1/431)	0.2% (1/445)
Grade 2	0.0% (0/431)	0.2% (1/445)
Grade 3	0.2% (1/431)	0.0% (0/445)
Fever (temperature ≥38ºC), % (n/N)	--	--
Any Fever: ≥38ºC	3% (13/431)	5.2% (23/445)
38-38.5 °C	1.4% (6/431)	2.2% (10/445)
38.51-39 °C	1.2% (5/431)	0.7% (3/445)
39.01-39.5 °C	0.2% (1/431)	0.9% (4/445)
39.51-40 °C	0.2% (1/431)	0.7% (3/445)
≥40.01 °C	0.0% (0/431)	0.7% (3/445)

Source: Adapted from STN 125748/0, MMR-159, Clinical Study Report, Table 9, Table 15 and MMR (RIT) Analysis #16 Table 15
Abbreviations: AE=adverse event; LAR=legally acceptable representative; N=number of participants in cohort; n=number of participants with available data for relevant endpoint; TVC=Total Vaccinated Cohort was used as the analyses set for safety
Note: For solicited local events, the N is the number of participants from the TVC with documented local events.
Note: For solicited systemic events, the N is the number of participants from the TVC with documented systemic events
a. Pain: Grade 0: none, Grade 1: Mild: Any pain neither interfering with nor preventing normal everyday activities; Grade 2: Moderate: Painful when limb was moved and interfered with everyday activities; Grade 3: Severe: Significant pain at rest. Prevented normal everyday activities
b. Other rash/Arthralgia/Joint pain/Irritability/Fussiness/Drowsiness/Loss of appetite/Meningism: Grade 1: caused minimal discomfort and did not interfere with everyday activities, Grade 2: sufficiently discomforting to interfere with normal everyday activities, Grade 3: prevented normal,

everyday activities (in a young child, such an AE would, for example, prevent attendance at school/day care and would cause the parent(s)/LAR(s) to seek medical advice); Note that drowsiness, loss of appetite, and irritability/fussiness were not collected in this study.
c. Parotid/salivary gland swelling: Grade 1: Swelling without difficulty moving the jaw, Grade 2: Swelling with difficulty moving the jaw, Grade 3: Swelling with accompanying general symptoms.

The incidences of solicited local symptoms were comparable between the groups. For both groups, the most frequently reported solicited local reaction was injection site erythema (PRIORIX 12.2%, vs. M-M-R II 11.7%). No participants reported severe (grade 3) injection site erythema.

Solicited Systemic Symptoms Specific to MMR Vaccination
Overall, the incidences of solicited general symptoms within 43 days post-vaccination were similar between the groups: fever was the most frequently reported (PRIORIX 3% vs. M-M-R II 5.2%), followed by other rash (PRIORIX 2.1% vs. M-M-R II 0.7%) and arthralgia/joint pain (PRIORIX 1.9% vs. M-M-R II 0.9%). Grade 3 fever (≥39.51°C) was reported in 0.2% of those who received PRIORIX as compared to 1.4% of those who received M-M-R II. No participants in the PRIORIX group reported fever ≥40.01 °C, compared to 0.7% in the M-M-R II group. Between 5- and 12-days post-vaccination, fever with causal relationship to the vaccine occurred in 0.5% of PRIORIX recipients as compared to 0.9% of M-M-R II recipients.

Joint pain/arthralgia were more often seen in the PRIORIX group compared to the M-M-R II group (1.9% vs. 0.9%, respectively) and was reported to have a causal relationship in more participants who received PRIORIX as compared to M-M-R II (0.7% vs. 0.2%, respectively). Although other rash was noted in a higher proportion of those who received PRIORIX as compared to M-M-R II (2.1% vs. 1.1%), confidence intervals were overlapping. Rash with causal relationship to the vaccine was reported in 1.4% of PRIORIX recipients and 0.4% in the M-M-R II recipients.

Rates of measles/rubella-like rash, parotid/salivary gland swelling, and signs of meningism/seizure (including febrile convulsions) were similar between the two groups. Meningism was reported in 1 participant in the PRIORIX group (0.2%) and was rated a grade 3 severity. The participant had non-epileptic seizures and it was assessed as unrelated to the study vaccine by the investigator. In the M-M-R II group, 1 participant reported a stiff neck which was also assessed as unrelated to the study vaccine by the investigator.

Reviewer Comment:

1. Overall, the occurrence of solicited reactions were similar between the two groups. The most frequently reported solicited local reactions was injection site erythema and the most frequently reported solicited general symptoms was fever. Most adverse reactions were Grade 1.
2. See Reviewer Comment 2 in Section 6.1.12.2 under the subsection Solicited Systemic Symptoms Specific to MMR Vaccination for an explanation of which events qualified as febrile convulsions. For study MMR-159, the proportion with each event were provided as follows:
    - Meningism excluding febrile convulsions:
        - PRIORIX: 0.23% (1/431 participants)
        - M-M-R II: 0.22% (1/445 participants)
    - Febrile convulsions:
        - PRIORIX: 0% (0/431 participants)
        - M-M-R II 0% (0/445 participants)

Ongoing Adverse Reactions and Adverse Reactions with Onset After Reporting Period

Overall, the proportion of participants with solicited reactions with onset during the solicited reporting period that were ongoing after the last day of the reporting period was similar across groups, low, and predominantly grade 1 to 2. The highest percentages for ongoing solicited ARs were for injection site erythema (PRIORIX 3.00% and M-M-R II 0.90%) and pain (PRIORIX 2.08% and M-M-R II 0.22%)

The proportion of any local solicited reaction with onset after the reporting period (Day 0 to Day 3) was 0% in both groups. The proportion of solicited systemic symptoms with onset after the reporting period (Day 0 to Day 14) and symptoms specific to MMR vaccination with onset after the reporting period (Day 0 to Day 42) was 0% in the PRIORIX group and 0-0.22% in the M-M-R II group, with rash being reported most frequently in the M-M-R II group.

See Reviewer Comment in Section 6.1.12.2 under the subsection *Ongoing Adverse Reactions and Adverse Reactions with Onset After Reporting Period* for an explanation of how duration was calculated.

Immediate AEs: within 30 minutes
The incidence of adverse events within 30 minutes of vaccination were similar between groups (PRIORIX 0.4% vs. pooled M-M-R II 1.1%). In the PRIORIX group, the two participants with immediate AEs reported MedDRA PTs of somnolence and oropharyngeal pain. In the M-M-R II group, 3 out of the 5 reported immediate AEs were erroneous entries.

Unsolicited AEs (Non-Serious): 0-42 days
The rates of unsolicited, non-serious AEs during the 43-day post-vaccination period were similar in both groups, with at least one unsolicited symptom reported in 20.9% of (PRIORIX recipients and 17.9% of M-M-R II. Unsolicited AEs were most frequently classified in MedDRA SOC *Nervous system disorders* (PRIORIX 4.7% vs. M-M-R II 1.5%), followed by SOC *Infections and infestations* (PRIORIX 9.5%, M-M-R II 10.3%). By MedDRA PT, the most common AE was headache (3.7% PRIORIX vs. 0.9% M-M-R II). The proportion of participants who reported a causal relationship between an unsolicited AE and the vaccination was 2.6% in the PRIORIX group and 3.3% in the M-M-R II group. Injection site reactions were the most commonly reported causally related AE in both groups (0.4% and 0.6%, respectively).

Adverse Events of Specific Interest
AEs considered AEs of specific interest are described in Section 6.1.12.2.

New Onset Chronic Disease (NOCD)
At least one NOCD was reported in 0.4% of participants in the PRIORIX group and 0.2% of participants in M-M-R II group. In both groups the NOCD reported was Diabetes mellitus and it was not considered to be related to the study vaccination in any of the reported cases.

AEs prompting ER Visit
Overall, 3.1% of participants in the PRIORIX group and 2.0% in M-M-R II experienced an AE that required an ER visit. The most frequent AEs that required an ER visit were laceration reported in 0.7% and 0% of PRIORIX and M-M-R II recipients, respectively; and pharyngitis reported in 0% and 0.4% of PRIORIX and M-M-R II recipients, respectively.

Medically Attended AEs
A total of 13.2% and 12.5% participants in the PRIORIX and M-M-R II groups, respectively, had at least one symptom that required medical attention during the entire study period. The most commonly reported symptoms requiring a medically attended visit in the PRIORIX group and M-M-R II group were as follows: nasopharyngitis (1.1% and 1.1%, respectively) and streptococcal pharyngitis (1.1% and 0.9%, respectively).

6.5.12.3 Deaths

There were no deaths reported in this study.

6.5.12.4 Nonfatal Serious Adverse Events

A total of 11 SAEs were reported by 10 participants during the study. Four SAEs were reported by 3 participants in the PRIORIX group (0.7%), and 7 SAEs were reported by 7 participants in the M-M-R II group (1.5%). The most frequently reported SAE was spontaneous abortion (0% PRIORIX, 0.4% M-M-R II), which is further described below. SAEs reported during this period resolved except for two: psychogenic seizure and jaw fracture which were resolving. Of the 11 SAEs reported, none were considered vaccine-related by the investigator.

