Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Division of Pharmacovigilance (DPV)

PHARMACOVIGILANCE PLAN REVIEW MEMORANDUM

From:	Yeowon A. Kim, MD, MHS Medical Officer, Pharmacovigilance Branch 1 (PB1) Division of Pharmacovigilance (DPV) Office of Biostatistics and Pharmacovigilance (OBPV)
To:	Luba Vujcic, MS Chair, Review Committee Division of Vaccines and Related Products Applications (DVRPA) Office of Vaccines Research and Review (OVRR)
Through:	Adamma Mba-Jonas, MD Branch Chief, PB1 DPV, OBPV Narayan Nair, MD Division Director, DPV OBPV
Subject:	Review of Pharmacovigilance Plan
Applicant:	GlaxoSmithKline Biologicals
Proprietary Name/ Established Name:	PRIORIX®/Measles, Mumps, and Rubella Vaccine, Live, Attenuated
BLA Number:	125748/0
Proposed Indication:	For active immunization for the prevention of measles, mumps, and rubella in individuals aged 12 months of age or older
Submission Date:	04 June 2021
Action Due Date:	03 June 2022

1. OBJECTIVE

This memo reviews the adequacy of the pharmacovigilance plan (PVP) submitted by GlaxoSmithKline Biologicals for the original BLA 125748/0. The proposed indication for PRIORIX is active immunization for the prevention of measles, mumps, and rubella in individuals aged 12 months of age or older.

2. INTRODUCTION

2.1 Background

Measles and mumps viruses can cause severe acute febrile illness while rubella, in addition to mild, acute febrile illness, can also cause congenital infection. Rubella infection can result in miscarriage, stillbirth, or congenital rubella syndrome (CRS). Measles is highly contagious and characterized by fever, rash, malaise, cough, coryza, and conjunctivitis. Complications include diarrhea, secondary infection (e.g., bacteremia, pneumonia, gastroenteritis, and otitis media), and neurologic manifestations (e.g., encephalitis, acute disseminated encephalomyelitis, and subacute sclerosing panencephalitis) (Gans et al. 2019). Mumps is typically self-limited and characterized by fever, headache, myalgia, fatigue, and parotitis. Complications include orchitis or oophoritis and neurologic manifestations (e.g., meningitis, encephalitis, and sensorineural hearing loss) (Albrecht 2020). The clinical manifestations of postnatally acquired rubella are generally mild, and include low grade fever, lymphadenopathy, maculopapular rash, arthritis, and arthralgia. Classic manifestations of CRS include deafness, cataracts, and cardiac disease (Edwards 2021).

The advent of universal vaccination campaigns in the U.S. against measles, mumps, and rubella (MMR) in 1963, 1967, and 1969, respectively, resulted in the elimination of endemic measles and rubella and a dramatic reduction in mumps cases (Jacobson 2020). The three vaccines were combined into a single trivalent vaccine in 1971. Despite over 50 years of widespread vaccination, the number of measles cases has recently increased, with most cases occurring in unvaccinated or under-vaccinated subpopulations; there were 1249 reported cases in 2019 (Patel et al. 2019). Multiple mumps outbreaks have been reported involving populations with high rates of vaccination with two doses of MMR vaccine. Cases of CRS have been rare; in the recent years, the few infants born in the U.S. with CRS were birthed by mothers who were infected with rubella while pregnant, prior to their arrival in the U.S. (CDC 2013; Jacobson 2020).

The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination with MMR vaccine, with the first dose administered in children 12-14 months and the second dose at ages 4-6 years. In addition, the ACIP recommends that a second dose of mumps-containing vaccine be considered in outbreak settings for children aged 1-4 years, and a third dose of mumps-containing vaccine in persons previously vaccinated with two doses of a mumps virus-containing vaccine who are identified by public health authorities as being at increased risk for acquiring mumps

due to an outbreak (Marin et al. 2018). Currently, there are two MMR-containing vaccines licensed in the U.S.:

- M-M-R II® (Measles, Mumps, and Rubella Virus Vaccine Live)[1]
- ProQuad® (Measles, Mumps, Rubella and Varicella Virus Vaccine Live)[2]

Both vaccines contain live, attenuated measles, mumps, and rubella viruses, and are manufactured by Merck Sharp & Dohme; ProQuad (MMRV) also contains live, attenuated varicella-zoster virus.

2.2 Product Information

PRIORIX is a live viral vaccine composed of 3 live attenuated viruses 1) measles (Schwarz strain), 2) mumps (RIT 4385 strain), and 3) rubella (Wistar RA 27/3 strain). Each virus strain is obtained separately by propagation in either chick embryo tissue cultures (mumps and measles) or MRC human diploid cells (rubella). The measles vaccine strains used in MMRII and PRIORIX are both derived from the Edmonston strain (Strebel et al. 2018). The mumps vaccine strain used in PRIORIX was derived from Merck's Jeryl Lynn strain (Rubin et al. 2018). MMRII and PRIORIX contain the same rubella vaccine strain. The final product is a sterile, single-dose, lyophilized formulation to be reconstituted with water for subcutaneous injection in a pre-filled syringe. The proposed indication is active immunization for the prevention of measles, mumps, and rubella in individuals aged 12 months or older. The proposed dosing regimen is a two-dose series, with the first dose administered at 12-15 months of age and the second dose administered at 4-6 years of age.

2.3 Regulatory History

The international birth date of PRIORIX is 25 November 1997; it was first licensed in Germany. PRIORIX is currently approved in all European Union (EU) countries as well as over 70 non-EU countries. Over 388 million doses have been distributed outside the U.S[3].

Pertinent review cycle history is summarized below:

- 19 December 2011 (End-of-Phase 2 Meeting): FDA stated that the proposed size of the safety database appears adequate provided that there are no unexpected safety concerns identified. Enrollment of U.S. subjects should be adequate to evaluate safety per the U.S. schedule of recommended vaccines and for each study to meet pre-specified safety endpoints.
- 26 January 2017 (Agreed Initial Pediatric Study Plan – Agreement Letter): FDA confirmed agreement with the submitted agreed initial Pediatric Study Plan (aiPSP), including the applicant's partial waiver request for the pediatric population <12 months of age.

[1] Referred to as MMRII for the remainder of the document
[2] Referred to as MMRV for the remainder of the document
[3] BLA 125748/0, Module 2.5, Clinical Overview.

- 06 June 2017 (Type C Meeting, CRMTS #10695): FDA stated that all safety data following a second dose of PRIORIX in Study MMR-161 will be considered in the evaluation of safety.
- 16 October 2020 (Type B Pre-BLA Written Responses, CRMTS #12804): FDA stated an integrated summary of safety (ISS) was not required due to differences across studies regarding 1) the potencies of the investigational vaccine used, 2) concomitant vaccines administered, 3) age of study participants. Postmarketing safety data from outside the U.S. may be considered for inclusion under Section 6.2 of the U.S. Package Insert (USPI); FDA agreed with the submission of the most current Periodic Safety Update Report (PSUR) for PRIORIX.

3. MATERIALS REVIEWED

Source	Subtype	Document Reviewed
GlaxoSmithKline	BLA 125748/0	Clinical Overview
GlaxoSmithKline	BLA 125748/0	Summary of Clinical Safety
GlaxoSmithKline	BLA 125748/0	Risk Management Plan, GRMP Version 1.0, dated 03 April 2018
GlaxoSmithKline	BLA 125748/0	Draft Labeling
GlaxoSmithKline	BLA 125748/0	Periodic Benefit Risk Evaluation Report (Reporting Period: 05 May 2015 to 04 May 2018), dated 25 July 2018
GlaxoSmithKline	BLA 125748/0	Synopses of Individual Studies (MMR-157, MMR-158, MMR-159, MMR-160, MMR-161, MMR-162)
GlaxoSmithKline	BLA 125748/0	Clinical Study Reports of Individual Studies (MMR-157, MMR-158, MMR-159, MMR-160, MMR-161, MMR-162)
GlaxoSmithKline	BLA 125748/0.4 (Sequence 5)	BLA Amendment, Response to 02 September 2021 request regarding rationale for inclusion of adverse reactions in Section 6.2 of draft USPI
GlaxoSmithKline	BLA 125748/0.12 (Sequence 13)	BLA Amendment, Response to 25 October 2021 request for information regarding select adverse reactions in Section 6.2 of draft USPI and brief analysis/summary of four previously important identified risks (e.g., hypersensitivity, syncope, febrile convulsions, and ITP)
GlaxoSmithKline	BLA 125748/0.15 (Sequence 16)	BLA Amendment, Response to 22 November 2021 request for information regarding Section 6.2 of the draft USPI and follow-up comments and questions regarding applicant's responses dated 08 November 2021
GlaxoSmithKline	BLA 125748/0.32 (Sequence 33)	BLA Amendment, Response to 24 March 2022 request for information regarding updated pregnancy outcome data relevant to Section 8.1 of the draft USPI
GlaxoSmithKline	BLA 125748/0.35 (Sequence 36)	BLA Amendment, Response to 18 April 2022 and 19 April 2022 requests for information regarding submission of individual case safety reports (ICSRs) from postmarketing sources according to CFR timelines and case narratives for reports of major and minor

		congenital anomalies and stillbirths from the Public Health England (PHE) registry.
GlaxoSmithKline	BLA 125748/0.38 (Sequence 39)	BLA Amendment, Response to 29 April 2022 request for information regarding PHE case narratives submitted in BLA Amendment 125748/0.35.
GlaxoSmithKline	BLA 125748/0.41 (Sequence 42)	BLA Amendment, Response to 10 May 2022 request for information regarding analysis of U.S.-specific safety data on febrile convulsions in future periodic safety reports for the next 3 years, should the PRIORIX be approved
Published literature	Various	See references

4. CLINICAL SAFETY DATABASE

The applicant submitted data from 6 completed clinical studies (Table 1); all studies were randomized, controlled, observer-blind studies that used MMRII as the active comparator. All studies enrolled both domestic and foreign subjects, except Study MMR-157, which was conducted in the U.S. and Puerto Rico. Across the 6 studies, 12,151 subjects received PRIORIX (6,391 from the U.S.[4]). The safety data were not pooled due to differences across studies regarding 1) potencies of the investigational vaccine used, 2) concomitant vaccines administered, and 3) age of study participants. Post-dose 1 studies (MMR-157, MMR-160, MMR-161[5], and MMR-162), were conducted in children 12-15 months of age while post-dose 2 studies (MMR-158, MMR-159, MMR-161) collectively enrolled subjects across the age range (12 months to adult). The duration of safety follow-up was 6 months after vaccination for all studies. Additionally, for MMR-157, the following serious adverse events (SAEs) were reported up to 2 years: events considered related to study participation by the investigator, prompted study withdrawal, led to death, and/or breakthrough cases of measles, mumps, and rubella,

Study MMR-162 had a safety-related primary objective (to compare rates of fever >102.2ºF and ≥100.4º occurring 5-12 days post-vaccination in the PRIORIX and MMRII groups), while the other 5 studies evaluated safety as a secondary objective using the following endpoints:

- Solicited local and general adverse events
  - Local symptoms within 4 days post-vaccination
  - General symptoms during 4 to 43 days post-vaccination
- Unsolicited adverse events (AEs) up to 43 days post-vaccination
- AEs of specific interest (AESIs): Occurrence of (NOCDs) up to 43 days after vaccination and throughout the study
- Serious AEs (SAEs) up to 43 days after vaccination and throughout the study

Additionally, MMR-162 evaluated the occurrence of measles-like illness (MLI) from Day 5 to Day 12 post-vaccination as a secondary endpoint.

[4] Subjects enrolled from Puerto Rico were considered together with U.S. subjects throughout this submission.
[5] Study MMR-161 evaluated both first and second doses of PRIORIX.

Regarding the statistical analyses of safety data, for the assessment of the primary safety-related endpoint in Study MMR-162 (rates of fever >102.2ºF and ≥100.4º occurring 5-12 days post-vaccination), 95% confidence intervals (CIs) were calculated for the difference in the rates of fever between PRIORIX and MMRII groups. A hierarchical procedure was used to account for Type I error (i.e., the objective on fever ≥100.4º could only be reached if the objective on fever >102.2ºF was met). For the assessment of secondary safety endpoints across the 6 studies, results were tabulated by group and 95% CIs were presented for the percentage of subjects reporting AEs (95% CIs were not presented for SAEs). Relative risk (RR) ratios (with 95% CIs) were calculated for PRIORIX over MMRII for all unsolicited AEs and NOCDs reported up to 43 days; the results were unadjusted for multiplicity. Non-overlapping CIs (indicating statistical significance) are noted in this memorandum where applicable. No statistical tests for significance were done for the SAE analyses.

The demographics and baseline characteristics were comparable between PRIORIX and MMRII groups across studies.

Table 1. Summary of Clinical Studies[6]

Study ID/ Phase	Description[7]	Countries/ Study Population	Vaccination Schedule	Study Groups	Number of Vaccinated Subjects (US Subjects)
MMR-157 Phase 2	Immunogenicity and antibody persistence of PRIORIX (3 lots of differing mumps potencies) vs. MMRII	United States Healthy children, 12-15 months	1 dose at Day 0, co-administered with HAV (HAVRIX), VV (VARIVAX), and PCV-7 (PREVNAR)	PRIORIX: Release potency (mumps strain): • INV_MMR_1: Lot 1 Low potency (mumps strain) • INV_MMR_2: Lot 2 • INV_MMR_3: Lot 3 MMRII: • MMRII (3 lots)	 304 (304) 304 (304) 304 (304) 308 (308)
MMR-158 Phase 3	Non-inferiority of a second dose of PRIORIX vs. MMRII	United States, South Korea, Taiwan Healthy children, 4-6 years, who previously received 1 dose of any MMR vaccine	1 dose at Day 0, co-administered with VV (VARIVAX) and DTaP-IPV (KINRIX) in a sub-cohort of U.S. subjects (Sub-cohort 1)	PRIORIX: Sub-cohort 1 (U.S. subjects only): • INV_MMR_CO: PRIORIX co-administered with VARIVAX and KINRIX Sub-cohort 2 • INV_MMR_I: PRIORIX given alone Sub-cohort 3: • INV-MMR_S: PRIORIX given alone MMRII:	 802 (802) 796 (412) 1,319 (736) 298 (298)

[6] Adapted from BLA 125748/0 Section 2.7.6 Synopses of Individual Studies, p 3-6.
[7] All studies were randomized, controlled, observer-blind studies that used MMRII as the active comparator

				Sub-cohort 1 (U.S. subjects only): • MMRII_CO: MMRII co-administered with VARIVAX and KINRIX Sub-cohort 2 • MMRII_I: MMRII given alone Sub-cohort 3: • MMRII_S: MMRII given alone	 303 (157) 489 (276)
MMR-159 Phase 3	Non-inferiority of a second dose of PRIORIX vs. MMRII	United States, Estonia, Slovakia Healthy children, adolescents, and adults 7 years of age and older, who previously received at least 1 dose of any MMR vaccine	1 dose at Day 0	PRIORIX: • INV_MMR MMRII: • MMR II (2 lots)	454 (293)** 457 (293)**
MMR-160 Phase 3	Immunogenicity and safety of PRIORIX compared to MMRII, as a first-dose	United States, Estonia, Finland, Mexico, Spain Healthy children, 12-15 months	1 dose at Day 0, co-administered with HAV (HAVRIX), VV (VARIVAX), and PCV-13 (PREVNAR 13); PREVNAR 13 administered in US subjects only	PRIORIX: • INV_MMR_1: Lot 1 • INV_MMR_2: Lot 2 • INV_MMR_3: Lot 3 • *INV_MMR: Total 3 lots* MMRII: • MMRII (2 lots)	1,239 (618) 1,232 (612) 1,243 (618) *3,714 (1,848)* 1,289 (654)
MMR-161 Phase 3	Immunogenicity and safety of PRIORIX at end of shelf-life potency compared to MMRII	United States, Czech Republic, Finland, Malaysia, Spain, Thailand	2 doses: • Day 0, co-administered with HAV (HAVRIX), VV (VARIVAX),	PRIORIX: • INV_MMR_MIN: Minimum potency lot at Day 0 and release potency at Day 42	1,493 (328) 1,497 (326)

		Healthy children, 12-15 months	and PCV-13 (PREVNAR 13); PREVNAR 13 administered in US subjects only • Day 42	• INV_MMR_MED: Medium potency lot at Day 0 and release potency at Day 42 MMRII: • MMRII (2 lots)	1,526* (346)
MMR-162 Phase 3	Safety and immunogenicity of PRIORIX at a potency used to define maximum release limits and MMRII	United States, Estonia, Finland, Taiwan Healthy children, 12-15 months	1 dose at Day 0, co-administered with HAV (HAVRIX), VV (VARIVAX), and PCV-13 (PREVNAR 13); PREVNAR 13 administered in US subjects only	PRIORIX: • INV_MMR MMRII: • MMRII (2 lots)	1,164 (734) 572 (357)
Total number of subjects for all studies (U.S. subjects)				**PRIORIX** **MMRII**	**12,151 (6,391)** **5,242 (2,689)**

*3 vaccinated subjects from MMR-161 (2 in the MIN group and 1 in the MMRII group) with invalid informed consent were excluded.
**Of the 994 vaccinated subjects in MMR-159, 83 subjects from 2 U.S. sites were excluded from the Total Vaccinated Cohort due to data integrity issues, resulting in 911 subjects.

4.1 Studies in Subjects Aged 12-15 Months

4.1.1 MMR-157 (Phase 2 Study)

Study Title:
A phase II, randomized, observer-blind, controlled, multi-center study to assess immunogenicity and antibody persistence following vaccination with GSK's candidate combined measles, mumps, and rubella vaccine (MMR) versus M-M-R®II as a first dose, both administered subcutaneously at 12 to 15 months of age, concomitantly with hepatitis A vaccine (HAV), varicella vaccine (VV), and pneumococcal conjugate vaccine (PCV) but at separate sites.

Study Design:
Three lots each of PRIORIX (with differing mumps virus potencies) and MMRII vaccine (pooled) were evaluated. Subjects were randomized in a (3:3:3:[1:1:1]) ratio to 4 parallel treatment groups (INV_MMR_1:INV_MMR_2:INV_MMR_3:MMRII) to receive a single dose of MMR vaccine on Day 0 co-administered with HAV (HAVRIX), VV (VARIVAX), and PCV (PREVNAR, pneumococcal 7-valent conjugate vaccine).

