Application Type	Original BLA
STN	125748/0
CBER Received Date	June 4, 2021
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Division / Office	DVRPA /OVRR
Committee Chair	Luba K. Vujcic
Clinical Reviewer(s)	Nadine Peart Akindele; Robin Wisch
Project Manager	Julianne C. M. Clifford, PhD
Priority Review	No
Reviewer Name(s)	Laura Thompson, PhD
Review Completion Date / Stamped Date	
Concurrence	Lei Huang, Ph.D. Concurring Reviewer, VEB, DB, OBPV
	Tsai-Lien Lin, Ph.D. Chief, VEB, DB, OBPV
	John Scott, Ph.D. Director, DB, OBPV
Applicant	GlaxoSmithKline Biologicals
Established Name	Measles, Mumps and Rubella Virus Vaccine Live
(Proposed) Trade Name	Priorix
Pharmacologic Class	Live attenuated combined viral vaccine
Formulation(s), including Adjuvants, etc	Lyophilized Powder for Injectable Suspension
Dosage Form(s) and Route(s) of Administration	Lyophilized Powder for Injectable Suspension, Subcutaneous
Dosing Regimen	0.5 mL
Indication(s) and Intended Population(s)	For active immunization for the prevention of measles, mumps, and rubella in individuals aged 12 months and older.

Table of Contents

Glossary

ATP	According to Protocol
Com_MMR	MMR-II vaccine, standard of care
D	Diphtheria
DTaP-IPV	Diphtheria, tetanus, acellular pertussis and inactivated polio vaccine
ELISA	Enzyme-linked Immunosorbent Assay
EOSL	End of Shelf Life
FHA	Filamentous hemagglutinin
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GSK	GlaxoSmith Kline
HAV	Hepatitus A Vaccine/Havrix
Inv_MMR	Priorix
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
MMR	Measles, mumps and rubella
PCV-13, PCV-7	Pneumococcal conjugate vaccine
PD1	Post-dose 1
PD2	Post-dose 2
PRN	Pertactin
(b) (4)	
PS	S. pneumoniae
PT	Pertussis toxoid
SRR	Sero-response rate
T	Tetanus
TVC	Total Vaccinated Cohort
VV	Varicella Vaccine/ Varivax
VZV	Varicella Zoster Vaccine
YOA	Years of age

1. Executive Summary

The applicant proposes the following indication for use of Priorix in the U.S.:

> *Priorix is a vaccine indicated for active immunization for the prevention of measles, mumps and rubella in individuals aged 12 months and older.*

Priorix was assessed to show non-inferiority to MMR-II, the current standard of care vaccine in the U.S. The following Phase 2 and Phase 3 pivotal clinical studies were conducted to compare immunogenicity and safety of Priorix to MMR-II.

MMR-157 (phase 2) evaluated immunogenicity and antibody persistence (descriptive analysis) of Priorix (3 lots with different mumps potencies) in comparison with MMR-II, in healthy children 12-15 months of age. Based on the comparison of sero-response rates

(SRRs) between Priorix lots and the pooled MMR-II lots, the applicant chose to use a mumps potency of 4.1 log10 $CCID_{50}$ for the minimum potency lot in study MMR-161.

MMR-158 (phase IIIa) evaluated immunogenicity and safety of Priorix versus MMR-II, when given as a second dose to children four to six years of age. The study design included three sub-cohorts:

1. Sub-cohort 1 compared immunogenicity of Priorix versus MMR-II when given with co-administration vaccines (Varicella and DTaP-IPV), in U.S. subjects only
2. Sub-cohort 2: compared immunogenicity of Priorix versus MMR-II when given without co-administrations
3. Sub-cohort 3: further assessed safety of Priorix versus MMR-II

Primary immunogenicity endpoints (non-inferiority of SRR and GMC ratio comparing Priorix to MMR-II) were met for sub-cohorts 1 and 2, according to the pre-specified success criteria. Secondary immunogenicity endpoints for sub-cohort 1 (non-inferiority of co-administration antibodies) were also met.

MMR-159 (phase III) assessed non-inferiority of immune response of Priorix compared to MMR-II when given as a second dose of MMR vaccine to healthy subjects 7 years of age (YOA) and older (both adults and children were included).

Primary (GMC ratio) and secondary immunogenicity endpoints (difference in SRRs across groups) were met, according to the pre-specified success criteria. The percentage of subjects who achieved at least a 4-fold rise in anti-measles antibody was smaller than for the other MMR antibodies, for both groups (Table 37). Subgroup analyses were largely consistent with the primary and secondary endpoint results.

MMR-160 (phase III) assessed consistency of immune response to 3 lots of Priorix at release potency. In addition, the study assessed non-inferiority of immunogenicity (GMC and SRR of MMR antibodies) of Priorix compared to MMR-II, when given as a first dose and co-administered with VV (Varivax), HAV (Havrix) and PCV-13 (Prevnar 13, in U.S. subjects only) in healthy children 12-15 months old.

Primary immunogenicity endpoints for lot consistency were met, according to the pre-specified success criteria. Secondary immunogenicity endpoints (assessing non-inferiority of co-administration antibodies) were also met.

The primary endpoints related to non-inferiority (difference in SRRs and GMC ratio) between Priorix and MMR-II were also met. The lower limit of the CI exceeded the non-inferiority margin of 0.67.

MMR-161 (phase III) assessed non-inferiority of the immunogenicity of Priorix at an end of shelf-life (EOSL) potency compared to MMR-II, when given as a first dose and co-administered with VV, HAV and PCV-13 (U.S. subjects only) in healthy children 12-15 months old. Two lots of Priorix, one at minimum potency (MIN) and another at medium

potency (MED), were evaluated to establish an EOSL potency. Children received a second dose of either MMR vaccine 6 weeks after the first dose.

For the MIN potency lot, primary immunogenicity endpoints were not met for the measles antibody nor mumps antibody measured using (b) (4). Therefore, the MED lot was tested. For the MED lot, primary immunogenicity endpoints were met, except for the mumps antibody. Specifically, the LL of the two-sided 97.5% CI for the difference in SRRs with respect to anti-mumps antibody measured using (b) (4) was < -10% (-10.94%). Also, the LL of the 95% CI on the GMC ratio was 0.57 using (b) (4), which is < 0.67, the non-inferiority margin (Table 69). These results are largely consistent across subgroups. Nevertheless, the anti-mumps immunogenicity endpoints using ELISA met the non-inferiority criteria.

MMR-162 (phase IIIa) evaluated the safety of Priorix at a potency that will be used to define maximum release limits in comparison to MMR-II in subjects 12-15 months of age. The study also evaluated immune response (GMC and SRR) of Priorix compared to MMR-II when co-administered with VV, HAV and PCV-13 (only in U.S. subjects), as non-confirmatory secondary endpoints.

Primary safety objectives were met according to the pre-specified success criteria. That is, the differences in rates of fever > 39.0°C and in fever ≥ 38.0°C from Day 5 through Day 12 after vaccination were within 5% based on the 95% confidence interval. Although secondary immunogenicity endpoints were not confirmatory, the GMC for the anti-rubella antibody was lower for Priorix vs. MMR-II. However, both 95% CIs were well above 10 IU/mL, the pre-specified sero-response threshold.

Overall, the primary immunogenicity and safety endpoints were largely met in the five phase III studies. One exception is that in MMR-161, non-inferiority between Priorix and MMR-II in anti-mumps antibody concentration using (b) (4) was not met.

Two studies (MMR-160 and MMR-161) showed slightly lower average anti-rubella antibody level from Priorix over MMR-II, as measured by GMC ratios and SRR differences. In these studies, the associated non-inferiority objectives were still met, and the SRRs were high for both groups. In a third study (MMR-162) the difference in percentage of subjects above a cut-off threshold for anti-rubella measured with ELISA increased as the threshold increased. However, immunogenicity endpoints were not confirmatory in MMR-162, and the respective LLs of the GMCs at day 42 were well above the pre-specified sero-response threshold. I defer to the clinical review team on the clinical significance of observed differences in anti-mumps and anti-rubella antibody concentrations in Priorix over MMR-II.

The safety profile of Priorix as compared to MMR-II appears to be satisfactory from a statistical perspective. Any observed differences in adverse event rates between groups have been considered acceptable by the clinical team.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Measles, mumps and rubella (MMR) are acute, systemic, highly contagious viral diseases with a worldwide distribution.

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

Merck & Co Inc.'s MMR vaccine, M-M-R II or M-M-R Vax Pro (referred to as MMR-II in this memo), was registered in the U.S. in 1978, and is currently the only licensed MMR vaccine in the U.S.

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

The trivalent measles, mumps and rubella (MMR) vaccine developed by GlaxoSmithKline (GSK) was first registered in Germany in 1997 under the trade name of Priorix and is currently licensed in more than 100 countries worldwide, including all European countries, Canada, Australia, and New Zealand. Priorix is currently not licensed in the U.S.

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

A pre-BLA meeting was held in mid-2020 to discuss outstanding review issues from the associated IND 7229. Activities from that meeting have been incorporated into this memo as appropriate.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review.

3.2 Compliance With Good Clinical Practices And Data Integrity

No data integrity issues with respect to immunogenicity and safety were found.

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

4.1 Chemistry, Manufacturing, and Controls (CMC)

Please see the CMC reviewer's memo.

4.2 Assay Validation

The applicant has reported that all proposed validation criteria were met. Please see my statistical review memo for non-clinical data for more details.

4.3 Nonclinical Pharmacology/Toxicology

NA

4.4 Clinical Pharmacology

NA

4.5 Clinical

Please see the clinical reviewers' memos.

4.6 Pharmacovigilance

NA

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

5.1 Review Strategy

This review focuses on six pivotal clinical studies as listed in Section 5.3 Table of Studies/Clinical Trials.

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

The following sections in STN 125748/0.0 were reviewed in detail:

- Module 2.7.3 Summary of Clinical Efficacy
- Module 2.5 Clinical Overview
- Module 5 Clinical Study Reports for MMR-157, MMR-158, MMR-159, MMR-160, MMR-161, MMR-162

In addition, I reviewed the information submitted in response to information requests (IRs) in amendments to the original BLA submission:

- 1.11.3 Clinical Information Amendment – Response to CBER Request 20Aug2021
- 1.11.3 Clinical Information Amendment – Response to CBER Request 26Oct2021
- 1.11.3 Clinical Information Amendment – Response to CBER Request 03Nov2021
- 1.11.3 Clinical Information Amendment – Response to CBER Request 10Nov2021
- 1.11.3 Clinical Information Amendment – Response to CBER Request 03Dec2021
- 1.11.3 Clinical Information Amendment – Response to CBER Request 25Mar2022

5.3 Table of Studies/Clinical Trials

There are six pivotal studies included in this submission to support the licensure application. See Table 1.

Table 1: Overview of studies

Study ID	Study countries	Study Design Objectives	Population (age) Schedule of vaccination	Study groups	Number of subjects (U.S. subjects)	
					ATP cohort of immunogenicity	TVC
MMR-157 (111870)	United States (including Puerto Rico)	Phase 2, observer-blind, randomized, controlled study to evaluate the immunogenicity and antibody persistence (descriptive analysis) of *Priorix* (3 lots with different mumps potencies) vs. *MMR-II*. Primary objective: • Immunogenicity of *Priorix* vs. *MMR-II* in terms of seroresponse rates for antibodies to measles, mumps and rubella viruses at Day 42	Healthy children (12-15 months) 1 dose at Day 0, co-administered with HAV (*Havrix*), VV (*Varivax*) and PCV-7 (*Prevnar*)	***Priorix:*** • **INV_MMR_1:** Lot 1 • **INV_MMR_2:** Lot 2 • **INV_MMR_3:** Lot 3 ***MMR-II:*** • MMRII (3 lots)	**261 (261)** **254 (254)** **251 (251)** 260 (260)	**304 (304)** **304 (304)** **304 (304)** 308 (308)
MMR-160 (115648)	United States (including Puerto Rico) Estonia Finland Mexico Spain	Phase 3, observer-blind, randomized, controlled, consistency and non-inferiority study to evaluate the immunogenicity and safety of *Priorix* compared to *MMR-II* pooled, as a first dose, both co-administered with *Varivax*, *Havrix* and *Prevnar 13* (subset of children enrolled in the U.S.). <u>Primary objectives (assessed in a hierarchical manner):</u> 1. Consistency of 3 lots of INV_MMR in terms of seroresponse rates for antibodies to measles, mumps and rubella viruses at Day 42 2. Consistency of 3 lots of INV_MMR in terms of GMCs for antibodies to measles, mumps and rubella viruses at Day 42 3. Non-inferiority of INV_MMR (3 lots pooled) to *MMR-II* in terms of seroresponse rates for antibodies to measles, mumps and rubella viruses at Day 42 4. Non-inferiority of INV_MMR (3 lots pooled) to *MMR-II* in terms of GMCs for antibodies to measles, mumps and rubella viruses at Day 42 5. Acceptability of immune response of INV_MMR in terms of seroresponse rates (≥ 90% with lower limit of 95% CI ≥ 90%) for antibodies to measles, mumps and rubella viruses at Day 42	Healthy children (12-15 months) 1 dose at Day 0, co-administered with HAV (*Havrix*) and VV (*Varivax*) (all subjects) and PCV-13 (*Prevnar 13*, administered in U.S. subjects only)	***Priorix:*** • **INV_MMR_1:** Lot 1 • **INV_MMR_2:** Lot 2 • **INV_MMR_3:** Lot 3 • *Total 3 lots INV_MMR_160* ***MMR-II:*** • MMRII (2 lots)	**1,108 (525)** **1,098 (516)** **1,130 (532)** *3,336 (1573)* 1,162 (559)	**1,239 (618)** **1,232 (612)** **1,243 (618)** *3,714 (1848)* 1,289 (654)
MMR-161 (115649)	United States (including Puerto Rico) Czech Republic Finland Malaysia Spain Thailand	Phase 3, observer-blind, randomized, controlled study to evaluate the immunogenicity and safety of *Priorix* at an end of shelf-life potency (established for each antigen) compared to *MMR-II* pooled when both are co-administered with *Varivax*, *Havrix* and *Prevnar 13* (subset of children enrolled in the U.S.) <u>Primary objectives</u>: Minimum potency vaccine (INV_MMR_MIN): 1. Non-inferiority of INV_MMR_MIN	Healthy children (12-15 months) 2 doses: • at Day 0, co-administered with HAV (*Havrix*) and VV (*Varivax*) (all subjects) and PCV-13 (*Prevnar 13*, administered in U.S. subjects only)	***Priorix:*** • **INV_MMR_MIN:** INV_MMR at minimum potency at Day 0 + INV_MMR lot at release potency range at Day 42 • **INV_MMR_MED:** INV_MMR at medium potency	Post-Dose 1: **1,363 (270)** Post-Dose 2: **245 (245)** Post-Dose 1: **1,373 (276)** Post-Dose 2: **261 (261)**	**1,493 (328)** **1,497 (326)**

Study ID	Study countries	Study Design Objectives	Population (age) Schedule of vaccination	Study groups	Number of subjects (U.S. subjects)	
					ATP cohort of immunogenicity	TVC
		to *MMR-II* in terms of sero-response rates for antibodies to measles, mumps and rubella viruses (by ELISA) at Day 42 2. Non-inferiority of INV_MMR_MIN to *MMR-II* in terms of GMCs for antibodies to measles, mumps and rubella viruses (by ELISA) at Day 42 3. Demonstrate acceptable Immune response of INV_MMR_MIN in terms of seroresponse rates for antibodies to measles, mumps and rubella viruses (by ELISA) at Day 42 4. Non-inferiority of INV_MMR_MIN to *MMR-II* in terms of seroresponse rates for antibodies to mumps virus (by (b) (4)) at Day 42 5. Non-inferiority of INV_MMR_MIN to *MMR-II* in terms of GMTs for antibodies to mumps virus (by (b) (4) at Day 42 Medium potency vaccine (INV_MMR_MED): 6. Non-inferiority of INV_MMR_MED to *MMR-II* in terms of seroresponse rates for antibodies to measles, mumps and rubella viruses (by ELISA) at Day 42 7. Non-inferiority of INV_MMR_MED to *MMR-II* in terms of GMCs for antibodies to measles, mumps and rubella viruses (by ELISA) at Day 42 8. Demonstrate acceptable Immune response of INV_MMR_MED in terms of seroresponse rates for antibodies to measles, mumps and rubella viruses (by ELISA) at Day 42 Non-inferiority of INV_MMR_MED to *MMR-II* in terms of seroresponse rates for antibodies to mumps virus (by (b) (4) at Day 42 9. Non-inferiority of INV_MMR_MED to *MMR-II* in terms of seroresponse rates for antibodies to mumps virus (by (b) (4)) at Day 42 10. Non-inferiority of INV_MMR_MED to *MMR-II* in terms of GMTs for antibodies to mumps virus (by (b) (4) at Day 42	• at Day 42	at Day 0 + INV_MMR lot at release potency range at Day 42 ***MMR-II:*** • MMRII (2 lots)	Post-Dose 1: 1,381 (280) Post-Dose 2: 258 (258)	1,526 (346)
MMR-162 (115650)	United States (including Puerto Rico) Estonia Finland Taiwan	Phase 3, observer-blind, randomized, controlled study to evaluate the safety and immunogenicity of *Priorix* and *MMR-II* as a first dose, both co-administered with *Varivax*, *Havrix* (all subjects) and *Prevnar 13* (U.S. subset). This study was intended to evaluate the safety of *Priorix* at a potency used to define maximum release limits. Primary objectives:	Healthy children (12-15 months) 1 dose at Day 0, co-administered with HAV (*Havrix*) and VV (*Varivax*) (all subjects) and PCV-13 (*Prevnar 13*, administered in U.S. subjects only)	***Priorix:*** • **INV_MMR** ***MMR-II:*** • MMRII (2 lots)	**1,045 (621)** 523 (313)	**1,164 (734)** 572 (357)