Within 43 days of study vaccination, 3 participants in the PRIORIX group and 4 participants in the M-M-R II reported SAEs. Of the eight SAEs reported, none was considered vaccine-related by the investigator.

Pregnancy
Abnormal pregnancy outcomes were considered SAEs. Two participants in the PRIORIX group and four in the M-M-R II group did report pregnancy. Of these reports, 2 participants of the 4 in the M-M-R II group reported spontaneous abortions. Both participants had vaccine exposure prior to pregnancy (ranging from 33 to 120 days between vaccine and last menstrual period). No congenital anomaly was noted in any of the remaining cases.

> Reviewer Comment: Overall, the unsolicited AEs occurring immediately and up to 42 days post-vaccination, were similar between the PRIORIX groups and M-M-R II groups. Injection site reactions were found to be the most commonly reported unsolicited adverse event that was likely related to vaccination and occurred at equal frequency in the PRIORIX group as compared to the M-M-R II group. There does not appear to be a greater likelihood of safety concerns with PRIORIX when compared to M-M-R II.

6.5.12.5 Dropouts and/or Discontinuations

Approximately 96.6% (N=880) of participants completed the Day 42 visit and 94.3% (N=859) completed day 180 phone contact, Table 57. No AEs leading to premature discontinuation of study vaccine and/or study were reported. The most common reason for exclusion from the ATP cohort or safety (6 participants) was a protocol violation (not meeting inclusion/exclusion criteria but still vaccinated).

Table 57. Discontinuations, All Randomized Participants, Study MMR-159

Population	PRIORIX N=497 % (n/N)	M-M-R II N=497 % (n/N)
Enrolled[a]	100% (497/497)	100% (497/497)
Vaccinated[b]	91.3% (454/497)	92.0% (457/497)
Completed study	85.7% (426/497)	87.1% (433/497)

Population	PRIORIX N=497 % (n/N)	M-M-R II N=497 % (n/N)
Withdrawal due to	--	--
Consent withdrawal	0.2% (1/497)	0.2% (1/497)
Lost to follow-up	5.2% (26/497)	4.4% (22/497)
Protocol deviation	0	0
Non-serious AE	0	0
Serious AE	0	0
Death	0	0
Other[c]	0.2% (1/497)	0.2% (1/497)

Source: Adapted from STN 125748/0, Study MMR-159, Clinical Study Report Amendment 1, Table 14, Table 15
Abbreviations: AE=adverse event; N=number of participants in population; n=number of participants who met given criteria
Note: Two different lots of M-M-R II were used during this study. Data from both lots were pooled for this summary.
a. A total of 996 participants were enrolled in this study. Two participants were enrolled but not randomized to a treatment group.
b. A total of 83 participants from 2 sites were excluded from the total vaccinated population due to GCP violations.
c. Other reasons included: Participant had been vaccinated later as new participant in the PRIORIX group and participant was incarcerated in the M-M-R II group.

6.5.13 Study Summary and Conclusions

Study MMR-159 was designed to demonstrate that PRIORIX as a second dose, is non-inferior to M-M-R II, a US-licensed MMR vaccine, in terms of GMCs and seroresponse rates for anti-measles, anti-mumps, and anti-rubella antibodies when administered to healthy children and adults, age 7 years or older. The primary objective evaluated GMCs and GMC ratios at Day 42, and the study met its predefined criteria for success for the primary objectives. The secondary objectives were to further evaluate immunogenicity, in terms of SRRs, as well as safety. The study met the predefined criteria for success of the first co-secondary objective of SRRs. The descriptive results of the percentage of participants who achieved a 4-fold increase in anti-measles, anti-mumps, and anti-rubella virus antibody concentrations at Day 42 were similar between the two groups. Safety parameters studied between the two groups were similar also. Although the upper age limit in this study was 59 years; data from this study are considered adequate to extrapolate to older persons. This study supports the safety and effectiveness of PRIORIX as a second dose in children and adults 7 years and older.

6.6 Trial #6 (Study MMR-157)

NCT00861744
"A Phase 2, randomized, observer blind, controlled, multicenter study to assess immunogenicity and antibody persistence following vaccination with GSK's MMR vaccine (PRIORIX) versus Merck's MMR vaccine (M-M-R II) as a first dose, both administered subcutaneously at 12 through 15 months of age, concomitantly with Havrix (HAV), Varivax (VV), and Prevnar 7 (PCV7)"

Study Overview: This study was a descriptive Phase 2 study designed to provide estimations of SRRs to develop statistical criteria for Phase 3 trials and to determine safety and reactogenicity of administration of PRIORIX (with three mumps virus potencies) compared to M-M-R II when concomitantly administered with routine vaccines for children 12 through 15 months of age.

6.6.1 Objectives

Primary Objective (Descriptive):

- To assess GSK's candidate MMR vaccine (PRIORIX) formulated with a range of mumps virus potencies, concomitantly administered with HAV, VV and PCV7, compared to M-M-R II

concomitantly administered with HAV, VV and PCV-7, with respect to the SRR for antibodies to measles virus, mumps virus and rubella virus at Day 42.

Secondary Objectives (Descriptive):

Active Phase (Day 0 to Day 42)

1. To assess PRIORIX, concomitantly administered with HAV, VV, and PCV7 in contrast to M-M-R II concomitantly administered with HAV, VV, and PCV7 with respect to the concentrations/titers of antibodies to measles virus, mumps virus and rubella virus at Day 42.
2. To assess the immunogenicity of VV with respect to the SRR and geometric mean concentration (GMC) for antibodies to varicella zoster virus (VZV) at Day 42 when concomitantly administered with HAV, PCV7, and PRIORIX or in contrast, M-M-R II
3. To assess the immunogenicity of HAV with respect to the SRR and GMC for antibodies to hepatitis A virus at Day 42 when concomitantly administered with VV, PCV7, and PRIORIX or in contrast, M-M-R II, in a randomly selected 50% subset.
4. To assess the immunogenicity of PCV7 with respect to the GMCs for antibodies to *S. pneumoniae* serotypes at Day 42 when concomitantly administered with VV, HAV, and PRIORIX, or in contrast, M-M-R II, in a randomly selected 50% subset.

Antibody persistence Phase (Day 0 to Day 365 and/or Day 730)

5. To assess the persistence of antibodies to measles, mumps and rubella viruses with respect to the antibody concentrations/titers one year after administration of the first dose of PRIORIX compared to M-M-R II.
6. To assess the persistence of antibodies to measles, mumps and rubella viruses with respect to the antibody concentrations/titers two years after administration of the dose of PRIORIX compared to M-M-R II.
7. To assess the persistence of antibodies to measles, mumps and rubella viruses with respect to one threshold for each component virus one year after administration of the dose of PRIORIX compared to M-M-R II.
8. To assess the persistence of antibodies to measles, mumps and rubella viruses with respect to one threshold for each component virus two years after administration of the dose of PRIORIX compared to M-M-R II.

> Reviewer Comment: Regarding the Antibody Persistence objective, the Applicant lists the 3rd and 4th point as "…with respect to one threshold…" The threshold being referred to here is the seroresponse threshold as defined for each vaccine antigen (See Section 6.1.1).

Safety and reactogenicity (Day 0 to Day 180)

9. To assess safety and reactogenicity of PRIORIX compared to M-M-R II.

6.6.2 Design Overview

Study MMR-157 was an observer blind, randomized, controlled, multicenter study with 6 parallel groups. Overall, participants were randomized 3:3:3:3 to received one of three PRIORIX lots or M-M-R II. Within each group, participants were randomized 3:3:3:[1:1:1] to receive one of the three PRIORIX lots (sub-groups identified as PRIORIX Lot 1, PRIORIX Lot 2, and PRIORIX Lot 3) or one of three M-M-R II (sub-groups identified as M-M-R II Lot 1, M-M-R II Lot 2, and M-M-R II Lot 3). The three lots of M-M-R II were analyzed as pooled lots.

Participants from each treatment group attended five study visits (Days 0, 42, 180, 365, and 730) that had the following major study activities:

- Day 0-Visit 1 at 12 through 15 months of age: Blood sampling; single vaccination with either one of the three PRIORIX lots or one of three M-M-R II lots, along with the concomitantly administered vaccines.
- Day 42-Visit 2, Day 365-Visit 4, Day 730-Visit 5: Blood samples

The study duration was approximately 2 years for each participant, ending with Visit 5 (Day 730).

6.6.3 Population

Eligibility Criteria

Individuals were eligible to be included if they were healthy male and female children 12 through 15 months of age who had previously received three doses of PCV7 within the first year of life with the third dose administered at least 30 days prior to enrollment and vaccination with study vaccines. Additionally, participants were eligible if the investigator believed their parents/guardians could and would comply with the requirements of the protocol and could provide written consent.