Immunogenicity and safety were evaluated from Day 0 to 42. The extended safety follow-up phase was up to 180 days, during which all SAEs, NOCDs, and conditions resulting in emergency room (ER) visits were reported. Antibody persistence was evaluated until 2 years after vaccination.

Safety Follow-up and Study Duration:
See above; 2 years (full study duration)

Objectives:

Safety (secondary)

- To assess safety and reactogenicity of PRIORIX compared to MMRII.

Primary

- To assess the seroresponse rate of PRIORIX across a range of mumps virus potencies compared to MMRII at Day 42, when co-administered with HAV, VV, and PCV.

Secondary

- To assess concentrations/titers of antibodies to measles, mumps, and rubella viruses at Day 42.
- To assess the immunogenicities of HAV, VV, and PCV when co-administered with other vaccines, including PRIORIX or MMRII.
- To assess the persistence of antibodies to measles, mumps, and rubella viruses 1 and 2 years after administration of the first dose of PRIORIX or MMRII.

Safety Endpoints:
Solicited and unsolicited AEs after vaccination (documented by subjects' parents/guardians on diary cards), SAEs, NOCDs, AEs resulting in ER visits.

- Solicited and unsolicited AEs:
  - Day 0 to 3: injection site reactions
  - Day 0 to 14: drowsiness, loss of appetite or irritability
  - Day 0 to 42: body temperature (recorded daily), rash, parotid/salivary gland swelling, febrile convulsion, any other AEs, concomitant medication/vaccination
    - Subjects were to return to the study site for all cases of rash, parotid/salivary gland swelling, and febrile convulsion for assessment by the investigator
- SAEs from Day 0 to 180; SAEs related to study participation, prompting study withdrawal, and leading to death were recorded up to Day 730 (2 years)
- NOCDs and AEs resulting in ER visits were recorded from Day 0 to Day 180

Study Population:

Eligibility Criteria
Males and females between 12 and 15 months of age, inclusive, who had previously received 3 doses of 7-valent PCV within the first year of life with the third dose administered ≥30 days prior to enrollment.

Demographics of Safety Population[8]:

	INV_MMR_1 N = 304	INV_MMR_2 N = 304	INV_MMR_3 N = 304	COM_MMR N = 308	Total N = 1220
Age (months)					
Mean (SD)	12.4 (0.75)	12.4 (0.73)	12.4 (0.56)	12.4 (0.75)	12.3 (0.71)
Range	12-15	12-15	12-15	12-15	12-15
Gender					
Female	51.3%	47.4%	51.6%	45.1%	48.9%
Male	48.7%	52.6%	48.4%	54.9%	51.1%
Race					
African/African-American	34 (11.2%)	23 (7.6%)	32 (10.5%)	44 (14.3%)	133 (10.9%)
American Indian or Alaskan Native	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)	1 (0.1%)
Asian or Native Hawaiian/Pacific Islander	3 (1.0%)	2 (0.7%)	2 (0.7%)	4 (1.3%)	11 (0.9%)
White	240 (78.9%)	233 (76.6%)	235 (77.3%)	228 (74.0%)	936 (76.7%)
Other	27 (8.9%)	46 (15.1%)	35 (11.5%)	31 (10.1%)	139 (11.4%)

Group naming:
PRIORIX: INV_MMR_1: PRIORIX at release potency for mumps strain (4.8 $\log_{10}$ $CCID_{50}$)
INV_MMR_2: PRIORIX below release potency for mumps strain (4.1 $\log_{10}$ $CCID_{50}$)
INV_MMR_3: PRIORIX below release potency for mumps strain (3.7 $\log_{10}$ $CCID_{50}$)
MMRII: COM MMR

Safety Conclusion (per Applicant):
PRIORIX, when co-administered with HAV, VV, and PCV, was well-tolerated and had a safety profile similar to MMRII.

The applicant excluded subjects who received low potency lots of PRIORIX (INV_MMR_2 and INV_MMR_3) from the safety evaluation, as these lots had potencies below the defined end of shelf life in the U.S. The applicant's discussion of safety data for the low potency lots were limited to SAEs assessed as vaccine-related by the investigator, withdrawals due to AEs, and deaths.

Solicited Adverse Events

Of note, AE comparisons between the PRIORIX and control groups for all solicited adverse events discussed below revealed overlapping confidence intervals unless otherwise noted.

[8] Adapted from BLA 125748/0, Study MMR-157 Clinical Study Report, Table 62: Summary of demographic characteristics (total vaccinated cohort), p 183. Under race, Asian-central/south Asian heritage, Asian – east Asian heritage, Asian – Japanese heritage, Asian – southeast Asian heritage, and Native Hawaiian or other Pacific Islander categories were collapsed into one category, "Asian or Native Hawaiian/Pacific Islander." White – Arabic/north African heritage and White – Caucasian/European heritage were collapsed into one category, "White."

Injection site reactions
Incidences of injection site pain, redness, or swelling within 4 days post-vaccination were comparable in the PRIORIX (INV_MMR_1) (24.8%, 16.0%, and 7.1%, respectively) and MMRII (COM_MMR) groups (24.5%, 17.2%, and 5.5%, respectively). The proportions of subjects experiencing grade 3 (severe) injection site pain, redness, or swelling were also similar between the PRIORIX (1.1%, 1.1%, and 0%, respectively) and MMRII (1.5%, 1.1%, and 0.4%, respectively) groups.

General symptoms
Incidences of drowsiness, loss of appetite, or irritability/fussiness during Days 0-14 were numerically higher in the PRIORIX (47.0%, 39.2%, and 63.6%, respectively) than in the MMRII group (39.4%, 33.9%, 55.2%, respectively). The majority of fever was reported between Days 5-12, with 14.8% of subjects in either group experiencing fever ≥100.4ºF during this interval. A higher percentage of subjects in the PRIORIX group experienced fever ≥100.4ºF during Days 0-14 and Days 0-42 (23.0% and 36.4%, respectively), compared to the MMRII group (20.2%, 30.7%, respectively). The proportion of subjects experiencing fever >103.1ºF was comparable between the two groups for all three time intervals (Table 2).

Table 2. Proportion of Subjects with Fever in MMR-157

	Temperature	**PRIORIX (INV_MMR_1)** (%)	**MMRII (COM_MMR)** (%)
Days 0-14	≥38.0ºC (≥100.4ºF)	23.0%	20.2%
	>39.5ºC (>103.1ºF)	3.5%	2.9%
Days 5-12	≥38.0ºC (≥100.4ºF)	14.8%	14.8%
	>39.5ºC (>103.1ºF)	2.1%	1.8%
Days 0-42	≥38.0ºC (≥100.4ºF)	36.4%	30.7%
	>39.5ºC (>103.1ºF)	7.1%	4.7%

The incidences of rash (any, measles/rubella-like, or grade 3) were comparable for the PRIORIX and MMRII groups. The proportions of subjects with any rash, measles/rubella-like rash, and grade 3 rash were 25.4%, 2.1%, and 3.9%, respectively, in the PRIORIX group and 24.9%, 3.2%, and 2.9%, respectively, in the MMRII group.

MMR-specific general symptoms
The incidence of parotid gland swelling within 43 days post-vaccination was 1.1% (3 subjects) in the PRIORIX group and 0.7% (2 subjects) in the MMRII group. One subject (0.4%) in the PRIORIX group had grade 3 swelling. No subjects in the PRIORIX group and one subject (0.4%) in the MMRII group had any meningism event.

Unsolicited Adverse Events
The percentage of subjects reporting the occurrence of at least one unsolicited AE during Days 0 to 42 was similar for the two groups: 55.9% for the PRIORIX and 54.9% for MMRII (RR=1.0, 95% CI: 0.8, 1.3). There were no statistically significant risk differences for any event. The most common (frequency ≥5.0% in either group) AEs were upper respiratory tract infection (13.2% for PRIORIX, 14.0% for MMRII), teething (11.5%, 11.4%), otitis media (8.2%, 7.8%),

diarrhea (8.2%, 6.8%), and cough (8.2%, 6.2%). Most AEs were mild or moderate in severity, with 5.9% of subjects in the PRIORIX group and 4.9% of subjects in the MMRII group experiencing at least 1 severe (grade 3) AE (RR=1.2, 95% CI: 0.6, 2.6). The most common (frequency ≥1.0% in either group) severe AEs were vomiting (1.3% for PRIORIX, 0.3% for MMRII) and otitis media (0.7%, 1.0%).

Serious Adverse Events

One subject (0.3%) in the PRIORIX group had a SAE (bronchiolitis, assessed as unrelated by the investigator) during the 6-month safety follow-up, compared to 10 subjects (3.3%) in the MMRII group. Excluding the low potency PRIORIX groups, one SAE was assessed to be vaccine-related by the investigator: febrile convulsion in a MMRII subject.

Two subjects in the low potency PRIORIX groups had SAEs that were assessed as vaccine-related by the investigator that were excluded from the safety analysis. One subject experienced immune thrombocytopenic purpura (ITP) 20 days post-vaccination, which resolved 7 months later; the subject was withdrawn after the Day 180 safety follow-up. The other subject had a SAE of lymphadenitis 68 days post-vaccination which resolved 2 weeks later.

There was one SAE during the extended safety follow-up. A subject in the MMRII group had a SAE of nephroblastoma which resulted in study withdrawal; the event was assessed as unrelated to vaccination by the investigator.

Deaths and Withdrawals

No deaths were reported. There were no withdrawals due to AEs in the INV_MMR_1 group. As previously discussed, one subject from the low potency PRIORIX group was withdrawn from the study due to a related SAE of ITP. One subject from the MMRII group was withdrawn due to a vaccine-related SAE of prolonged atypical febrile seizures.

Adverse Events of Specific Interest

New Onset Chronic Diseases (NOCD)

One subject in the PRIORIX group had a NOCD (seasonal allergy) within 43 days of vaccination (RR=INF, 95% CI: 0.05, INF). No subjects in the MMRII group had a NOCD during this interval. Five subjects (1.6%, 95% CI: 0.5, 3.8) in the PRIORIX group and two subjects (0.6%, 95% CI: 0.1, 2.3) in the MMRII group reported at least one NOCD during the 6-month study period; the confidence intervals overlapped. Asthma was the only event reported in more than 1 subject (it was reported in 2 subjects in the PRIORIX group).

4.1.2 MMR-160 (Phase 3a Study)

Study Title: A phase IIIA, randomized, observer-blind, controlled, multi-national consistency study to evaluate the immunogenicity and safety of GSK Biologicals' MMR Vaccine (109762) (Priorix®) compared to Merck & Co., Inc.'s MMR Vaccine (M-M-R®II) as a first dose, both co-administered with Varivax®, Havrix®, and Prevnar 13® (subset of children) to healthy children 12 to 15 months of age.
Study Design:

The study was designed to evaluate the consistency of the immune response to 3 different lots of PRIORIX manufactured to target potencies. Subjects were randomized in a (2:2:2:[1:1]) ratio to 5 parallel treatment groups: INV_MMR_L1:INV_MMR_L2:INV_MMR_L3:MMRII_L1:MMRII:L2). The 2 MMRII groups were pooled for analyses. Subjects received a single dose of MMR vaccine on Day 0 co-administered with HAV (HAVRIX) and VV (VARIVAX). U.S. subjects also received PCV-13 (PREVNAR, pneumococcal 13-valent conjugate vaccine).

Immunogenicity and safety (e.g., solicited and unsolicited AEs) were evaluated from Day 0 to 42. SAEs and AESIs (i.e., NOCDs, AEs resulting in emergency room (ER) visits) were reported during the entire study period.

Safety Follow-up and Study Duration:
See above; 6 months (full study duration)

Objectives:

Safety (secondary)

- To assess safety and reactogenicity of PRIORIX compared to MMRII when co-administered with VARIVAX, HAVRIX, and PREVNAR 13 (the latter in U.S. subjects-only)

Primary (5 co-primary objectives, in descending hierarchical order)

- To demonstrate consistency of 3 lots of PRIORIX in terms of seroresponse rates to measles, mumps, and rubella viruses at Day 42.
- To demonstrate consistency of 3 lots of PRIORIX in terms of geometric mean concentrations (GMCs) for antibodies to measles, mumps, and rubella viruses at Day 42.
- To demonstrate non-inferiority of PRIORIX (pooled) compared to MMRII (pooled) in terms of seroresponse rates to measles, mumps, and rubella viruses at Day 42.
- To demonstrate non-inferiority of PRIORIX (pooled) compared to MMRII (pooled) in terms of GMCs for antibodies to measles, mumps, and rubella viruses at Day 42.
- To demonstrate acceptable immune response for PRIORIX in terms of seroresponse rates to measles, mumps, and rubella viruses at Day 42.

Secondary (to be assessed only if all co-primary objectives were met)

- To demonstrate non-inferiority of PRIORIX (pooled) compared to MMRII (pooled) in terms of seroresponse rate and GMC for antibodies to varicella zoster virus (VZV) at Day 42 (in a subset of U.S. subjects)
- To demonstrate non-inferiority of PRIORIX (pooled) compared to MMRII (pooled) in terms of GMC for antibodies to hepatitis A virus (HAV) at Day 42 (in a subset of U.S. subjects)
- To demonstrate non-inferiority of PRIORIX (pooled) compared to MMRII (pooled) in terms of seroresponse rate and GMC for antibodies to *S. pneumoniae* (PS, 13 serotypes) at Day 42 (in a subset of U.S. subjects who received Prevnar 13)
- To assess the immunogenicity of HAVRIX with respect to the seroresponse rates for antibodies to HAV in the pooled PRIORIX compared to the pooled MMRII groups at Day 42 (in a subset of U.S. subjects).

Safety Endpoints:
Solicited and unsolicited AEs after vaccination (documented by subjects' parents/guardians on diary cards), SAEs, and AESIs (e.g., NOCDs, AEs resulting in ER visits).

- Solicited and unsolicited AEs:
  - Day 0 to 3: injection site reactions
  - Day 0 to 14: drowsiness, loss of appetite or irritability
  - Day 0 to 42: body temperature ≥100.4ºF, rash, parotid/salivary gland swelling, signs of meningism (including febrile convulsion), any other AEs
- SAEs from Day 0 to 180

- NOCDs and AEs resulting in ER visits from Day 0 to 180

Study Population:

Eligibility Criteria

Males and females aged 12 and 15 months. For U.S. sites only: subjects who received all routine vaccinations as per the Advisory Committee on Immunization Practices (ACIP) recommendations prior to study entry.

Demographics of Safety Population[9]:

	INV_MMR_1 N = 1239	INV_MMR_2 N = 1232	INV_MMR_3 N = 1243	INV_MMR (Pooled) N = 3714	COM_MMR N = 1289	Total N = 5003
Age (months)						
Mean (SD)	12.3 (0.7)	12.3 (0.7)	12.3 (0.7)	12.3 (0.7)	12.3 (0.7)	12.3 (0.7)
Range	12-16	12-15	12-16	12-16	11-15	11-16
Gender						
Female	49.0%	48.2%	49.5%	48.9%	47.9%	48.7%
Male	51.0%	51.8%	50.5%	51.1%	52.1%	51.3%
Race						
African/African-American	60 (4.8%)	52 (4.2%)	57 (4.6%)	169 (4.6%)	70 (5.4%)	239 (4.8%)
American Indian or Alaskan Native	25 (2.0%)	37 (3.0%)	33 (2.7%)	95 (2.6%)	31 (2.4%)	126 (2.5%)
Asian or Native Hawaiian/Pacific Islander	47 (3.8%)	44 (3.6%)	45 (3.6%)	136 (3.7%)	48 (3.7%)	184 (3.7%)
White	937 (75.6%)	944 (76.6%)	946 (76.1%)	2,827 (76.1%)	977 (75.8%)	3804 (76.0%)
Other	170 (13.7%)	155 (12.6%)	162 (13.0%)	487 (13.1%)	163 (12.6%)	650 (13.0%)
U.S. Subjects						
	618 (49.9%)	612 (49.7%)	618 (49.7%)	1848 (49.8%)	654 (50.7%)	2502 (50.0%)

Group naming:

PRIORIX: INV_MMR_1: PRIORIX Lot 1
INV_MMR_2: PRIORIX Lot 2
INV_MMR_3: PRIORIX Lot 3
INV_MMR: PRIORIX lots pooled (3 lots)
MMRII: COM_MMR: MMR lots pooled (2 lots)

Safety Conclusion (per Applicant):

PRIORIX, when co-administered with HAV, VV, and PCV, had an acceptable safety profile similar to MMRII.

The 3 PRIORIX groups[10] (INV_MMR_1, INV_MMR_2, INV_MMR_3) were pooled (INV_MMR) for the safety analysis.

[9] Adapted from BLA 125748/0, Study MMR-160 Clinical Study Report, Report Amendment 2 Final, Table 6.5: Summary of demographic characteristics (total vaccinated cohort), p 311-312. Under race, Asian-central/south Asian heritage, Asian – east Asian heritage, Asian – Japanese heritage, Asian – southeast Asian heritage, and Native Hawaiian or other Pacific Islander categories were collapsed into one category, "Asian or Native Hawaiian/Pacific Islander." White – Arabic/north African heritage and White – Caucasian/European heritage were collapsed into one category, "White."

[10] The formulation of the 3 PRIORIX lots was the same: 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) $\geq 10^{3.0}$ $CCID^{50}$ (Source: BLA 125748/0, Study MMR-160 Clinical Study Report, p 69).

Solicited Adverse Events

Of note, AE comparisons between the PRIORIX and control groups for all solicited adverse events discussed below revealed overlapping confidence intervals unless otherwise noted.

Injection site reactions

Incidences of injection site pain, redness, or swelling in the first 4 days after vaccination were comparable in the PRIORIX (INV_MMR) (25.9%, 24.5%, and 8.9%, respectively) and MMRII (28.1%, 25.2%, and 10.7%, respectively) groups. Proportions of subjects experiencing grade 3 (severe) injection site pain, redness, or swelling were also similar for the two groups: 0.7%, 0.4%, and 0.3%, respectively, for PRIORIX, and 1.0%, 0.6%, and 0.4%, respectively, for MMRII.