Study ID	Study countries	Study Design Objectives	Population (age) Schedule of vaccination	Study groups	Number of subjects (U.S. subjects)	
					ATP cohort of immunogenicity	TVC
		• Safety profile of INV_MMR versus *MMR-II* in terms of fever rates > 39°C (>102.2°F) and > 38°C (>100.4°F) Secondary immunogenicity objectives: • Immunogenicity in terms of seroresponse rates and GMCs for antibodies to measles, mumps and rubella viruses at Day 42 • Safety and reactogenicity • Any measles-like illness within 5-12 days after vaccination				
MMR-158 (115158)	United States Republic of Korea Taiwan	Phase 3, observer-blind, randomized, controlled study to evaluate non-inferiority of a second dose of *Priorix* vs. a second dose of *MMR-II*.3 sub-cohorts were defined for the analyses. Primary objectives: Non-inferiority of INV_MMR to *MMR-II* with or without *Varivax* and *Kinrix* in terms of: • seroresponse rates for antibodies to measles, mumps and rubella viruses at Day 42 • antibody concentrations to measles, mumps and rubella viruses at Day 42	Healthy children previously primed with 1 dose of any MMR vaccine (4-6 years) 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:** INV_MMR co-administered with *Varivax* and *Kinrix* **Sub-cohort 2:** • **INV_MMR_I:** INV_MMR given alone **Sub-cohort 3:** • **INV_MMR_S:** INV_MMR given alone ***MMR-II:*** **Sub-cohort 1 (U.S. s ubjects only):** • MMRII_CO (2 lots): *MMR-II* co-administered with *Varivax* and *Kinrix* **Sub-cohort 2:** • MMRII_I (2 lots): *MMR-II* given alone **Sub-cohort 3:** • MMRII_S (2 lots): *MMR-II* given alone	**698 (698)** **742 (369)** Not applicable (safety assessment only) 250 (250) 283 (142) Not applicable (safety assessment only)	**802 (802)** **796 (412)** **1,319 (736)** 298 (298) 303 (157) 489 (276)
MMR-159 (115231)	United States Estonia Slovakia	Phase 3, observer-blind, randomized, controlled study to evaluate non-inferiority of a second dose of *Priorix* vs. a second dose of *MMR-II*. Primary objective: – Non-inferiority of INV_MMR to *MMR-II* in terms of GMCs for antibodies to measles, mumps and rubella viruses at Day 42	Healthy children, adolescents and adults previously primed with at least 1 dose of any MMR vaccine (7 years of age and older) 1 dose at Day 0	***Priorix:*** • **INV_MMR** ***MMR-II:*** – MMRII (2 lots)	**433 (272)** 436 (272)	**454 (293)** 457 (293)

ATP = according-to-protocol; D = diphtheria; DTaP = diphtheria, tetanus, acellular pertussis; DTaP-IPV = diphtheria, tetanus, acellular pertussis and inactivated polio virus; ELISA = enzyme-linked immunosorbent assay; FHA = filamentous hemagglutinin; GMC = geometric mean concentration; GMT = geometric mean titer; HAV = hepatitis A vaccine/*Havrix*; INV_MMR = *Priorix*; MMRII = *MMR-II*; PRN = pertactin; (b) (4) ; PT = pertussis toxoid; T = tetanus; TVC = total vaccinated cohort; VV = varicella vaccine/*Varivax*; VZV = varicella zoster virus

Source: Adapted from Table 1 in m2.7.3 Summary of Clinical Efficacy

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 MMR-157

This phase 2 study evaluated immunogenicity and antibody persistence (descriptive analysis) of Priorix (3 lots with different mumps potencies) in comparison with MMR-II, in healthy children 12-15 months old. Both vaccines were administered concomitantly with a pneumococcal conjugate vaccine (PCV; PCV-7, Prevnar), hepatitis A vaccine (HAV, Havrix) and live attenuated varicella vaccine (VV, Varivax).

6.1.1 Primary Objectives

- Assess immunogenicity of Priorix formulated with a range of mumps virus potencies vs. MMR-II, both co-administered with HAV, VV and PCV-7, with respect to sero-response rate (SRR) for antibodies to measles, mumps and rubella (MMR) viruses at Day 42, as measured by ELISA for measles and rubella and by (b) (4) for mumps.
- Establish the mumps virus potency of Priorix to be evaluated in MMR U.S. Phase 3 studies

Reviewer comment*: Because this was a phase II study, I did not critically review secondary endpoints from a statistical perspective. See the clinical reviewer's memo for details.*

6.1.2 Design Overview

This study was an exploratory Phase 2, observer-blind, randomized, controlled clinical trial conducted in the U.S. A total of 1,224 subjects 12-15 months old were randomized in a 3:3:3:3 ratio to 4 vaccine groups (3 Priorix lot groups and 1 MMR-II). In addition, subjects within the MMR-II group were randomized 1:1:1 to one of the 3 vaccine lots used in the study (which were pooled together for analyses). A total of 1,220 subjects received one dose of one of the 3 lots of Priorix with differing mumps virus potencies or MMR-II, both co-administered with HAV, VV and PCV-7. The active phase of the study went from Day 0 to Day 42. The antibody persistence phase ended 2 years after vaccination (Day 730).

Data were collected in an observer-blinded manner. That is, vaccine recipients, parents/ guardians and those responsible for evaluation of any study endpoint were unaware of which MMR vaccine was administered to a particular subject. The laboratory in charge of testing was blinded to the treatment.

The randomization algorithm used a minimization procedure accounting for center. In addition, subjects in all treatment groups were randomly selected for immunogenicity testing. All subjects were tested for antibodies against MMR viruses and varicella zoster virus (VZV). A subset of 50% of subjects was randomly selected to be tested for antibodies against hepatitis A virus; the remaining 50% were to be tested for antibodies to the 7 Streptococcus pneumoniae serotypes.

Sero-responses for the MMR vaccines were defined as follows:

- Measles: post-vaccination concentration ≥200 mIU/mL (ELISA) in subjects below the assay cut-off of 150 mIU/mL before vaccination
- Mumps: post-vaccination concentration ≥1:51 (enhanced (b) (4) in subjects below the assay cut-off of 1:24 before vaccination.
- Mumps (ELISA): post-vaccination concentration ≥10 EU/mL in subjects with antibody concentration < 5 EU/mL before vaccination
- Rubella: post-vaccination concentration ≥10 IU/mL (ELISA) in subjects below the assay cut-off of 4 IU/mL before vaccination
- Since only available baseline samples from the HAV subcohort were tested using the unenhanced mumps (b) (4), seroresponse using the unenhanced (b) (4) was not defined in the protocol. Instead, the percentage of subjects with a titer ≥ 4 ED50 at year 1 and year 2 is presented in the clinical study report.

Sero-responses for the co-administered vaccines were defined as follows:

- Varivax: Anti-VZV antibody concentrations ≥75 mIU/mL for initially seronegative subjects (antibody concentrations <25 mIU/mL prior to vaccination).
- Havrix: Anti-hepatitis A virus antibody concentrations ≥15 mIU/mL for initially seronegative subjects (antibody concentrations <15 mIU/mL prior to vaccination).
- Prevnar: Antibody concentrations to the 7 *S. pneumoniae* serotypes above pre-defined cut-offs (≥0.05 or ≥0.2 μg/mL depending on serotypes).

6.1.3 Population

Healthy children 12-15 months old having previously received 3 doses of PCV-7 within the first year of life, and living in the U.S.

6.1.4 Study Treatments or Agents Mandated by the Protocol

There were four parallel groups:

- INV_MMR_1: 300 subjects receiving one dose of Priorix Lot 1 (RIT 4385 mumps strain $10^{4.8}$ $CCID_{50}$)
- INV_MMR_2: 300 subjects receiving one dose of Priorix Lot 2 (RIT 4385 mumps strain $10^{4.1}$ $CCID_{50}$)
- INV_MMR_3: 300 subjects receiving one dose of Priorix Lot 3 (RIT 4385 mumps strain $10^{3.7}$ $CCID_{50}$)
- MMRII: 300 subjects receiving one dose of MMR-II from one of 3 different commercial lots (Jeryl Lynn mumps strain $10^{4.8}$ $CCID_{50}$)

All 4 groups received HAV, PCV-7, and VV concomitantly.

6.1.5 Sites and Centers

51 centers in the U.S. (including 3 centers in Puerto Rico)

6.1.6 Endpoints and Criteria for Study Success

Primary immunogenicity endpoints
For each Priorix lot compared to MMR-II (at Day 42 post-vaccination), exploratory null hypotheses were as follows:

- Sero-response to anti-measles virus antibody concentration
  Null hypothesis: Difference in SRR < -5.0%
- Sero-response to anti-mumps virus antibody titer as measured by enhanced (b) (4)
  Null hypothesis: Difference in SRR < -10.0%
- Sero-response to anti-rubella virus antibody concentration
  Null hypothesis: Difference in SRR < -5.0%

  The null hypothesis would be rejected if the lower limit (LL) of the 95% CI on the difference in SRRs (Priorix – MMR-II) exceeded the specified value.

6.1.7 Statistical Considerations & Statistical Analysis Plan

The GMT/GMC ratios between groups (MMR over MMRII) were obtained using an ANOVA model on log-transformed antibody concentrations/titers at Day 42 for subjects who were sero-negative pre-vaccination, with vaccine group as a fixed effect.

6.1.8 Study Population and Disposition

6.1.8.1 Populations Enrolled/Analyzed

The total vaccinated cohort (TVC) included all vaccinated subjects.

- The TVC safety analysis included all vaccinated subjects with at least one vaccine administration documented.
- The TVC immunogenicity analysis included all vaccinated subjects for whom immunogenicity data were available.

The according-to-protocol (ATP) cohort for safety included all eligible subjects

- who received study vaccine/comparator
- who had not received a vaccine unspecified or forbidden in the protocol
- for whom the randomization code had not been broken
- for whom the administration route of study vaccine(s) was correct

The ATP cohort for immunogenicity included all subjects in the ATP cohort for safety

- with pre- and post-vaccination serology results available
- who were below the assay cut-off for at least one vaccine antigen for MMR at baseline
- who had not received medication/vaccine forbidden in the protocol
- who had no underlying medical condition forbidden in the protocol
- with no important protocol violation

Table 2 shows the number of subjects who were included in the cohorts. See the clinical reviewer's memo for details about exclusions from each cohort.

Table 2: Number of subjects included per cohort

	Total	MMR_1	MMR_2	MMR_3	MMRII
Total cohort	1259	304	305	305	310
Total vaccinated cohort	1220	304	304	304	308
ATP cohort for safety	1147	285	287	283	292
ATP cohort for immunogenicity	1026	261	254	251	260

Source: Table 15 in Clinical Study Report MMR-157

6.1.8.1.1 Demographics

Overall, the mean age (± standard deviation [SD]) of subjects in the TVC was 12.3 months ±0.71 months. The TVC cohort was 75.8% White/Caucasian and 51.1% male. The mean age of subjects in the ATP cohort for immunogenicity was 12.3 months ±0.69 months, and the cohort was 75.6% White/Caucasian and 51.3% male. Demographics were similar across treatment groups.

6.1.8.1.2 Subject Disposition

A total of 1,220 subjects were enrolled and vaccinated, of which 304 subjects were included in each of the three Priorix lot groups and 308 in the MMR-II control group. Of these, 1,067 (87.5%) subjects completed the study and 1117 subjects (91.6%) completed the active phase of the study. A total of 103 subjects were withdrawn from the active phase of the study for the reasons shown in Table 3.

Table 3: Number of subjects vaccinated, completed and withdrawn with reason for withdrawal between Day 0 and Day 42 (Total vaccinated cohort)

Cohort Exclusion/Reason for Exclusion	MMR_1	MMR_2	MMR_3	MMRII	Total
Number of subjects vaccinated	304	304	304	308	1220
Number of subjects completed	287	275	280	275	1117
Number of subjects withdrawn	17	29	24	33	103
Reasons for withdrawal :					
Serious Adverse Event	0	0	0	1	1
Non-serious adverse event	0	0	0	0	0
Protocol violation	0	1	0	0	1
Consent withdrawal (not due to an adverse event)	10	6	6	19	41
Migrated/moved from study area	0	3	1	0	4
Lost to follow-up (subjects with incomplete vaccination course)	0	0	0	0	0
Lost to follow-up (subjects with complete vaccination course)	7	19	17	12	55
Others	0	0	0	1	1

Source: Table 12 in Clinical Study Report MMR-157

6.1.9 Immunogenicity Analyses

6.1.9.1 Analyses of Primary Endpoint(s)

The primary analysis of immunogenicity was based on the ATP cohort for immunogenicity.

The large majority of subjects in all groups (>99%) were seronegative at baseline prior to vaccination, against anti-measles, anti-rubella, and anti-VZV antibodies. For anti-mumps antibodies, 85.7%, 88.3%, 86.6%, and 84.2% for the MMR_1, MMR_2, MMR_3, and MMR-II groups were seronegative.

Anti-measles virus antibody response

Table 4 compares the anti-measles virus SRRs between Priorix and MMRII at Day 42 in subjects who were seronegative prior to vaccination. The LL of the 95% CI was above the limit of -5.0% for each Priorix lot.

Table 4: Difference between each Priorix lot group and the MMRII group in percentage of subjects with an anti-measles virus concentration ≥ 200 mIU/mL at PI (D42) (ATP cohort for immunogenicity)

MMR_1 (N)	n	SRR	MMRII (N)	n	SRR	Difference	95% LL	95% UL	P-value
247	245	99.2%	249	248	99.6%	-0.41%	-2.55%	1.50%	<0.001
MMR_2 (N)	**n**	**SRR**	**MMRII (N)**	**n**	**SRR**	**Difference**	**95% LL**	**95% UL**	**P-value**
240	236	98.3%	249	248	99.6%	-1.27%	-3.85%	0.74%	0.006
MMR_3 (N)	**n**	**SRR**	**MMRII (N)**	**n**	**SRR**	**Difference**	**95% LL**	**95% UL**	**P-value**
240	236	98.3%	249	248	99.6%	-1.27%	-3.85%	0.74%	0.006

P-value = One-sided asymptotic standardized test for H0: MMR lot minus MMRII < -5.00 %
Source: Adapted from Tables 21 and 143 in Clinical Study Report MMR-157

Anti-mumps virus antibody response (enhanced (b) (4)

Table 5 compares the anti-mumps virus SRRs between Priorix and MMRII at Day 42 in subjects who were seronegative prior to vaccination. The LL of the 95% CI was above the limit of -10.0% for each Priorix lot.

Table 5: Difference between each Priorix lot group and the MMRII group in percentage of subjects with anti-mumps virus titer ≥51 ED_{50} at PI(D42) (ATP cohort for immunogenicity)

MMR_1 (N)	n	SRR	MMRII (N)	n	SRR	Difference	95% LL	95% UL	P-value
193	175	90.7%	192	175	91.1%	-0.47%	-6.42%	5.46%	0.001
MMR_2 (N)	**n**	**SRR**	**MMRII (N)**	**n**	**SRR**	**Difference**	**95% LL**	**95% UL**	**P-value**
202	183	90.6%	192	175	91.1%	-0.55%	-6.41%	5.35%	0.001
MMR_3 (N)	**n**	**SRR**	**MMRII (N)**	**n**	**SRR**	**Difference**	**95% LL**	**95% UL**	**P-value**
195	175	89.7%	192	175	91.1%	-1.40%	-7.47%	4.62%	0.003

P-value = One-sided asymptotic standardized test for H0: MMR lot minus MMRII < -10.0 %
Source: Adapted from Tables 23 and 146 in Clinical Study Report MMR-157

Anti-rubella virus antibody response

Table 6 compares the anti-rubella virus SRRs between Priorix and MMRII at Day 42 in subjects who were seronegative prior to vaccination. The LL of the 95% CI was above -5.0% for two of three Priorix lots compared to MMRII. For the comparison of MMR_3 vs. MMRII, the LL was -5.37%, below the criterion of -5.0%.