Exclusion criteria is as described previously (Section 6.1.3) with the addition of the following exclusion criteria:

- major congenital defects or serious chronic illness;
- history of any neurologic disorders or seizures, including febrile seizures

6.6.4 Study Treatments or Agents Mandated by the Protocol

PRIORIX: investigational measles, mumps, and rubella vaccine

- Dose/RoA/Presentation: see Section 6.1.4.
- Lot/Formulation:
  - Lot #1: AMJRB721A
    - $10^{3.8}$ $CCID_{50}$ Measles virus (Schwarz strain), $10^{4.8}$ $CCID_{50}$ Mumps virus (RIT 4385 strain), $10^{3.9}$ $CCID_{50}$ Rubella virus (Wistar RA 27/3 strain).
  - Lot #2: DMJRA002A
    - $10^{4.1}$ $CCID_{50}$ Measles virus (Schwarz strain), $10^{4.1}$ $CCID_{50}$ Mumps virus (RIT 4385 strain), $10^{3.9}$ $CCID_{50}$ Rubella virus (Wistar RA 27/3 strain).
  - Lot #3: DMJRA003A
    - $10^{4.0}$ $CCID_{50}$ Measles virus (Schwarz strain), $10^{3.7}$ $CCID_{50}$ Mumps virus (RIT 4385 strain), $10^{4.1}$ $CCID_{50}$ Rubella virus (Wistar RA 27/3 strain).

M-M-R II: comparator measles, mumps, and rubella vaccine

- Dose/RoA/Presentation/Formulation: Section 6.1.4.
  - Lots:
    - Lot #1: 1291X
    - Lot #2: 1255X
    - Lot #3: 1362X

Varivax

- Dose/RoA/Presentation/Formulation: see Section 6.1.4.
- Lots: 1323X, 0778Y and 0158Z; Diluent lots: 4091X, 6014Y, 6101Y

Havrix

- Dose/RoA/Presentation/Formulation: see Section 6.1.4.
- Lot: AHAVB330AA

Prevnar 7

- Dose/RoA/Presentation: see Section 6.1.4.
- Lot #: D06803

Reviewer Comment:

1. The study protocol included an option for revaccination with MMR-II and VV at Day 365 if the Day 42 immune response data suggested a suboptimal immunologic response. A second dose of HAV was administered as per the protocol at Day 180, though it was not considered part of study procedures (documented in the eCRF). No study vaccines were administered during the antibody persistence evaluation period.
2. Storage: M-M-R II was stored at ~4°C and PRIORIX was stored at ~ (b) (4), though it can be stored at 4°C. This was done to preserve the defined mumps potencies. Temperature deviations occurred with 6 blocks of PRIORIX at one site and GSK Quality assurance deemed these vaccines unusable.

6.6.5 Directions for Use

The lyophilized PRIORIX vaccine was reconstituted by injecting the entire volume of diluent (WFI) in a pre-filled syringe into the vial of lyophilized vaccine. The entire contents of the reconstituted vaccine were withdrawn into a syringe. After the needle was changed, the total volume of reconstituted vaccine was administered subcutaneously via the syringe.

6.6.6 Sites and Centers

There were 51 sites in the continental United States and Puerto Rico with a total vaccinated cohort of 1,220 participants.

6.6.7 Surveillance/Monitoring

The study was monitored in three Phases:

- Active Phase – Day 0 to Day 42,
- Extended safety follow-up Phase – Day 0 to Day180
- Antibody persistence Phase – Day 0 to Day 730

Safety Monitoring:
See Section 6.1.7.

Immunogenicity monitoring
Table 58 includes the serological assays used in the measurement of immunogenicity endpoints.

Table 58. Summary of Serological Assays, Study MMR-157

Component	Method	Unit	Cut-Off	Threshold	Kit/ Manufacturer	Location
Measles Virus Ab.IgG	ELISA	mIU/mL	150	200	(b) (4)	
Rubella Virus Ab.IgG	ELISA	IU/mL	4	10		

Component	Method	Unit	Cut-Off	Threshold	Kit/ Manufacturer	Location
Mumps Virus Ab.IgG	ELISA	EU/mL	5	10	(b) (4)	
Mumps virus strain Mu90 Ab	(b) (4)	ED_{50}	2.5	4		
Varicella Zoster Virus Ab.IgG	(b) (4)	mIU/mL	25	75		
Hepatitis A Virus Ab	(b) (4)	mIU/mL	15	--		

Source: Adapted from STN 125748/0, Clinical Overview, Table 4
Abbreviations: Ab=antibodyELISA=enzyme-linked immunosorbent assay; IgG=immunoglobulin G; IU-international unit

Reviewer Comment: After completion of this Phase 2 study, the Applicant developed a new (b) (4) which was more reflective of mumps-specific antibody responses. CBER agreed on the use of this new (b) (4), and antibody testing with the (b) (4) assay was performed post-hoc on participants in the HAV subset (randomized subset of 50% of the TVC) for Day 0 and Day 42 and on all participants in Year 1 and Year 2 samples. After an End of Phase 2 meeting, in planning for the Phase 3 studies, CBER agreed to the use of the (b) (4) ELISA as the mumps primary clinical readout assay in the MMR US development program; therefore, post-hoc testing was done with (b) (4) ELISA on all available samples in this Phase 2 study.

6.6.8 Endpoints and Criteria for Study Success

See Section 6.6.1.

6.6.10 Study Population and Disposition

A total of 1,259 participants were enrolled in the study. The first participant was enrolled in the study on June 3, 2009, and the last study visit was on June 18, 2012.

6.6.10.1 Populations Enrolled/Analyzed

The analysis of the Day 180 extended safety follow-up data was based on the TVC. The analyses of the antibody persistence Phase at Year 1 and Year 2 were based on the ATP vaccinated cohort.

The *Total Vaccinated Cohort (TVC)*: see Section 6.1.10.1.

According to Protocol (ATP) Cohort for Analysis of Safety: see Section 6.1.10.1.

According to Protocol (ATP) Cohort for Analysis of Immunogenicity included all eligible participants from the ATP Cohort for Safety:

- Had pre-vaccination and post-vaccination serology results available

- Who were below the assay cut-off for at least one vaccine antigen (MMR) at baseline
- Who had not received medication/vaccine forbidden in the protocol
- Who had no underlying medical condition forbidden in the protocol
- Who had no protocol violations

The ATP cohort for immunogenicity analysis was the primary analysis for immunogenicity. If >5% of the vaccinated participants were not eligible for inclusion in his cohort, a second analysis based on the TVC was to be performed.

According to Protocol (ATP) Cohort for Analysis of Antibody Persistence at Year 1 and/or Year 2 included all eligible participants from the ATP Cohort for Immunogenicity:

- Who were vaccinated with M-M-R II or PRIORIX
- Who had data concerning immunogenicity endpoint measures available for Day 0, Day 42 and Year 1 and/or 2
- Who complied with blood sampling schedules

6.6.10.1.1 Demographics

Table 59. Demographic Characteristics, TVC, Study MMR-157

Characteristic	Pooled PRIORIX N=912	M-M-R II N=308
Sex	--	--
Ratio male:female	455:457	169:139
% male: % female	49.9%:50.1%	54.9%:45.1%
Age, months		--
Mean (SD)	12.3 (0.69)	12.4 (0.75)
Median	12.0	12.0
Range	12, 15	12, 15
Ethnicity, n (%)	--	--
American Hispanic/Latino	NA	NA
Not American Hispanic/Latino	NA	NA
Racial Origin (Geographic Ancestry), n (%)	--	--
Am. Indian/A.N.	0 (0)	1 (0.3%)
All Asian	4 (0.4%)	2 (0.6%)
Central/South Asian	0 (0)	0 (0)
East Asian	0 (0)	0 (0)
Japanese	0 (0)	0 (0)
South East Asian	4 (0.4%)	2 (0.6%)
African/A.A.	89 (9.8%)	44 (14.3%)
All White	708 (77.6%)	228 (74.0%)
Arabic/North African	8 (0.9%)	3 (1.0%)
Caucasian/European	700 (76.6%)	225 (73.1%)
N. Hawaiian/P.I.	3 (0.3%)	2 (0.6%)
Other	108 (11.8%)	31 (10.1%)
Country, n (%)	--	--
United States	912 (100%)	308 (100%)

Source: Adapted from STN 125748/0, Study MMR-157, Clinical Study Report, Table 62, pooled analysis by FDA reviewer
Abbreviations: A.A.=African American; Am. Indian/A.N=American Indian/Alaskan Native; N=total number of participants in the TVC; n=number of participants with indicated characteristic; NA=not available (ethnicity information was not collected in this study) N. Hawaiian/P.I=Native Hawaiian/Pacific Islander; Other=mixed race or not otherwise specified; SD=standard deviation; TVC=total vaccinated cohort (participants with at least 1 vaccination of either PRIORIX or M-M-R II)
Note: Three different lots of M-M-R II were used during this study. Data from all lots were pooled for this summary.

The median age of participants in the TVC was 12 months with a range of 12 through 15 months at the time of the first study vaccination. Overall, in the study, the majority of participants were White/Caucasian (75.8%) and male (51.1%). Each study group was also predominantly White/Caucasian; however, the predominant gender was female in the groups PRIORIX lot 1 and lot 3. In general, demographic and baseline characteristics were similar across study groups. The demographic characteristics in the TVC were comparable to those observed in the ATP Cohort for Immunogenicity and the ATP Cohorts for Antibody Persistence at 1 and 2 years.