General symptoms

The incidences of drowsiness, loss of appetite, or irritability/fussiness during Days 0-14 were similar in both groups: 44.9%, 45.1%, and 63.3%, respectively, for PRIORIX, and 47.1%, 44.1%, and 65.9% for MMRII. The majority of fever was reported between Days 5-12, with 19.7% of subjects in the PRIORIX group and 18.2% of subjects in the MMRII experiencing fever ≥100.4ºF during this interval. The percentage of subjects experiencing fever ≥100.4ºF during Days 0-14 and Days 0-42 were comparable for the two groups: 23.7% and 34.7%, respectively, for PRIORIX, and 21.8% and 33.1%, respectively, for MMRII. The percentage of subjects experiencing fever >103.1ºF was comparable between the two groups for all three time intervals (Table 3).

Table 3. Proportion of Subjects with Fever in MMR-160

	Temperature	**PRIORIX (INV_MMR)** (%)	**MMRII (COM_MMR)** (%)
Days 0-14	≥38.0ºC (≥100.4ºF)	23.7%	21.8%
	>39.5ºC (>103.1ºF)	1.6%	1.4%
Days 5-12	≥38.0ºC (≥100.4ºF)	19.7%	18.2%
	>39.5ºC (>103.1ºF)	1.4%	1.1%
Days 0-42	≥38.0ºC (≥100.4ºF)	34.7%	33.1%
	>39.5ºC (>103.1ºF)	2.9%	2.6%

The incidences of rash (any, measles/rubella-like, or grade 3) were comparable for the PRIORIX and MMRII groups. The proportions of subjects with any rash, measles/rubella-like rash, and grade 3 rash were 29.2%, 6.6%, and 3.0%, respectively, in the PRIORIX group and 30.4%, 6.2%, and 2.0%, respectively, in the MMRII group.

MMR-specific general symptoms

There were no reports of parotid gland swelling within 43 days post-vaccination in either group. The incidence of meningism was low and was similar in both groups. The proportions of subjects experiencing meningism (any) and grade 3 meningism were 0.3% (10 subjects) and 0.1% (4 subjects), respectively, in the PRIORIX group and 0.2% (3 subjects) and 0%, respectively, in the MMRII group.

Unsolicited Adverse Events

The percentage of subjects reporting the occurrence of at least one unsolicited AE during Days 0 to 42 was comparable for the two treatment groups: 50.0% for PRIORIX and 47.9% for MMRII (RR=1.0, 95% CI: 1.0, 1.1). There was an increased frequency of abdominal pain upper and influenza in the MMRII group. The most common (frequency ≥5.0% in either group) AEs were upper respiratory tract infection (9.5% for both groups), teething (7.0% for PRIORIX, 7.4% for MMRII), otitis media (5.9%, 6.8%), nasopharyngitis (6.0%, 5.0%), and diarrhea (4.6%, 5.0%).

Most AEs were mild or moderate in severity, with 6.1% of subjects in the PRIORIX group and 6.6% of subjects in the MMRII group experiencing at least 1 severe (grade 3) AE (RR=0.9, 95% CI: 0.7, 1.2). The most common (frequency ≥1.0% in either group) severe AEs were otitis media (1.7% for PRIORIX, 2.1% for MMRII) and upper respiratory tract infection (1.3%, 0.5%). There was an increased risk of severe upper respiratory tract infection in the PRIORIX group (1.3% (47/3714 subjects) and 0.5% (6/1289 subjects) in the PRIORIX and MMRII groups respectively [RR = 2.7; 95% CI: 1.2, 7.8]).

Reviewer Comment: *There was an increased risk of severe upper respiratory tract infections in the PRIORIX group. The wide 95% CIs of the RR ratio is reflective of the degree of uncertainty regarding the small number of subjects reporting the AEs. The clinical significance of these results are unclear. Of note, there were no risk differences between the PRIORIX and MMRII groups for upper respiratory infections, regardless of severity, occurring within 43 days post-vaccination.*

Serious Adverse Events

The percentages of subjects reporting at least 1 SAE during the 6-month study period were similar for the two groups: 2.1% (77/3,714 subjects) for PRIORIX and 1.9% (25/1,289 subjects) for MMRII. The most common SAEs (reported in ≥5 subjects in either group) were bronchitis (8 subjects, 0.2% for PRIORIX; 2 subjects, 0.2% for MMRII), pneumonia (6 subjects, 0.2% for PRIORIX; 0 subjects for MMRII), dehydration (5 subjects, 0.1% for PRIORIX; 3 subjects, 0.2% for MMRII), and febrile convulsion (1 subject, <0.1% for PRIORIX; 5 subjects, 0.4% for MMRII).

Two subjects in the PRIORIX group had SAEs assessed as vaccine-related by the investigator: one subject had gastroenteritis occurring on the day of vaccination which resolved after 14 days, and the other subject had febrile convulsion on Day 9 which resolved after one day.

Reviewer Comment: *A higher proportion of subjects in the PRIORIX group (0.2%) reported a SAE of pneumonia compared to subjects in the MMRII group (0%). Tests for statistical significance were not done by the applicant, and it is unknown whether the small absolute percentage difference (0.2%) could be explained by random chance or is of clinical significance. Of note, there were no significant risk differences between the PRIORIX and MMRII groups for pneumonia, regardless of severity, occurring within 43 days post-vaccination.*

Deaths and Withdrawals

No deaths were reported. Two subjects withdrew due to AEs: both subjects were in the PRIORIX group, and the AEs (gastroesophageal reflux, gastroenteritis) were non-serious and assessed as unrelated to vaccination by the investigator.

Adverse Events of Specific Interest

New Onset Chronic Diseases (NOCD)

The percentage of subjects with NOCDs within 43 days of vaccination was 0.8% and 1.0% for the PRIORIX and MMRII groups, respectively (RR = 0.80, 95% CI: 0.41, 1.67). The relative risk (RR) analyses did not show any imbalances between the PRIORIX and MMRII groups for any NOCDs occurring within 43 days of vaccination. The most common (occurring in ≥4 subjects in either group) NOCDs were food allergy (6 subjects in the PRIORIX group and 4 subjects in the MMRII group), rhinitis allergic (4 and 0 subjects, respectively), eczema (4 and 2 subjects, respectively), and asthma (2 and 4 subjects, respectively). The percentages of subjects reporting NOCDs during the 6-month study period were similar (3.4% for PRIORIX and 3.7% for MMRII). Dermatitis atopic was the most frequent NOCD, reported by 0.7% (26 subjects) and 0.5% (7 subjects) of subjects in the PRIORIX and MMRII groups, respectively.

4.1.3 MMR-161 (Phase 3a Study Evaluating PRIORIX at End of Shelf Life Potencies)

Study Title: A phase IIIA, randomized, observer-blind, controlled, multi-national study to evaluate the immunogenicity and safety of GSK Biological's MMR vaccine (209762) (*Priorix*®) at an end of shelf-life potency compared to Merck & Co., Inc.'s MMR vaccine (*M-M-R®II*) when both are co-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 Design: Two lots each of PRIORIX (one minimum potency and one medium potency) and MMRII vaccine (pooled) were evaluated. Subjects were randomized in a 2:2:1:1 ratio to 4 parallel treatment groups (Inv_MMR_Min:Inv_MMR_Med:Com_MMR_L1:Com_MMR_L2) to receive two doses of vaccinations 6 weeks apart. For the second dose, subjects who were randomized to either PRIORIX group received PRIORIX at a release lot potency. All subjects were co-administered HAV (HAVRIX) and VV (VARIVAX) with their first dose of MMR vaccine; U.S. subjects also received PCV-13 (PREVNAR 13). Immunogenicity (primary analyses) was evaluated at Day 42. Solicited and unsolicited AEs were evaluated from Day 0 to 42, following each dose. SAEs and AESIs (i.e., NOCDs, AEs resulting in emergency room (ER) visits) were reported during the entire study period.
Safety Follow-up and Study Duration: See above; 7 months (full study duration)
Objectives: **Safety (Secondary)** • To assess safety and reactogenicity of the two lots (minimum and medium potencies) of PRIORIX and MMRII when co-administered with VARIVAX, HAVRIX, and PREVNAR 13 (the latter in U.S. subjects-only) **Primary (applicable to each lot of PRIORIX)** • To demonstrate non-inferiority of PRIORIX compared to MMRII in terms of seroresponse rates to measles, mumps, and rubella viruses at Day 42.

- To demonstrate non-inferiority of PRIORIX compared to MMRII in terms of GMCs for antibodies to measles, mumps, and rubella viruses at Day 42.
- To demonstrate an acceptable immune response of PRIORIX in terms of seroresponse rates to measles, mumps, and rubella viruses at Day 42.
- To demonstrate non-inferiority of PRIORIX compared to MMRII in terms of seroresponse rates for mumps virus (by (b) (4)) at Day 42
- To demonstrate non-inferiority of PRIORIX compared to MMRII in terms of geometric mean titer (GMT) for antibodies to mumps virus (by (b) (4) at Day 42.

Secondary

- To assess the immunogenicities of both lots of PRIORIX (minimum and medium potencies) when followed by a second dose with PRIORIX at release lot potency in terms of seroresponse rate and GMCs for antibodies to measles, mumps, and rubella viruses at Day 84 (in a sub-cohort of U.S. subjects)

Safety Endpoints:

Solicited and unsolicited AEs after vaccination (documented by subjects' parents/guardians on diary cards), SAEs, and AESIs (e.g., NOCDs, AEs resulting in ER visits).

- Solicited and unsolicited AEs:
  - Day 0 to 3: injection site reactions
  - Day 0 to 14: drowsiness, loss of appetite or irritability
  - Day 0 to 42: body temperature ≥100.4ºF, rash, parotid/salivary gland swelling, signs of meningism (including febrile convulsion), any other AEs
- SAEs from Day 0 to 180
- NOCDs and AEs resulting in ER visits from Day 0 to 180

Study Population:

Eligibility Criteria

Males and females between 12 and 15 months of age. For U.S. sites only: subjects who received all routine vaccinations as per the Advisory Committee on Immunization Practices (ACIP) recommendations prior to study entry.

Demographics of Safety Population[11]:

	INV_MMR_MIN N = 1493	**INV_MMR_MED N = 1497**	**COM_MMR N = 1526**	**Total N = 4516**
Age (months)				
Mean (SD)	12.6 (0.9)	12.6 (0.9)	12.6 (0.9)	12.6 (0.9)
Range	11-15	12-16	11-15	11-16
Gender				
Female	47.2%	48.0%	49.7%	48.3%
Male	52.8%	52.0%	50.3%	51.7%
Race				
African/African-American	45 (3.0%)	53 (3.5%)	46 (3.0%)	144 (3.2%)
American Indian or Alaskan Native	2 (0.1%)	1 (0.1%)	1 (0.1%)	4 (0.1%)

[11] Adapted from BLA 125748/0, Study MMR-161 Clinical Study Report, Report Amendment 2 Final, Table 6.5: Summary of demographic characteristics (total vaccinated cohort, without subjects excluded from all stat analysis), p 541-542. Under race, Asian-central/south Asian heritage, Asian – east Asian heritage, Asian – Japanese heritage, Asian – southeast Asian heritage, and Native Hawaiian or other Pacific Islander categories were collapsed into one category, "Asian or Native Hawaiian/Pacific Islander." White – Arabic/north African heritage and White – Caucasian/European heritage were collapsed into one category, "White."

Asian or Native Hawaiian/Pacific Islander	366 (24.5%)	367 (24.5%)	370 (24.4%)	1103 (24.4%)
White	1025 (68.7%)	1030 (68.8%)	1060 (69.5%)	3115 (69.0%)
Other	55 (3.7%)	46 (3.1%)	49 (3.2%)	150 (3.3%)
U.S. Subjects				
	328 (22.0%)	326 (21.8%)	346 (22.7%)	1000 (22.1%)
Group naming: PRIORIX: INV_MMR_MIN: Minimum potency PRIORIX INV_MMR_MED: Medium potency PRIORIX MMRII: COM_MMR				
Safety Conclusion (per Applicant): Both lots of PRIORIX had an acceptable safety profile that was similar to MMRII when co-administered with the same vaccines.				

The applicant excluded subjects who received the minimum potency lot of PRIORIX (INV_MMR_MIN) from the post-dose 1 safety evaluation, as the potency of the lot was below the defined end of shelf life in the U.S. The applicant's discussion of safety data for the minimum potency lot was limited to SAEs assessed as vaccine-related by the investigator, withdrawals due to AEs, and deaths. The post-dose 2 safety evaluation included subjects who received minimum potency PRIORIX for the first dose, since all subjects randomized to PRIORIX received release lot potency PRIORIX for the second dose.

Solicited Adverse Events

Of note, AE comparisons between the PRIORIX and control groups for all solicited adverse events discussed below revealed overlapping confidence intervals unless otherwise noted.

Injection site reactions

Post-dose 1

Incidences of injection site pain, redness, and swelling, both any and grade 3, were numerically higher in the MMRII group than in the medium potency PRIORIX group (INV_MMR_MED). The incidences of any injection site pain, redness and swelling were 17.9%, 17.5%, and 6.6%, respectively, for the medium potency PRIORIX group, and 20.3%, 19.3%, and 8.2%, respectively, for the MMRII group. The incidences of grade 3 injection site pain, redness, and swelling were 0.1%, 0.2%, and 0.2%, respectively, for the medium potency PRIORIX group, and 0.3%, 1.1%, and 0.4%, respectively, for the MMRII group.

Post-dose 2

Overall, the frequencies of injection site reactions were numerically lower post-dose 2 compared to post-dose 1. Injection site reactions were less frequent in the PRIORIX groups (for both minimum and medium potencies) compared to the MMRII group. Comparing PRIORIX groups, injection site reactions were numerically higher in the medium potency group than in the minimum potency group. The incidences of any injection site pain, redness and swelling were 11.9%, 11.1%, and 4.7%, respectively, for the minimum potency PRIORIX

group; 12.7%, 13.6%, and 6.3%, respectively, for the medium potency PRIORIX group; and 13.5%, 14.9%, and 6.6%, respectively, for the MMRII group. The incidences of Grade 3 redness and swelling were numerically higher in the MMR II group but were low across the groups. The incidences of grade 3 injection site pain, redness, and swelling were 0.2%, 0.1%, and 0.1%, respectively, for the minimum potency PRIORIX group; 0.3%, 0.2%, and 0%, respectively, for the medium potency PRIORIX group; and 0.2%, 0.9%, and 0.5%, respectively, for the MMRII group.

General symptoms

The incidences of drowsiness, loss of appetite, or irritability/fussiness during Days 0-14 post-dose 1 were similar for the medium potency PRIORIX and MMRII groups: 38.5%, 40.2%, and 54.0%, respectively, for medium potency PRIORIX, and 39.2%, 39.8%, and 53.0% for MMRII. CIs for incidences of these AEs overlapped between the PRIORIX and control groups.

The incidence of fever was comparable across groups. Overall, the incidence of fever was numerically lower post-dose 2 compared to post-dose 1. The majority of fever was reported 5-12 days post-vaccination, with 22.3% of subjects in the medium potency PRIORIX group and 23.1% of subjects in the MMRII group experiencing fever ≥100.4ºF during this interval post-dose 1, and 10.0% of subjects in the minimum potency PRIORIX group, 10.7% of subjects in the medium potency PRIORIX group, and 9.3% of subjects in the MMRII group experiencing fever ≥100.4ºF during this interval post-dose 2 (Table 4). The incidence of fever >103.1ºF was similar across groups except during Days 5-12, post-dose 2; 0.7% and 0.8% of subjects in the minimum and medium potency PRIORIX groups, respectively, had a fever >103.1ºF during this period, compared to 0.3% of subjects in the MMRII group.

Table 4. Proportion of Subjects with Fever in MMR-161

		PRIORIX Min Potency (INV_MMR_MIN) (%)	**PRIORIX Med Potency (INV_MMR_MED)** (%)	**MMRII (COM MMR)** (%)
Post-dose 1[12]				
Days 0-14	≥38.0ºC (≥100.4ºF)	26.3%	27.1%	27.7%
	>39.5ºC (>103.1ºF)	2.3%	2.3%	2.3%
Days 5-12	≥38.0ºC (≥100.4ºF)	20.8%	22.3%	23.1%
	>39.5ºC (>103.1ºF)	1.6%	2.0%	1.7%
Days 0-42	≥38.0ºC (≥100.4ºF)	39.9%	42.0%	41.5%
	>39.5ºC (>103.1ºF)	3.4%	4.3%	4.1%
Post-dose 2				
Days 0-14	≥38.0ºC (≥100.4ºF)	15.4%	16.6%	16.1%
	>39.5ºC (>103.1ºF)	1.0%	1.3%	0.8%
Days 5-12	≥38.0ºC (≥100.4ºF)	10.0%	10.7%	9.3%
	>39.5ºC (>103.1ºF)	0.7%	0.8%	0.3%
Days 0-42	≥38.0ºC (≥100.4ºF)	31.9%	32.5%	34.3%
	>39.5ºC (>103.1ºF)	2.8%	3.5%	3.2%

[12] The shaded values indicate incidences of fever, post-dose 1, for the low potency PRIORIX group that were excluded from the safety evaluation by the applicant. For the second dose, subjects who were randomized to either PRIORIX group (low or medium potencies) received PRIORIX at a release lot potency.

The incidences of rash (any, measles/rubella-like, or grade 3) were comparable for the PRIORIX and MMRII groups post-dose 1. The proportions of subjects with any rash, measles/rubella-like rash, and grade 3 rash post-dose 1 were 22.0%, 4.2%, and 1.4%, respectively, in the medium potency PRIORIX group and 22.4%, 4.6%, and 1.6%, respectively, in the MMRII group. Rash was less frequent post-dose 2 compared to post-dose 1. The proportions of subjects with any rash, measles/rubella-like rash, and grade 3 rash post-dose 2 were 9.0%, 1.5%, and 0.6%, respectively, in the minimum potency PRIORIX group; 10.4%, 1.0%, and 0.6%, respectively, in the medium potency PRIORIX group; and 9.7%, 1.0%, and 0.8%, respectively, in the MMRII group.