Table 6: Difference between each Priorix lot group and the MMRII group in percentage of subjects with an anti-rubella virus concentration ≥10 IU/mL at PI(D42) (ATP cohort for immunogenicity)

MMR_1 (N)	n	SRR	MMRII (N)	n	SRR	Difference	95% LL	95% UL	P-value
247	244	98.8%	249	249	100%	-1.21%	-3.51%	0.32%	0.003
MMR_2 (N)	**n**	**SRR**	**MMRII (N)**	**n**	**SRR**	**Difference**	**95% LL**	**95% UL**	**P-value**
238	235	98.7%	249	249	100%	-1.26%	-3.64%	0.27%	0.004
MMR_3 (N)	**n**	**SRR**	**MMRII (N)**	**n**	**SRR**	**Difference**	**95% LL**	**95% UL**	**P-value**
239	233	97.5%	249	249	100%	-2.51%	-5.37%	-0.97%	0.039

Source: Adapted from Tables 27 and 149 in Clinical Study Report MMR-157

Choice of mumps virus potency to be used in future U.S. MMR trials

Based on the comparison of SRRs between Priorix lots and the pooled MMR-II lots, the applicant chose to use a mumps potency of 4.1 log10 $CCID_{50}$ (MMR_2 lot) for the MIN potency lot in study MMR-161.

6.1.9.2 Analyses of Secondary Endpoints

See the clinical reviewer's memo for details on exploratory secondary analyses.

6.1.10 Safety Analyses

The primary analysis of safety was based on the TVC safety cohort.

6.1.10.1 Overall Incidence of AEs

Table 7 provides the incidence of all reported (solicited and unsolicited) generalized and local symptoms over the 43-day follow-up (Day 0-42) after vaccination in the four groups.

Table 7: Incidence of symptoms (solicited and unsolicited) reported during the 43-day (Days 0-42) post-vaccination period (TVC)

Group	N	Any Symptom	LL	UL	General symptoms	LL	UL	Local symptoms	LL	UL
MMR_1	304	80.9%	76.0%	85.2%	78.6%	73.6%	83.1%	30.9%	25.8%	36.4%
MMR_2	304	75.7%	70.4%	80.4%	74.0%	68.7%	78.9%	29.3%	24.2%	34.7%
MMR_3	304	74.0%	68.7%	78.9%	72.0%	66.6%	77.0%	31.3%	26.1%	36.8%
MMRII	308	75.3%	70.1%	80.0%	73.7%	68.4%	78.5%	29.9%	24.8%	35.3%

Source: Adapted from Table 40 in Clinical Study Report MMR-157

Table 8 summarizes the incidence of solicited local symptoms (pain, redness, swelling) at the Priorix and MMR-II injection sites. All solicited local injection site symptoms were considered causally related to vaccination.

Table 8: Incidence of solicited local symptoms reported during the 4-day (Days 0-3) post-vaccination period (TVC)

Symptom	MMR_1[1]	MMR_2[1]	MMR_3[1]	MMRII[1]
All Pain	24.8%[1]	25.5%	28.0%	24.5%
Grade 2 or 3 Pain	7.1%	7.7%	6.4%	5.8%
Grade 3 Pain	1.1%	1.5%	0.4%	1.5%
All Redness	16.0%	17.2%	14.5%	17.2%

Symptom	MMR_1[1]	MMR_2[1]	MMR_3[1]	MMRII[1]
Redness >5.0 mm	3.5%	6.2%	4.3%	2.9%
Redness >20.0 mm	1.1%	1.5%	0.4%	1.1%
All Swelling	7.1%	9.5%	6.7%	5.5%
Swelling >5.0 mm	0.4%	1.1%	0.4%	1.1%
Swelling >20.0 mm	0.0%	0.4%	0.0%	0.4%

[1]MMR_1 (N=282); MMR_2 (N=274); MMR_3 (N=282); MMR_II (N=274). Sample sizes reflect compliance in completing symptom sheets
Source: Adapted from Table 41 in Clinical Study Report MMR-157

With respect to solicited general symptoms, during the 43-day post-vaccination period, the reported incidence of any fever (rectal temperature ≥38.0°C) was somewhat higher in the Priorix groups (36.4% to 37.8%) than in the MMRII group (30.7%). Rates of fever attributed a causal relationship to vaccination by the investigator were 15.2%, 17.1%, 14.1%, and 12.6% in the MMR_1 (n=283), MMR_2 (n=275), MMR_3 (n=283), and MMRII (n=277) groups, respectively. Rates of fever that caused the parent/guardian to seek medical advice were 11.3%, 12.4%, 14.8%, and 12.6%, respectively.

Rates of febrile convulsions and localized or generalized rash over the 43-day vaccination period were similar between Priorix and MMR-II. A febrile convulsion was reported in two subjects (one each in the MMR_2 and MMRII groups). See the clinical reviewers' memos for further discussion of solicited AEs.

Reviewer comment*: Table 8 shows generally similar rates between Priorix and MMR-II, with the exception of swelling, where the Priorix groups have somewhat higher rates. With respect to general solicited symptoms, there was a slightly higher incidence of fever in the Priorix groups versus the MMR-II group. Also, there were slightly higher rates of unsolicited grade 3 symptoms from Priorix subjects than MMR-II subjects. At least one unsolicited grade 3 symptom was reported by 5.9%, 7.2%, 7.9%, and 4.9% of subjects in the three Priorix and MMRII groups, respectively. However, clinical reviewers considered the rates to be acceptable.*

6.1.10.2 Deaths

There were no deaths in the study.

6.1.10.3 Nonfatal Serious Adverse Events

At least one SAE with onset between vaccination/Day 0 and Day 180 was reported in:

- 1/304 (0.3%) subjects in Group MMR_1
- 6/304 (2.0%) subjects in Group MMR_2 (6 SAEs total)
- 7/304 (2.3%) subjects in Group MMR_3 (9 SAEs total)
- 9/308 (2.9%) subjects in the MMRII group (18 SAEs total)

6.1.10.4 Adverse Events of Special Interest (AESI)

Please see the clinical reviewers' memos for discussion of AESIs.

6.1.10.5 Dropouts and/or Discontinuations

Between vaccination/Day 0 and the Day 180 follow-up, an AE was the reason for premature discontinuation of study in two subjects (one in MMR_2, one in MMRII group). Both events were considered vaccine-related by the investigator.

6.2 MMR-158

This study evaluated immunogenicity of Priorix versus Com_MMR (MMR II), when given as a second dose to children four to six years old with documented one dose immunization with MMR-II, MMR VaxPro or ProQuad. The study also evaluated immune responses of co-administered DTaP-IPV vaccines when given with either Priorix or Com_MMR in the U.S. population.

6.2.1 Objectives

Primary Objectives (Day 42)

- Demonstrate non-inferiority of Priorix to Com_MMR, when administered with VV and DTaP-IPV vaccines in terms of SRRs and antibody concentrations to MMR viruses
- Demonstrate non-inferiority of Priorix to Com_MMR, when administered *without* VV and DTaP-IPV vaccines in terms of SRRs and antibody concentrations to MMR viruses

Secondary Immunogenicity Objectives (Day 42)

- Demonstrate non-inferiority in terms of SRRs and antibody concentrations to VZV when VV is administered with Priorix and DTaP-IPV vaccines as compared to Com_MMR and DTaP-IPV vaccines
- Demonstrate non-inferiority in terms of antibody booster response to diphtheria (D), tetanus (T), pertussis Toxin (PT), Filamentous Hemagglutinin (FHA) and Pertactin (PRN) when DTaP-IPV is administered with Priorix and VV as compared to Com_MMR and VV
- Demonstrate non-inferiority in terms of antibody titers to poliovirus types 1, 2 and 3 when DTaP-IPV is administered with Priorix and VV as compared to Com_MMR and VV
- Demonstrate non-inferiority in terms of anti-PT, anti-FHA and anti-PRN antibody concentrations when DTaP-IPV is administered with Priorix and VV as compared to Com_MMR and VV

6.2.2 Design Overview

This was a phase IIIa, randomized, observer-blind, controlled, multicenter, multi-country study with nine parallel groups. The study period was six months starting at Visit 1 (day 0) and ending at day 180.

The study design included three sub-cohorts:

1. Sub-cohort 1: (for immunogenicity and safety when given with co-administrations, in U.S. subjects only):

- INV_MMR_CO: subjects receiving one dose of Priorix co-administered with DTaP-IPV (Kinrix) and VV (Varivax)
- Com_MMR_L1_co: subjects receiving one dose of MMR-II Lot 1 co-administered with DTaP-IPV (Kinrix) and VV (Varivax)
- Com_MMR_L2_co: subjects receiving one dose of MMR-II Lot 2 co-administered with DTaP-IPV (Kinrix) and VV (Varivax)

2. Sub-cohort 2: (for immunogenicity and safety when given without co-administrations)
   - INV_MMR_I: subjects receiving one dose of Priorix
   - Com_MMR_L1_I: subjects receiving one dose of MMR-II Lot 1
   - Com_MMR_L2_I: subjects receiving one dose of MMR-II Lot 2
3. Sub-cohort 3: (for safety assessment)
   - INV_MMR_S: subjects receiving one dose of Priorix
   - Com_MMR_L1_S: subjects receiving one dose of MMR-II Lot 1
   - Com_MMR_L2_S: subjects receiving one dose of MMR-II Lot 2

Approximately 4000 subjects were randomized in a 3:1 ratio to receive Priorix or Com_MMR. Randomization was stratified by sub-cohort. Within each stratification level, a minimization procedure accounted for center. Once a subject was placed into a sub-cohort, randomization was done in a 6:1:1 ratio across the 3 groups.

Table 9 contains the sample sizes per cohort group.

Table 9: Study groups

Cohort	Group name (identifier)	Number of subjects
1	Inv _MMR_co	822
1	Com_MMR_L1_co	137
1	Com_MMR_L2_co	137
2	Inv_MMR_i	822
2	Com_MMR_L1_i	137
2	Com_MMR_L2_i	137
3	Inv_MMR_s	1356
3	Com_MMR_L1_s	226
3	Com_MMR_L2_s	226

Source: Adapted from Table 2 in Clinical Study Report MMR-158

Post-vaccination antibody thresholds that defined sero-response were the same for study MMR-157. Pre-vaccination concentrations were not considered in the definitions. In addition, for anti-poliovirus types 1, 2, and 3, titers ≥8 ED_{50} indicated sero-response.

Booster responses for pertussis antigens (PT, FHA and PRN) were defined as below.

- For subjects with pre-vaccination antibody concentration
  - below the assay cut-off: post-vaccination antibody concentration ≥ 4 times assay cut-off

- between the assay cut-off and below 4 times the assay cut-off: post-vaccination antibody concentration ≥ 4 times pre-vaccination antibody concentration
- ≥ 4 times the assay cut-off: post-vaccination antibody concentration ≥ 2 times pre-vaccination antibody concentration

Booster responses for D and T antigens were defined as below:

- For subjects with pre-vaccination concentration < 0.1 IU/mL (below the sero-protection cut-off), antibody concentrations at least ≥ 0.4 IU/mL one month post vaccination
- For subjects with pre-vaccination concentration ≥ 0.1 IU/mL, an increase in antibody concentrations of at least 4 times the pre-vaccination concentration one month post vaccination

6.2.3 Population

Children 4 to 6 years old who received either a single dose of MMRII, MMR VaxPro or ProQuad in the second year of life, and have not yet received a second dose

For sub-cohort 1, subjects had to have received previous doses of DTaP-IPV and VV vaccinations.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Treatment: Inv_MMR: Priorix MMR vaccine

Control: Com_MMR: two lots designated Com_MMR_L1 and Com_MMR_L2 (analyzed as pooled lots)

Co-administered vaccines (sub-cohort 1 only): DTaP-IPV and VV were administered with the MMR vaccines at Visit 1

6.2.5 Sites and Centers

There were 70 centers (52 in the U.S., 12 in South Korea, and 6 in Taiwan). Each center contributed to either:

1) a single sub-cohort or
2) an immunogenicity sub-cohort (first) and Sub-cohort #3 (thereafter)

6.2.6 Endpoints and Criteria for Study Success

Primary Endpoints (Day42)

- Subcohort 1: Non-inferiority of immunogenicity of Inv_MMR compared to Com_MMR when given *with* VV and DTaP-IPV vaccines in terms of:
  - Sero-response to MMR viruses:
    - Criterion: Lower limit (LL) of two-sided 97.5% CI for group difference (Inv_MMR_co minus Com_MMR_co) in SRRs is ≥ -5%
  - MMR virus antibody concentrations:
    - Criterion: LL of two-sided 97.5% CI for the adjusted GMC ratio (Inv_MMR_co divided by Com_MMR_co) is ≥ 0.67

- Subcohort 2: Non-inferiority of immunogenicity of Inv_MMR compared to Com_MMR when given *without* VV and DTaP-IPV in terms of:
  - Sero-response to MMR viruses:
    - Criterion: LL of two-sided 97.5% CI for group difference (Inv_MMR_i minus Com_MMR_i) in SRRs is ≥ -5%
  - MMR virus antibody concentrations:
    - Criterion: LL of two-sided 97.5% CI for the adjusted GMC ratio (Inv_MMR_i divided by Com_MMR_i) is ≥ 0.67

For the study to be successful, all co-primary objectives in sub-cohort 1 or all co-primary objectives in sub-cohort 2 had to be met. If the co-primary objectives for sub-cohort 1 were met, the five confirmatory immunogenicity secondary endpoints (related to co-administrations) were to be tested hierarchically as described in Section 6.2.7 Statistical Considerations & Statistical Analysis Plan.

Secondary Immunogenicity Endpoints (Day 42)

- Non-inferiority of sero-response and antibody concentrations to VZV
  - Inv_MMR_co versus Com_MMR_co:
    - Criterion: The LL of the 2-sided 97.5% CI for the difference in SRR across groups ≥ -5%.
    - Criterion: The LL of the 2-sided 97.5% CI for adjusted GMC ratio (Inv_MMR_co divided by Com_MMR_co) ≥ 0.67
- Non-inferiority of immunogenicity with respect to the components of DTaP-IPV vaccine:
  - anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN booster response
    - Criterion: The LL of the 2-sided 97.5% CI for difference in booster response rates (Priorix minus MMR-II) is ≥-10%.
  - anti-PT, anti-FHA, anti-PRN titers
    - The LL of the two-sided 97.5% CI for the adjusted GMC ratio between groups ≥ 0.67
- Non-inferiority of immunogenicity with respect to the components of polio vaccine at day 42
  - anti-poliovirus types 1, 2 and 3 titers
    - Criterion: The LL of the two-sided 97.5% CI for the adjusted GMC ratio between groups ≥ 0.67

6.2.7 Statistical Considerations & Statistical Analysis Plan

The CIs for adjusted GMC/GMT ratios were calculated using an ANCOVA model on log-transformed concentrations/titers, with vaccine group and country as fixed effects and pre-vaccination concentration/titer as a regressor.

To control the familywise type I error rate below 2.5%, a Bonferroni adjustment was used to compare groups in either sub-cohort 1 or 2, independently. Each group comparison was based on a 1.25% nominal type I error. In addition, a hierarchical procedure was used for the secondary objectives for sub-cohort 1. Table 10 shows the order in which each of the primary and secondary objectives was assessed.

Table 10: Sequence for evaluating study objectives to control type I error rate below 2.5%

	Sub-cohort 1	Sub-cohort 2	Significance level
Primary Endpoint (Inv_MMR vs. Com_MMR)	Non-inferiority with respect to SRR for measles, mumps, and rubella	Non-inferiority with respect to SRR for measles, mumps, and rubella	1.25%
Primary Endpoint (Inv_MMR vs. Com_MMR)	Non-inferiority with respect to GMC for measles, mumps, and rubella	Non-inferiority with respect to GMC for measles, mumps, and rubella	1.25%
Secondary Endpoint #1	Non-inferiority with respect to SRR for VZV	NA	1.25%
Secondary Endpoint #2	Non-inferiority with respect to GMC for VZV	NA	1.25%
Secondary Endpoint #3	Non-inferiority with respect to booster response for DTaP (D, T, PT, FHA, PRN)	NA	1.25%
Secondary Endpoint #4	Noninferiority with respect to GMT for polio	NA	1.25%
Secondary Endpoint #5	Noninferiority with respect to GMC for anti-PT, anti-FHA, anti-PRN	NA	1.25%

Source: Reviewer-created table using information from Figure 2 in Clinical Study Report MMR-158

6.2.8 Study Population and Disposition

6.2.8.1 Populations Enrolled/Analyzed

The total vaccinated cohort (TVC) was defined as per study MMR-157.