6.6.10.1.2 Participant Disposition

A total of 1,259 participants were enrolled into the study and 1,220 participants received a study vaccination. Of those vaccinated, 1,117 (91.6%) completed the Active Phase of the study (to Day 42). The primary reason for withdrawal between Day 0 and Day 42 (103 participants) was lost to follow up (55 participants). One participant in the M-M-R II group was withdrawn due to an SAE which was a complex febrile convulsion on Day 0.

Of those vaccinated, 1,067 (87.5%) completed the study to the Day 180 safety follow up and 880 (72.1%) completed the entire study. For the 340 participants withdrawn over the entire study period, the reasons were primarily lost to follow up. There was one additional study withdrawal due to an SAE (grade 2 idiopathic thrombocytopenic purpura in a 13-month-old on Day 20 in the PRIORIX Lot 2 group).

The primary reason for exclusion from the ATP cohort for immunogenicity was missing essential serological data (88 participants overall). Participants excluded from antibody persistent Phase ATP immunogenicity cohort were primarily missing serological data.

6.6.11 Immunogenicity Analyses

The study design did not include clinical efficacy endpoints, rather safety and immunologic endpoints were used to assess the response to the vaccine.

The primary analysis of immunogenicity was performed on the ATP cohort for immunogenicity. Since more than 5% of vaccinated participants with immunogenicity results were not eligible for inclusion in the ATP cohort, a secondary analysis on the TVC was performed. The analysis of antibody persistence was performed on the ATP cohort for antibody persistence for Years 1 and 2.

6.6.11.1 Analyses of Primary Endpoint(s)

The primary immunogenicity endpoints descriptively evaluated the immune responses at 42 days post-vaccination to the measles, mumps and rubella virus in PRIORIX compared to M-M-R II based on the percentage of participants with antibody concentrations above seroresponse thresholds.

Primary Objective 1 (Descriptive): Seroresponse rate (Active Phase)

Anti-Measles antibody response
The results show that the percentages of participants with antibodies to measles ≥200 mIU/mL were ≥98.3% and 99.6% of participants in the three PRIORIX lot groups and the pooled M-M-R II group, respectively. All 95% CIs were overlapping.

Anti-Mumps antibody response
The results show that the percentages of participants with antibodies to mumps measured by ELISA that were ≥10 EU/mL were ≥90.8% and 94.6% of participants in the three PRIORIX lot groups and the pooled

M-M-R II group, respectively. The 95% CIs of the PRIORIX lot groups were overlapping with the M-M-R II group.

The percentage of participants with antibodies to mumps measured by (b) (4) that were ≥4 ED_{50} were comparable across groups, (73.6, 85.4, and 81.7% in the PRIORIX Lot group 1, 2, and 3 respectively vs. 81.4% in the pooled M-M-R II group) each with overlapping 95% CIs when compared to the pooled M-M-R II group ([63.3, 82.3; 76.3, 92; 81.7, 72.4] in the PRIORIX Lot group 1, 2, and 3 respectively vs. [72.4, 88.4] in the pooled M-M-R II group).

> Reviewer Comment: These data indicate there was no obvious potency-response relationship in terms of observed antibody responses to the mumps component of MMR.

Anti-Rubella antibody response
The results show that the percentages of participants with antibodies to rubella ≥10 IU/mL were ≥94.67% and 98.5% of participants in the three PRIORIX lot groups and the pooled M-M-R II group, respectively. The 95% CIs of the PRIORIX lot groups were overlapping with the M-M-R II group.

> Reviewer Comment: The data generated in this study, including the percent of participants who achieved antibody concentrations above the seroresponse thresholds described, were used to confirm that the thresholds proposed for each assay reflected a statistically significant difference between seronegative participants and those above the defined seroresponse thresholds. Based on these results, CBER agreed on the assay cut-offs used by the Applicant to define seroresponse for each vaccine antigen, as described in Table 4.

6.6.11.2 Analyses of Secondary Endpoints

Secondary Objective 1 (Descriptive): GMCs (Active Phase)

The first secondary immunogenicity endpoints descriptively evaluated the immune responses at 42 days post-vaccination to the measles, mumps and rubella virus in PRIORIX compared to M-M-R II based on GMCs.

Anti-Measles antibody response
The anti-measles antibody GMCs were ≥2593.1 mIU/mL and 2949.5 mIU/mL in the three PRIORIX lot groups and the pooled M-M-R II group, respectively, with 95% CIs for GMCs that were overlapping.

Anti-Mumps antibody response
As measured by ELISA, the anti-mumps antibody GMCs were ≥45.2 EU/mL and 57.9 EU/mL in all three PRIORIX lot groups and the pooled M-M-R II group, respectively.

As measured by (b) (4), GMCs were comparable across groups (12.5, 20.3, and 14.1 in the PRIORIX lot group 1,2 and 3 respectively vs. 16.3 in the M-M-R II group), each with overlapping 95% CIs when compared to the pooled M-M-R II group ([9.2, 16.8; 15.1, 27.4; and 10.7, 18.6] in the PRIORIX lot group 1,2 and 3 respectively vs. [12.1, 21.8] in the pooled M-M-R II group).

> Reviewer Comment: These data indicate there was no obvious potency-response relationship in terms of observed antibody responses to the mumps component of MMR.

Anti-Rubella antibody response
The anti-rubella antibody GMCs were >45 IU/mL in the PRIORIX lot groups and 66.8 IU/mL, in the M-M-R II groups.

Secondary Objectives 2, 3, and 4 (Descriptive): Concomitantly administered vaccines (Active Phase)
Anti-varicella, Anti-hepatitis, Anti-Seven pneumococcal serotypes
At Day 42, observed antibody response to the concomitantly administered vaccines (VV, HAV, PCV7) in terms of seroresponse (VV and HAV), seroprotection (PCV) rates, and GMCs was considered consistent across the four groups. Seroresponse rates and GMCs were comparable between the three PRIORIX Lot groups and the M-M-R II group, with overlapping CIs for each measure.

Secondary Objectives 5, 6, 7, and 8 (Descriptive): Antibody responses at Year 1 and Year 2
At Year 1 and Year 2 post-vaccination, seroresponse rates as measured by ELISA for measles, mumps, and rubella viruses were similar between the PRIORIX lots (≥98.3%, ≥90.1%, and ≥98.9%, respectively) and the M-M-R II pooled lot (≥99.4%, ≥95.7%, and 100% respectively). GMCs as measured by ELISA were overall similar between the PRIORIX groups and M-M-R II as displayed in Table 60.

Table 60. Seroresponse Rate and GMC at 1 Year Post-Vaccination, ATP Cohort for Antibody Persistence, Study MMR-157

Antibody	PRIORIX Lot 1 N=141 to 189	PRIORIX Lot 2 N=142 to 186	PRIORIX Lot 3 N=154 to 191	M-M-R II N=146 to 183
Anti-Measles antibody	--	--	--	--
% ≥200 mIU/mL (95% CI)	99.4% (96.9, 100)	98.3% (95.1, 99.6)	100% (98.1, 100)	99.4% (96.9, 100)
GMC (95% CI)	3230.2 (2820.4, 3699.7)	3766.9 (3245.6, 4372.0)	3521.5 (3094.6, 4007.3)	3930.4 (3423.3, 4512.7)
Anti-Mumps antibody (ELISA)	--	--	--	--
% ≥10 EU/mL (95% CI)	90.1% (83.9, 94.5)	90.8% (84.9, 95.0)	90.3% (84.4, 94.4)	95.9% (91.3, 98.5)
GMC (95% CI)	47.0 (37.9, 58.2)	40.1 (33.4, 48.0)	43.9 (36.5, 52.9)	57.4 (49.1, 67.0)
Anti-Mumps antibody (b) (4)	--	--	--	--
% ≥4 ED_{50}, % (95% CI)	88.2% (82.2, 92.7)	89.4% (83.8, 93.6)	87.5% (81.8, 91.9)	88.6% (82.8, 93.0)
Anti-Rubella antibody	--	--	--	--
% ≥10 IU/mL (95% CI)	98.9% (96.0, 99.9)	99.4% (96.8, 100)	99.5% (97.1, 100)	100% (97.9, 100)
GMC (95% CI)	136.4 (121.4, 153.3)	134.8 (121.4, 149.8)	135.6 (122.0, 150.7)	165.7 (149.4, 183.9)

Source: Adapted from STN 125748/0, MMR-157, Clinical Study Report Amendment 1 (Integrated), Table 33, Table 34, Table 35, Table 36, Table 37
Abbreviations: ATP=According to protocol; CI=confidence interval; ED_{50}=endpoint dilution 50%; ELISA=enzyme-linked immunosorbent assay; EU=ELISA unit; GMC=geometric mean concentration (GMC calculations were performed by taking the anti-log of the mean of the log concentration transformations. Antibody concentrations below the assay cut-off were given an arbitrary value of one-half the assay cut-off for the purpose of GMC calculation); IU=international unit; N=number of participants in ATP; (b) (4) test; Seroresponse Rate: percentage of initially seronegative participants with concentration above seroresponse threshold for each assay; Assays: Anti-Measles, (b) (4) ELISA; Anti-Mumps, (b) (4) ELISA and (b) (4); Anti-Rubella, (b) (4) ELISA
(For each assay - seroresponse thresholds are 200 mIU/mL, 10 EU/mL, 10 IU/mL, and 4 ED_{50} for anti-measles, anti-mumps (b) (4), anti-rubella, and anti-mumps (b) (4) antibodies respectively)
Note: Three different lots of M-M-R II were used during this study. Data from these lots were pooled for this summary.
CBER agreed to the use of the (b) (4) ELISA as the mumps primary clinical readout and a (b) (4) for detection of functional antibodies. See Reviewer comment in Section 6.6.7.