MMR-specific general symptoms
The incidences of parotid gland swelling and meningism reported within 43 days of post-dose 1 were similar for the medium potency PRIORIX and MMRII groups. Parotid gland swelling was reported for 0.1% (2 subjects) in the medium potency PRIORIX group and for 0.2% (3 subjects) in the MMRII group. No subjects had grade 3 parotid gland swelling. Meningism was reported for 0.3% (4 subjects) in the medium potency PRIORIX group and 0.2% (3 subjects) in the MMRII group; grade 3 meningism was reported for 0.2% (3 subjects) in the medium potency PRIORIX group and 0.1% (1 subject) in the MMRII group. The incidences of parotid gland swelling reported after post-dose 2 were similar: 0.1% (1 subject) in the minimum potency PRIORIX group, 0.1% (2 subjects) in the medium potency PRIORIX group, and 0% in the MMRII group. No subjects had grade 3 parotid gland swelling. The incidence of meningism post-dose 2 was numerically higher in the medium potency PRIORIX group than in the other two groups: 0.4% (6 subjects) in the medium potency PRIORIX group, compared to 0.1% (2 subjects) in the minimum potency PRIORIX group and 0.3% (4 subjects) in the MMRII group. Grade 3 meningism was reported for 2 subjects (0.1%) in the medium potency PRIORIX group, no subjects in the minimum potency PRIORIX group, and 1 subject (0.1%) in the MMRII group.

Unsolicited Adverse Events
The percentages of subjects reporting the occurrence of at least one unsolicited AE within 43 days post-dose 1 were comparable for the two groups: 53.0% for medium potency PRIORIX and 50.9% for MMRII (RR=1.0, 95% CI: 0.9, 1.2). The relative risk (RR) analyses did not show any imbalances between the PRIORIX and MMRII groups for any AEs occurring within 43 days of vaccination. The most common (frequency ≥5.0% subjects in either group) AEs were upper respiratory tract infection (14.6% for medium potency PRIORIX, 15.0% for MMRII) and nasopharyngitis (6.4% for medium PRIORIX, 4.7% for MMRII).

The percentages of subjects reporting at least one unsolicited AE within 43 days post-dose 2 were comparable for the two groups: 47.0% for pooled (minimum and medium potencies) PRIORIX and 46.5% for MMRII (RR=1.0, 95% CI: 0.9, 1.1). There was a statistically significant increased frequency of ear infection in the pooled PRIORIX group (0.8%, 23/2,913 subjects) compared to the MMRII group (0.2%, 3/1,483 subjects) (RR=3.9; 95% CI: 1.2, 20.3)), The most common (frequency ≥5.0% subjects in either group) AEs were upper respiratory

tract infection (13.3% for pooled PRIORIX, 13.1% for MMRII) and nasopharyngitis (5.6%, 5.2%).

Most AEs were mild or moderate in severity, with 3.5% of subjects in the medium potency PRIORIX group and 4.0% of subjects in the MMRII group experiencing at least 1 severe (grade 3) AE within 43 days post-dose 1 (RR=0.9, 95% CI: 0.6, 1.3). There were no grade 3 AEs reported at a frequency ≥1.0% in either group or risk imbalances for any PT. The percentage of subjects reporting at least 1 severe AE within 43 days of post-dose 2 was 4.5% for pooled PRIORIX and 3.8% for MMRII (RR=1.2, 95% CI: 0.9, 1.6). There were no grade 3 AEs reported at a frequency ≥1.0% in either group or any risk imbalances for any PT.

Reviewer Comment: *The increased frequency of ear infection 43 days post-dose 2 in the pooled PRIORIX group compared to the MMRII group is of unclear significance. Although the increased frequency of ear infection 43 days post-dose 2 was statistically significant, it is unknown whether the small absolute difference (0.6%) between the percentages of subjects experiencing the ear infection and the wide 95% CI of the RR ratio are of clinical significance. In general, ear infections are typically self-resolving without serious sequelae.*

Serious Adverse Events

The percentage of subjects reporting at least 1 SAE during the entire study period was similar across the 3 groups: 6.1% (91/1493 subjects) for the minimum potency PRIORIX group, 6.8% (102/1497) for the medium potency PRIORIX group, and 6.0% (92/1526 subjects) for MMRII. The 3 most frequently reported SAEs were gastroenteritis (1.0%, 16 subjects for minimum potency PRIORIX; 1.3%, 19 subjects for medium potency PRIORIX; 0.7%, 10 subjects for MMRII), pneumonia (0.5%, 7 subjects for minimum potency PRIORIX; 0.9%, 14 subjects for medium potency PRIORIX; 0.7%, 10 subjects for MMRII), and febrile convulsion (0.5%, 7 subjects for minimum potency PRIORIX; 0.9%, 13 subjects for medium potency PRIORIX; 0.5%, 8 subjects for MMRII).

Additionally, there were 3 SAEs that were notable to this reviewer for which causality could not be assessed by the investigator due to insufficient clinical documentation (meningitis, encephalitis) or are known to be drug-induced (Stevens-Johnson Syndrome):

- Subject (b) (6) was a 17-month-old male in the Czech Republic in the medium potency PRIORIX group who developed grade 3 meningitis 61 days post-dose 1 (along with concomitant HAVRIX and VARIVAX)/20 days post-dose 2. The subject was hospitalized and treated with corticosteroids and antibiotics. No pathogen was identified and the subject recovered 31 days after onset. Causality could not be assessed by the investigator because of insufficient clinical documentation.
- Subject (b) (6) was a 15-month-old male in the U.S. in the medium potency PRIORIX group who developed grade 2 encephalitis (cerebellitis) 70 days post-dose 1 (along with concomitant HAVRIX, VARIVAX, PREVNAR 13)/23 days post-dose 2. The subject presented with fever 1 week prior to hospitalization; CT scan was notable for absence of the septum pellucidum although MRI did not show septo-optic dysplasia, and a CSF testing was unremarkable. The event resolved without sequelae 2 weeks after onset.

Causality could not be assessed by the investigator because of insufficient clinical documentation.

- Subject (b) (6) was an 18-month-old male in the U.S. in the medium potency PRIORIX group who developed grade 3 Stevens-Johnson Syndrome 138 days post-dose 2 (along with concomitant HAVRIX and VARIVAX). The event resolved after 61 days. Prior to the event, the patient had fever and rash, which was treated with ondansetron and ibuprofen. The event was assessed as unrelated and likely due to other causes (e.g., ondansetron, ibuprofen) by the investigator.

Reviewer Comment: *The 3 SAEs discussed above were notable to this reviewer, as the SAEs are labeled AEs (meningitis, encephalitis) for other MMR-containing vaccines or are known to be drug-induced (Stevens-Johnson Syndrome). It is unlikely that the SAE of Stevens-Johnson Syndrome is related to PRIORIX, considering the prolonged time interval between vaccine administration and event onset and the presence of other probable causes (odansetron, ibuprofen). A potential contributory role of PRIORIX for the SAEs of meningitis and encephalitis cannot be ruled out. It is noted that meningitis and encephalitis are included in Section 6.2 Postmarketing Experience in the proposed PRIORIX USPI.*

Deaths and Withdrawals

There were 3 deaths during the study, with 1 death in each of the 3 groups. None of the AEs with a fatal outcome were assessed as vaccine-related by the investigator.

- Subject (b) (6) was a 12-month-old female in Finland with a past medical history of suspected autosomal recessive polycystic kidney disease, urinary tract infection, and febrile convulsion in the medium potency PRIORIX group. She died 14 days post-dose 1 from pyelonephritis, which started 5 days prior to dose 1. An autopsy showed postmortem signs suggestive of epilepsy. Infectious disease work-up of samples taken from the lungs, heart, kidneys, and CSF were negative. Histology did not show any findings consistent with measles, mumps, rubella, or varicella infection. The immediate cause of death was determined to be acute pyelonephritis due to cystic renal dysplasia, although per the neuropathologist, epilepsy was the likely cause of death.
- Subject (b) (6) was a 19-month-old male in Thailand in the minimum potency PRIORIX group who died from drowning 171 days post-dose 2. An autopsy was not performed.
- Subject (b) (6) was a 21-month old male in the Czech Republic in the MMRII group who died from drowning and multiple injuries 153 days post-dose 2.

Reviewer Comment: *Regarding Subject (b) (6), it is not possible to conclude whether PRIORIX contributed to the underlying disorder (epilepsy). There is a known increased risk of febrile seizures in the first 2 weeks following immunization with measles, mumps, and rubella-containing vaccines. However, febrile seizures are typically a benign phenomenon (Millichap 2021). A large population-based cohort study showed that the long-term rate of epilepsy was not increased in children who had febrile seizures following vaccination compared with children who had febrile seizures of a different etiology (Vestergaard et al. 2004). The other deaths are assessed by this reviewer as unrelated to the product.*

In addition to the 3 deaths above, 2 subjects had SAEs leading to study withdrawal. Both SAEs were assessed as unrelated to vaccine, and both subjects recovered from the events.

- Subject (b) (6) was a 12-month-old male in the minimum potency PRIORIX group who developed thrombocytopenia and petechiae 21 days post-dose 1. The subject was hospitalized and the event resolved after 42 days. The investigator thought that the events were possibly due to a viral infection.
- Subject (b) (6) was a 12-month-old male in the MMRII group who developed petechiae and was found to have Henoch-Schönlein purpura 21 days post-dose 1. The subject was not hospitalized but was being monitored by hospital and outpatient visits.

Additionally, 3 subjects in the PRIORIX minimum potency group and 1 subject in the PRIORIX medium potency group withdrew from the study due to non-serious AEs. The non-serious AEs leading to withdrawal were diarrhea, otitis media, and worsening of congenital hypertrophy of lymph node (behind left ear) in the PRIORIX minimum potency group and vomiting in the PRIORIX medium potency group. Only the AE of worsening lymph node hypertrophy was assessed as vaccine-related by the investigator.

Adverse Events of Specific Interest

New Onset Chronic Diseases (NOCD)

There were no imbalances in risk for any PTs defined as NOCDs occurring within 43 days post-vaccination (post-dose 1 or 2). The percentage of subjects with NOCDs occurring within 43 days of post-dose 1 was 0.5% (8/1497) for medium potency PRIORIX and 0.4% (6/1526 subjects) for MMRII (RR=1.36; 95% CI: 0.4, 4.8). The only NOCD reported for more than 1 subject in either group was bronchial hyperreactivity, which was reported for 2 subjects in the medium potency PRIORIX group and no subjects in the MMRII group. The percentage of subjects with NOCDs occurring within 43 days post-dose 2 was 0.8% (24/2913) for pooled (minimum and medium potencies) PRIORIX and 0.6% (9/1483 subjects) for MMRII (RR=1.36; 95% CI: 0.6, 3.3). NOCDs reported for more than 1 subject in either group were dermatitis atopic (0.2%, 7 subjects in pooled PRIORIX group; 0.3%, 4 subjects in MMRII group), wheezing (0.1%, 3 subjects; 0.1%, 2 subjects), bronchial hyperreactivity (0.1%, 3 subjects; 0 subjects), eczema (0.1%, 3 subjects; 0 subjects), drug hypersensitivity (<0.1%, 1 subject; 0.1%, 2 subjects), rhinitis allergic (<0.1%. 1 subject; 0.1%, 1 subject).

The percentages of subjects reporting NOCDs during the 6-month study period were comparable across the 3 groups: 2.3% for minimum potency PRIORIX, 2.6% for medium potency PRIORIX, and 2.2% for MMRII. The most frequently reported NOCD during the entire study period was dermatitis atopic, experienced by 0.9% (13 subjects), 0.7% (11 subjects), and 0.9% (13 subjects) of subjects in the minimum potency PRIORIX, medium potency PRIORIX, and MMRII groups, respectively. Other NOCDs reported in 3 or more subjects in a group were bronchial hyperreactivity (0.3%, 5 subjects in minimum potency PRIORIX; 0.2%, 3 subjects in medium potency PRIORIX; 0.1%, 1 subject in MMRII), eczema (0.3%, 4 subjects; 0.3%, 5 subjects; 0.1%, 2 subjects), wheezing (0.1%, 1 subject; 0.3%, 4 subjects; 0.3%, 4 subjects), asthma (0.2%, 3 subjects; 0.2%, 3 subjects; 0.1%, 2 subjects), rhinitis allergic (0.2%, 3 subjects; 0.1%, 2 subjects; 0.2%, 3 subjects), urticaria (0.2%, 3 subjects; 0.1%, 1 subject;

0.1%, 2 subjects); the 95% CIs for the incidences of all these AEs overlapped amongst the 3 groups.

4.1.4 MMR-162 (Phase 3a Study Evaluating PRIORIX at Maximum Release Potency)

Study Title:
A phase IIIa, randomized, observer-blind, controlled, multi-national study to evaluate the safety and immunogenicity of GSK Biologicals' MMR vaccine (209762) (Priorix®) compared to Merck & Co., Inc.'s MMR vaccine (*M-M-R®II* or *VaxPro*), as a first dose, both co-administered with *Varivax*, *Havrix* (all subjects), and *Prevnar 13* (U.S. subset) in healthy children 12 to 15 months of age.

Study Design:
Subjects were randomized in a 4:1:1 ratio to 3 parallel treatment groups, Inv_MMR (PRIORIX at a maximum release limit potency):Com_MMR_L1:Com_MMR_L2. The 2 MMRII groups (Com_MMR_L1, Com_MMR_L2) were pooled for analysis. Subjects received a single dose of MMR vaccine on Day 0 co-administered with VV (VARIVAX) and HAV (HAVRIX). U.S. subjects also received PCV-13 (PREVNAR, pneumococcal 7-valent conjugate vaccine).

Immunogenicity and safety were evaluated from Day 0 to 42. Solicited and unsolicited AEs were evaluated from Day 0 to 42, following each dose. SAEs and AESIs (i.e., NOCDs, AEs resulting in emergency room (ER) visits) were reported during the entire study period.

Safety Follow-up and Study Duration:
See above; 6 months (full study duration)

Objectives:
Co-Primary (Safety)

- To demonstrate the safety profile (fever >102.2ºF) of PRIORIX compared to MMRII (pooled) when co-administered with VV and HAV (all subjects) and PCV-13 (only U.S. subjects)
- To demonstrate the safety profile (fever ≥100.4ºF) of PRIORIX compared to MMRII (pooled) when co-administered with VV and HAV (all subjects) and PCV-13 (only U.S. subjects)

Secondary (Safety and Efficacy)

- To assess the immunogenicity of PRIORIX and MMRII in terms of seroresponse and GMCs for anti-measles, anti-mumps, and anti-rubella virus antibodies at Day 42.
- To assess safety and reactogenicity of PRIORIX compared to MMRII when co-administered with VV, HAV, and PCV-13.
- To assess any measles-like illness occurring within 5 to 12 days after vaccination.

Safety Endpoints:

- Occurrence of fever after MMR vaccination
  - Fever >102.2ºF from Day 5 to 12
  - Fever ≥100.4ºF from Day 5 to 12
- Solicited and unsolicited AEs after vaccination (documented by subjects' parents/guardians on diary cards), SAEs, NOCDs, conditions resulting in ER visits.
  - Solicited and unsolicited AEs:
    - Day 0 to 3: injection site reactions
    - Day 0 to 14: drowsiness, loss of appetite or irritability
    - Day 0 to 42: temperature ≥100.4ºF, rash, parotid/salivary gland swelling, febrile convulsion, any other AEs
- SAEs from Day 0 to 180
- NOCDs and AEs resulting in ER visits from Day 0 to 180

- Measles-like illness (MLI) from Day 5 to 12 post-vaccination. MLI was defined as the occurrence of the following signs and symptoms in absence of another confirmed diagnosis:
    - Temperature ≥100.4ºF and
    - Maculopapular rash and
    - At least one of the following: cough, coryza, conjunctivitis or diarrhea with fever or rash occurring during the period of Day 5 through Day 12 post-vaccination

Study Population:
Eligibility Criteria
Males and females between 12 and 15 months of age. For U.S. sites only: subjects who received all routine vaccinations as per the Advisory Committee on Immunization Practices (ACIP) recommendations prior to study entry.

Demographics of Safety Population[13]:

	INV_MMR N = 1164	**COM_MMR N = 572**	**Total N = 1736**
Age (months)			
Mean (SD)	12.3 (0.7)	12.3 (0.7)	12.3 (0.7)
Range	12-16	12-16	12-16
Gender			
Female	47.3%	47.2%	47.3%
Male	52.7%	52.8%	52.7%
Race			
African/African-American	64 (5.5%)	38 (6.6%)	102 (5.9%)
American Indian or Alaskan Native	29 (2.5%)	16 (2.8%)	45 (2.6%)
Asian or Native Hawaiian/Pacific Islander	171 (14.7%)	83 (17.5%)	254 14.6%)
White	811 (69.7%)	388 (67.8%)	1199 (69.0%)
Other	89 (7.6%)	47 (8.2%)	136 (7.8%)
U.S. Subjects			
	734 (63.1%)	357 (62.4%)	1091 (62.8%)

Group naming:
PRIORIX: INV_MMR
MMRII: COM_MMR

Safety Conclusion (per Applicant):
The safety profile of the high potency formulation of PRIORIX was acceptable and similar to MMRII, when both vaccines were co-administered with VV, HAV, and PCV-13.

Solicited Adverse Events

[13] Adapted from BLA 125748/0, Study MMR-162 Clinical Study Report, Report Amendment 2 Final, Table 20: Summary of demographic characteristics (total vaccinated cohort), p 89. Under race, Asian-central/south Asian heritage, Asian – east Asian heritage, Asian – Japanese heritage, Asian – southeast Asian heritage, and Native Hawaiian or other Pacific Islander categories were collapsed into one category, "Asian or Native Hawaiian/Pacific Islander." White – Arabic/north African heritage and White – Caucasian/European heritage were collapsed into one category, "White."

Of note, AE comparisons between the PRIORIX and control groups for all solicited adverse events discussed below revealed overlapping confidence intervals unless otherwise noted.

Injection site reactions
Incidences of injection site pain, both any and grade 3, were numerically higher in the maximum potency PRIORIX group (27.8% and 0.5%, respectively) than in the MMRII group (23.7% and 0.4%, respectively). Occurrences of injection site redness and swelling (any and grade 3) were numerically higher in the MMRII group; the incidences of redness, any and grade 3, were 24.8% and 1.3%, respectively, for the MMRII group, and 23.2% and 0.7%, respectively, for the PRIORIX group. The incidences of swelling, any and grade 3, were 10.5% and 0.4%, respectively, for the MMRII group, and 8.5% and 0.3% for the PRIORIX group.