The ATP cohort for safety was the same as for MMR-157, but included all eligible subjects who had not received a prohibited vaccine up to Visit 2 (day 42).

The ATP cohort for immunogenicity included all evaluable subjects from the ATP cohort for analysis of safety:

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

The immunogenicity subset for evaluation of the immune responses to co-administered vaccines only included children from the U.S. whose DTaP, IPV and VV vaccination history is known. These subjects would have received GSK products.

6.2.8.1.1 Demographics

Demographic characteristics were largely similar across groups within sub-cohorts, with the exception of a slight imbalance in gender. Table 11 shows gender composition of the ATP cohort for immunogenicity for each of the sub-cohorts.

Table 11: Summary of gender composition (ATP cohort for immunogenicity)

Gender	Inv_MMR_CO N=698	Com_MMR_CO N=250	Total N=948*
Female	n=350 (50.1%)	n=110 (44.0%)	n=460 (48.5%
Male	n=348 (49.9%)	n=140 (56.0%)	n=488 (51.5%)
Gender	**Inv_MMR_I N=742**	**Com_MMR_I N=283**	**Total N=1025**
Female	n=340 (45.8%)	n=140 (49.5%)	n=480 (46.8%)
Male	n=402 (54.2%)	n=143 (50.5%)	n=545 (53.2%)
Gender	**Inv_MMR_S N=1319**	**Com_MMR_S N=489**	**Total N=1808**
Female	n=632 (47.9%)	n=225 (46.0%)	n=857 (47.4%)
Male	n=687 (52.1%)	n=264 (54.0%)	n=951 (52.6%)

*Sub-cohort 1 consisted of subjects enrolled only in the U.S.
N=total number of subjects
n/%=number/percentage of subjects in a given category
Source: Reviewer-created table using Table 30, 31, and 32 in Clinical Study Report MMR-158

Reviewer comment: *There are slight discrepancies in gender balance across groups in Sub-cohort 1. However, based on subgroup analyses presented later, despite males in general having lower GMCs than females, overall conclusions within subgroups were not materially different.*

6.2.8.1.3 Subject Disposition

Table 12 shows subject disposition by treatment group and sub-cohort.

Table 12: Participant Disposition & Data Analyses Sets for Priorix and MMR II Study Groups, All Randomized Participants, Study MMR-158

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

Population	Priorix Sub-cohort 1 n (%) [N=802]	MMR II Sub-cohort 1 n (%) [N=299]	Priorix Sub-cohort 2 n (%) [N=796]	MMR II Sub-cohort 2 n (%) [N=303]	Priorix Sub-cohort 3 n (%) [N=1,320]	MMR II Sub-cohort 3 n (%) [N=489]
Maximum % of subjects eliminated for ATP-Imm analyses***	4.32%	4.35%	2.41%	2.44%	NA	NA

*Includes participants with important protocol violations that resulted in exclusion from the ATP-Imm. analysis population.
**Includes participants with important protocol violations that resulted in exclusion from the ATP-Safety analysis population.
***For each antigen and each confirmatory objective, the percentage of subjects who had the necessary immunogenicity results to contribute to the TVC analysis but were eliminated for the ATP analysis was computed. This value represents the maximum over all confirmatory objectives and antigens
Source: 1.11.3 Clinical Information Amendment Response to CBER request 20Aug2021

6.2.9 Immunogenicity Analyses

The analysis of immunogenicity was based on the primary ATP cohort for immunogenicity.

6.2.9.1 Analyses of Primary Endpoints

6.2.9.1.1 Immunogenicity analyses of Inv_MMR and Com_MMR co-administered with VV and DTaP-IPV vaccines (sub-cohort 1)

The SRRs to MMR viruses for groups Inv_MMR_co and Com_MMR_co at day 42 following vaccination are given in Table 13. The LLs of the two-sided 97.5% CIs for the differences in SRRs between the groups were > -5% for all three antibodies.

Table 13: Non-inferiority of INV_MMR_CO vs COM_MMR_CO in terms of SRR when co-administered with Varicella and DTaP-IPV vaccines (ATP cohort for immunogenicity, sub-cohort 1)

Antibody	INV_MMR_CO SRR %	COM_MMR_CO SRR %	Difference	97.5% CI LL	97.5% CI UL
anti-measles antibody	100	100	0.00	**-0.72**	1.98
anti-mumps (PPD) antibody	100	100	0.00	**-0.72**	1.97
anti-rubella antibody	99.9	100	-0.14	**-0.98**	1.84

SRR=Seroresponse rate (percentage of subjects with concentration above seroresponse threshold for each assay
Source: Adapted from Table 36 in Clinical Study Report MMR-158

The GMCs against MMR viruses are given in Table 14. The LLs of the two-sided 97.5% CIs for the adjusted GMC ratios between the groups were > 0.67 for all three antibodies.

Table 14: Non-inferiority of INV_MMR_CO vs COM_MMR_CO in terms of GMC ratios of antibodies when co-administered with Varicella and DTaP-IPV vaccines (ATP cohort for immunogenicity, sub-cohort 1)

Antibody	INV_MMR_CO Adjusted GMC	COM_MMR_CO Adjusted GMC	Ratio	97.5% CI LL	97.5% CI UL
anti-measles antibody (mIU/mL)	4285.0	4333.5	0.99	**0.92**	1.06
anti-mumps (PPD) antibody (EU/mL)	171.3	188.5	0.91	**0.83**	1.00
anti-rubella antibody (IU/mL)	97.1	94.5	1.03	**0.97**	1.09

Adjusted GMC/GMT=geometric mean antibody concentration/titer adjusted for pre-vaccination concentration
Source: Adapted from Table 37 in Clinical Study Report MMR-158

6.2.9.1.2 Immunogenicity analyses of Inv_MMR and Com_MMR administered without VV and DTaP-IPV vaccines (sub-cohort 2)

The SRRs to MMR viruses for groups Inv_MMR_i and Com_MMR_i are given in Table 15. The LLs of the two-sided 97.5% CIs for the differences in SRRs between the groups were > -5% for all three antibodies.

Table 15: Non-inferiority of INV_MMR_I vs COM_MMR_I in terms of SRR when administered alone (ATP cohort for immunogenicity, sub-cohort 2)

Antibody	INV_MMR_I SRR %	COM_MMR_I SRR %	Difference	97.5% CI LL	97.5% CI UL
anti-measles antibody	100	99.3	0.71%	**0.02%**	2.97%
anti-mumps (PPD) antibody	100	100	0.00%	**-0.68%**	1.75%
anti-rubella antibody	100	100	0.00%	**-0.68%**	1.75%

SRR=Seroresponse rate (percentage of subjects with concentration above seroresponse threshold for each assay
Source: Adapted from Table 52 in Clinical Study Report MMR-158

The GMCs are given in Table 16. The LLs of the two-sided 97.5% CIs for the adjusted GMC ratios between the Inv_MMR_co group and the Com_MMR_co group were > 0.67 for all three antibodies.

Table 16: Non-inferiority of INV_MMR_I vs COM_MMR_I in terms of GMC ratios when administered alone (ATP cohort for immunogenicity, sub-cohort 2)

Antibody	INV_MMR_I Adjusted GMC	COM_MMR_I Adjusted GMC	Ratio	97.5% CI LL	97.5% CI UL
anti-measles antibody (mIU/mL)	3600.3	3504.3	1.03	**0.96**	1.10
anti-mumps (PPD) antibody (EU/mL)	167.7	174.6	0.96	**0.87**	1.06
anti-rubella antibody (IU/mL)	99.3	98.6	1.01	**0.95**	1.07

Adjusted GMC=geometric mean antibody concentration adjusted for country and pre-vaccination concentration
Source: Adapted from Table 53 in Clinical Study Report MMR-158

6.2.9.2 Analyses of Secondary Endpoints

Because the success criteria of primary endpoints for sub-cohort 1 were met, the secondary endpoints for sub-cohort 1 were tested according to the hierarchy in Table 10.

The assessment of non-inferiority of immune response to VV and DTaP-IPV vaccines when coadministered with Inv_MMR compared to that when coadminstered with Com_MMR with respect to SRR is provided in Table 17, and with respect to GMC ratio is in Table 18. Because all LLs of the CIs for the difference in SRR were > -10%, and all LLs of the CIs for the ratios of GMCs were > 0.67, all secondary endpoint success criteria were met.

Table 17: Difference between groups (INV_MMR_CO minus COM_MMR_CO) in percent of subjects with seroresponse to anti-VZV and booster response to anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibody at Day 42 (ATP cohort for immunogenicity, Sub-cohort 1)

Secondary Endpoint	Antibody	Inv_MMR_CO	%	Com_MMR_CO	%	Difference	97.5% CI LL	97.5% CI UL
3	anti-D (IU/ml)	N=659	99.7	N=233	100	-0.30%	**-1.29**%	1.81%
3	anti-FHA (IU/ml)	N=659	94.1	N=234	94.4	-0.36%	**-3.90**%	4.34%

Secondary Endpoint	Antibody	Inv_MMR_CO	%	Com_MMR_CO	%	Difference	97.5% CI LL	97.5% CI UL
3	anti-PRN (IU/ml)	N=660	99.5	N=234	99.6	-0.03%	**-1.17**%	2.44%
3	anti-PT (IU/ml)	N=659	97.6	N=233	96.6	1.01%	**-1.54**%	4.95%
3	anti-T (IU/ml)	N=661	93.9	N=234	95.7	-1.78%	**-5.08**%	2.60%
1	anti-VZV (IU/ml)	N=695	99.7	N=247	100	-0.29%	**-1.22**%	1.71%

N = number of subjects with pre- and post-vaccination results available
% = percentage of subjects with a sero or booster response
Source: Adapted from Tables 7.15 and 7.17 in Clinical Study Report MMR-158

Table 18: Non-inferiority of INV_MMR_CO vs COM_MMR_CO in terms of GMC ratios of antibodies (VZV, Poliovirus type 1, 2 and 3 and pertussis) to co-administered vaccines (ATP cohort for immunogenicity, sub-cohort 1)

Secondary Endpoint	Antibody	INV_MMR_CO Adjusted GMC/GMT	COM_MMR_CO Adjusted GMC/GMT	Ratio	97.5% CI LL	97.5% CI UL
2	anti-VZV (mIU/mL)	879.7	830.1	1.06	**0.95**	1.18
4	Polio 1 (ED_{50})	1636.5	1558.4	1.05	**0.88**	1.25
4	Polio 2 (ED_{50})	2032.7	2197.3	0.93	**0.78**	1.09
4	Polio 3 (ED_{50})	2794.4	2978.8	0.94	**0.77**	1.14
5	anti-PT (IU/mL)	76.1	73.0	1.04	**0.92**	1.18
5	anti-FHA (IU/mL)	313.7	323.3	0.97	**0.88**	1.07
5	anti-PRN (IU/mL)	399.9	417.6	0.96	**0.84**	1.09

Adjusted GMC/GMT=geometric mean antibody concentration/titer adjusted for pre-vaccination concentration
Source: Adapted from Table 42 in Clinical Study Report MMR-158

6.2.9.3 Subpopulation Analyses

By country

Sub-cohort 2 was the only cohort with non-U.S. subjects for immunogenicity endpoints. The differences in SRRs at Day 42 across groups are shown in Table 19.

Table 19: Non-inferiority of INV_MMR_I vs COM_MMR_I in terms of SRRs when administered alone (ATP cohort for immunogenicity, sub-cohort 2)

Antibody	Sub-group	INV_MMR_I	SRR	COM_MMR_I	SRR	Diff	97.5% LL	97.5% UL
anti-measles	Country: United States	N=365	100%	N=142	99.3%	0.7%	-0.66%	4.68%
anti-measles	Country: Republic of Korea	N=152	100%	N=62	98.4%	1.61%	-1.64%	10.28%
anti-measles	Country: Taiwan	N=219	100%	N=79	100%	0%	-2.25%	6%
anti-mumps (PPD)	Country: United States	N=365	100%	N=142	100%	0%	-1.36%	3.42%
anti-mumps (PPD)	Country: Republic of Korea	N=152	100%	N=62	100%	0%	-3.21%	7.53%
anti-mumps (PPD)	Country: Taiwan	N=219	100%	N=79	100%	0%	-2.25%	6%
anti-rubella	Country: United States	N=365	100%	N=142	100%	0%	-1.36%	3.42%
anti-rubella	Country: Republic of Korea	N=152	100%	N=62	100%	0%	-3.21%	7.53%
anti-rubella	Country: Taiwan	N=219	100%	N=79	100%	0%	-2.25%	6%

N = number of subjects with post-vaccination results available
Source: Table 5 in 1.11.3 Clinical Information Amendment – Response to CBER Request 10Nov2021 (MMR-158 (115158) – Analysis 7)

***Reviewer comment**: The only antibody with slight observed differences across countries in SRR was anti-measles. However, the increases in GMC from prevaccination to post day 42 between groups were similar across countries (Table 20).*

Table 20: GMC of anti-Measles antibody concentration by country, treatment group, and time point (ATP cohort for immunogenicity, Sub-cohort 2)

Group	Timing	Taiwan GMC	95% CI LL	95% CI UL	Korea GMC	95% CI LL	95% CI UL	U.S. GMC	95% CI LL	95% CI UL
Inv_MMR_I	PRE	2017.2	1774.1	2293.5	2704.0	2316.7	3156.1	3338.1	2989.4	3727.6
Inv_MMR_I	PI(D42)	3188.5	2922.5	3478.8	3291.4	2917.9	3712.7	4124.7	3803.5	4473.0
Com_MMR_I	PRE	1987.4	1602.2	2465.1	2633.8	2028.1	3420.4	3321.7	2715.8	4062.6
Com_MMR_I	PI(D42)	2905.3	2499.7	3376.6	3286.6	2637.1	4096.1	3999.1	3444.7	4642.9

Source: Reviewer-created using information from Tables 7.41, 7.42, and 7.43 in Clinical Study Report MMR-158

By gender

Table 21 through Table 24 show primary endpoint results by gender, for sub-cohorts 1 and 2, at day 42.