Table 61. Seroresponse Rate and GMC at 2 Years Post-Vaccination, ATP Cohort for Antibody Persistence, Study MMR-157

Antibody	PRIORIX Lot 1 N=136 to 171	PRIORIX Lot 2 N=130 to 159	PRIORIX Lot 3 N=141 to 169	M-M-R II N=140 to 166
Anti-Measles antibody	--	--	--	--
% ≥200 mIU/mL (95% CI)	100% (97.9, 100)	100% (97.7, 100)	99.4% (96.7, 100)	100% (97.8, 100)
GMC (95% CI)	3361.1 (2922.3, 3865.6)	3963.8 (3479.3, 4515.7)	3360.3 (2923.3, 3862.7)	4022.1 (3507.7, 4611.9)
Anti-Mumps antibody (ELISA)	--	--	--	--
% ≥10 EU/mL (95% CI)	94.1% (88.7, 97.4)	96.2% (91.3, 98.7)	96.5% (91.9, 98.8)	95.7% (90.9, 98.4)
GMC (95% CI)	47.8 (40.2, 56.9)	50.2 (42.1, 59.9)	54.0 (46.1, 63.3)	59.2 (50.1, 70.0)
Anti-Mumps antibody (b) (4)	--	--	--	--
% ≥4 ED_{50} (95% CI)	91.7% (86.3, 95.5)	93.1% (87.6, 96.6)	96.8% (92.7, 99.0)	94.7% (89.9, 97.7)
Anti-Rubella antibody	--	--	--	--
% ≥10 IU/mL (95% CI)	100% (97.9, 100)	100% (97.7, 100)	100% (97.8, 100)	100% (97.8, 100)
GMC (95% CI)	78.0 (69.7, 87.2)	79.5 (71.7, 88.2)	81.7 (73.8, 90.4)	93.1 (83.6, 103.6)

Source: Adapted from STN 125748/0, MMR-157, Clinical Study Report Amendment 1 (Integrated), Table 33, Table 35, Table 36, Table 37
Abbreviations: ATP=According to protocol; CI=confidence interval; ED_{50}=endpoint dilution 50%; ELISA=enzyme-linked immunosorbent assay; EU=ELISA unit; GMC=geometric mean concentration (GMC calculations were performed by taking the anti-log of the mean of the log concentration transformations. Antibody concentrations below the assay cut-off were given an arbitrary value of one-half the assay cut-off for the purpose of GMC calculation); IU=international unit; N=number of participants in ATP; (b) (4) test; Seroresponse Rate: percentage of initially seronegative participants with concentration above seroresponse threshold for each assay; Assays: Anti-Measles, (b) (4) ELISA; Anti-Mumps, (b) (4) ELISA and (b) (4); Anti-Rubella, (b) (4) ELISA
(For each assay - seroresponse thresholds are 200 mIU/mL, 10 EU/mL, 10 IU/mL, and 4 ED_{50} for anti-measles, anti-mumps (b) (4), anti-rubella, and anti-mumps (b) (4) antibodies respectively)
Note: Three different lots of M-M-R II were used during this study. Data from these lots were pooled for this summary.
CBER agreed to the use of the (b) (4) ELISA as the mumps primary clinical readout and a (b) (4) for detection of functional antibodies. See Reviewer comment in Section 6.6.7.

Complement analysis on TVC cohort for immunogenicity
Since more than 5% of vaccinated participants with immunogenicity results were not eligible for inclusion in the ATP cohort for immunogenicity (10.5%), a secondary analysis on the TVC was performed. Results of this analysis were consistent with those obtained from the analysis of immunogenicity in the ATP cohort.

> Reviewer Comment: The complementary analysis in the TVC Cohort for immunogenicity and the ATP Cohort for immunogenicity was comparable, suggesting that the ATP cohort was a representative sample of the larger TVC.

6.6.11.3 Subpopulation Analyses

No sub-group analyses were performed

6.6.11.4 Dropouts and/or Discontinuations

Approximately 72% of enrolled participants completed the study (to Day 730).

6.6.12 Safety Analyses

Primary analysis of safety was performed on the TVC and the ATP Cohort for Safety. Since more than 5% of the vaccinated participants were not eligible for inclusion in the ATP Cohort for Safety, a secondary analysis based on the ATP Cohort for Safety was performed to complement the TVC analysis. The results of the ATP Cohort for Safety were consistent with those obtained from the analysis of the TVC.

6.6.12.1 Methods

See Section 6.6.2.

6.6.12.2 Overview of Adverse Events

Safety Overview
The rates for any reported AE, including local and systemic solicited reactions, unsolicited AEs, and SAEs, were similar between the pooled PRIORIX Lot groups and M-M-R II pooled groups. Overall, ≥74.0% and 75.3% of participants, respectively, reported at least one solicited or unsolicited symptom during the 43-day post-vaccination period. No subpopulation analyses were performed.

Solicited Adverse Reactions
The incidences of solicited local symptoms were comparable across the groups. For all four groups injection site pain was the most frequently reported local reaction (in all three PRIORIX groups ≥24.8 vs. pooled M-M-R II 24.5%). The percentage of participants reporting severe (grade 3) injection site pain was low (in all three PRIORIX groups ≤1.5% vs pooled M-M-R II 1.5%).

Solicited Systemic Symptoms Specific to MMR Vaccination
Overall, the most frequently reported solicited general symptom within 15 days post-vaccination was irritability or fussiness in all four groups (≥38.5% in all three PRIORIX Groups vs 39.4% M-M-R II). The percentage of participants reporting severe (grade 3) irritability or fussiness was as high as 6% among the PRIORIX Lot groups compared to 1.4% in the M-M-R II group

In the 15 days post-vaccination, fever occurred in ≥22.6% of those in the PRIORIX Lot groups compared to 20.2% of those in the M-M-R II groups. In the 43 days post-vaccination, Fever occurred in ≥36.4% and 30.7% of those in the PRIORIX groups and the M-M-R II groups, respectively. Post hoc analyses evaluated the fever rates overall and also assessed temperature measurements (0.5°C increments) between Day 5 and Day 12, irrespective of primary investigator assessment, as well as for events considered related to vaccination by the investigator. The incidence of any fever during the Day 5 to Day 12 period was <23.3% in any group. Grade 3 fever (rectal temperature >39.5°C) was reported in <3% of participants in all four groups during this period. When looking at any fever within Day 0 to Day 42 period, the peak prevalence of fever was Day 6 to Day 10 in all four groups.

Reviewer Comment:

1. Overall, the occurrence of solicited reactions were similar between the two groups. The most frequently reported solicited local reactions was injection site pain and the most frequently reported solicited general symptoms was irritability or fussiness. Most adverse reactions were Grade 1.
2. See Reviewer Comment 2 in Section 6.1.12.2 under the subsection Solicited Systemic Symptoms Specific to MMR Vaccination for an explanation of which events qualified as febrile convulsions. For study MMR-157, the proportion with each event were provided as follows:
    - Meningism excluding febrile convulsions:

  - Pooled PRIORIX: 0% (0/842 participants)
  - M-M-R II: 0% (0/277 participants)
- Febrile convulsions:
  - Pooled PRIORIX: 0.1% (1/842 participants)
  - M-M-R II 0% (0/277 participants)

Ongoing Adverse Reactions and Adverse Reactions with Onset After Reporting Period
Overall, the proportion of participants with solicited reactions with onset during the solicited reporting period that were ongoing after the last day of the reporting period was similar across groups, low, and predominantly grade 1 to 2. The highest percentages for ongoing solicited ARs were for rash (PRIORIX Lot 1: 3.18, Lot 2: 4.71, Lot 3: 2.83 and M-M-R II 4.33%) and irritability/fussiness (PRIORIX Lot 1: 3.53, Lot 2: 3.26, Lot 3: 1.77% and M-M-R II 2.53%)

In general, the proportion of participants with solicited symptoms with onset after the reporting period was low. The proportion of any local solicited reaction with onset after the reporting period (Day 0 to Day 3) was 0%in all three PRIORIX lot groups and in the M-M-R II group. The proportion of solicited systemic symptoms with onset after the reporting period (Day 0 to Day 14) and symptoms specific to MMR vaccination with onset after the reporting period (Day 0 to Day 42) ranged from 0-1.64% across all three PRIORIX lot groups and 0-0.65% in the M-M-R II group.