General symptoms
The incidences of drowsiness, loss of appetite, or irritability/fussiness during Days 0-14 were numerically higher in the maximum potency PRIORIX group (46.8%, 43.8%, and 64.1%, respectively, for PRIORIX; 42.9%, 41.8%, and 62.2%, respectively, for MMRII).

The majority of fever was reported between Days 5-12, with 18.2% of subjects in the PRIORIX group and 17.1% of subjects in the MMRII experiencing fever ≥100.4ºF during this interval (Table 5). The difference (PRIORIX minus MMRII) in the proportion of subjects with fever was 1.1%, which is below the pre-specified criterion of 10%; hence the co-primary objective was met. The incidence of fever >102.2ºF was 4.2% for the PRIORIX group and 3.1% for the MMRII group. The difference was 1.1%, which was also below the criterion of 5% for meeting the co-primary objective. The incidences of fever during Days 0-14 and Days 0-42 were comparable between the two groups.

Table 5. Proportion of Subjects with Fever in MMR-162

	Temperature	**PRIORIX (INV MMR)** (%)	**MMRII (COM MMR)** (%)	**Difference (INV MMR minus COM_MMR) (95% CI)***
Days 0-14	≥38.0ºC (≥100.4ºF)	21.6%	21.1%	
	>39.5ºC (>103.1ºF)	2.0%	1.6%	
Days 5-12	≥38.0ºC (≥100.4ºF)	18.2%	17.1%	1.1% (-2.9%, 4.9%)
	>39.0ºC (>102.2ºF)	4.2%	3.1%	1.1% (-0.9, 2.9%)
	>39.5ºC (>103.1ºF)	1.5%	1.3%	
Days 0-42	≥38.0ºC (≥100.4ºF)	31.2%	32.3%	
	>39.5ºC (>103.1ºF)	4.0%	2.7%	

*The differences were only calculated for the co-primary objectives

The incidences of rash (any, measles/rubella-like, or grade 3) were comparable for the PRIORIX and MMRII groups. The proportions of subjects with any rash, measles/rubella-like rash, and grade 3 rash within 43 days were 24.4%, 5.8%, and 2.0%, respectively, in the PRIORIX group and 27.4%, 4.7%, and 1.4%, respectively, in the MMRII group.

MMR-specific general symptoms

The incidence of measles-like illness (MLI) was 1.5% (95% CI: 0.9, 2.4) in the PRIORIX group and 0.9% (95% CI: 0.3, 2.0) in the MMRII group. Measles-like illness was defined as the occurrence of the following signs and symptoms during Days 5 to 12 without another confirmed diagnosis: maculopapular rash and fever (≥100.4ºF), and at least one other symptom of cough, coryza, conjunctivitis, or diarrhea. There were no reports of parotid gland swelling occurring within 43 days in either group. The incidence of meningism was 0.2% (2 subjects) in the PRIORIX group and 0% in the MMRII group; one subject in the PRIORIX group had a grade 3 event.

Reviewer Comment: *The maximum potency PRIORIX group had numerically higher incidences of injection site pain, drowsiness, loss of appetite, irritability/fussiness, fever during Days 5-12, measles-like illness, and meningism, compared to the MMRII group. However, the absolute differences in the proportion of subjects experiencing AEs between the PRIORIX and MMRII groups were small to moderate (<4.0%) and 95% CIs were overlapping. Additionally, the differences between the proportions of subjects (1.1%) experiencing fever between Days 5-12 were below the pre-specified criteria. Since the potency of the lot used for the maximum potency PRIORIX group is at the maximum release limit, it is expected that most lots of commercially available PRIORIX will be below this potency level.*

Unsolicited Adverse Events

The percentages of subjects reporting the occurrence of at least one unsolicited AE during Days 0 to 42 were comparable for the two groups: 51.4% for PRIORIX and 48.4% for MMRII (RR=1.1, 95% CI: 0.9, 1.2). The most common (frequency ≥5.0% in either group) AEs were upper respiratory tract infection (9.5% for PRIORIX, 12.8% for MMRII), diarrhea (8.2%, 8.0%), otitis media (7.4%, 6.1%), cough (6.9%, 5.2%), and teething (5.1%, 2.6%). Of note, the relative risk analysis showed an increased frequency only for teething in the PRIORIX group (RR=1.9, 95% CI: 1.1, 3.7) and pharyngitis in the MMRII group.

Most AEs were mild or moderate in severity, with 4.6% of subjects in the PRIORIX group and 3.8% of subjects in the MMRII group experiencing at least 1 severe (grade 3) AE (RR=1.2, 95% CI: 0.7, 2.1). The only severe AE that occurred at a frequency ≥1.0% in either group was otitis media (0.9% for PRIORIX, 1.2% for MMR)[14].

Serious Adverse Events

The percentage of subjects reporting at least 1 SAE during the 6-month study period was comparable for the two groups: 2.1% (24/1,164 subjects) for PRIORIX and 1.6% (9/572 subjects) for MMRII. The 3 most frequent SAEs were pneumonia (n=4 subjects, 0.3% for PRIORIX; n=1 subject, 0.2% for MMRII), dehydration (n=3, 0.3% for PRIORIX; none for MMRII), and bronchitis (n=1, 0.1% for PRIORIX; n=2, 0.4% for MMRII).

There was 1 SAE assessed as vaccine-related by the investigator: immune thrombocytopenic purpura occurring in a MMRII subject.

[14] Source: BLA 125748/0, Study MMR-162 Clinical Study Report, Report Amendment 2 Final, Table 7.7. It is noted that the main body of the CSR and the Summary of Clinical Safety incorrectly states that no grade 3 AE occurred at frequency ≥1.0%.

Deaths and Withdrawals

No deaths were reported. There were no withdrawals due to AEs.

Adverse Events of Specific Interest

New Onset Chronic Diseases (NOCD)

The percentages of subjects with NOCDs within 43 days of vaccination were similar for the two groups: 0.6% for PRIORIX and 0.7% for MMRII (RR=0.9, 95% CI: 0.2, 4.0). There were no imbalances in risk for any PTs defined as NOCDs occurring within 43 days post-vaccination. Two NOCDs were reported for more than 1 subject in either group: drug hypersensitivity (2 subjects in the PRIORIX group and 1 subject in the MMRII group; RR=1.0, 95% CI: 0.1, 58.0)) and multiple allergies (2 subjects in the PRIORIX group; RR=INF, 95% CI: 0.1, INF). The percentage of subjects reporting NOCDs during the 6-month study period was 2.5% and 1.9% for the PRIORIX and MMRII groups, respectively. The most frequent NOCD during the entire study period was dermatitis atopic, which was reported by 0.8% (9/1,164 subjects) and 0.3% (2/572 subjects) of subjects in the PRIORIX and MMRII groups, respectively.

Reviewer Comment: *Although the proportion of subjects experiencing NOCDs during the 6-month study period and the proportion of subjects reporting dermatitis atopic were numerically higher in the PRIORIX compared to the MMRII group, the absolute differences between the percentages were small and 95% CIs overlapped.*

4.2 MMR-158: Phase 3a Study in Subjects Aged 4 to 6 Years

Study Title:

A phase IIIa, observer-blind, randomized study to evaluate non-inferiority of a second dose of GSK Biologicals' measles-mumps-rubella vaccine vs. a second dose of Merck & Co., Inc.'s MMR vaccine when administered with and without diphtheria, tetanus, acellular pertussis and inactivated polio (DTaP-IPV) vaccine and varicella vaccine (VV) to healthy children four to six years of age.

Study Design:

Subjects were randomized in a 3:1 ratio to either the PRIORIX or MMRII groups (2 lots of MMRII were used and results were pooled for analyses). Within each group, there were three sub-cohorts; subjects were randomized in a 6:1:1 ratio within each sub-cohort.

- Sub-cohort 1: immunogenicity and safety in the setting of co-administered DTaP-IPV and VV
- Sub-cohort 2: immunogenicity and safety without co-administered vaccines
- Sub-cohort 3: safety without co-administered vaccines

Immunogenicity and safety were evaluated from Day 0 to 42. Solicited and unsolicited AEs were evaluated from Day 0 to 42, following each dose. SAEs and AESIs (i.e., NOCDs, AEs resulting in emergency room (ER) visits) were reported during the entire study period.

Safety Follow-up and Study Duration:

See above; 6 months (full study duration)

Objectives:

Safety (Secondary)

- To assess safety and reactogenicity of PRIORIX compared to MMRII in each sub-cohort separately.

Primary

- To demonstrate non-inferiority of PRIORIX to MMRII, when co-administered with VV and DTaP-IPV vaccines, in terms of seroresponse rates to measles, mumps, and rubella viruses at Day 42.

- To demonstrate non-inferiority of PRIORIX to MMRII, when co-administered with VV and DTaP-IPV vaccines, in terms of antibody concentrations to measles, mumps, and rubella viruses at Day 42.
- To demonstrate non-inferiority of PRIORIX to MMRII, when administered without VV and DTaP-IPV vaccines, in terms of seroresponse rates to measles, mumps, and rubella viruses at Day 42.
- To demonstrate non-inferiority of PRIORIX to MMRII, when administered without VV and DTaP-IPV vaccines, in terms of antibody concentrations to measles, mumps, and rubella viruses at Day 42.

Secondary

- To demonstrate non-inferiority of PRIORIX to MMRII in terms of seroresponse rates and antibody concentrations to VZV at Day 42.
- To demonstrate non-inferiority of PRIORIX to MMRII in terms of antibody booster response to diphtheria, tetanus, pertussis toxin, filamentous hemagglutinin, and pertactin.
- To demonstrate non-inferiority of PRIORIX to MMRII in terms of antibody titers to poliovirus types 1, 2, and 3.

Safety Endpoints:

Solicited and unsolicited AEs after vaccination (documented by subjects' parents/guardians on diary cards), SAEs, and AESIs (e.g., NOCDs, AEs resulting in ER visits).

- Solicited and unsolicited AEs:
  - Day 0 to 3: injection site reactions
  - Day 0 to 3: drowsiness, loss of appetite (sub-cohort 1 only)
  - Day 0 to 42: body temperature ≥100.4ºF, rash, parotid/salivary gland swelling, signs of meningism (including febrile convulsion), any other AEs
- SAEs from Day 0 to 180
- NOCDs and AEs resulting in ER visits from Day 0 to 180

Study Population:

Eligibility Criteria

Males and females aged 4-6 years, who had received either a single dose of MMRII, M-M-RVaxPro (live attenuated measles, mumps, and rubella vaccine; Merck Sharp & Dohme Corp.), or ProQuad (live attenuated measles, mumps, rubella, and varicella virus vaccine; Merck Sharp & Dohme Corp.) in the second year of life.

Demographics of Safety Population[15]:

	INV_MMR_CO N = 802	COM_MMR_CO N = 298	INV_MMR_I N = 796	COM_MMR_I N = 303	INV_MMR_S N = 1319	COM_MMR_S N = 489	Total N = 4007
Age (years)							
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)	4.3 (0.6)
Range	4-6	4-6	3-6	4-6	4-6	4-6	3-6
Gender							
Female	49.6%	45.0%	45.4%	50.5%	47.9%	46.0%	47.5%
Male	50.4%	55.0%	54.6%	49.5%	52.1%	54.0%	52.5%
Race							
African/African-American	96 (12.0%)	39 (13.1%)	48 (6.0%)	19 (6.3%)	94 (7.1%)	32 (6.5%)	328 (8.2%)

[15] Adapted from BLA 125748/0, Study MMR-158 Clinical Study Report, Report Amendment 2 Final, Tables 34 (p 118), 6.11 (p 273), 6.12 (p 274), 6.13 (p 275), 8.1 (p 340). Under race, Asian-central/south Asian heritage, Asian – east Asian heritage, Asian – Japanese heritage, Asian – southeast Asian heritage, and Native Hawaiian or other Pacific Islander categories were collapsed into one category, "Asian or Native Hawaiian/Pacific Islander." White – Arabic/north African heritage and White – Caucasian/European heritage were collapsed into one category, "White."

American Indian or Alaskan Native	130 (16.2%)	38 (12.8%)	15 (1.9%)	3 (1.0%)	4 (0.3%)	0 (0%)	190 (4.7%)
Asian or Native Hawaiian/Pacific Islander	96 (12.0%)	38 (12.8%)	404 (50.8%)	152 (50.2%)	593 (45.0%)	217 (44.4%)	1500 (37.4%)
White	368 (45.9%)	138 (46.3%)	294 (36.9%)	120 (39.6%)	576 (43.7%)	218 (44.6%)	1714 (42.8%)
Other	112 (14.0%)	45 (15.1%)	35 (4.4%)	9 (3.0%)	52 (3.9%)	22 (4.5%)	275 (6.9%)
U.S. Subjects							
	802 (100%)	209 (100%)	412 (51.8%)	157 (51.8%)	736 (55.8%)	276 (56.4%)	2592 (64.7%)

Group naming:
PRIORIX: INV_MMR_CO: PRIORIX co-administration sub-cohort (sub-cohort 1)
INV_MMR_I: PRIORIX immunogenicity sub-cohort (sub-cohort 2)
INV_MMR_S: PRIORIX safety sub-cohort (sub-cohort 3)
MMRII: COM_MMR_CO: MMRII co-administration sub-cohort (sub-cohort 1)
COM_MMR_I: MMRII immunogenicity sub-cohort (sub-cohort 2)
COM_MMR_S: MMRII safety sub-cohort (sub-cohort 3)

Safety Conclusion (per Applicant):
No safety concerns were identified regarding PRIORIX. The safety profile of PRIORIX was similar to that of MMRII, when administered with or without VV and DTaP-IPV.

Safety data was presented by sub-cohort. Sub-cohort 1 (co-administration cohort) consisted of U.S. subjects who also received diphtheria, tetanus, acellular pertussis, and inactivated polio (DTaP-IPV) and varicella (VV) vaccines. The other 2 sub-cohorts (sub-cohort 2: immunogenicity cohort, sub-cohort 3: safety cohort) received the MMR vaccine without other concomitant vaccines.

Solicited Adverse Events

Of note, AE comparisons between the PRIORIX and control groups for all solicited adverse events discussed below revealed overlapping confidence intervals unless otherwise noted.

Injection site reactions

Sub-cohort 1 (co-administration cohort)

Incidences of injection site pain and swelling in the first 4 days after vaccination were comparable for the two groups: 40.6% and 11.3%, respectively, for PRIORIX, and 40.8%, 10.5%, respectively, for MMRII. Grade 3 injection site pain and swelling occurred in 3.0% and 0.4%, respectively, in the PRIORIX group, and 1.5% and 1.1%, respectively, in the MMRII group. Injection site redness was higher in the MMRII group. Proportions of subjects with any injection site redness and grade 3 redness were 21.6% and 1.2%, respectively, in the PRIORIX group, and 25.8% and 1.5%, respectively, in the MMRII group.

Sub-cohort 2 (immunogenicity cohort)

Incidences of injection site redness and swelling were comparable for the two groups: 19.1% and 8.4%, respectively, for PRIORIX, and 18.3% and 8.0%, respectively, for MMRII. There was no Grade 3 injection site redness or swelling in either group. The incidence of any injection site pain was higher in the MMRII group. Proportions of subjects with any injection

site pain and grade 3 pain were 22.1% and 0.7%, respectively, in the MMRII group, and 19.8% and 0.8%, respectively, in the PRIORIX group.

Sub-cohort 3 (safety cohort)
Incidences of injection site redness and swelling were similar for the two groups: 18.8% and 8.4%, respectively, for PRIORIX, and 18.8% and 8.8%, respectively, for MMRII. There was no Grade 3 injection site redness or swelling in either group. The incidence of any injection site pain was higher in the MMRII group. Proportions of subjects with any injection site pain and grade 3 pain were 25.6% and 0.4%, respectively, in the MMRII group, and 21.6% and 0.4%, respectively, in the PRIORIX group.

Reviewer Comment: *Overall, injection site reactions were not higher for the PRIORIX group compared to the MMRII group across the 3 sub-cohorts. Injection site redness was more frequent in the MMRII group in the co-administration cohort, and injection site pain was more frequent in the MMRII group in the immunogenicity and safety cohorts. However, the small to moderate absolute differences between the percentages (≤4.0%) and overlapping 95% CIs are of unclear clinical significance.*

General symptoms
Drowsiness and loss of appetite within 4 days post-vaccination were only assessed in sub-cohort 1. The incidences of drowsiness and loss of appetite were similar for the two groups: 27.2% and 21.2%, respectively, for PRIORIX, and 26.9% and 22.0%, respectively, for MMRII.

The incidence of fever ≥100.4ºF during Days 0-42 were comparable for the two groups across the 3 sub-cohorts (Tables 6-8). A higher proportion of subjects in the PRIORIX group experienced fever ≥100.4ºF during Days 5-12 across the 3 sub-cohorts.