Table 21: Non-inferiority of INV_MMR_CO vs COM_MMR_CO in terms of SRR when co-administered with Varicella and DTaP-IPV vaccines by gender (ATP cohort for immunogenicity, sub-cohort 1)

Antibody	Sub-group	INV_MMR_CO	SRR	COM_MMR_CO	SRR	Diff	97.5% LL	97.5% UL
anti-measles	Sex: Male	N=347	100%	N=139	100%	0	-1.43%	3.5%
anti-measles	Sex: Female	N=350	100%	N=110	100%	0	-1.42%	4.38%
anti-mumps (PPD)	Sex: Male	N=348	100%	N=140	100%	0	-1.43%	3.47%
anti-mumps (PPD)	Sex: Female	N=350	100%	N=110	100%	0	-1.42%	4.38%
anti-rubella	Sex: Male	N=347	100%	N=139	100%	0	-1.43%	3.5%
anti-rubella	Sex: Female	N=350	99.7%	N=110	100%	-0.29%	-1.94%	4.09%

Source: Adapted from Table 1 in 1.11.3 Clinical Information Amendment – Response to CBER Request 10Nov2021 (MMR-158 (115158) – Analysis 7)

Table 22: Non-inferiority of INV_MMR_CO vs COM_MMR_CO in terms of GMC ratios when co-administered with Varicella and DTaP-IPV vaccines by gender (ATP cohort for immunogenicity, sub-cohort 1)

Antibody	Sub-group	INV_MMR_CO	Adjusted GMC	COM_MMR_CO	Adjusted GMC	Ratio	LL	UL
anti-measles (mIU/mL)	Sex: Male	N=345	4047.9	N=136	4077.2	0.99	0.91	1.08
anti-measles (mIU/mL)	Sex: Female	N=345	4551.1	N=109	4627.2	0.98	0.87	1.11
anti-mumps (PPD) (EU/mL)	Sex: Male	N=346	160.1	N=138	186.1	0.86	0.75	0.98
anti-mumps (PPD) (EU/mL)	Sex: Female	N=345	183.8	N=110	189.8	0.97	0.84	1.12
anti-rubella (IU/mL)	Sex: Male	N=345	88.2	N=136	86.5	1.02	0.95	1.1
anti-rubella (IU/mL)	Sex: Female	N=345	107.3	N=109	104.2	1.03	0.95	1.11

Adjusted GMC/GMT = geometric mean antibody concentration/titer adjusted for pre-vaccination concentration

Source: Table 2 in 1.11.3 Clinical Information Amendment – Response to CBER Request 10Nov2021 (MMR-158 (115158) – Analysis 7)

Table 23: Non-inferiority of INV_MMR_I vs COM_MMR_I in terms of SRR when administered alone by gender (ATP cohort for immunogenicity, sub-cohort 2)

Antibody	Sub-group	INV_MMR_I	SRR	COM_MMR_I	SRR	Diff	97.5% LL	97.5% UL
anti-measles	Sex: Male	N=397	100%	N=143	99.3%	0.7%	-0.56%	4.65%
anti-measles	Sex: Female	N=339	100%	N=140	99.3%	0.71%	-0.76%	4.75%
anti-mumps (PPD)	Sex: Male	N=397	100%	N=143	100%	0	-1.25%	3.4%
anti-mumps (PPD)	Sex: Female	N=339	100%	N=140	100%	0	-1.46%	3.47%
anti-rubella	Sex: Male	N=397	100%	N=143	100%	0	-1.25%	3.4%
anti-rubella	Sex: Female	N=339	100%	N=140	100%	0	-1.46%	3.47%

Source: Adapted from Table 5 in 1.11.3 Clinical Information Amendment – Response to CBER Request 10Nov2021 (MMR-158 (115158) – Analysis 7)

Table 24: Non-inferiority of INV_MMR_I vs COM_MMR_I in terms of GMC ratios when administered alone by gender (ATP cohort for immunogenicity, sub-cohort 2)

Antibody	Sub-group	INV_MMR_I	Adjusted GMC	COM_MMR_I	Adjusted GMC	Ratio	LL	UL
anti-measles (mIU/mL)	Sex: Male	N=392	3406.9	N=141	3258.8	1.05	0.96	1.13
anti-measles (mIU/mL)	Sex: Female	N=337	3839.1	N=139	3777.5	1.02	0.92	1.12
anti-mumps (PPD) (EU/mL)	Sex: Male	N=394	154.4	N=143	164.1	0.94	0.82	1.08
anti-mumps (PPD) (EU/mL)	Sex: Female	N=338	185	N=139	185.9	1	0.86	1.15
anti-rubella (IU/mL)	Sex: Male	N=392	91.4	N=141	89.7	1.02	0.94	1.11
anti-rubella (IU/mL)	Sex: Female	N=337	109.5	N=139	109	1	0.92	1.1

Adjusted GMC/GMT = geometric mean antibody concentration/titer adjusted for pre-vaccination concentration

Source: Table 6 in 1.11.3 Clinical Information Amendment – Response to CBER Request 10Nov2021 (MMR-158 (115158) – Analysis 7)

Reviewer comment: *Although males have somewhat lower adjusted GMCs than females, the difference between groups is roughly similar for males and females.*

By race

Table 25 and Table 26 show primary endpoint results by race, for sub-cohort 2. Sub-cohort 1 only had subjects of White Caucasian/European race.

Table 25: Non-inferiority of INV_MMR_I vs COM_MMR_I in terms of SRR when administered alone (ATP cohort for immunogenicity, sub-cohort 2)

Antibody	Sub-group	INV_MMR_I	SRR	COM_MMR_I	SRR	Diff	97.5% LL	97.5% UL
anti-measles	Race: White Caucasian/ European	N=258	100%	N=105	99.0%	0.95	-0.98%	6.26%
anti-measles	Race: East Asian	N=371	100%	N=141	99.3%	0.71	-0.64%	4.71%
anti-mumps(PPD)	Race: White Caucasian/ European	N=258	100%	N=105	100%	0	-1.92%	4.58%
anti-mumps(PPD)	Race: East Asian	N=371	100%	N=141	100%	0	-1.34%	3.45%
anti-rubella	Race: White Caucasian/ European	N=258	100%	N=105	100%	0	-1.92%	4.58%
anti-rubella	Race: East Asian	N=371	100%	N=141	100%	0	-1.34%	3.45%

Source: Adapted from Table 5 in 1.11.3 Clinical Information Amendment – Response to CBER Request 10Nov2021 (MMR-158 (115158) – Analysis 7)

Table 26: Non-inferiority of INV_MMR_I vs COM_MMR_I in terms of GMC ratios when administered alone (ATP cohort for immunogenicity, sub-cohort 2)

Antibody	Sub-group	INV_MMR_I	Adjusted GMC	COM_MMR_I	Adjusted GMC	Ratio	LL	UL
anti-measles (mIU/mL)	Race: White Caucasian/ European	N=253	3897.4	N=102	3894.6	1	0.89	1.12
anti-measles (mIU/mL)	Race: East Asian	N=371	2904.8	N=141	2777.2	1.05	0.96	1.14
anti-mumps (PPD)(EU/mL)	Race: White Caucasian/	N=255	159.5	N=104	182.8	0.87	0.74	1.03
anti-mumps (PPD)(EU/mL)	Race: East Asian	N=371	140.6	N=141	140.2	1	0.87	1.15
anti-rubella (IU/mL)	Race: White	N=253	99.9	N=102	97.3	1.03	0.93	1.14
anti-rubella (IU/mL)	Race: East Asian	N=371	85.3	N=141	85.1	1	0.91	1.1

Source: Table 6 in 1.11.3 Clinical Information Amendment – Response to CBER Request 10Nov2021 (MMR-158 (115158) – Analysis 7)

Reviewer comment*: White subjects had higher adjusted GMCs at Day 42 than East Asian subjects. However, from further information in the CSR for MMR-158, White subjects also tended to start with higher GMCs at baseline.*

6.2.9.4 Dropouts and/or Discontinuations

See Section 6.2.8 Study Population and Disposition for details on discontinuations and dropouts.

6.2.9.5 Exploratory and Post Hoc Analyses

The confirmatory objectives were re-analyzed accounting for the randomization process with a minimization algorithm. The p-value for each confirmatory objective was recomputed accounting for center as a minimization factor, country and the sub-cohort (sub-cohorts 1, 2 and 3) as stratification factors. A total of 5000 rerandomizations were performed to compute each p-value as the proportion of rerandomizations leading to a re-estimated value greater than the observed one. All p-values were below the one-sided nominal significance level.

6.2.10 Safety Analyses

The TVC-Safety analysis set was used for safety assessments.

6.2.10.1 Overall incidence of AEs

During the 43-day (day 0-42) post-vaccination follow-up period:

- 72.2% and 68.1% of subjects in the TVC reported at least one AE in the Inv_MMR_co and Com_MMR_co groups, respectively.
- 59.7% and 58.4% of subjects in the TVC reported at least one AE in the Inv_MMR_i group and Com_MMR_i group, respectively.
- 60.5% and 64.6% of subjects in the TVC reported at least one AE in the Inv_MMR_s group and Com_MMR_s group, respectively.

Percentages of subjects in the TVC reporting select types of grade 3 solicited local and general AEs are provided in Table 27, Table 28, and Table 29 by treatment group, for each subcohort. Differences in sample sizes reflect compliance with reporting on solicited symptoms sheets.

Table 27: Percentage of subjects reporting grade 3 AEs by group (Subcohort 1)

Category of grade 3 AE	Inv_MMR	Com_MMR
Grade 3 pain (through Day 3)	3.0% (22/727)	1.5% (4/267)
Grade 3 fever (> 39.5°C) (Day 5 – 12)	0.4% (3/731)	0.4% (1/268)
Fever ≥38°C related to study vaccines	3.8% (28/731)	3.0% (8/268)
Sought medical advice for fever	0.8% (6/731)	0.4% (1/268)
Grade 3 unsolicited AEs (through Day 42)	3% (24/802)	3.7% (11/298)

Source: Reviewer-created table

Table 28: Percentage of subjects reporting grade 3 AEs by group (Subcohort 2)

Category of grade 3 AE	Inv_MMR	Com_MMR
Grade 3 pain (through Day 3)	0.8% (6/766)	0.7% (2/289)
Grade 3 fever (> 39.5°C) (Day 5 – 12)	0.4% (3/767)	1.4% (4/291)
Fever ≥38°C related to study vaccines	1.2% (9/767)	0% (0/291)
Sought medical advice for fever	2.1% (16/767)	1.4% (4/291)
Grade 3 unsolicited AEs (through Day 42)	2.4% (19/796)	3.3% (10/303)

Source: Reviewer-created table

Table 29: Percentage of subjects reporting grade 3 AEs by group (Subcohort 3)

Category of grade 3 AE	Inv_MMR	Com_MMR
Grade 3 pain (through Day 3)	0.4% (5/1289)	0.4% (2/480)
Grade 3 fever (> 39.5°C) (Day 5 – 12)	0.5% (7/1291)	0% (0/481)
Fever ≥38°C related to study vaccines	1.3% (17/1291)	1.9% (9/481)
Sought medical advice for fever	3.0% (39/1291)	2.1% (10/481)
Grade 3 unsolicited AEs (through Day 42)	2.2% (29/1319)	2.2% (11/489)

Source: Reviewer-created table

***Reviewer comment**: The reporting rate of Grade 3 pain in sub-cohort 1 was somewhat higher in Priorix than in Com_MMR . A 95% asymptotic CI on the difference between groups is (-0.6%, 3.7%). Clinical reviewers have determined that the AE rates are acceptable*

The percentage of unsolicited AEs occurring during the 43-day post-vaccination period for all three sub-cohorts is given in Table 30. The Priorix group reported a slightly higher percent of unsolicited AEs than did the MMR-II group. See the clinical reviewers' memos for details and discussion about specific unsolicited AEs.

Table 30: Percentage of subjects with unsolicited adverse events during the 43-day (days 0-42) post-vaccination period (TVC)

Sub-cohort	Inv_MMR	Com_MMR
Sub-cohort 1	34.4% (276/802)	30.2% (90/298)
Sub-cohort 2	39.4% (314/796)	37.0% (112/303)
Sub-cohort 3	38.5% (508/1319)	38.0% (186/489)

Source: Reviewer-created table using information from Table 75 in Clinical Study Report MMR-158

6.2.10.3 Deaths

No deaths were reported in the study.

6.2.10.4 Nonfatal Serious Adverse Events

- In sub-cohort 1, five SAEs were reported in four subjects (0.5%) in the Inv_MMR_co group and none in the Com_MMR_co group.
- In sub-cohort 2, 21 SAEs were reported in 14 subjects (1.75%) in the Inv_MMR_i group and one SAE was reported in one subject (0.33%) in the Com_MMR_i group.
- In sub-cohort 3, 37 SAEs were reported in 25 subjects (3%) in the Inv_MMR_s group and 16 SAEs reported in nine subjects (3%) in the Com_MMR_s group.

6.2.10.5 Adverse Events of Special Interest (AESI)

Table 31, Table 32, and Table 33 provide the percentage of subjects in each sub-cohort who reported at least one new onset chronic disease (NOCD), who reported at least one AE prompting an ER visit, and who reported at least one AE leading to a medically attended visit, respectively.

Table 31: Percentage of subjects in each sub-cohort reporting NOCD from day 0 through the end of the study (TVC)

Sub-cohort	Inv_MMR	Com_MMR
Sub-cohort 1	1.0% (8/802)	1.3% (4/298)
Sub-cohort 2	0.8% (6/796)	0% (0/303)
Sub-cohort 3	0.8% (11/1319)	0.6% (3/489)

Source: Reviewer-created table

Table 32: Percentage of subjects in each sub-cohort reporting at least one AE prompting an ER visit from day 0 through the end of the study (TVC)

Sub-cohort	Inv_MMR	Com_MMR
Sub-cohort 1	7.6% (61/802)	9.7% (29/298)
Sub-cohort 2	8.0% (64/796)	7.3% (22/303)
Sub-cohort 3	7.7% (102/1319)	7.4% (36/489)

Source: Reviewer-created table

Table 33: Percentage of subjects in each sub-cohort reporting at least one AE leading to a medically attended visit from day 0 through the end of the study (TVC)

Sub-cohort	Inv_MMR	Com_MMR
Sub-cohort 1	34.7% (278/802)	33.6% (100/298)
Sub-cohort 2	45.1% (359/796)	41.6% (126/303)
Sub-cohort 3	48.8% (644/1319)	47.2% (231/489)

Source: Reviewer-created table

***Reviewer comment**: For sub-cohort 2, the difference in percentages reporting at least one AE leading to a medically attended visit across groups is 3.5% with asymptotic 95%*

CI of (-3.2%, 10.3%). I defer to clinical reviewers as to whether the magnitude of difference is clinically relevant.

6.2.10.6 Dropouts and/or Discontinuations

There were no AEs leading to premature discontinuation of study vaccine and/or withdrawal from the study.

6.3 MMR-159

MMR-159 assessed non-inferiority of immune response from Priorix compared to MMR-II when given as a second dose of MMR vaccine to healthy subjects 7 YOA and older (both adults and children were included).

6.3.1 Objectives

Primary Objective (Day 42)
Demonstrate non-inferiority of Priorix to MMR-II in terms of GMC ratio for anti-measles, anti-mumps and anti-rubella antibodies.

Secondary Immunogenicity Objectives (Day 42)

- Demonstrate non-inferiority of Priorix to MMR-II in terms of SRR for antibodies to MMR viruses
- Assess the percentage of subjects who achieve a minimum 4-fold rise in anti-measles, anti-mumps or anti-rubella virus antibody concentrations

6.3.2 Design Overview

This study was a Phase 3, observer-blind, randomized, controlled, multi-country study to demonstrate non-inferiority of Priorix (at release potency) compared to MMR-II and to assess the safety of Priorix, when both vaccines were given as a second dose of MMR vaccine to subjects ≥ 7 YOA who were previously primed with at least one dose of any MMR vaccine.

A total of 996 subjects were randomized in a 2:1:1 ratio to 3 parallel treatment groups (Priorix and two different lots of MMR-II, which were pooled for analysis). Of them, 911 subjects were included in the TVC including 586 subjects enrolled in the U.S.

The randomization algorithm used a minimization procedure accounting for center, country, gender and age. Minimization factors had equal weights in the algorithm. In addition, to ensure sufficient sample size for subgroup analyses, the enrollment was constrained to at least:

- 334 subjects <18 years of age with a target to enroll 28 of these subjects in the U.S.
- 334 subjects ≥ 18 years of age from the U.S.
- 334 females and 334 males

The antibody thresholds used to define sero-response were the same as those used in MMR-158.

6.3.3 Population

Persons (≥ 7 YOA) with either a history or formal documentation of at least one dose immunization with any MMR vaccine

6.3.4 Study Treatments or Agents Mandated by the Protocol

Treatment groups:

- INV_MMR: 500 subjects to receive one dose of the Priorix MMR vaccine
- COM_MMR_L1: 250 subjects to receive one dose of Lot 1 of the MMR-II vaccine
- COM_MMR_L2: 250 subjects to receive one dose of Lot 2 of the MMR-II vaccine

6.3.5 Sites and Centers

17 centers (10 in the U.S., 6 in Slovakia, and 1 in Estonia)

6.3.6 Endpoints and Criteria for Study Success

Primary Endpoint (Day 42)
Immunogenicity of the study vaccines in terms of antibody concentration (GMC)

- Criterion: The LL of the 2-sided 95% CI for the adjusted GMC ratios (Priorix over MMR-II) between groups is ≥ 0.67.

Secondary (Immunogenicity) Endpoints (Day 42)

- Non-inferiority in SRR across groups:
  - Criterion: The LL of the 2-sided standardized asymptotic 95% CI for the difference (INV_MMR minus MMRII) in SRRs to MMR viruses is ≥ -5%
- 4-fold or greater rise in anti-measles, anti-mumps, and anti-rubella virus antibody concentration

6.3.7 Statistical Considerations & Statistical Analysis Plan

The 2-sided CIs for the adjusted GMC ratios were calculated using an ANCOVA model on log-transformed concentrations/titers, with vaccine group and country as fixed effects and pre-vaccination log-transformed concentration/titer as a regressor. Gender and age stratum (< 18 years versus ≥ 18 years) were also included in the model. For analyses of sero-response, pre-vaccination concentrations were not taken into account.

6.3.8 Study Population and Disposition

6.3.8.1 Populations Enrolled/Analyzed

The TVC was defined in the same way as in study MMR-157. A total of 83 subjects were excluded from the TVC due to GCP violations observed at 2 U.S. study sites. No

additional subjects were enrolled to compensate for the loss of subjects. Sensitivity analyses of selected safety/immunogenicity endpoints for these two sites were conducted.

The ATP cohort for analysis of safety was defined in the same way as in study MMR-157, but included eligible subjects from the TVC who remained blinded to study treatment and who had not received a vaccine leading to exclusion from the ATP cohort in the protocol up to the post-vaccination blood sampling.