See Reviewer Comment in Section 6.1.12.2 under the subsection Ongoing Adverse Reactions and Adverse Reactions with Onset After Reporting Period for an explanation of how duration was calculated.

Solicited and Unsolicited AEs (Non-Serious): Day 0 to Day 42
The most commonly reported solicited general symptom, Day 0 to Day 42 post-vaccination, across all four groups was irritability/fussiness, occurring in ≥51.3% across all four groups. Febrile convulsions were reported in 2 participants. One participant in PRIORIX Lot 2 group developed a grade 1 febrile convulsion that was not considered vaccine related by the investigator. One participant in M-M-R II group developed a grade 2 febrile convulsion and required hospitalization. This was considered vaccine related by the investigator and lead to participant withdrawal.

> Reviewer Comment: The grade 1 febrile convulsion described occurred in a 12-month-old female on Day 29 post-vaccination. She had been diagnosed with a UTI on Day 22, Her fever on Day 28 and Day 29 post-vaccination were 38.6°C and 39.3°C rectal, respectively. The grade 2 febrile convulsion described occurred in a 12-month-old female the evening of vaccination with a temperature of 38.2°C at the time of the convulsion. She was hospitalized for treatment. The clinical reviewer agrees with the assessment of the investigator.

6.6.12.3 Deaths

There were no deaths reported in this study (Day 0 until Day 730).

6.6.12.4 Nonfatal Serious Adverse Events

A total of 34 SAEs were reported in 23 participants in the entire study period, with similar incidence across groups (PRIORIX Lot 1, 0.3%; PRIORIX Lot 2, 2.0%; PRIORIX Lot 2.3%; M-M-R II, 2.9%). Three of the 34 reported SAEs were considered vaccine-related by the investigator: grade 2 idiopathic thrombocytopenic purpura onset Day 20 in a 13-month-old female (PRIORIX Lot 2 group), grade 2 febrile convulsion on Day 0 in a 12-month-old female (M-M-R II) and grade 3 lymphadenitis with onset Day 68 in a 14-month-old male (PRIORIX Lot 3 group).

Reviewer Comment: The clinical reviewer agrees with two of the 34 reported SAEs (the case of idiopathic thrombocytopenic purpura and the case of febrile convulsions as being likely related to study vaccination, however given the timing of onset of the case of lymphadenitis (68 days post-vaccination), the location (right inguinal- near the site of PCV7 vaccination) with associated elevation of inflammatory markers (neutrophilia and bandemia), there is a possibility that the study vaccination was not related to this event.

6.6.12.5 Dropouts and/or Discontinuations

The most common reasons for study discontinuation (Table 62) were lost to follow-up with complete vaccination course (208 participants) followed by consent withdrawal, not due to an adverse event (97 participants). The rate of those lost to follow-up with complete vaccination course was comparable across groups.

Two participants were withdrawn due to an SAE (Section 6.6.12.4): a participant with complex febrile seizures and a participant with idiopathic thrombocytopenic purpura. Both were considered by the investigator to be causally related to vaccination and both resolved prior to study completion.

Table 62. Discontinuations, All Randomized Participants, Study MMR-157

Population	PRIORIX Lot 1 N=304 % (n/N)	PRIORIX Lot 2 N=305 % (n/N)	PRIORIX Lot 3 N=305 % (n/N)	M-M-R II N=310 % (n/N)
Enrolled[a]	100% (304/304)	100% (305/305)	100% (305/305)	100% (310/310)
Vaccinated	100% (304/304)	99.7% (304/305)	99.7% (304/305)	99.4% (308/310)
Completed study[b]	73.0% (222/304)	71.4% (217/304)	75.0% (228/304)	69.2% (213/308)
Withdrawal due to	--	--	--	--
Consent withdrawal	6.6% (20/304)	6.3% (19/304)	6.9% (21/304)	12.0% (37/308)
Lost to follow-up	--	--	--	--
Migrated/moved from study area	1.6% (5/304)	3.0% (9/304)	3.0% (9/304)	1.0% (3/308)
Lost to follow-up (participants with incomplete vaccination course)	0	0	0	0
Lost to follow-up (participants with complete vaccination course)	18.8% (57/304)	18.1% (55/304)	14.8% (45/304)	16.6% (51/308)
Protocol deviation	0	0.3% (1/304)	0	0
Non-serious AE	0	0	0	0
Serious AE[c]	0	0.3% (1/304)	0	0.3% (1/308)
Death	0	0	0	0
Other[d]	0	0.7% (2/304)	0.3% (1/304)	1.0% (3/308)

Source: Adapted from STN 125748/0, MMR-157 Clinical Study Report Amendment 1 (Integrated), Table 14, Table 15, Synopsis Table 5
Abbreviations: AE=adverse event; N=number of participants in population; n=number of participants who met given criteria
Note: Three different lots of M-M-R II were used during this study. Data from these lots were pooled for this summary
a. A total of 1,259 participants were enrolled in this study. Thirty-five participants were enrolled but not randomized to a treatment group.
b. Table shows disposition through Day 730 (entire study period).
c. SAEs were Grade 3 idiopathic thrombocytopenic purpura in the PRIORIX Lot 2 group and Grade 2 febrile convulsion in the M-M-R II group.
d. Other reasons included: One participant each moved to another doctor and unable to draw labs (i.e., drawing blood in lab) in the PRIORIX Lot 2 group; difficulty drawing blood in labs in the PRIORIX Lot 3 group; and blood draws (i.e., no blood draw), parent did not want to continue due to scheduling, and withdrawn as no guardian for consent in the M-M-R II group.

6.6.13 Study Summary and Conclusions

Study MMR-157 was designed to demonstrate the safety of a modified mumps vaccine virus manufacturing process, the immunogenicity and reactogenicity of the three components of PRIORIX and the duration of the antibody responses following vaccination as a single dose in children 12 through 15 months of age compared to M-M-R II, a licensed MMR vaccine, while concomitantly administered with routinely recommended vaccines for age. The primary objectives were descriptive and showed similar SRRs across three lots of PRIORIX and M-M-R II, including for the seroresponse rates as measure by (b) (4) to mumps virus and ELISA. The secondary objectives were also descriptive and demonstrated overall similar GMCs between the PRIORIX groups and M-M-R II. The humoral immune responses to concomitantly administered vaccine antigens were also similar across groups, (Varivax, Havrix, and Prevnar 7) compared to when M-M-R II was concomitantly administered with these vaccines. Additionally, SRRs when compared between PRIORIX and M-M-R II groups, were similar at 1- and 2-years post-vaccination. The safety profile of PRIORIX was comparable to the safety profile of the M-M-R II and did not demonstrate any safety concerns. The data from this study provided estimations of seroresponse thresholds, a determination of mumps potency, and provided data to guide development of statistical criteria for Phase 3 trials.

7. Integrated Overview of Efficacy

The studies in this BLA did not include clinical efficacy endpoints. Serological immune endpoints were used to assess the response to vaccination. Comparisons of vaccine-specific antibody responses to measles, mumps, and rubella in terms of GMCs and SRRs to those of the US-licensed trivalent combined MMR vaccine, M-M-R II were provided to support the effectiveness of PRIORIX. Formal evaluations of antibody responses to each vaccine antigen via hypothesis testing of PRIORIX compared to M-M-R II in non-inferiority analyses were performed with individual studies as described in the study objectives for MMR-158, MMR-159, MMR-160, and MMR-161. These four studies with formal hypothesis testing met the protocol-defined statistical criteria for success for PRIORIX at the planned commercial potency, when evaluated by ELISA, when compared to M-M-R II.

8. Integrated Overview of Safety

CBER advised that an Integrated Summary of Safety would not be necessary and that a Summary of Clinical Safety summarizing the safety data by study would be considered adequate to review the overall safety of PRIORIX. In follow-up responses dated November 18, 2020, CBER agreed that safety results would be provided for each individual study with 95% CIs for relative risk between groups for unsolicited AEs and for NOCD.

8.1 Safety Assessment Methods

Safety data included in this application and reviewed to characterize the safety profile of the final formulation of PRIORIX were from the following sources:
Main trials: MMR-160, MMR-158, MMR-161, MMR-162, MMR-159, MMR-157.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

There were 6 studies (MMR-160, MMR-158, MMR-161, MMR-162, MMR-159, MMR-157) included in this application to describe the safety profile of PRIORIX. The safety database across these 6 trials included children 12 through 15 months of age and children and adults 4 years of age and older. The database included 17,393 participants who were enrolled in 11 countries, of which, 12,151 participants received PRIORIX.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Across these 6 studies, 71.7% were 12 through 15 months of age, 23.0% were 4 through 6 years of age, and 5.2% were 7 years of age and older. The PRIORIX exposure by age is presented in Table 63. Across the six studies, 44.0-56.4%% were female, and 43.6-54.6% were male. The majority of the participants were White/Caucasian (67.5-77.3%). The majority of PRIORIX recipients (6,391) were enrolled in sites in the United States (52.6%).