Table 6. Proportion of Subjects with Fever in MMR-158: Sub-cohort 1 (Co-Administration Cohort)

	Temperature	PRIORIX (INV_MMR_CO) (%)	MMRII (COM_MMR_CO) (%)
Days 0-14	≥38.0ºC (≥100.4ºF)	13.4%	11.6%
	>39.5ºC (>103.1ºF)	0.4%	0.4%
Days 5-12	≥38.0ºC (≥100.4ºF)	4.8%	3.4%
	>39.5ºC (>103.1ºF)	0.4%	0.4%
Days 0-42	≥38.0ºC (≥100.4ºF)	24.1%	24.6%
	>39.5ºC (>103.1ºF)	1.0%	2.2%

Table 7. Proportion of Subjects with Fever in MMR-158: Sub-cohort 2 (Immunogenicity Cohort)

	Temperature	PRIORIX (INV_MMR_I) (%)	MMRII (COM_MMR_I) (%)
Days 0-14	≥38.0ºC (≥100.4ºF)	7.8%	9.3%
	>39.5ºC (>103.1ºF)	0.7%	1.4%
Days 5-12	≥38.0ºC (≥100.4ºF)	4.3%	2.7%

	>39.5ºC (>103.1ºF)	0.4%	1.4%
Days 0-42	≥38.0ºC (≥100.4ºF)	19.0%	19.9%
	>39.5ºC (>103.1ºF)	1.8%	3.1%

Table 8. Proportion of Subjects with Fever in MMR-158: Sub-cohort 3 (Safety Cohort)

	Temperature	PRIORIX (INV_MMR_S) (%)	MMRII (COM_MMR_S) (%)
Days 0-14	≥38.0ºC (≥100.4ºF)	10.0%	8.9%
	>39.5ºC (>103.1ºF)	0.9%	0.4%
Days 5-12	≥38.0ºC (≥100.4ºF)	5.9%	5.0%
	>39.5ºC (>103.1ºF)	0.5%	0.0%
Days 0-42	≥38.0ºC (≥100.4ºF)	19.9%	20.0%
	>39.5ºC (>103.1ºF)	1.6%	1.7%

Generally, the incidences of rash (any, measles/rubella-like, or grade 3) within 43 days of vaccination were comparable in both groups across the 3 cohorts, except for any rash, which was higher in the MMRII group in sub-cohort 1. In sub-cohort 1, the proportions of subjects with any rash, measles/rubella-like rash, and grade 3 rash were 8.3%, 1.9%, and 0.4%, respectively, in the PRIORIX group and 10.4%, 1.9%, and 0%, respectively, in the MMRII group. In sub-cohort 2, the proportions of subjects with any rash, measles/rubella-like rash, and grade 3 rash were 4.8%, 0.4%, and 0.1%, respectively, in the PRIORIX group and 4.1%, 0.7%, and 0%, respectively, in the MMRII group. In sub-cohort 3, the proportions of subjects with any rash, measles/rubella-like rash, and grade 3 rash were 4.3%, 0.3%, and 0.2%, respectively, in the PRIORIX group and 4.8%, 0.4%, and 0%, respectively, in the MMRII group.

MMR-specific general symptoms

Parotid gland swelling and meningism occurring within 43 days post-vaccination were infrequent. In the pooled sub-cohorts, the incidence of parotid gland swelling was <0.1% (1 subject) in the PRIORIX groups and 0.2% (2 subjects) in the MMRII groups. There was no grade 3 parotid gland swelling in either treatment group. The incidence of meningism was <0.1% (1 subject) in the PRIORIX groups and 0.2% (2 subjects) in the MMRII groups. There was no grade 3 meningism in either treatment group.

Unsolicited Adverse Events

The percentage of subjects reporting at least one unsolicited AE within 43 days post-vaccination was 37.6% for pooled PRIORIX and 35.6% for pooled MMRII groups (RR=1.0; 95% CI: 0.9, 1.2). The only AE reported by ≥5.0% of subjects in either group was nasopharyngitis, which was reported by 7.3% of subjects in the pooled PRIORIX and 7.0% in the pooled MMRII groups (RR=1.1; 95% CI: 0.8, 1.4). There was an increased risk of ear infection (0.4% (12/2,917 subjects) for pooled PRIORIX, 0% for pooled MMRII (RR = infinity; 95% CI: 1.3, infinity)) and influenza (0.6% (18/2,917 subjects) for pooled PRIORIX, 0.1% (1/1,090 subjects) for pooled MMRII (RR = 6.7; 95% CI: 1.1, 280.2)) in the pooled PRIORIX group. Most AEs were mild or moderate in severity, with 2.5% of subjects in the pooled PRIORIX group and 2.9% of subjects in the MMRII group experiencing at least 1 severe

(grade 3) AE (RR=0.8; 95% CI: 0.6, 1.3). There were no grade 3 AEs reported with a frequency ≥1.0% in either group or imbalances for any PT.

Reviewer Comment: *The exploratory RR analyses showed an increased risk of ear infection and influenza in the pooled PRIORIX group. The wide 95% CIs of the RR ratios are reflective of the degree of uncertainty regarding the small number of subjects reporting the AEs. The clinical significance of these results are unclear.*

Serious Adverse Events

The percentage of subjects reporting at least 1 SAE during the 6-month study period was 1.5% (43/2,917 subjects) for the pooled PRIORIX group and 0.9% (10/1,090 subjects) for the pooled MMRII group. The percentage of subjects reporting at least 1 SAE by sub-cohort was as follows: sub-cohort 1 (0.5%, 4/802 subjects for PRIORIX; 0 subjects for MMRII), sub-cohort 2 (1.8%, 14/796 subjects for PRIORIX; 0.3%, 1/303 subjects for MMRII), sub-cohort 3 (1.9%, 25/1319 subjects for PRIORIX; 1.8%, 9/489 subjects for MMRII). The 3 most common SAEs were gastroenteritis (0.2%, 7 subjects for pooled PRIORIX; 0.1%, 1 subject for pooled MMRII), asthma (0.2%, 6 subjects for pooled PRIORIX; 0.2%, 2 subjects for pooled MMRII), and gastritis (0.1%, 3 subjects for pooled PRIORIX; 0 subjects for pooled MMRII).

One SAE was assessed as vaccine-related by the investigator: an event of rash generalized in a PRIORIX recipient in sub-cohort 3.

Reviewer's Comment: *The percentage of subjects reporting SAEs was greater in the pooled PRIORIX group (1.5%) compared to the pooled MMRII group (0.9%). Tests for statistical significance were not done by the applicant, and it is unknown whether the small absolute percentage difference (0.6%) could be explained by random chance or is of clinical significance.*

Deaths and Withdrawals

No deaths were reported. There were no withdrawals due to AEs.

Adverse Events of Specific Interest

New Onset Chronic Diseases (NOCD)

The percentages of subjects reporting NOCDs 43 days post-vaccination were 0.3% (9/2,917 subjects) and 0.1% (1/1,090 subjects) for the pooled PRIORIX and MMRII groups, respectively (RR=3.4; 95% CI: 0.5, 147.4). The relative risk (RR) analyses did not show any imbalances between the PRIORIX and MMRII groups for any NOCDs occurring within 43 days of vaccination. NOCDs reported by more than 1 subject in either group were rhinitis allergic (2 subjects in the pooled PRIORIX group and 1 subject in the pooled MMRII group) (RR=0.8; 95% CI: <0.1, 44.1) and dermatitis atopic (3 subjects, all in the pooled PRIORIX group) (RR=infinity; 95% CI: 0.2, infinity).

The occurrence of NOCDs during the entire study period was analyzed by sub-cohort. In-sub-cohort 1, NOCDs were reported by 1.0% (8/802 subjects) in the PRIORIX group and 1.3% (4/298) subjects in the MMRII group. The NOCDs reported for >1 subject (in any group) in

sub-cohort 1 were rhinitis allergic (3 subjects, 0.4% in PRIORIX group and 2 subjects, 0.7% in MMRII group) and drug hypersensitivity (2 subjects, 0.2% in PRIORIX group, and 0 subjects in MMRII group). In-sub-cohort 2, NOCDs were reported by 0.8% (6/796 subjects) in the PRIORIX group and no subjects in the MMRII group. The only NOCD reported for >1 subject (in any group) in sub-cohort 2 was eczema (2 subjects, 0.3% in the PRIORIX group). In-sub-cohort 3, NOCDs were reported by 0.8% (11/1,319 subjects) in the PRIORIX group and 0.6% (3/489) subjects in the MMRII group. The NOCDs reported for >1 subject (in any group) in sub-cohort 3 were rhinitis allergic (6 subjects, 0.5% in PRIORIX group and 2 subjects, 0.4% in MMRII group), dermatitis (4 subjects, 0.3% in PRIORIX group and 0 subjects in MMRII group), and asthma (2 subjects, 0.2% in PRIORIX group and 1 subject, 0.2%) in MMRII group.

4.3 : MMR-159: Phase 3a Study in Subjects Aged 7 Years and Older

Study Title:
A phase IIIA, observer-blind, randomized study to evaluate non-inferiority of a second dose of GlaxoSmithKline (GSK) Biological's measles-mumps-rubella vaccine vs. a second dose of Merck & Co., Inc.'s measles, mumps, and rubella vaccine when administer to healthy subjects seven years of age and older.

Study Design:
The study evaluated one lot of PRIORIX and two lots of MMRII. Subjects were randomized in a 2:1:1 ratio to 3 parallel treatment groups (INV_MMR:COM_MMR_L1:COM_MMR_L2) to receive a single dose of MMR vaccine on Day 0. No other vaccines were co-administered.

Immunogenicity and safety were evaluated from Day 0 to 42. Solicited and unsolicited AEs were evaluated from Day 0 to 42, following each dose. SAEs and AESIs (i.e., NOCDs, AEs resulting in emergency room (ER) visits) were reported during the entire study period.

Study Duration and Safety Follow-up
See above; 6 months (full study duration)

Objectives:
Safety (Secondary)
- To assess safety and reactogenicity of PRIORIX compared to MMRII.

Primary
- To demonstrate the non-inferiority of PRIORIX to MMRII in terms of GMCs for anti-measles, anti-mumps, and anti-rubella antibodies at Day 42.

Secondary
- To demonstrate the non-inferiority of PRIORIX to MMRII in terms of seroresponse rates to measles, mumps, and rubella viruses at Day 42.
- To assess the percentage of subjects who achieve a minimum 4-fold rise in anti-measles, anti-mumps, or anti-rubella virus antibody concentrations at Day 42.

Safety Endpoints:
Solicited and unsolicited AEs after vaccination (documented by the subject or subjects' parents/guardians on diary cards), SAEs, and AESIs (e.g., NOCDs, AEs resulting in ER visits).
- Solicited and unsolicited AEs:
  - Day 0 to 3: injection site reactions
  - Day 0 to 42: body temperature ≥100.4ºF, rash, parotid/salivary gland swelling, signs of meningism (including febrile convulsion), joint pain, any other AEs
- SAEs from Day 0 to 180
- NOCDs and AEs resulting in ER visits from Day 0 to 180

Study Population:
Eligibility Criteria

Males and females aged ≥7 years who had previously received one dose of any MMR vaccine (for subjects 7-17 years, the dose should have been administered on or after the subject's first birthday). Adults ≥18 years who were born outside the U.S. were excluded.

Demographics of Safety Population[16]:

	INV_MMR N = 454	**COM_MMR N = 457**	**Total N = 911**
Age (years)			
Mean (SD)	25.9 (13.9)	25.6 (13.8)	25.7 (13.8)
Range	7-59	7-59	7-59
Gender			
Female	55.1%	55.1%	55.1%
Male	44.9%	44.9%	44.9%
Race			
African/African-American	108 (23.8%)	103 (22.5%)	211 (23.2%)
American Indian or Alaskan Native	2 (0.4%)	4 (0.9%)	6 (0.7%)
Asian or Native Hawaiian/Pacific Islander	3 (6.6%)	1 (2.2%)	4 (4.4%)
White	334 (73.6%)	345 (75.5%)	679 (74.5%)
Other	7 (1.5%)	4 (0.9%)	11 (1.2%)
U.S. Subjects			
	293 (64.5%)	293 (64.1%)	586 (64.3%)

Group naming:
PRIORIX: INV_MMR
MMRII: COM_MMR

Safety Conclusion (per Applicant):
PRIORIX had an acceptable safety profile that was similar to MMRII in subjects ≥7 years old.

Solicited Adverse Events

Of note, AE comparisons between the PRIORIX and control groups for all solicited adverse events discussed below revealed overlapping confidence intervals unless otherwise noted.

Injection site reactions

Incidences of injection site pain, redness, or swelling in the first 4 days after vaccination were comparable for the two groups: 11.8%, 12.2%, and 5.3%, respectively, for PRIORIX (INV_MMR) and 11.5%, 11.7%, and 6.5%, respectively, for MMRII. One subject (0.2%) in the PRIORIX group had grade 3 injection site pain; there were no other instances of grade 3 solicited symptoms in either group.

General symptoms

[16] Adapted from BLA 125748/0, Study MMR-159 Clinical Study Report, Report Amendment 1 Final, Table 14.1.2.1 Summary of demographic characteristics (total vaccinated cohort), p 106.

The incidence of fever (≥ 100.4ºF and >103.1ºF) during Days 0-14 was similar for the two groups (Table 9). A numerically greater proportion of subjects in the MMRII group experienced fever during Days 5-12 and Days 0-42.

Table 9. Proportion of Subjects with Fever in MMR-159

	Temperature	PRIORIX (INV_MMR) (%)	MMRII (COM_MMR) (%)
Days 0-14	≥38.0ºC (≥100.4ºF)	1.9%	2.0%
	>39.5ºC (>103.1ºF)	0.2%	0.0%
Days 5-12	≥38.0ºC (≥100.4ºF)	0.5%	1.6%
	>39.5ºC (>103.1ºF)	0.0%	0.0%
Days 0-42	≥38.0ºC (≥100.4ºF)	3.0%	5.2%
	>39.5ºC (>103.1ºF)	0.2%	1.3%

The incidences of rash (any, measles/rubella-like, or grade 3) were low in both groups. The proportions of subjects with any rash, measles/rubella-like rash, and grade 3 rash were 2.1%, 0%, and 0%, respectively, in the PRIORIX group and 1.1%, 0.4%, and 0%, respectively, in the MMRII group.

MMR-specific general symptoms
The incidence of joint pain during Days 0 to 42 was 1.9% in the PRIORIX and 0.9% in the MMRII group. There were no reports of grade 3 joint pain. One subject (0.2% for each) in each group had parotid gland swelling; the event was severe in the subject that received PRIORIX. Similarly, one subject (0.2% for each) in each group had meningism, with the event being severe in the subject that received PRIORIX.

Unsolicited Adverse Events
There was no statistical difference in the percentage of subjects reporting at least one unsolicited AE during Days 0 to 42 between recipients of PRIORIX vs MMRII (20.9% for PRIORIX and 17.9% for MMRII, RR=1.2; 95% CI: 0.9, 1.6). No AEs were reported by ≥5.0% of subjects in either group. The most common AEs (frequency ≥1.0% in either group) were headache (3.7% in PRIORIX group, 0.9% in MMRII group), nasopharyngitis (2.9%, 1.3%), diarrhea (1.3%, 0%), sinusitis (1.1%, 0%), upper respiratory tract infection (0.9%, 1.1%), viral upper respiratory tract infection (0.7%, 1.1%), and cough (0.4%, 1.1%). There was an increased risk of diarrhea (1.3% (6/454 subjects) for PRIORIX, 0% for MMRII (RR = infinity; 95% CI: 1.6, infinity)) and sinusitis (1.1% (5/454 subjects) for PRIORIX and 0% in MMRII (RR = infinity; 95% CI: 1.2, infinity)) in the PRIORIX group. Most AEs were mild or moderate in severity, with 1.5% of subjects in the PRIORIX group and 1.1% of subjects in the MMRII group experiencing at least 1 severe (grade 3) AE (RR = 1.4; 95% CI: 0.4, 5.6). No grade 3 AEs were reported with a frequency ≥1.0% in either group, and there were no risk imbalances for any PTs.

Reviewer Comment: *The exploratory RR analyses showed an increased risk of diarrhea and sinusitis in the PRIORIX group. The wide 95% CIs of the RR ratios are reflective of the degree*

of uncertainty regarding the small number of subjects reporting the AEs. The clinical significance of these results are unclear.

Serious Adverse Events

The percentage of subjects reporting at least 1 SAE during the 6-month study period was 0.7% (3/454 subjects) for PRIORIX and 1.3% (6/457) for MMRII. The only SAE reported in more than 1 subject was spontaneous abortion, which was reported for 2 subjects in the MMRII group. None of the SAEs were assessed as vaccine-related by the investigator.

Deaths and Withdrawals

No deaths were reported. There were no withdrawals due to AEs.

Adverse Events of Specific Interest

New Onset Chronic Diseases (NOCD)

One subject in the PRIORIX group reported a NOCD of type 2 diabetes mellitus within 43 days of vaccination. No subjects in the MMRII group reported a NOCD within 43 days of vaccination (RR=infinity, 95% CI: 0.05, infinity). The percentage of subjects reporting NOCDs during the 6-month study period was 0.4% (2/454 subjects) and 0.2% (1/457 subjects) for the PRIORIX and MMRII groups, respectively. These reports included the aforementioned event of type 2 diabetes mellitus in the PRIORIX group, as well as 1 additional event of diabetes mellitus (type not specified) in each group.

***Reviewer Comment**: Given that type 1 diabetes is one of the most common chronic illnesses in the pediatric population and the increasing incidence of type 2 diabetes, it is not possible to conclude that there is a causal relationship between PRIORIX and diabetes. Additionally, the small number of subjects reporting diabetes make these numbers difficult to interpret. Controlled epidemiologic studies (Blom et al. 1991, DeStefano et al 2001) did not show a causal association between type 1 diabetes and MMR-containing vaccines; on the contrary, one study (Blom et al. 1991) reported a decreased risk of type 1 diabetes with measles vaccination. A comprehensive review conducted by the Institute of Medicine concluded that the evidence favored rejection of a causal relationship between type 1 diabetes and MMR vaccines (IOM 2011).*

Use During Pregnancy

Study MMR-159 was the only study that included subjects of childbearing age. Pregnant subjects were excluded; however, there were 6 subjects who became pregnant during the study: 2 subjects in the PRIORIX group and 4 subjects in the MMRII group. All reported pregnancies were in U.S. subjects. One subject received PRIORIX 8 weeks into her pregnancy and delivered a live infant at term without congenital abnormalities. The other subject was exposed to PRIORIX 2 months prior to pregnancy and also delivered a live infant at term without congenital abnormalities. The 4 subjects reporting pregnancy in the MMRII group were exposed prior to pregnancy, with the interval between exposure and last menstrual period ranging from 33 to 120 days. Of the 4 subjects, 2 subjects experienced spontaneous abortion (at 6 and 7 weeks gestation) without apparent congenital abnormalities, 1 subject

underwent elective termination for non-medical reasons, and 1 subject delivered a live infant at term without congenital abnormalities.