The ATP cohort for analysis of immunogenicity included eligible subjects from the ATP cohort for analysis of safety who had no protocol deviation and meet the following criteria:

- had post-vaccination serology results for at least one of the three vaccine components (measles, mumps or rubella)
- did not meet any elimination criteria up to the Visit 2 blood sample
- had no intercurrent medical conditions leading to elimination before the post-vaccination blood sample

6.3.8.1.1 Demographics

The mean age (SD) of the total population was 25.7 (13.8) years; 64.3% of subjects were from the U.S., 12.0% from Estonia, and 23.7% from Slovakia; 74.4% of subjects were of White – Caucasian/European ancestry; and 55.1% of subjects were female. Demographics were similar across study groups.

6.3.8.1.2 Subject Disposition

Of the 911 subjects in the TVC, 880 subjects (96.6%) completed the phase from Day 0 to Day 42; 28 subjects were withdrawn from the study. The principal reason for withdrawal in both treatment groups was lost to follow-up after receiving the study vaccination (3.5% versus 2.4%). A total of 24 subjects (11 + 13) were withdrawn between Day 42 and Day 180. The principal reason was also lost to follow-up after Day 42 (10 versus 11 subjects). See Table 34.

Table 34: Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (TVC)

Description of subjects	INV_MMR n	%	COM_MMR n	%	Total n	%
Subjects vaccinated	454	100%	457	100%	911	100
Subjects completed the last phone contact (end of study)	426	93.8%	433	94.7%	859	94.3
Subjects withdrawn by Visit 2 (Day 42) †	17	3.7%	11	2.4%	28	3.1
Reasons for withdrawal by Visit 2:	--	--	--	--	--	--
Lost to follow-up	16	3.5%	11	2.4%	27	3.0
Subject had previously enrolled in this study as subject (b) (6)	1	0.2%	0	0.0%	1	0.1
Subjects withdrawn by the last phone contact ‡	11	2.4%	13	2.8%	24	2.6
Reasons for withdrawal by last phone contact:	--	--	--	--	--	--
Consent withdrawal (not due to an adverse event)	1	0.2%	1	0.2%	2	0.2

Description of subjects	INV_MMR n	%	COM_MMR n	%	Total n	%
Lost to follow-up	10	2.2%	11	2.4%	21	2.3
Patient is now incarcerated	0	0.0%	1	0.2%	1	0.1
Subjects completed Visit 2 (Day 42)	435	95.8%	445	97.4%	880	96.6

† Subjects who were vaccinated but did not return for visit 2.
‡ Subjects who completed visit 2 but did not participate in the last phone contact (end of study).
Source: Table 14 in Clinical Study Report MMR-159

See Table 35 for disposition with respect to analysis cohorts.

Table 35: Summary of analysis cohorts and reasons for exclusion (Total enrolled cohort)

Description of subjects	Total	%	INV_MMR n	COM_MMR n	No Group n
Total cohort	996		497	497	2
Questionable subject	83		43	40	0
Study vaccine dose not administrated but subject enrolled	2		0	0	2
Total Vaccinated cohort	911	100	454	457	0
Protocol violation (inclusion/exclusion criteria)	6		3	3	0
ATP cohort for safety	905	99.3	451	454	0
Administration of any medication forbidden by the protocol	1		1	0	0
Non-compliance with blood sampling schedule (including wrong and unknown dates)	2		0	2	0
Essential serological data missing	33		17	16	0
ATP cohort for immunogenicity	869	95.4	433	436	0

% = percentage of subjects in the considered ATP cohort relative to the Total Vaccinated cohort
No Group = Enrolled subjects who were not randomized to a study group
Source: Table 15 in Clinical Study Report MMR-159

6.3.9 Immunogenicity Analyses

The analysis of immunogenicity was based on the ATP cohort for immunogenicity.

6.3.9.1 Analyses of Primary Endpoint(s)

To address the primary objective, the 2-sided 95% CI for the adjusted GMC ratio (INV_MMR divided by COM_MMR) was calculated using an ANCOVA model on log-transformed titer, including the minimization factors and log-transformed titer at pre-vaccination. The LLs of the CIs on the GMC ratios were >0.67 for anti-measles, anti-mumps, and anti-rubella antibodies (See Table 36).

Table 36: Non-inferiority of Priorix versus MMR-II in terms of SRR and GMC ratios for antibodies to MMR viruses at Day 42 (ATP cohort for immunogenicity)

	Priorix (N=433) SRR (%)	*MMR-II (N=436)* SRR (%)	Diff	95% LL (%)	95% UL (%)	*Priorix* Adjusted GMC	*MMR-II* Adjusted GMC	Ratio	95% LL	95% UL
Anti-measles	98.8%	99.1%	-0.24%	**-1.87**	1.32	1790.2	1781.5	1.00	**0.91**	1.11
Anti-mumps	98.4%	99.5%	-1.16%	**-2.90**	0.23	113.5	107.8	1.05	**0.96**	1.16
Anti-rubella	99.5%	99.8%	-0.23%	**-1.46**	0.86	76.1	74.6	1.02	**0.93**	1.11

N = Number of subjects with both pre and post-vaccination results available

Source: Adapted from Table 9 in m2.5 Clinical Overview

6.3.9.2 Analyses of Secondary Endpoints

To address the first secondary objective, the standardized asymptotic 95% CI was calculated for the group difference in SRRs. Results are provided in Table 36, above. The LLs of the CIs for the differences were > -5% for all three antibodies.

The percentages of subjects achieving a 4-fold or greater rise in antibody concentration at Day 42 by treatment group are given in Table 37.

Table 37: Percentage of subjects with a 4-fold or greater rise in anti-measles, anti-mumps and anti-rubella virus antibody concentrations at Day 42 (ATP cohort for immunogenicity)

Antibody	INV_MMR	%	95% CI LL	95% CI UL	COM_MMR	%	95% CI LL	95% CI UL
Anti-measles	N=432	9.7	7.1%	12.9%	N=435	11.0	8.2%	14.4%
Anti-mumps	N=432	35.2	30.7%	39.9%	N=435	29.4	25.2%	34.0%
Anti-rubella	N=432	41.4	36.7%	46.2%	N=435	37.0	32.5%	41.7%

For subjects with seronegative status at pre-vaccination, a 4-fold rise in antibody concentration is defined as 4 times the cut-off level of the assay.
95% CI = Two-sided 95% confidence interval using the Clopper Pearson method
Source: Adapted from Table 19 in Clinical Study Report MMR-159

6.3.9.3 Subpopulation Analyses

Subgroup analyses by age (< 18 years, >=18 years), gender, country, and pre-vaccination status were also provided. Analyses by country, age and gender are presented below. Despite some small numerical differences, results are generally consistent across subgroups.

In Table 38 are the adjusted GMC ratios between groups by country.

Table 38: Adjusted ratios of anti-measles, anti-mumps and anti-rubella GMCs at Day 42 between INV_MMR and COM_MMR by country subgroup (ATP cohort for immunogenicity)

Antibody	Country	INV_MMR	Adjusted GMC	95% CI LL	95% CI UL	COM_MMR	Adjusted GMC	95% CI LL	95% CI UL	Ratio	95% CI LL	95% CI UL
Anti-measles (mIU/mL)	United States	N=271	1809.3	1652.6	1981.0	N=271	1927.7	1760.7	2110.6	0.94	0.83	1.07
Anti-measles (mIU/mL)	Estonia	N=54	1441.7	1213.7	1712.6	N=55	1011.8	853.2	1200.0	1.42	1.12	1.82
Anti-measles (mIU/mL)	Slovakia	N=107	1922.7	1679.7	2200.8	N=109	1968.8	1722.2	2250.8	0.98	0.81	1.18
Anti-mumps (EU/mL)	United States	N=271	103.1	94.6	112.4	N=271	98.8	90.6	107.6	1.04	0.92	1.18
Anti-mumps (EU/mL)	Estonia	N=54	133.6	111.9	159.6	N=55	119.7	100.3	142.7	1.12	0.87	1.43
Anti-mumps (EU/mL)	Slovakia	N=107	133.8	116.9	153.2	N=109	126.5	110.7	144.7	1.06	0.87	1.28
Anti-rubella (IU/mL)	United States	N=271	78.6	72.5	85.2	N=271	79.5	73.3	86.1	0.99	0.88	1.11
Anti-rubella (IU/mL)	Estonia	N=54	68.2	58.2	80.0	N=55	55.2	47.1	64.6	1.24	0.99	1.55

Antibody	Country	INV_MMR	Adjusted GMC	95% CI LL	95% CI UL	COM_MMR	Adjusted GMC	95% CI LL	95% CI UL	Ratio	95% CI LL	95% CI UL
Anti-rubella (IU/mL)	Slovakia	N=107	74.1	65.8	83.5	N=109	74.4	66.1	83.7	1.00	0.84	1.18

Source: Adapted from Table 14.2.1.4 in Clinical Study Report MMR-159

***Reviewer comment**: Estonia appears to have higher adjusted GMC ratios than the other regions, with the GMC for INV_MMR higher than for MMR II for each antibody. The sample size in Estonia was much smaller than for the two other countries, however, with wider CIs of the individual GMCs.*

Subgroup analyses of the difference in SRRs across vaccine groups were also provided. Table 39 shows the differences in SRRs by age, and Table 40 shows the differences by gender. Results are similar across subgroups.

Table 39: Difference of anti-measles, anti-mumps and anti-rubella SRRs at Day 42 between INV_MMR and COM_MMR by age subgroup (ATP cohort for immunogenicity)

Antibody	Age	INV_MMR	SRR	COM_MMR	SRR	Difference	95% CI LL	95% CI UL
Anti-measles (≥200 mIU/mL)	<18	N=162	98.1%	N=165	98.8%	-0.64%	-4.24%	2.68%
Anti-measles (≥200 mIU/mL)	≥18	N=271	99.3%	N=271	99.3%	0.00%	-1.99%	1.99%
Anti-mumps (≥10 EU/mL)	<18	N=162	98.8%	N=165	99.4%	-0.63%	-3.85%	2.23%
Anti-mumps (≥10 EU/mL)	≥18	N=271	98.2%	N=271	99.6%	-1.48%	-3.92%	0.40%
Anti-rubella (≥10 IU/mL)	<18	N=162	98.8%	N=165	99.4%	-0.63%	-3.85%	2.23%
Anti-rubella (≥10 IU/mL)	≥18	N=271	100%	N=271	100%	0.00%	-1.40%	1.40%

Source: Adapted from Table 14.2.2.2 in Clinical Study Report MMR-159

Table 40: Difference of anti-measles, anti-mumps and anti-rubella SRRs at Day 42 between INV_MMR and COM_MMR by gender subgroup (ATP cohort for immunogenicity)

Antibody	Sex	INV_MMR	SRR	COM_MMR	SRR	Difference	95% CI LL	95% CI UL
Anti-measles (≥200 mIU/mL)	Male	N=189	98.4%	N=192	99.5%	-1.07%	-4.11%	1.45
Anti-measles (≥200 mIU/mL)	Female	N=244	99.2%	N=244	98.8%	0.41%	-1.85%	2.83
Anti-mumps (≥10 EU/mL)	Male	N=189	99.5%	N=192	100%	-0.53%	-2.94%	1.44%
Anti-mumps (≥10 EU/mL)	Female	N=244	97.5%	N=244	99.2%	-1.64%	-4.54%	0.77%
Anti-rubella (≥10 IU/mL)	Male	N=189	99.5%	N=192	99.5%	-0.01%	-2.46%	2.41%
Anti-rubella (≥10 IU/mL)	Female	N=244	99.6%	N=244	100%	-0.41%	-2.29%	1.15%

Source: Adapted from Table 14.2.2.3 in Clinical Study Report MMR-159

6.3.9.4 Dropouts and/or Discontinuations

Results from the sensitivity analyses of primary and secondary endpoints for the 83 subjects from sites 102914 and 102915 who were excluded from the main analyses were compared to primary analyses using the ATP cohort for immunogenicity in terms of adjusted GMC ratios and SRRs (see Table 41 and Table 42).

The applicant noted that compared with the ATP cohort, a higher percentage of subjects from sites 102914 and 102915 had a minimum 4-fold rise in anti-measles virus antibody concentrations, while a lower percentage had a minimum 4-fold rise in anti-mumps and anti-rubella virus antibody concentrations (see Table 43).

Table 41: Adjusted ratios of anti-measles, anti-mumps and anti-rubella GMCs at Day 42 between INV_MMR and COM_MMR (Vaccinated subjects in sites 102914 and 102915)

Antibody	INV_MMR	Adj GMC	LL	UL	COM_MMR	Adj GMC	LL	UL	Ratio	LL	UL
Anti-measles (mIU/mL)	N=43	1194.3	835.1	1708.1	N=40	1232.5	850.4	1786.2	0.97	0.58	1.63
Anti-mumps (EU/mL)	N=43	111.7	90.4	138.1	N=38	107.9	86.1	135.3	1.04	0.76	1.41
Anti-rubella (IU/mL)	N=43	48.7	37.6	62.9	N=40	43.5	33.3	56.7	1.12	0.77	1.62

Source: Table 14.2.1.1.2 in Clinical Study Report MMR-159

Table 42: Difference of anti-measles, anti-mumps and anti-rubella SRRs at Day 42 between INV_MMR and COM_MMR (Vaccinated subjects in sites 102914 and 102915)

Antibody	INV_MMR	%	COM_MMR	%	Difference	95% CI LL	95% CI UL
Anti-measles (≥200 mIU/mL)	N=43	95.3	N=40	97.5	-2.15%	-13.41%	8.86%
Anti-mumps (≥10 EU/mL)	N=43	100.0	N=40	100.0	0.00%	-8.29%	8.86%
Anti-rubella (≥10 IU/mL)	N=43	97.7	N=40	92.5	5.17%	-5.60%	17.98%

N = number of subjects with available results
95% CI = Two-sided 95% confidence interval using the Miettinen & Nurminen method
Source: Adapted from Table 14.2.2.1.2 in Clinical Study Report MMR-159

Table 43: Number and percentage of subjects who achieved a 4-fold or greater rise in anti-measles, anti-mumps and anti-rubella virus antibody concentrations at Day 42 (Vaccinated subjects in sites 102914 and 102915

Antibody	INV_MMR	%	95% LL	95% UL	COM_MMR	%	95% LL	95% UL
Anti-measles	N=43	20.9	10.0%	36.0%	N=40	22.5	10.8%	38.5%
Anti-mumps	N=43	18.6	8.4%	33.4%	N=38	18.4	7.7%	34.3%
Anti-rubella	N=43	14.0	5.3%	27.9%	N=40	15.0	5.7%	29.8%

Source: Adapted from Table 14.2.9.1.2 in Clinical Study Report MMR-159

***Reviewer comment**: As alluded to by the applicant, the percentages of subjects who achieved a 4-fold or greater rise in the two excluded sites are more consistent across antibodies than they are for the ATP cohort. In particular, the percentage in the anti-measles antibody category is much higher in the excluded sites, roughly double that in the ATP cohort for both treatment groups (despite the GMCs being lower than in the ATP cohort and in the other U.S. sites, as shown in Table 38). However, the excluded sites show similar treatment differences and ratios to what the ATP cohort shows.*

6.3.9.5 Exploratory and Post Hoc Analyses

The confirmatory objectives were re-analyzed accounting for the randomization process. The p-value of each confirmatory objective was recomputed accounting for the 3 minimization factors in the study (age group, country, gender). A total of 5000 rerandomizations were performed to compute the p-value as the proportion of rerandomizations leading to a re-estimated value greater than the observed one. All p-values were below the one-sided nominal significance level.

6.3.10 Safety Analyses

The analysis set for safety was the TVC.

6.3.10.1 Overall Incidence of AEs

During the 43-day follow-up period, at least one adverse event (solicited or unsolicited) was reported in 35.7% of subjects in the INV_MMR group and in 33.9% of subjects in the COM_MMR group (See Table 44).

Table 44: Incidence of symptoms (solicited and unsolicited) reported during the 43-day (Days 0-42) post-vaccination period (TVC)

Group	N	Any Symptoms	LL	UL	General Symptoms	LL	UL	Local Symptoms	LL	UL
INV_MMR	454	35.7%	31.3%	40.3%	22.7%	18.9%	26.8%	18.7%	15.2%	22.6%
COM_MMR	457	33.9%	29.6%	38.5%	21.2%	17.6%	25.3%	19.5%	15.9%	23.4%

N = number of subjects with the administered dose.
% = percentage of subjects presenting at least one type of symptom whatever the study vaccine administered.
Source: Table 14.3.1.3.1 in Clinical Study Report MMR-159

Incidence rates of local solicited AEs such as injection site pain, redness and swelling during the four-day post-vaccination period (Day 0 to Day 3) were largely similar across groups.