Table 63. PRIORIX Exposure by Age

Age Group	Studies	Number of Participants
12 to 15 months	MMR-160, MMR-161, MMR-162, MMR-157	8780
4 through 6 years	MMR-158	2917
7 years of age and older	MMR-159	454

8.2.3 Categorization of Adverse Events

Safety data collected across each study included the following:

- Solicited local and general symptoms.
  - Occurrence of solicited local symptoms in terms of injection site redness, pain, and swelling from Day 0 to Day 3 after vaccination.
  - Occurrence of solicited general symptoms in terms of drowsiness, loss of appetite, and irritability from Day 0 to Day 14 after vaccination.
  - Occurrence of solicited general symptoms in terms of fever (temperature ≥38.0°C/100.4°F), rash, parotid/salivary gland swelling, any sign of meningism (including febrile convulsions) from Day 0 to Day 42 after vaccination.
- Unsolicited adverse events.
  - Occurrence of unsolicited symptoms, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification, from Day 0 to Day 42 after vaccination.
- Adverse events of specific interest.
  - Occurrence of NOCD (e.g., autoimmune disorders, asthma, type I diabetes, vasculitis, celiac disease, conditions associated with subacute or chronic thrombocytopenia and allergies) and AEs prompting ER visits from Day 0 through the EOS.
- Serious adverse events.
- Occurrence of serious adverse events from Day 0 through the EOS.

Joint pain was additionally considered as a solicited systemic symptom in study MMR-159 due to the inclusion of adults and older children.

8.4 Safety Results

8.4.1 Deaths

Across all six studies, there were 3 deaths throughout the entire study period: two deaths among PRIORIX recipients and 1 death among M-M-R II recipients. Upon careful review of the case narratives, it was determined that none were considered related to study vaccination by the clinical review team.

8.4.2 Nonfatal Serious Adverse Events

Case narratives for SAEs reported by PRIORIX recipients are described in the review of individual studies (Section 6). Rates of SAEs following administration of PRIORIX as compared to M-M-R II were similar and <2.3% within each study. The types of SAEs observed in the clinical trials were events that

have been reported previously with other MMR-containing vaccines. All SAEs considered related to the administration of PRIORIX resolved without sequelae by the end of the study period.

8.4.3 Study Dropouts/Discontinuations

Dropouts and Discontinuations are described in the review of individual studies (Section 6).

8.4.4 Common Adverse Events and Solicited Adverse Events

Across all studies, the rates of AEs were comparable; 20.9-55.9% of PRIORIX recipients and 17.9-54.9% of M-M-R II recipients reported ≥1 solicited AE. The most frequently reported solicited AEs included injection site pain (11.8-40.6%), followed by injection site redness (11.1-24.5%), and injection site swelling (4.7-11.3%). For all studies the most frequently reported events in children 12 through 15 months of age after a first dose of PRIORIX were of SOC *Infections and Infestations* with the PT of URIs (PRIORIX 9.5-14.6% vs. M-M-R II 9.5-15.0%). After a second dose of PRIORIX, the most frequently reported events were of SOC *Infections and Infestations* with the PTs of URIs (PRIORIX 6.9-13.2% vs. M-M-R II 4.3-13.1%) and nasopharyngitis (5.6-9.7% vs. 5.2-9.2%, respectively).

8.5 Safety Conclusions

In a total of 6 randomized clinical trials conducted in 11 countries, 12,151 participants received at least 1 dose of PRIORIX and provided post-vaccination safety data. Overall, the reactogenicity profile was similar to that of the licensed comparator vaccine, M-M-R II. No safety concerns were identified when a single dose of PRIORIX was administered to children 12 through 15 months of age, and children and adults 4 years of age and older, with or without prior exposure to an MMR-containing vaccine. Rates of fever (>39.0°C and ≥38.0°C) following administration of PRIORIX (release potency) and M-M-R II (commercial lots), were similar after a first dose to children 12 through 15 months of age. Safety for children who begin vaccination after 15 months of age but before 4 years of age was extrapolated from the data generated in clinical studies in children 12 through 15 months of age and 4 through 6 years of age.

Review of the post-marketing safety data from the EU and other countries by the CBER OBPV/DPV reviewer did not identify additional safety concerns or risks that have not been previously described for other MMR-containing vaccines.

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 memo.

9.1.1 Human Reproduction and Pregnancy Data

PRIORIX contains live attenuated measles, mumps, and rubella viruses. Similar to M-M-R II, the vaccine should be contraindicated for use in pregnant women because infection during pregnancy with the wild-type viruses is associated with maternal and fetal adverse outcomes.

Pregnancy should be avoided for 1 month after vaccination as per the Centers for Disease Control and Prevention (CDC, 2013). For women who are inadvertently vaccinated when pregnant or who become pregnant within 1 month of administration of PRIORIX, the healthcare provider should be aware of the following: Reports have indicated that contracting wild-type measles during pregnancy increases fetal risk. Mumps infection during the first trimester of pregnancy may increase the rate of spontaneous

abortion. Pregnant women infected with rubella are at increased risk for miscarriage or stillbirth, and their infants are at risk for congenital rubella syndrome.

Available data on inadvertent administration of PRIORIX to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

There are no animal studies with PRIORIX to inform use during pregnancy.

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the general US population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

9.1.2 Use During Lactation

The application did not contain data from clinical studies specifically addressing whether the vaccine viruses are excreted in human breast milk. The following language is proposed for inclusion in the PRIORIX prescribing information based on literature reviewed:

"It is not known whether the vaccine components of PRIORIX are excreted in human milk. Data are not available to assess the effects of PRIORIX on the breastfed infant or on milk production and excretion. Studies have shown that lactating postpartum women vaccinated with live attenuated rubella vaccine may secrete the virus in breast milk and transmit it to breast-fed infants. In the breast-fed infants with serological evidence of rubella virus vaccine strain antibodies, none exhibited severe disease; however, one exhibited mild clinical illness typical of acquired rubella. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PRIORIX and any potential adverse effects on the breastfed child from PRIORIX or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine."

9.1.3 Pediatric Use and PREA Considerations

Safety and effectiveness of PRIORIX in infants younger than 12 months of age have not been established.

As specified in the Pediatric Research Equity Act (PREA), the Applicant requested that the assessment of PRIORIX 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

Most infants receive passive protection against measles, mumps, and rubella in the form of antibodies from their mothers via trans-placental transmission. These antibodies can prevent vaccine virus replication if they are present when the vaccine is given and, thus, can cause the vaccine to be less effective. By 12 months of age, almost all infants have lost this passive protection. For this reason, ACIP recommends that children in the US receive a first dose of MMR vaccine at ≥12 months of age once maternal antibodies have been lost.

ACIP does recommend vaccination below 12 months of age in the event of an outbreak or if the child would be traveling to an area where measles infection is endemic. However, in these situations ACIP

considers these young children are still susceptible to all three diseases and recommends revaccination at ≥12 months of age (considered as their first dose) (CDC, 2013). Consequently, in the US, unless there is an outbreak, few children less than 12 months of age are likely to be vaccinated with MMR vaccine; therefore, the vaccine does not represent a therapeutic benefit to children in this age group.

The Applicant's request for a partial waiver in infants less than 12 months of age was presented to FDA's Pediatric Review Committee (PeRC). PeRC agreed with the partial waiver request in a letter dated January 26, 2017.

9.1.4 Immunocompromised Patients

Administration of PRIORIX poses a potential risk to immunocompromised individuals due to the live replication-competent virus strains contained in the vaccine. The following language is proposed for inclusion in the PRIORIX prescribing information:

"Due to the risk of disseminated vaccine virus infection, do not administer to individuals with severe humoral or cellular (primary or acquired) immunodeficiency."

9.1.5 Geriatric Use

Clinical studies of PRIORIX did not include participants 65 years of age and older. The upper age limit across studies was 59 years. The data from study MMR-157 (age range: 7 to 59 years) are considered adequate to extrapolate safety and effectiveness to older persons.

9.2 Ungraduated Pre-Filled Syringe Presentation

With this BLA, the Applicant submitted clinical trial data from Phase 2 Study MMR-157 that utilized the lyophilized vaccine antigen in a vial plus the diluent in an ungraduated pre-filled syringe (PFS) presentation for use in a Whole Content/Whole Content (WC/WC) approach for PRIORIX reconstitution and administration. The safety and immunogenicity data generated from this study using the ungraduated PFS presentation are consistent with the Phase 3 clinical trial data findings using the vial/vial presentation (See Section 6.6), thus providing evidence to support the commercial use of the diluent in an ungraduated PFS presentation and the Whole Content/Whole Content (WC/WC) approach for PRIORIX reconstitution and administration. The Applicant submitted a Use Related Risk Analysis (URRA) to their IND which included information that the ungraduated PFS presentation has been used in PRIORIX marketed in other countries (e.g., PRIORIX Australia, AUS). Due to the similar presentation characteristics between PRIORIX US and PRIORIX AUS and the Applicant's report of the medication errors associated with use of PRIORIX AUS, the clinical reviewer assessed that the risk of medication errors associated with WC/WC administration is low. A formal consultation with the Division of Medication Error Prevention and Analysis (DMEPA) at CDER/FDA, will be completed post-licensure but is not considered essential for the approval of PRIORIX. Any recommendations from the DMEPA consultation will be communicated to the Applicant as appropriate.