Reviewer Comment: *Overall, the data for the 6 clinical studies indicate that the reactogenicity and safety profiles of PRIORIX are comparable to that of MMRII across the age groups studied (e.g., 12-15 months, 4-6 years, and ≥7 years), whether given as a first or second dose, and with or without other concomitantly administered vaccines (e.g., varicella virus, hepatitis A virus, and pneumococcal vaccines for 12-15-month-olds; varicella virus and DTaP-IPV vaccines for 4-6-year-olds). There are no new safety concerns or signals concerning PRIORIX that have not been previously reported with the two approved MMR-containing vaccines (e.g., MMRII, ProQuad) in the U.S.*

5. POSTMARKETING DATA

PRIORIX is currently approved in all EU countries as well as over 70 non-EU countries. Over 388 million doses have been distributed outside the U.S[17]. The submitted Periodic Benefit Risk Evaluation Report (PBRER) (reporting period: 05 May 2015 to 04 May 2018), dated 25 July 2018, was reviewed. Adverse reactions (ARs) reported in the post-marketing setting outside the U.S. are summarized below:

Table 10: Adverse Reactions Reported in the Postmarketing Setting Outside the U.S.[18]

System Organ Class (SOC)	Adverse Reactions
Infections and infestations	Meningitis, measles-like syndrome, mumps-like syndrome (including orchitis, epididymitis, and parotitis)
Blood and lymphatic system disorders	Thrombocytopenia, thrombocytopenic purpura
Immune system disorders	Anaphylactic reactions
Nervous system disorders	Encephalitis, cerebellitis, cerebellitis like symptoms (including transient gait disturbance and transient ataxia), Guillain-Barré syndrome, transverse myelitis, peripheral neuritis
Vascular disorders	Vasculitis (including Henoch-Schönlein purpura and Kawasaki syndrome)
Skin and subcutaneous tissue disorders	Erythema multiforme
Musculoskeletal and connective tissue disorders	Arthralgia, arthritis

Reviewer Comment: *The ARs reported in the postmarketing setting for PRIORIX are also labeled for MMRII, except for meningitis. Meningitis is labeled for PROQUAD (measles, mumps, rubella, and varicella virus vaccine live).*

During the reporting period, there were no new important risks or safety issues identified and there were no safety-related changes to the reference safety information. Two actions were taken for safety reasons: 1) at the European Medicines Agency's (EMA's) request, a dear healthcare provider letter regarding a product quality issue of leaking syringes was issued, and 2) a manufacturing investigation of a lot associated with the death of a 6-year-old female in Belarus did not find any quality-related issues. Four signals (encephalitis/cerebellitis,

[17] BLA 125748/0, Module 5.3.6, Periodic Benefit Risk Evaluation Report, data lock point 04 May 2018.
[18] BLA 125748/0, Module 2.7.4, Summary of Clinical Safety, Table 93, p213.

stomatitis, uveitis, “feeling bad’ involving a specific lot in Estonia) were evaluated and closed/refuted during the reporting period. The evaluation of a potential signal of pneumonia was inconclusive and was ongoing at the time of the report. The evaluation was prompted by an abstract from an academic meeting regarding a 2-year-old male without significant medical history who developed vaccine-strain measles-positive pneumonia post-vaccination with PRIORIX TETRA (live, attenuated measles, mumps, rubella, and varicella vaccine). The applicant reported that there were no spontaneous case reports in which vaccine measles virus was confirmed as a direct causal pathogen for pneumonia or pneumonitis. Subsequent observed/expected (O/E) analyses of PRIORIX and PRIORIX TETRA and pneumonia showed that the numbers of observed cases were much lower than the expected number of cases for children 1 year of age as well as for those <5 years of age[19]. Across the 6 clinical studies, there were no significant risk differences between the PRIORIX and MMRII groups regarding pneumonia within 43 days post-vaccination.

As of 18 April 2022, there were 5,837 AE reports for PRIORIX in the VAERS database. Table 11 lists the 10 most frequently reported preferred terms (PTs) for PRIORIX. The majority of the PTs were included in the proposed PRIORIX USPI, except vomiting, headache, and pallor. Pallor is conceptually related to syncope, which is included in the PRIORIX USPI. Vomiting and headache are labeled AEs for other MMR-containing vaccines.

Table 11: Top 10 Most Frequently Reported Preferred Terms for PRIORIX in VAERS

PT	N
Pyrexia	311
Rash	93
Vomiting	85
Injection site erythema	55
Diarrhea	53
Febrile convulsion	52
Headache	49
Pallor	46
Injection site swelling	45
Body temperature increased	43

Data mining of the VAERS database was performed on 24 February 2022, using Empirica 8.0 with a data lock date of 20 February 2022[20]. Table 12 lists the preferred terms (PTs) and SMQ - narrow reported disproportionately (EB05 >2) for PRIORIX.

Table 12: Results of Data Mining for PRIORIX

PT or Narrow_Alg SMQ	N	EB05
Vaccination failure	6	176.3
Juvenile idiopathic arthritis	4	3.47
Product deposit	3	3.31

[19] Source: BLA 125748/0, Module 5.3.6, Periodic Benefit Risk Evaluation Report, reporting period 05 May 2018 to 04 May 2021.

[20] Data mining was performed in Empirica Signals Management “Product (S)” run for PRIORIX. Data mining findings are subject to several potential limitations. Data mining scores do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation

Arthritis (SMQ) [narrow]	5	2.55
Nodule	3	2.26

Vaccination failure is not an AE and is related to efficacy; vaccination failure can occur with any vaccine since no vaccine is 100% efficacious or effective. Arthritis is a known adverse reaction that is also labeled for MMRII. The VAERS reports of "product deposit" and "nodule" were reviewed and likely represent AEs to other concomitant medications; the reports were duplicates of a single case of an infant female with a medical history of juvenile arthritis on multiple medications (methotrexate, etanercept, and infliximab) who developed a growth on ankle and knee swelling after articular injection with an unspecified drug. Per the report, "the drug did not absorb but crystallized."

Reviewer Comment: *The data mining results for PRIORIX are of limited applicability since the VAERS reports for PRIORIX represent a small and potentially unrepresentative fraction of all postmarketing reports for PRIORIX. Overall, the pattern of VAERS reports for PRIORIX are consistent with the clinical safety database and the safety profile of other MMR-containing vaccines.*

6. PHARMACOVIGILANCE PLAN

6.1 Summary of Pharmacovigilance Plan

The applicant submitted a pharmacovigilance plan (PVP) proposing routine pharmacovigilance (PV) activities, which includes the review and reporting of adverse reactions from the postmarketing setting, signal detection, periodic aggregate safety reports, and literature review. The applicant's summary of important identified risks, important potential risks, and missing information is summarized in Table 13.

Table 13: Summary of Safety Concerns

Safety Concern	Risk Minimization Activities
Important Identified Risks	
None	• N/A
Important Potential Risks	
None	• N/A
Missing Information	

Use in pregnant or lactating patients	• Routine PV activities
	• Routine risk communication in USPI
	  ○ The Highlights of Prescribing Information and Section 4.3 list pregnancy as a contraindication
	  ○ Sections 8.1 and 8.2 summarize the lack of data regarding use of PRIORIX during pregnancy and/or lactation

There are no important identified or important potential risks in the submitted PVP. At the time of the PBRER dated 25 July 2018, important identified risks consisted of hypersensitivity, syncope/vasovagal response to injection, febrile convulsions, and immune thrombocytopenic purpura (ITP)/thrombocytopenia. There were no important potential risks. The applicant removed the four previously important identified risks from the safety specifications of the

current PVP, stating that the risks are well-characterized, the frequencies have remained the same, are labeled, and do not require additional measures beyond routine pharmacovigilance. The applicant did not mention any ongoing studies in in the PVP that will yield additional safety information.

7. ASSESSMENT OF PHARMACOVIGILANCE PLAN

Overall, the clinical trial safety database does not indicate any new safety issues for PRIORIX which have not been previously described for MMR-containing vaccines. Since there are no important identified or important potential risks in the submitted PVP, the discussion below focuses on the four previously important identified risks that were removed from the safety specifications of the current PVP.

7.1 Important Identified Risks

There are no important identified risks in the submitted PVP. The four previously important identified risks (hypersensitivity, syncope/vasovagal response to injection, febrile convulsions, and immune thrombocytopenic purpura (ITP)/thrombocytopenia) are no longer listed under the safety specifications of the current PVP; they are discussed below. Hypersensitivity and syncope/vasovagal reactions can occur with any vaccine, while febrile convulsions and ITP/thrombocytopenia are known to occur with MMR-containing vaccines.

Hypersensitivity

Hypersensitivity can occur with any vaccine, although anaphylaxis after vaccination is rare in the U.S. (Su et al. 2019). Anaphylaxis has been reported with MMRII by individuals with allergies to vaccine components, including neomycin and gelatin. PRIORIX may contain trace amounts of neomycin (≤25 mcg) but does not contain gelatin[21]. MMR vaccines have been safely administered in individuals with egg allergies (Aickin et al. 1994; Carapetis et al. 2001). Table 14 summarizes the incidences of hypersensitivity reactions during the 43-day post-vaccination period across the 6 clinical studies (subjects who received low potency lots of PRIORIX are excluded). Overall, the incidences of hypersensitivity reactions across the 6 studies were low (<1%) and comparable between the PRIORIX and MMRII groups. One subject in the PRIORIX group experienced an anaphylactic reaction.

Table 14: Occurrence of Hypersensitivity During the 43-Day Post-Vaccination Period Across the 6 Clinical Studies[22]

	Preferred Term	PRIORIX N (%)	MMRII N (%)	Relative Risk (95% CI)
Study MMR-157	Hypersensitivity	0 (0%)	2 (0.65%)	0.00 (0.00, 3.52)
Study MMR-158	Hypersensitivity	4 (0.14%)	0 (0%)	INF (0.34, INF)
	Anaphylactic reaction	1 (0.03%)	0 (0%)	INF (0.02, INF)
Study MMR-159	Hypersensitivity	0 (0%)	0 (0%)	
Study MMR-160	Hypersensitivity	4 (0.11%)	2 (0.16%)	0.69 (0.10, 7.67)
	Drug hypersensitivity	2 (0.05%)	1 (0.08%)	0.69 (0.04, 40.95)

[21] Source: BLA 125748/0, Module 1.14.1.3 Draft Labeling Text

[22] Source: BLA 125748/0.12. Excludes subjects who received low potency lots (e.g., lots INV_MMR_2 and INV_MMR_3 for Study MMR-157 and INV_MMR_MIN for Study MMR-161) of PRIORIX. There were 304 subjects each in groups INV_MMR_2 and INV_MMR_3 and 1,493 subjects in INV_MMR_MIN.

Study MMR-161				
Post-dose 1	Application site hypersensitivity	0 (0%)	1 (0.07%)	0.00 (0.00, 19.37)
	Drug hypersensitivity	1 (0.07%)	1 (0.07%)	1.02 (0.01, 80.02)
Post-dose 2	Hypersensitivity	1 (0.03%)	0 (0.00%)	INF (0.03, INF)
	Drug hypersensitivity	2 (0.07%)	2 (0.13%)	0.51 (0.04, 7.02)
Study MMR-162	Drug hypersensitivity	2 (0.17%)	1 (0.17%)	0.98 (0.05, 57.98)

Of the subjects receiving low potency lots of PRIORIX, in Study MMR-157, hypersensitivity was reported by 2 (0.7%) subjects in the PRIORIX INV_MMR_L2 lot group and by 1 (0.3%) subject in the PRIORIX INV_MMR_L3 lot group[23]. For Study MMR-161, hypersensitivity was reported by 1 (0.1%) subject in the PRIORIX INV_MMR_MIN lot.

Hypersensitivity, including anaphylaxis, has been reported with PRIORIX in the postmarketing setting. The number of cumulative spontaneous reports[24] (total number of reports, number of serious reports) of hypersensitivity and similar terms are as follows: hypersensitivity (213, 42), anaphylactic reaction (75, 75), anaphylactic shock (11, 11), anaphylactoid reaction (5, 5), and allergy to vaccine (3, 1). In the submitted PBRER, the applicant stated that there has been no significant change in the nature or frequency of hypersensitivity events.

Considering that hypersensitivity events have been infrequent and are addressed in the draft USPI, the classification of hypersensitivity as a non-important risk and routine pharmacovigilance are acceptable. The draft USPI addresses hypersensitivity in the Warnings and Precautions ("Use caution when administering PRIORIX to persons anaphylaxis or immediate hypersensitivity to eggs or contact hypersensitivity to neomycin.") and anaphylactic reactions are listed in Section 6.2 Postmarketing Experience.

Syncope/vasovagal response to injection

Vaccine administration may elicit vasovagal reactions and fall-related injuries. Vasovagal reactions occur most commonly in adolescents (Braun MM et al. 1997), while the similar clinical presentation of sudden onset of reduced muscle tone, hyporesponsiveness, and change of skin color, is referred to as hypotonic-hyporesponsive episodes (HHE) in children younger than 2 years of age (Buettcher et al. 2007). Across the 6 clinical studies, syncope/vasovagal response to injection occurring within the 43-day post-vaccination period was only reported for 1 subject; the subject received PRIORIX from a low potency lot (INV_MMR_MIN) in Study MMR-161[25].

Syncope/vasovagal response has been reported with PRIORIX in the postmarketing setting. The number of cumulative spontaneous reports[23] (total number of reports, number of serious reports) of syncope and similar terms are as follows: syncope (156, 117), loss of consciousness (241, 238), hypotonic-hypotensive episode (44, 20), and altered state of consciousness (27, 27). In the submitted PBRER, the applicant stated that the reporting rate

[23] Source: BLA 125748/0.15, BLA Amendment, Module 1.11.3 Clinical Information Amendment.
[24] Source: BLA 125748/0, Module 5.3.6 PRIORIX Periodic Benefit Risk Evaluation Report (Reporting Period 05 May 2015 to 04 May 2018), dated 25 July 2018, Appendix 2B.
[25] Sources: BLA Amendments 125748/0.12 and 125748/0.15

for vaccination anxiety-related events, which includes syncope, is 0.03 per 100,000 doses distributed since the launch of PRIORIX and that the rate has not increased with time.

Considering that syncope/vasovagal reactions have been infrequent and are addressed in the draft USPI, the classification of syncope as a non-important risk and routine pharmacovigilance are acceptable. The Warnings and Precautions section of the draft USPI states that fainting can occur with vaccine administration so procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope.

Febrile convulsions

Febrile convulsions (or febrile seizures) are the most common neurologic disorders of infants and young children, occurring in 2-4% of children less than 5 years of age. Febrile convulsions recur in one-third of young children but are otherwise a benign phenomenon (Millichap 2021). There is an increased risk of febrile convulsions in the first 2 weeks following immunization with MMR-containing vaccines (Barlow et al. 2001; Miller et al. 2007; Vestergaard et al. 2004; Ward et al. 2007), with approximately 1 case of febrile convulsion for every 3,000-4,000 doses of MMR-vaccine administered (Barlow et al. 2001; Farrington et al. 1995).

Table 15 summarizes the incidences of meningism, including febrile convulsions, during the 43-day post-vaccination period across the 6 clinical studies. Overall, the incidences of meningism, including febrile convulsions, across the 6 studies were low (<0.5%) and comparable between the PRIORIX and MMRII groups.

Table 15: Occurrence of Meningism Including Febrile Convulsions During the 43-Day Post-Vaccination Period Across the 6 Clinical Studies[26]

	PRIORIX N (%)	**MMRII N (%)**
Study MMR-157	L1 lot: 0 (0%) L2 lot (low potency lot): 1 (0.36%) L3 lot (low potency lot): 0 (0%)	1 (0.36%)
Study MMR-158	1 (0.04%)	2 (0.19%)
Study MMR-159	1 (0.23%)	1 (0.22%)
Study MMR-160	10 (0.28%)	3 (0.24%)
Study MMR-161		
Post-dose 1	MIN lot (low potency lot): 3 (0.21%) MED lot: 4 (0.27%)	3 (0.20%)
Post-dose 2	MIN lot: 2 (0.14%) MED lot: 6 (0.42%)	4 (0.27%)
Study MMR-162	2 (0.18%)	0 (0.0%)

Febrile convulsions have been reported with PRIORIX in the postmarketing setting. Cumulatively, there have been 891 spontaneous reports of febrile convulsion, of which 887 reports are serious[23]. In the submitted PBRER, the applicant stated that the reporting rate for febrile convulsion is 0.28 cases per 100,000 doses distributed since the launch of PRIORIX,

[26]Sources: BLA Amendments 125748/0.12 and 125748/0.15

and that the proportion of febrile convulsion reports (as compared to all AE reports) has not increased over time.

Considering that febrile convulsions are a well-known adverse reaction of MMR vaccination and are addressed in the draft USPI, the classification of febrile convulsions as a non-important risk and routine pharmacovigilance are acceptable. The Warnings and Precautions section of the draft USPI states that caution should be used with administering PRIORIX to individuals with an individual or family history of convulsions. Febrile convulsions are also included in Section 6.1, and seizures are included in Section 6.2 of the draft USPI. In order to facilitate the monitoring of febrile convulsions in the U.S. population, in the event that PRIORIX is approved, the applicant agreed to perform an analysis of U.S.-specific safety data pertaining to febrile convulsion and include the results in each future periodic safety report submissions for a period of 3 years following approval in the U.S.[27]

Immune thrombocytopenic purpura (ITP)/thrombocytopenia

Thrombocytopenia, including ITP, is a known AR associated with MMR-containing vaccines. A review conducted by the Institute of Medicine concluded that there is a causal relationship between the MMR vaccine and thrombocytopenia (IOM 1994). A review of 12 studies reported a median incidence of 2.6 cases of ITP per 100,000 MMR vaccine doses (Mantadakis et al. 2010). Severe bleeding was rare, and thrombocytopenia resolved within 6 months from diagnosis in 93% of children. Notably, MMR vaccination of individuals with ITP or revaccination of those with prior ITP did not lead to recurrence of thrombocytopenia. A Vaccine Safety Datalink project found an attributable risk of 1 case per 40,000 doses of MMR, with cases resolving within 7 days, on average (France et al, 2008).

Across the 6 clinical studies, ITP/thrombocytopenia occurring within the 43-day post-vaccination period was reported for 1 MMRII subject and 2 subjects who received low potency lots of PRIORIX (1 subject in the PRIORIX L2 lot group in Study MMR-157 and 1 subject in the PRIORIX MIN lot group in Study MMR-161)[28]. Thrombocytopenia and ITP have been reported with PRIORIX in the postmarketing setting. The number of cumulative spontaneous reports[23] (total number of reports, number of serious reports) of thrombocytopenia, ITP, and conceptually related terms are as follows: ITP (222, 221), thrombocytopenia (207,180), thrombocytopenic purpura (71, 66), and platelet count decreased (41, 13). In the PBRER dated 25 July 2018, the applicant stated that the reporting rate for ITP/thrombocytopenia for PRIORIX is 0.17 cases per 100,000 doses distributed since the launch of PRIORIX, and that the rate has not increased over time.