During the 43-day post-vaccination period, the observed incidence of any fever was reported by 3.0% of INV_MMR subjects and by 5.2% of COM_MMR subjects (out of 431 and 445 subjects, respectively, with the general symptoms sheets completed). Grade 3 fever (temperature > 39.5°C) occurred in one subject (0.2%) in the INV_MMR group and six subjects (1.3%) in the COM_MMR group.

Joint pain was reported by eight (1.9%) subjects in the INV_MMR group and by four (0.9%) subjects in the COM_MMR group. No subject reported Grade 3 joint pain.

Rash or exanthem was reported by 2.1% of subjects in the INV_MMR group (8 out of 9 were localized rashes) and 1.1% of subjects in the COM_MMR group (3 of 5 were localized). No subject reported Grade 3 rash.

Signs of meningism/seizure were reported by one subject in each of the two groups. The one reported in the INV_MMR group was considered grade 3.

At least one unsolicited symptom was reported by 20.9% (95/454) and 17.9% (82/457) of TVC subjects in the INV_MMR and COM_MMR groups, respectively. A 95% asymptotic CI on the groups difference is (-2.3%, 8.4%).

6.3.10.3 Deaths

No deaths were reported in this study.

6.3.10.4 Nonfatal Serious Adverse Events

One or more SAEs from Day 0 until Day 180 were reported by 10 subjects: three (0.7%) subjects in the INV_MMR group and seven (1.5%) in the COM_MMR group. The SAEs

were considered unrelated to the study vaccine by the investigators. See the clinical reviewers' memos for more details.

6.3.10.5 Adverse Events of Special Interest (AESI)

Table 45 provides the percentage of subjects in each group who reported at least one AE related to a NOCD, at least one AE prompting an ER visit, and at least one AE leading to a medically attended visit, from Day 0 to Day 180.

Table 45: Percentage of subjects reporting AESIs from Day 0 to Day 180

Adverse Event	Inv_MMR (N=454)	Com_MMR (N=457)
At least one AE related to a NOCD	0.44%	0.22%
At least one AE prompting an ER visit	3.1%	2.0%
At least one AE leading to a medically attended visit	13.2%	12.5%

Source: Reviewer-created table

Reviewer comment*: The rates are slightly higher in the Priorix group. However, clinical reviewers have determined the rates to be acceptable.*

6.3.10.6 Dropouts and/or Discontinuations

No AEs leading to premature discontinuation of study vaccine and/or study were reported.

6.4 MMR-162

This study evaluated the safety of the Inv_MMR vaccine at maximum release potency compared to the U.S. standard of care (MMR II/ MMR VaxPro vaccine). The study also evaluated the immune response of Inv_MMR versus the standard of care vaccine (Com_MMR) when co-administered with Varivax (VV), Havrix (HAV) and Prevnar 13 (PCV-13, only in U.S. subjects).

6.4.1 Objectives

Primary Objectives

- Demonstrate the safety profile (fever > 39.0°C) of Inv_MMR compared to Com_MMR (pooled lots) when co-administered with VV and HAV (to all subjects) and PCV-13 (only to subjects enrolled in the U.S.)
- Demonstrate the safety profile (fever ≥ 38.0°C) of Inv_MMR compared to Com_MMR (pooled lots) when co-administered with VV and HAV (to all subjects) and PCV-13 (subjects enrolled in the U.S.)

Secondary Immunogenicity Objectives

- Assess immunogenicity of Inv_MMR and Com_MMR in terms of sero-response and GMCs for anti-measles, anti-mumps and anti-rubella virus antibodies at Day 42

6.4.2 Design Overview

This was a Phase IIIA, observer-blind, randomized, controlled, multicenter, multi-country, study with three parallel groups. A total of 1734 healthy subjects 12 to 15 months old were randomized in a 4:1:1 ratio to receive either one dose of Inv_MMR (1156 subjects), or one dose of either Com_MMR_L1 (289 subjects) or Com_MMR_L2 (289 subjects). The vaccines HAV, VV and PCV-13 were co-administered with the Inv_MMR or Com_MMR vaccine. Overall, the randomization ratio was 2:1 for Inv_MMR versus Com_MMR.

The randomization algorithm used a minimization procedure accounting for center and country. Minimization factors had equal weights in the algorithm.

Antibody thresholds for defining sero-response were the same as for study MMR-157.

Temperature was to be recorded daily, from Day 0 through Day 42. Parent(s) or legal guardian(s) were requested to record on the diary card the subject's body temperature measured each evening at bedtime.

6.4.3 Population

Healthy children 12-15 months of age. For U.S. study centers, subjects needed to have received all routine vaccinations.

6.4.4 Study Treatments or Agents Mandated by the Protocol

- INV_MMR: subjects received one dose of Priorix at maximum release potency
- MMRII_1: subjects received one dose of MMR-II Lot 1 (Com_MMR_L1)
- MMRII_2: subjects received one dose of MMR-II Lot 2 (Com_MMR_L2)

Com_MMR_L1 and Com_MMR_L2 were pooled for analyses.

A single vaccination, with either Inv_MMR or Com_MMR was to be administered at Visit 1, along with the appropriate co-administered vaccines.

6.4.5 Sites and Centers

104 centers (91 in the U.S., 6 each in Finland and Taiwan, and 1 in Estonia)

6.4.6 Surveillance/Monitoring

Because the viral potencies of the MMR lot to define maximum release limits were higher than a typically released lot, safety monitoring was performed by an IDMC external to the applicant.

6.4.7 Endpoints and Criteria for Study Success

Primary Endpoints
- Occurrence of fever > 39.0°C from Day 5 through Day 12 after vaccination

Criterion: The rates of fever > 39.0°C were considered comparable across groups if the UL of the 2-sided 95% CI for the group difference (Inv_MMR - Com_MMR) in incidence was ≤ 5%.

- Occurrence of fever ≥ 38.0°C from Day 5 through Day 12 after vaccination
  Criterion: The rates of fever ≥ 38.0°C were considered comparable across groups if the UL of the 2-sided 95% CI for the group difference (Inv_MMR - Com_MMR) in incidence was ≤ 10%.

Secondary Immunogenicity Endpoints
- Immunogenicity of the MMR vaccines at Day 42 in terms of sero-response and antibody concentrations.

6.4.8 Statistical Considerations & Statistical Analysis Plan

To control the type I error rate below 2.5%, a hierarchical procedure was used for the primary objectives. The objective on fever ≥ 38.0°C could only be tested if the first primary objective on fever > 39.0°C was met.

No statistical modeling was done for the immunogenicity analyses.

6.4.9 Study Population and Disposition

6.4.9.1 Populations Enrolled/Analyzed

The TVC was the same as for study MMR-157.

The ATP cohort for analysis of safety was the same as for study MMR-157, but excluded subjects who received a vaccine leading to exclusion from the ATP cohort up to Visit 2.

The ATP cohort for analysis of immunogenicity included all eligible subjects from the ATP cohort for safety:
- with pre-vaccination and post-vaccination serology results available for at least one antigen of measles, mumps, or rubella
- who were below the assay cut-off for at least one antigen for MMR at pre-vaccination
- who did not meet any elimination criteria up to the Visit 2 blood draw
- who complied with the post-vaccination blood sample schedule

The total number of subjects included in each cohort and the deviations leading to elimination are shown in Table 46. Of the 1742 enrolled subjects, 1736 received a study vaccination (1164 subjects in Inv_MMR and 572 subjects in Com_MMR). A total of 1659 subjects (1117 in Inv_MMR, and 542 in Com_MMR) completed the study until Visit 3 (day 180). A total of 1707 subjects (98.3%) were included in the ATP cohort for safety, and 1568 subjects (90.3%) were included in the ATP cohort for immunogenicity.

Table 46: Number of subjects enrolled into the study and number excluded from ATP analyses with reasons for exclusion

Cohort / Reason for Exclusion	Total n	%	INV_MMR n	COM_MMR n	No Group n
Total cohort	1742		1165	575	2
Study vaccine dose not administrated but subject number allocated	6		1	3	2
Total Vaccinated cohort	1736	100	1164	572	0
Administration of vaccine(s) forbidden in the protocol	8		5	3	0
Randomization code broken at the investigator site	1		1	0	0
Study vaccine dose not administered according to protocol	4		4	0	0
Others including violation of inclusion/exclusion criteria	16		12	4	0
ATP cohort for safety	1707	98.3	1142	565	0
Initially seropositive or initially unknown antibody status	53		38	15	0
Administration of any medication forbidden by the protocol	2		0	2	0
Non-compliance with blood sampling schedule	10		6	4	0
Essential serological data missing	74		53	21	0
ATP cohort for immunogenicity	1568	90.3	1045	523	0

No Group = No assigned group
% = percentage of subjects in the considered ATP cohort relative to the Total vaccinated cohort
Source: Adapted from Table 18 in Clinical Study Report MMR-162

6.4.9.1.1 Demographics

Demographic and other baseline characteristics of the TVC were similar across treatment groups. The mean age of subjects included in the TVC was 12.3 months in both study groups at the time of the first study vaccination (i.e., at enrollment). Overall, 1193 subjects (68.7%) were White/Caucasian with a male: female ratio of 1.0:0.9 (52.7% vs 47.3%). In the TVC, 62.8% of subjects were from the U.S.

6.4.10 Safety Analyses

The primary objective of the study was to demonstrate the safety profile in terms of fever >39.0°C and ≥38.0°C within 5 to 12 days post-vaccination in subjects receiving the Inv_MMR vaccine as compared to Com_MMR, when co-administered with VV, HAV and PCV-13.

6.4.10.1 Analysis of Primary Endpoint

The TVC for safety included 1164 Priorix subjects and 572 MMR II subjects (Table 46). Table 47 shows compliance with respect to local and general solicited AEs.

Table 47: Compliance in returning symptom information (TVC)

Group	Number of doses	Doses not according to protocol	Number of general SS	Compliance % general SS	Number of local SS	Compliance % local SS
INV_MMR	1164	15	1126	96.7	1123	96.5
COM_MMR	572	3	555	97.0	553	96.7

SS = Symptom screens/sheets used for the collection of local and general solicited AEs

Compliance % = (number of doses with symptom screen/sheet return / number of administered doses) X 100

Source: Table 7.1 in Clinical Study Report MMR-162

The percentages of subjects reporting fever from Day 5 to Day 12 following vaccination, as well as the difference between the 2 groups are given in Table 48.

Incidences of fever >39.0°C were reported in 4.2% of subjects in Inv_MMR and 3.1% of subjects in Com_MMR, with a difference between groups of 1.11% (95% CI: -0.93%, 2.89%). The UL of the 2-sided 95% CI for the difference between groups was ≤ 5%.

The percentages of subjects reporting fever >39.0°C considered related to the study vaccination were 3.2% in Inv_MMR and 2.2% in Com_MMR, with the 95% CI of the difference being (-0.75, 2.57%).

Incidences of fever ≥38.0°C were reported in 18.2% of subjects in Inv_MMR and in 17.1% of subjects in Com_MMR, with a difference between groups of 1.09% (95%CI: -2.89%, 4.85%). The UL of the 2-sided 95% CI for the difference was ≤ 10%.

The percentages of subjects reporting fever ≥38.0°C considered related to the study vaccination were 14.1% in Inv_MMR and 12.8% in Com_MMR, with the 95% CI of the difference being (-2.26%, 4.66%).

Table 48: Difference between groups (INV_MMR minus COM_MMR) in percentage of subjects reporting a fever during the Day 5 to Day 12 post vaccination period (TVC)

Temperature	INV_MMR (N=1126)	COM_MMR (N=555)	Diff	95% LL(%)	95% UL(%)
All	22.2%	22.2%	0.04%	-4.28	4.17
≥38	18.2%	17.1%	1.09%	-2.89	4.85
>38.5	9.6%	7.9%	1.66%	-1.33	4.39
>39.0	4.2%	3.1%	1.11%	-0.93	2.89
>39.5	1.5%	1.3%	0.25%	-1.18	1.37
>40.0	0.1%	0.7%	-0.63%	-1.76	-0.08
≥38 Related	14.1%	12.8%	1.33%	-2.26	4.66
>38.5 Related	6.9%	5.6%	1.34%	-1.25	3.66
>39.0 Related	3.2%	2.2%	1.03%	-0.75	2.57
>39.5 Related	1.2%	1.1%	0.16%	-1.18	1.19
>40.0 Related	0.1%	0.5%	-0.45%	-1.49	0.05
Medical advice	6.2%	4.0%	2.25%	-0.07	4.33

N = Number of subjects with the documented dose

n/% = number/percentage of subjects reporting a specified symptom.

Co-primary objectives: UL of 95% CI is equal to or below 5% for Fever >39C and equal to or below 10% for Fever ≥38.0°C.

Note: The 'All' category also includes any subject with one or more missing daily temperature recordings within the considered period (Days 5 to 12) but having one or more days recorded with fever within the Day 0 to 42 reporting period.

Source: Table 22 in Clinical Study Report MMR-162

6.4.10.2 Subpopulation Analyses

Safety analyses were repeated by country, gender and geographic ancestry. The overall results were generally similar across subgroups. Please see the clinical reviewers' memos for details.

6.4.11 Immunogenicity Analyses

The analysis of immunogenicity was performed on the ATP cohort for immunogenicity.

6.4.11.1 Analyses of Secondary Immunogenicity Endpoint(s)

Each immunogenicity analysis included only subjects who were seronegative based on the specific immunogenicity assay prior to first vaccination. The majority of subjects in both groups (>95%) were seronegative at baseline prior to vaccination, against anti-measles, anti-mumps and anti-rubella antibodies.

Anti-measles antibody response

The GMCs of anti-measles antibodies and percentages of subjects with concentrations equal to or above thresholds of 150 and 200 mIU/ml at Day 42 in initially seronegative subjects are given in Table 49.

Table 49: Percentage of subjects with an Anti-Measles antibody concentration ≥ 150 and 200 mIU/mL and GMCs (ATP cohort for immunogenicity)

Group	Timing	N	≥ 150 mIU/mL	LL	UL	≥ 200 mIU/mL	LL	UL	GMC	LL	UL
INV_MMR	PI(D42)	1043	99.3%	98.6%	99.7%	99.0%	98.2%	99.5%	2751.9	2618.3	2892.2
COM_MMR	PI(D42)	521	96.7%	94.8%	98.1%	96.5%	94.6%	97.9%	3133.3	2878.6	3410.6

N = number of subjects with available results
LL = 95% confidence interval Lower Limit, UL = Upper Limit 95% confidence interval
PI(D42) = Post-vaccination blood sample at Day 42
Source: Adapted from Table 34 in Clinical Study Report MMR-162

Anti-mumps antibody response

Percentages of subjects with anti-mumps concentrations equal to or above the threshold of 5 and 10 EU/mL and GMCs in initially seronegative subjects at Day 42 are presented in Table 50.

Table 50: Percentage of subjects with an Anti-Mumps (PPD) antibody concentration ≥ 5 and 10 ELU/ML and GMCs (ATP cohort for immunogenicity)

Group	Timing	N	≥ 5 EU/mL	LL	UL	≥ 10 mIU/mL	LL	UL	GMC	LL	UL
INV_MMR	PI(D42)	964	99.8%	99.3%	100%	99.4%	98.7%	99.8%	86.0	82.0	90.3
COM_MMR	PI(D42)	483	99.4%	98.2%	99.9%	97.9%	96.2%	99.0%	82.6	76.5	89.2

N = number of subjects with available results
LL = 95% confidence interval Lower Limit, UL = Upper Limit 95% confidence interval
PI(D42) = Post-vaccination blood sample at Day 42
Source: Adapted from Table 35 in Clinical Study Report MMR-162

Anti-rubella antibody response

Percentages of subjects with anti-rubella concentrations equal to or above the thresholds of 4 and 10 IU/ml and GMCs in initially seronegative subjects are given in Table 51. Although responses against rubella were lower in Inv_MMR group, the applicant did not

consider this to be clinically relevant as 95.7% of INV_MMR subjects had concentrations above the pre-defined sero-response threshold of 10 IU/mL.