10. Conclusions

The US clinical development plan for PRIORIX consisted of six studies that enrolled 17,393 participants (9,080 in the US) of whom 12,151 received at least 1 dose of PRIORIX (6,391 in the US). Of those vaccinated, 8,780 were 12 through 15 months of age and received PRIORIX as a first dose (4,148 in the US), and 6,284 received PRIORIX as a second dose at varying ages (2,845 in the US).

The proposed indication for PRIORIX, active immunization for the prevention of measles, mumps, and rubella in persons 12 months of age and older, is supported by demonstration of non-inferior antibody

responses compared to M-M-R II in terms of SRRs and GMC/GMT for antibodies to measles, mumps, and rubella viruses in four Phase 3 studies. PRIORIX was evaluated among participants 12 through 15 months of age after a single dose of PRIORIX (study MMR-160), in participants 4 through 6 years of age (study MMR-158), and ≥7 years of age (study MMR-159). In study MMR-161, a second dose (planned commercial potency) of PRIORIX, spaced 6 weeks later, PRIORIX elicited antibody responses to all 3 viruses in terms of SRRs and GMCs comparable to those elicited by M-M-R II. Clinical consistency in terms of immune response across the three PRIORIX lots manufactured with targeted release potencies for use in the US was demonstrated in study MMR-160.

The Phase 2 Study, MMR-157 demonstrated that PRIORIX is immunogenic when administered as a single dose in participants 12 through 15 months of age with seroresponse rates that remained nominally above 90% for 2 years for all antigens. The antibody responses to vaccine virus antigens and the concomitantly administered vaccine antigens were comparable between PRIORIX and MMR-II when concomitantly administered with routine US pediatric vaccines. Based on the immune response to measles, mumps, and rubella antigens post-dose 1 in participants 12 through 15 months of age in study MMR-161, the EOSL specifications for use of PRIORIX in the US were defined as 3.4 $\log_{10}$ $CCID_{50}$ per dose for measles, 4.2 $\log_{10}$ $CCID_{50}$ per dose for mumps, and 3.3 $\log_{10}$ $CCID_{50}$ per dose for rubella.

Across all studies, the safety data collected in the PRIORIX US CDP did not differ from the known and acceptable safety profile of M-M-R II. No safety signals were detected that would require further assessment in post-marketing safety studies. PRIORIX was generally well tolerated when given as a first or second dose. The second dose of PRIORIX had a safety profile comparable to that of the first dose. The reactogenicity and safety profile following co-administration of PRIORIX and ACIP-recommended routine childhood vaccinations was comparable to the reactogenicity and safety profile of M-M-R II concomitantly administered with the same vaccines. The reactogenicity and safety profile of PRIORIX in participants enrolled in the US was comparable to the reactogenicity and safety profile of PRIORIX in the overall population. Similarly, the reactogenicity and safety profile of PRIORIX in sub-groups of participants by gender and race was comparable to that of the overall population. The safety data reported during the post-marketing surveillance of PRIORIX used outside the US are consistent with safety reporting following post-marketing use of M-M-R II.

Overall, the safety and effectiveness data provided in the application support the safety and effectiveness of PRIORIX for the proposed Indication and Usage.

11. Risk-Benefit Considerations and Recommendations

11.1 Risk-Benefit Considerations

Table 64. Risk-Benefit Summary

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Measles is a highly contagious viral disease primarily affecting children. Common complications from measles include pneumonia and diarrhea, which can lead to significant morbidity and mortality. Measles still causes over 140,000 deaths world-wide, with the highest disease incidence by age occurring among children under 5 years of age. Children under 5 years, pregnant women, immunocompromised individuals, and adults are at highest risk for measles complications and death. • Mumps is an acute viral illness that results in inflammation of the salivary glands and most often presents as parotitis. Other manifestations of the infection include orchitis (in post-pubertal males), oophoritis (in post-pubertal females), and meningoencephalitis. • Rubella is a viral disease primarily affecting children, which manifests clinically with rash, low-grade fever, lymphadenopathy, and malaise. Fetal infection, particularly in the first trimester, can result in miscarriages, stillbirths, and Congenital Rubella Syndrome (CRS), the latter of which can present with cataracts, hearing loss, mental retardation, and congenital heart defects.	• Prevention of these highly infectious childhood diseases by vaccination would 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.
Unmet Medical Need	• Although there is one manufacturer of licensed MMR-containing vaccines in the US, a second MMR vaccine by a different manufacturer would provide additional options and access to vaccination, particularly in the setting of vaccine shortages or outbreaks.	• An alternative vaccine option in the setting of an outbreak or shortage makes the availability of additional MMR vaccines relevant.
Clinical Benefit	• The immunogenicity of PRIORIX, administered as either a first or second dose was evaluated in 6 randomized, double blind clinical trials, compared to M-M-R II. Altogether, a total of 12,485 children ages 12 through 15 months of age and 4,007 children 4 through 6 years of age participated in these trials, as well as 911 children and adults 7 years of age and older. In these trials 12,151 individuals received PRIORIX and 5,242 individuals received M-M-R II. • The effectiveness of PRIORIX in prevention of measles, mumps, or rubella was inferred from antigen specific serological responses compared to responses induced by M-M-R II. Immunological evaluations included non-inferiority of immunogenicity of PRIORIX in terms of SRR and GMCs: o After a first dose in MMR-naïve children, 12 through 15 months of age o As a second dose in MMR-primed children, 4 through 6 years of age • Immunological interference was not observed when PRIORIX was concomitantly administered with age-appropriate vaccines at 12 through 15 months of age (Varivax, Havrix, Prevnar 13) and 4 through 6 years of age (Varivax. DTaP), based on antibody responses of MMR, VZV, Hepatitis A, 13 pneumococcal serotypes, diphtheria (D), tetanus (T), pertussis	• The immunogenicity data support the effectiveness of PRIORIX by demonstrating comparable antibody responses to M-M-R II, a US-licensed measles, mumps, and rubella virus-containing vaccine. • The data submitted in this application also support the preservation of the humoral immune response induced by PRIORIX and by ACIP-recommended routine childhood vaccinations when concomitantly administered.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	toxoid (PTx), Filamentous Hemagglutinin (FHA), and Pertactin (PRN) in terms of SRRs and GMCs.	
Risk	• The rates of solicited injection site and systemic adverse reactions (AR) after PRIORIX were as follows: local pain 11.8-40.6%; local erythema 11.1-24.9%; local swelling 4.7-11.3%; Most solicited ARs were reported as mild or moderate with <4.9% reporting Grade 3/severe solicited ARs. The rates of reported SAEs were low (<2.3% across all studies). Across all six studies, there were 3 deaths throughout the entire study period. There were two deaths in PRIORIX recipients and 1 death in M-M-R II recipients; none were considered related to study vaccination. • PRIORIX is approved in all EU countries and over 70 non-EU countries. Over 388 million doses have been distributed outside the US. Post-marketing safety data from the EU and other countries did not identify safety concerns or risks that have not been previously described for other MMR-containing vaccines. • The most common risks of PRIORIX vaccination were described above	• The data from PRIORIX clinical studies adequately characterize the safety of PRIORIX. Overall, the safety results were comparable to those of M-M-R II. The safety profile of PRIORIX is acceptable for its intended use. • The post-marketing safety experience outside the US provides additional reassurance regarding the safety of PRIORIX.
Risk Management	• The most common risks of PRIORIX vaccination were described above.	• The risks of PRIORIX are adequately characterized in the USPI. Routine pharmacovigilance to monitor adverse events in accordance with 21 CFR 600.80 is sufficient.

11.2 Risk-Benefit Summary and Assessment

The overall clinical benefit of PRIORIX in individuals 12 months of age and older in prevention of measles, mumps, and rubella is favorable compared to the risks associated with vaccination. Data submitted to this BLA establish the safety and effectiveness of PRIORIX among individuals in the age groups for which it is indicated. The safety of PRIORIX 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

Due to the low incidence of disease caused by measles, mumps and rubella, clinical studies designed to prevent clinical disease endpoints are not feasible. PRIORIX induces an immune response to the viral antigens contained within the vaccine. The effectiveness of PRIORIX is based on determination of non-inferior antibody responses compared to the US-licensed vaccine, M-M-R II, for which effectiveness for the prevention of clinical disease has previously been demonstrated in children. PRIORIX contains similar virus strains as M-M-R II and similar virus potencies.

Safety data and analyses provided in the BLA 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 PRIORIX for the prevention of measles, mumps, and rubella in individuals 12 months of age and older.

11.5 Labeling Review and Recommendations

The proprietary name PRIORIX was reviewed by the Advertising and Promotional Labeling Branch and found acceptable. 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 Post-marketing 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 adverse event reporting as required under 21 CFR 600.80.