Considering that thrombocytopenia, including ITP, is a well-known adverse reaction of MMR vaccination and is addressed in the draft USPI, the classification of thrombocytopenia/ITP as a non-important risk and routine pharmacovigilance are acceptable. The Warnings and Precautions section of the draft USPI states that caution should be used with administering PRIORIX to individuals with thrombocytopenia or history of thrombocytopenia after MMR

[27] Source: BLA Amendments 125748/0.41.
[28] Sources: BLA Amendments 125748/0.12 and 125748/0.15

vaccination. This is consistent with the ACIP recommendations, which list a history of thrombocytopenia or thrombocytopenic purpura as a precaution for MMR-containing vaccines. Although two published studies have reported that children with ITP post-MMR vaccination did not have any vaccine-associated recurrences (Mantadakis et al. 2010; Miller et al. 2001), the draft PRIORIX USPI states that are postmarketing reports of worsening or recurrence of thrombocytopenia with revaccination in individuals who have experienced thrombocytopenia after the first dose of MMR.

7.2 Important Potential Risks

There are no important potential risks in the submitted PVP. Of note, due to the theoretical concern of disseminated viral infections of vaccine origin, immunosuppression (primary or acquired) is listed as a contraindication in the USPI.

7.3 Missing Information

Use in Pregnant or Lactating Patients

Infection during pregnancy with wild-type measles and rubella viruses have been associated with adverse maternal and fetal outcomes. Measles infection during pregnancy is associated with an increased risk of miscarriage, preterm birth, neonatal low birth weight, and maternal death (Atmar et al. 1992; Eberhart-Phillips et al. 1993; Ogbuanu et al. 2014; Gershon et al. 2015; Rasmussen et al. 2015; as cited in Strebel et al. 2018). There is no clear evidence that measles is associated with congenital malformations (Jesperson et al. 1997; Siegel et al. 1966; Siegel 1973; as cited in Strebel et al. 2018). There is conflicting data regarding mumps infection during pregnancy and adverse pregnancy outcomes (Marlow et al. 2021). A prospective, controlled study did not find an increased risk of congenital malformations with mumps infection during pregnancy (Siegel 1973). Rubella infection can result in miscarriage, stillbirth, or CRS. Although the wild-type rubella virus often infects the placenta in the setting of viremia in pregnant women, there is no evidence for fetal damage by vaccine-derived rubella virus (Reef et al. 2018). A recent review of pregnancy outcomes following rubella virus vaccination found no cases of CRS across 42 studies (Mangtani et al. 2020). There is a lack of data regarding the secretion of vaccine-derived measles and mumps viruses in breast milk. Studies have shown that although lactating women vaccinated with rubella may secrete the virus in breast milk and transmit it to their breast-fed infants, no infants have developed severe disease (Buimovici-Klein et al. 1977; Landes et al. 1980; Losonsky et al. 1982; Losonsky et al. 1982; as cited in Reef et al. 2018).

PRIORIX has not been studied in pregnant or lactating subjects, and animal studies on reproductive toxicity were not conducted. Since PRIORIX is a live-virus vaccine, pregnancy is listed as a contraindication in the proposed USPI; Sections 8.1 (Pregnancy) and 8.2 (Lactation) of the USPI address the lack of information in pregnant or lactating populations. As described in Section 4.3 of this memorandum, in Study MMR-159, there was one case of inadvertent PRIORIX exposure during pregnancy and one case two months prior to pregnancy; both pregnancies resulted in live births without congenital abnormalities. Per the PVP and the submitted PBRER, the limited data on exposure to the vaccine during the risk period (defined as 30 days prior to pregnancy to the end of pregnancy), have not indicated a safety concern with respect to adverse pregnancy outcomes, low birth weight, or congenital malformations.

No cases of CRS have been reported. The applicant has not proposed additional activities beyond routine pharmacovigilance.

Table 16 summarizes the postmarketing pregnancy exposure data for PRIORIX. Cases of PRIORIX exposure during pregnancy from launch to 04 May 2021 are listed by data source. Data from Public Health England (PHE) were received by the applicant as part of a safety data agreement that was effective during 2010 to 2018 to facilitate the sharing of information and data regarding PRIORIX exposure during pregnancy. It is noted that intrauterine deaths were defined as spontaneous abortions in pregnancies <22 weeks gestation and stillbirths in pregnancies ≥22 weeks gestation, according to the European Medicines Agency (EMA) guidelines. The following figures were used for denominators in calculating percentages of cases resulting in specific adverse pregnancy outcomes: the total number of cases with known pregnancy outcome was used to calculate the percentage of spontaneous abortions, the total number of cases resulting in live births or stillbirths was used to calculate the percentage of stillbirths, and the total number of cases resulting in live births was used to calculate the percentage of minor and major congenital anomalies (CA).

Table 16: Postmarket Pregnancy Exposure Data for PRIORIX through 04 May 2021[29]

	Spontaneous abortion **N (%)**	**Stillbirth** **N (%)**	**Major congenital anomalies** **N (%)**	**Minor congenital anomalies** **N (%)**
Spontaneous Postmarketing Cases (from Global Safety Database)	47/268 (17.5%)	1/199 (0.5%)	4/198 (2.0%)	0/198 (0.0%)
Public Health England (PHE)	39/246 (15.9%)	3/196 (1.5%)	13/193 (6.7%)	18/193 (9.3%)
Published Background Rates	15-20% of clinically recognized pregnancies[30]	6 per 1,000 (0.6%) live births and stillbirths[31]	2-4% of live births[32]	14-40% of live births[33]

[29] Source: BLA Amendment 125748/0.32
[30] FDA Draft Guidance for Industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (July 2020).
[31] Source: UpToDate, https://www.uptodate.com/contents/stillbirth-incidence-risk-factors-etiology-and-prevention?search=rate%20of%20miscarriage&source=search_result&selectedTitle=8~150&usage_type=default&display_rank=8, accessed 21 April 2022. Per the CDC, rate of stillbirth varies by race and Hispanic origin, and ranges from 4.29 per 1000 (0.4%) live births and still births in Asian and Pacific Islander women to 10.32 per 1000 (1.0%) in non-Hispanic black women. See https://www.cdc.gov/ncbddd/stillbirth/data.html, accessed 21 April 2022.
[32] FDA Draft Guidance for Industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (July 2020).
[33] FDA Reviewer Guidance *Evaluating the Risks of Drug Exposure in Human Pregnancies* (April 2005).

For both sources of data, the percentages of adverse pregnancy outcomes were within published background rates except for the percentages of stillbirths and major congenital anomalies which were elevated for the PHE data. There are several limitations associated with the PHE data. The PHE data consist of spontaneous reports of drug exposures during pregnancy; limitations with spontaneous reporting include bias, lack of denominator/inability to calculate rates, incomplete data, and underreporting. It is noted that the PHE data includes both prospectively and retrospectively reported exposures during pregnancy; retrospective reports are subject to bias. Overall, for the PHE data, there was only one case of major CA and one case of minor CA which potentially shared clinical findings with CRS. For the case of major CA, an 18-year-old female was exposed to PRIORIX prior to pregnancy and delivered a live infant at 41 weeks GA. One year after birth, a cardiac anomaly of atrial septal defect or patent foramen ovale was identified in the infant. It is noted that neither cardiac defect is commonly associated with CRS (patent ductus arteriosus and branch pulmonary artery stenosis are most common)[34]. For the case of minor CA, a 28-year-old female was exposed to PRIORIX during the first trimester and delivered an infant weighing 2050 grams at 40 weeks GA. One year after birth, unspecified eye abnormalities were reported in the infant. Rubella antibody testing for the infant was not reported in both cases.

Given that PRIORIX is contraindicated for pregnant women and that there have been no documented cases of CRS following rubella vaccination in pregnant women across multiple epidemiological studies or in the postmarketing safety database, the applicant's proposal to conduct routine pharmacovigilance is acceptable.

Other Populations Not Included in the Clinical Studies

Other populations that were excluded from the clinical studies and were not mentioned in the missing information section of the RMP include children aged <1 year, elderly individuals (the maximum age of subjects in Study MMR-159 was 59 years), and immunocompromised individuals. Since routine vaccination consists of a two-dose series, with the first dose administered at 12-15 months and the second dose at 4-6 years, it is anticipated that most individuals receiving the MMR vaccine will be children aged ≥1 year. It is noted that children aged <1 year and elderly individuals may be vaccinated under special circumstances; specifically, the first dose of MMR vaccine may be given to infants aged 6-11 months in the setting of international travel and a third dose may be given to populations at increased risk for mumps during an outbreak. However, these circumstances are anticipated to arise infrequently. Section 8 (Use in Specific Populations) of the proposed USPI states that safety and effectiveness of PRIORIX in infants younger than 12 months have not been established and that clinical studies did not include subjects aged ≥65 years. Immunocompromised individuals were also excluded from the clinical studies; however, this is because immunodeficiency and immunosuppression are a contraindication for the MMR vaccine.

[34] Source: UpToDate, https://www.uptodate.com/contents/congenital-rubella?search=congenital%20rubella&source=search_result&selectedTitle=1~46&usage_type=default&display_rank=1, accessed 27 April 2022.

8. CONCLUSION/RECOMMENDATION

- Overall, the review of the clinical and postmarketing safety database does not indicate new safety issues for PRIORIX which have not been previously described for MMR-containing vaccines.
- At this time, review of the clinical and postmarketing safety databases does not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS) or a new postmarketing requirement (PMR) for a safety-related study under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA), or a postmarketing commitment (PMC).
- OBPV/DPV agrees with the pharmacovigilance activities proposed by the applicant in the PVP along with adverse event reporting as required under 21 CFR 600.80.

REFERENCES

1. Aickin R, Hill D, Kemp A. Measles immunisation in children with allergy to egg. BMJ 1004;309:223-225.
2. Atmar RL, Englund JA, Hammill H. Complications of measles in pregnancy. Clin Infect Dis. 1992;14:217-226.
3. Albrecht M. Mumps. In *UpToDate*. Topic lasted updated 29 July 2020. Retrieved 30 June 2021 from https://www.uptodate.com/contents/mumps?search=mumps&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1
4. Barlow WE, Davis RL, Glasser JW, et al. The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. N Engl J Med 2001;345:656-661.
5. Blom L, Nyström L,. Dahlquist G. The Swedish childhood diabetes study: vaccinations and infections as risk determinants for diabetes in childhood, Diabetologica 1991;34:176-181.
6. Braun MM, Patriarca PA, Ellenberg SS. Syncope after immunization. Arch Pediatr Adolesc Med 1997;151:255-259.
7. Buettcher M, Heininger U, Braun M, et al. Hypotonic-hyporesponsive episode (HHE) as an adverse event following immunization in early childhood: Case definition and guidelines for data collection, analysis, and presentation. Vaccine 2007;25:5875-5881.
8. Buimovici-Klein E, Hite RL, Byrne T, et al. Isolation of rubella virus in milk after postparturm immunization. J Pediatr. 1977;91:939-941.
9. Carapetis JR, Curtis N, Royle J. MMR immunization: true anaphylaxis to MMR vaccine is extremely rare. BMJ 2001;323:869.
10. Centers for Disease Control and Prevention (CDC). Three cases of congenital rubella syndrome in the postelimination era – Maryland, Alabama, and Illinois, 2012. MMWR Morb Mortal Wkly Rep. 2013;62:226-229.
11. DeStefano F, Mullooly JP, Okoro CA, et al. Childhood vaccinations, vaccination timing, and risk of type 1 diabetes mellitus. Pediatrics 2001;108:E112.
12. Eberhart-Phillips JE, Frederick PD, Baron RC, et al. Measles in pregnancy: a descriptive study of 58 cases. Obstet Gynecol. 1993;82:797-801.
13. Edwards MS. Rubella. In *UpToDate*. Topic lasted updated 28 June 2021. Retrieved 30 June 2021 from https://www.uptodate.com/contents/rubella?search=rubella&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H8
14. Farrington P, Pugh S, Colville A, et al. A new method for active surveillance of adverse events from diphtheria/tetanus/pertussis and measles/mumps/rubella vaccines. Lancet 1995;345:567-569.
15. France EK, Glanz J, Xu S, et al. Risk of immune thrombocytopenic purpura after measles-mumps-rubella immunization in children. Pediatrics 2008;121:e687-e692.
16. Gans H and Maldonado YA. Measles: Clinical manifestations, diagnosis, treatment, and prevention. In *UpToDate.* Topic last updated 05 December 2019. Retrieved 30 June 2021 from https://www.uptodate.com/contents/measles-clinical-manifestations-diagnosis-treatment-and-prevention?search=measles&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

17. Gershon AA, Marin M, Seward JF. Measles and mumps. In: Wilson CB, et al. eds. Remington and Klein's Infectious Disease of the Fetus and Newborn Infant. 8th ed. Philadelphia, PA: Elsevier; 2015:675-723.
18. Institute of Medicine. Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality. Washington, DC: National Academies Press; 1994.
19. Institute of Medicine. Adverse Effects of Vaccines: Evidence and Causality. Washington, DC: National Academies Press; August 2011.
20. Jacobson RM. Routine Childhood Vaccines Given from 1 through 18 Years of Age. Mayo Clin Proc. 2020;95:1780-1795.
21. Jesperson CS, Littover J, Saglid V. Measles as a cause of fetal defects: a retrospective study of ten measles epidemics in Greenland. Acta Paediatr Scand. 1977;66:367-376.
22. Landes RD, Bass JW, Millunchick EW, et al. Neonatal rubella following postpartum maternal immunization. J Pediatr. 1980;97:465-467.
23. Losonky GA, Fishaut JM, Strussenberg J, et al. Effect of immunization against rubella on lactation products. I. Development and characterization of specific immunologic reactivity in breast milk. J Infect Dis. 1982;145:654-656.
24. Losonky GA, Fishaut JM, Strussenberg J, et al. Effect of immunization against rubella on lactation products. II. Maternal-neo-natal interactions. J Infect Dis. 1982;145:661-666.
25. Mangtani P, Evans S, Lange B, et al. Safety profile of rubella vaccine administered to pregnant women: a systematic review of pregnancy related adverse events following immunisation, including congenital rubella syndrome and congenital rubella infection in the foetus or infant. Vaccine 2020;38:963-978.
26. Mantadakis E, Farmaki E, Buchanan GR. Thrombocytopenic purpura after measles-mumps-rubella vaccination: a systematic review of the literature and guidance for management. J Pediatr 2010;156:623-628.
27. Marin M et al. Recommendation of the Advisory Committee on Immunization Practices for use of a third dose of mumps virus-containing vaccine in persons at increased risk for mumps during an outbreak. MMWR Morb Mortal Wkly Rep 2018;67:33-38.
28. Marlow M, Leung J, Marin M. et al. Chapter 9: Mumps. In: Roush SW et al (Eds.). Manual for the Surveillance of Vaccine-Preventable Diseases. Page last reviewed 30 June 2021. Retrieved 17 August 2021 from https://www.cdc.gov/vaccines/pubs/surv-manual/chpt09-mumps.html
29. McLean HQ, Fiebelkorn AP, Temte JL, et al. Prevention of Measles, Rubella, Congenital Rubella Syndrome, and Mumps, 2013: Summary Recommendations of the Advisory Committee on Immunization Practices (ACIP). 14 June 2013. Retrieved 18 August 2021 from https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6204a1.htm
30. Miller E, Waight P, Farrington P, et al. Idiopathic thrombocytopenic purpura and MMR vaccine. Arch Dis Child 2001;84:227-229.
31. Miller E, Andrews N, Stowe J, et al. Risks of convulsion and aseptic meningitis following measles-mumps-rubella vaccination in the United Kingdom. American Journal of Epidemiology 2007;165:704-709.
32. Millichap J. Clinical features and evaluation of febrile seizures. In *UpToDate*. Topic last updated 06 May 2021. Retrieved 01 September 2021 from https://www.uptodate.com/contents/clinical-features-and-evaluation-of-febrile-

seizures?search=febrile%20seizures&source=search_result&selectedTitle=1~140&usage_type=default&display_rank=1
33. Ogbuanu IU, Zeko S, Chu SY, et al. Maternal, fetal, and neonatal outcomes associated with measles during pregnancy: Namibia, 2009-2010. Clin Infect Dis. 2014;58:1086-1092.
34. Patel M, Lee AD, Clemmons NS, et al. National update on measles cases and outbreaks – United States, January 1 – October 1, 2019. MMWR Morb Mortal Wkly Rep. 2019;68:893-896.
35. Rasmussen SA, Jamieson DJ. What obstetric health care providers need to know about measles and pregnancy. Obstet Gynecol. 2015;126:163-170.
36. Reef SE and Plotkin SA (2018). Rubella Vaccines. In: Plotkin SA et al (Eds.). Plotkin's Vaccines, 7th edition. https://doi.org/10.1016/C2013-0-18914-3
37. Rubin SA. Mumps Vaccines. In: Plotkin SA et al (Eds.). Plotkin's Vaccines, 7th edition. https://doi.org/10.1016/C2013-0-18914-3
38. Siegel M, Fuerst HT, Peress NS. Comparative fetal mortality in maternal virus diseases: a prospective study on rubella, measles, mumps, chicken pox, and hepatitis. N Engl J Med. 1966;274:768-771.
39. Siegel M. Congenital malformations following chicken pox, measles, mumps, and hepatitis: results of a cohort study. JAMA 1973;226:1521-1524.
40. Strebel PM, Papania MJ, Gastanaduy PA, et al (2018). Measles Vaccines. In: Plotkin SA et al (Eds.). Plotkin's Vaccines, 7th edition. https://doi.org/10.1016/C2013-0-18914-3
41. Su JR, Moro PL, Ng CS, et al. Anaphylaxis after vaccination reported to the Vaccine Adverse Event Reporting System, 1990-2016. J Allergy Clin Immunol 2019;143:1465-1473.
42. Vestergaard M, Madsen A, Wohlfahrt J, et al. MMR vaccination and febrile seizures: evaluation of susceptible subgroups and long-term prognosis. JAMA 2004;292:351-357.
43. Ward KN, Bryant NJ, Andrews NJ, et al. Risk of serious neurologic disease after immunization of young children in Britain and Ireland. Pediatrics 2007;120:314-321.