Table 51: Percentage of subjects with an Anti-Rubella antibody concentration ≥ 4 and 10 IU/mL and GMCs (ATP cohort for immunogenicity)

Group	Timing	N	≥ 4 EU/mL	LL	UL	≥ 10 mIU/mL	LL	UL	GMC	LL	UL
INV_MMR	PI(D42)	1043	99.6%	99.0%	99.9%	95.7%	94.3%	96.8%	45.0	42.8	47.2
COM_MMR	PI(D42)	521	99.8%	98.9%	100%	98.3%	96.7%	99.2%	66.8	62.3	71.7

N = number of subjects with available results
LL = 95% confidence interval Lower Limit, UL = Upper Limit 95% confidence interval
PI(D42) = Post-vaccination blood sample at Day 42
Source: Adapted from Table 36 in Clinical Study Report MMR-162

***Reviewer comment**: The anti-rubella GMC is lower for INV_MMR vs. COM_MMR. However, the confidence intervals are both well above 10 IU/mL. As the cutoff threshold increases, the difference between COM_MMR and INV_MMR increases, as seen in Table 52. below. The difference between groups in percentage above 64 IU/mL rises to 20.7% (57.0% – 36.3%). A similar pattern holds across country, gender, and geographic ancestry subgroups. I defer to clinical reviewers as to the clinical interpretation of the observed differences as concentration increases.*

Table 52: Distribution of Anti-Rubella antibody concentrations (ATP cohort for immunogenicity)

Group	N	≥ 4 IU/mL	≥8 IU/mL	≥ 10 mIU/mL	≥16 IU/mL	≥32 IU/mL	≥64 IU/mL
INV_MMR	1043	99.6%	98.0	95.7%	89.9%	70.4%	36.3%
COM_MMR	521	99.8%	98.8	98.3%	94.2%	84.1%	57.0%

Source: Adapted from Table 8.4 in Clinical Study Report MMR-162

6.4.11.2 Subpopulation Analyses

The analyses of immunogenicity were also repeated for subjects in each country, by gender and by geographic ancestry. See the clinical reviewer's memo for details.

6.4.11.4 Dropouts and/or Discontinuations

See Section 6.4.9.1 Populations Enrolled/Analyzed for discontinuations.

6.4.11.5 Exploratory and Post Hoc Analyses

The confirmatory objectives were re-analyzed accounting for the randomization process. The p-value for each confirmatory objective was recomputed accounting for the two minimization factors in the study (country and center). A total of 5000 rerandomizations were performed to compute the p-value as the proportion of rerandomizations leading to a re-estimated value greater than the observed one. All p-values are below the one-sided nominal significance level.

6.4.12 Additional Safety Results

Of the number of subjects who returned solicited symptoms forms (Table 47), the most frequently reported solicited local symptoms within four days of vaccination were pain

(27.8% and 23.7%) and redness (23.2% and 24.8%), in groups Inv_MMR and Com_MMR, respectively. Within the 15-day period post-vaccination, the most frequently reported general symptoms were irritability or fussiness, seen in 64.1% of subjects in Inv_MMR and 62.2% in Com_MMR, drowsiness (46.8% and 42.9%) and loss of appetite (43.8% and 41.8%).

6.4.12.1 Deaths

No deaths were reported in this study.

6.4.12.2 Nonfatal Serious Adverse Events

In Inv_MMR, 39 SAEs were reported by 24 subjects (2.1%) while 12 SAEs were reported by 9 subjects (1.6%) in Com_MMR. Other than pneumonia (4 subjects in Inv_MMR and 1 subject in COM_MMR group), dehydration (3 subjects in Inv_MMR and 0 in Com_MMR) and bronchitis (1 subject in INV_MMR group and 2 subjects in Com_MMR group), all SAEs were reported by only a single subject.

Overall, 51.4% of subjects in Inv_MMR and 48.4% in Com_MMR reported any unsolicited AE, with 4.6% and 3.8% reporting grade 3 unsolicited AEs, respectively (Table 53).

Table 53: Percent of subjects reporting unsolicited adverse events during the 43-day (Days 0-42) post-vaccination period (TVC)

Adverse Event	INV_MMR (N = 1164)	COM_MMR (N = 572)
Unsolicited AEs	51.4%	48.4%
Grade 3 Unsolicited AEs	4.6%	3.8%

Source: Reviewer-created table

6.4.12.3 Adverse Events of Special Interest (AESI)

Table 54 gives the percentage of subjects reporting at least one AESI, by study group, from Day 0 to the end of the study.

Table 54: Percentage of subjects reporting AESIs from Day 0 to Day 180 (TVC)

Adverse Event	Inv_MMR (n=1154)	Com_MMR (n=572)	Asymptotic 95% CI on group difference
At least one AE related to a NOCD	2.5%	1.9%	(-1.0%, 2.2%)
At least one AE prompting an ER visit	14.3%	9.6%	(1.4%, 9.6%)
At least one AE leading to a medically attended visit	61.7%	55.6%	(1.0%, 11.2%)

Source: Reviewer-created table

***Reviewer comment**: There are slightly more AEs and AESIs reported in the Priorix group. For the AESIs, asymptotic 95% CIs on the group differences were computed. Clinical reviewers have determined that the safety profile of Priorix is acceptable.*

6.4.12.4 Dropouts and/or Discontinuations

No subjects were withdrawn due to an AE or an SAE.

6.5 MMR-160

MMR-160 assessed consistency of immune response to three lots of Priorix. In addition, the study assessed non-inferiority of immunogenicity of Priorix compared to MMR-II, when given as a first dose and co-administered with VV, HAV and PCV-13 (administered in U.S. subjects only) in healthy children 12-15 months old.

6.5.1 Objectives

Primary Objectives (Day 42)

1. Demonstrate consistency of 3 manufacturing lots of Priorix in terms of SRR for antibodies to MMR viruses
2. Demonstrate consistency of 3 manufacturing lots of Priorix in terms of GMC for antibodies to MMR viruses
3. Demonstrate non-inferiority of Priorix (for the 3 pooled lots) compared to MMR-II (for the 2 pooled lots) in terms of SRR for antibodies to MMR viruses
4. Demonstrate non-inferiority of Priorix (for the 3 pooled lots) compared to MMR-II (for the 2 pooled lots) in terms of GMC for antibodies to MMR viruses
5. Demonstrate an acceptable immune response for Priorix in terms of SRR for antibodies to MMR viruses

Confirmatory Secondary Objectives (Day 42)

1. Demonstrate non-inferiority of the pooled Priorix groups compared to the pooled MMR-II groups in terms of SRR and GMC for antibodies to VZV in a subset comprising the first 2500 children enrolled in the U.S.
2. Demonstrate non-inferiority of the pooled Priorix groups compared to the pooled MMR-II groups in terms of GMC for antibodies to hepatitis A virus in a subset of the first 1250 children enrolled in the U.S. – subset A
3. Demonstrate non-inferiority of the pooled Priorix groups compared to the pooled MMR-II groups in terms of GMC for antibodies to S. pneumoniae (PS) (13 serotypes) in a subset comprising the second set of 1250 children enrolled in the U.S. – subset B

6.5.2 Design Overview

This study was a Phase 3, observer-blind, randomized, controlled, multi-country study to evaluate the clinical consistency in terms of immunogenicity and safety of 3 manufacturing lots of Priorix (at release potency) and the non-inferiority of Priorix compared to MMR-II when both vaccines were co-administered with VV, HAV and PCV-13 (U.S. subset only) to subjects 12-15 months old.

A total of 5,016 subjects were enrolled and randomized in a 2:2:2:1:1 ratio to one of the 5 study groups (3 different lots of Priorix and 2 lots of MMR-II), and 5,003 subjects were vaccinated and included in the TVC, of whom 2,502 subjects were enrolled in the U.S. Overall, the randomization was 3:1 for Inv_MMR versus Com_MMR.

The randomization algorithm used a minimization procedure accounting for center and country. Minimization factors had equal weights in the algorithm.

The study was double-blind with respect to lot. The study was observer-blind for the comparison of Priorix to MMR-II because of the difference in presentation of the investigational Priorix vaccine and the commercial MMR-II vaccine.

The same antibody thresholds for sero-response with respect to MMR used for study MMR-157 were used in MMR-160. In addition, for PCV-13, antibody concentrations to the 13 *S. pneumoniae* serotypes above pre-defined (b) (4) assay cut-offs indicated sero-response.

6.5.3 Population

Healthy children 12-15 months old, with all routine vaccinations (U.S. only).

6.5.4 Study Treatments or Agents Mandated by the Protocol

Five parallel groups:

- INV_MMR_1: subjects receiving one dose of Priorix Lot 1
- INV_MMR_2: subjects receiving one dose of Priorix Lot 2
- INV_MMR_3: subjects receiving one dose of Priorix Lot 3
- Com_MMR_L1: subjects receiving one dose of MMR-II Lot 1
- Com_MMR_L2: subjects receiving one dose of MMR-II Lot 2

Pooled results for the Com_MMR lots are presented.

All subjects received VV and HAV vaccines concomitantly with an MMR vaccine at 12 to 15 months of age. PCV-13 was co-administered only to U.S. subjects.

6.5.5 Sites and Centers

92 centers (64 in the U.S., 11 in Finland, 9 in Spain, 6 in Estonia, and 2 in Mexico)

6.5.6 Endpoints and Criteria for Study Success

Primary Endpoints

The success criteria to demonstrate consistency of the 3 lots in terms of antibodies to MMR viruses were as follows:

- For each pair-wise lot comparison, the 2-sided 95% CI on the lot difference in SRRs had to be within [-5%; 5%].
- For each pair-wise lot comparison, the 2-sided 95% CI on the GMC lot ratio had to be within [0.67; 1.5]

Non-inferiority criteria for comparing Priorix to MMR-II were

- The LL of the 2-sided 95% CI of the group difference (pooled INV_MMR minus pooled MMRII) in SRR had to be ≥ -5% for antibodies to MMR viruses.
- The LL of the 2-sided 95% CI on GMC ratio (pooled INV_MMR over pooled MMR-II) had to be ≥ 0.67 for antibodies to MMR viruses.

Acceptable immune response was defined as

- The LL of the 2-sided 95% CI for the SRR for the pooled INV_MMR lots is ≥90% for antibodies to MMR viruses.

Secondary Endpoints

The success criteria to demonstrate non-inferiority in terms of immune response to the co-administered VV, HAV and PCV-13 vaccine antigens were as follows:

- LL of the 2-sided 95% CI for difference in SRRs (Priorix minus MMR-II) to anti-VZV antibodies had to be ≥-10%.
- LL of the 2-sided 95% CI for the GMC ratios (Priorix over MMR-II) for anti-VZV antibodies had to be ≥0.67.
- LL of the 2-sided 95% CI for the GMC ratios (Priorix over MMR-II) for anti-hepatitis A antibodies had to be ≥ 0.5.
- LL of the 2-sided 95% CI for the adjusted GMC ratios (Priorix over MMR-II) for antibodies to the 13 S. pneumoniae serotypes had to be ≥ 0.5.

6.5.7 Statistical Considerations & Statistical Analysis Plan

To control familywise type I error rate, the between group comparisons for consistency and non-inferiority were based on a 2.5% nominal type I error rate. A hierarchical procedure was used for primary and secondary objectives. Each co-primary objective could only be tested if all previous co-primary objectives were reached. The confirmatory secondary immunogenicity objectives were only assessed when all co-primary objectives were met. No hierarchy among secondary endpoints was made.

Reviewer comment*: If there was no hierarchy to the three confirmatory secondary endpoints (with criteria pre-specified), then the overall type I error rate for confirmatory secondary endpoints may not be controlled at the 2.5% nominal level.*

6.5.8 Study Population and Disposition

6.5.8.1 Populations Enrolled/Analyzed

The TVC cohort was the same as that defined in study MMR-157. The ATP cohort for analysis of safety was the same as that defined in study MMR-157.

The ATP cohort for analysis of immunogenicity included all eligible subjects from the ATP cohort for safety:

- with pre-vaccination and post-dose serology results available for at least one antigen of measles, mumps, or rubella
- who were below the assay cut-off for at least one vaccine antigen for MMR at pre-vaccination
- who did not meet any elimination criteria up to the Visit 2 (Day 42) blood sample
- who complied with the post-vaccination blood sample schedule

6.5.8.1.1 Demographics

Overall, the mean age (± SD) of subjects in the TVC was 12.3 months ±0.7 months; the cohort was 75.6% White/Caucasian and 51.3% male. The mean age of subjects in the ATP cohort for immunogenicity was 12.3 months ±0.7 months, and the cohort was 76.6% White/Caucasian and 51.5% male. Demographics were similar across study groups.

6.5.8.1.2 Subject Disposition

A total of 5,003 subjects were enrolled and vaccinated, of whom 1,239 were in the INV_MMR_1 group, 1,232 in the INV_MMR_2 group, 1,243 in the INV_MMR_3 group and 1,289 in the MMR-II control group (Table 55, below). Of these, 94.8%, 94.3%, 95.7%, and 95.6% of subjects in the respective groups completed the study. The most common reasons for withdrawal were loss to follow-up with complete vaccination course (26, 38, 31, and 38 subjects across respective groups) and consent withdrawal (21, 23, and 14 subjects in the Inv_MMR groups versus 10 subjects in the Com_MMR group). See Table 55 for reasons for exclusion from analysis cohorts.

Table 55: Number of subjects enrolled into the study as well as the number excluded from ATP analyses with reasons for exclusion

Cohort/Reason for Exclusion	Total	%	INV_MMR_1 n	INV_MMR_2 n	INV_MMR_3 n	COM_MMR n	No Group n
Total cohort	**5016**		**1239**	**1234**	**1246**	**1291**	**6**
Study vaccine dose not administrated but subject enrolled	13		0	2	3	2	6
Total Vaccinated cohort	**5003**	**100**	**1239**	**1232**	**1243**	**1289**	**0**
Administration of vaccine(s) forbidden in the protocol	22		8	4	5	5	0
Randomization code broken at the investigator site	1		0	1	0	0	0
Study vaccine dose not administered according to protocol	4		1	1	2	0	0
Vaccine temperature deviation	12		2	3	2	5	0
Expired vaccine administered	3		1	1	0	1	0
Others	3		1	0	1	1	0
ATP cohort for safety	**4958**	**99.1**	**1226**	**1222**	**1233**	**1277**	**0**
Protocol violation (eligibility criteria)	4		1	1	2	0	0
Initially seropositive or initially unknown antibody status	139		40	34	28	37	0
Administration of any medication forbidden by the protocol	1		0	0	0	1	0
Underlying medical condition forbidden by the protocol	1		1	0	0	0	0
Non-compliance with blood sampling schedule (including wrong and unknown dates)	39		8	10	11	10	0
Essential serological data missing	276		68	79	62	67	0
ATP cohort for immunogenicity	**4498**	**89.9**	**1108**	**1098**	**1130**	**1162**	**0**

No Group = No assigned group
% = percentage of subjects in the considered ATP cohort relative to the Total vaccinated cohort

Source: Table 24 in Clinical Study Report MMR-160

***Reviewer comment**: There were relatively more consent withdrawals in the Priorix group than in the MMR-II group. Nevertheless, the withdrawal rates are generally low (<2%) across treatment groups.*

6.5.9 Immunogenicity Analyses

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

6.5.9.1 Analyses of Primary Endpoints

The 95% CIs of the GMC/GMT ratio were computed using an ANOVA model on the log-transformed concentrations/titers, including vaccine group and country (only for measles, mumps and rubella) as fixed effects. In addition, for pneumococcal immunogenicity assessment, the pre-vaccination log titer was included as a regressor.

Each immunogenicity analysis included only subjects who were seronegative for that assay prior to first vaccination. The majority of subjects in both groups (>95%) were seronegative at baseline, against anti-measles, anti-mumps and anti-rubella antibodies.

The first co-primary endpoint assessed clinical lot consistency among the three Priorix lots. Table 56 shows results of pairwise comparisons between lots in terms of difference in SRRs and adjusted GMC ratio for antibodies to MMR. For each pair-wise lot comparison, the two-sided 95% CI for the difference in SRRs was within the (-5%, 5%) margin, and the two-sided 95% CI for the adjusted GMC ratio was within (0.67, 1.5) for all three antibodies.

Table 56: Consistency of *Priorix* lots in terms of SRR and GMC ratios at Day 42 (ATP cohort for immunogenicity)

Antibody	First Lot	Second Lot	Diff in SRR (First lot minus Second lot)	95% CI LL	95% CI UL	Adjusted GMC ratio (First lot over Second lot)	95% CI LL	95% CI UL
anti-Measles	Lot 1	Lot 2	-0.54%	**-1.69%**	**0.58%**	0.99	**0.91**	**1.06**
anti-Measles	Lot 1	Lot 3	0.25%	**-0.98%**	**1.50%**	0.97	**0.90**	**1.05**
anti-Measles	Lot 2	Lot 3	0.79%	**-0.35%**	**1.98%**	0.99	**0.91**	**1.06**
anti-Mumps	Lot 1	Lot 2	0.02%	**-1.05%**	**1.09%**	0.93	**0.87**	**1.00**
anti-Mumps	Lot 1	Lot 3	0.63%	**-0.50%**	**1.81%**	1.04	**0.97**	**1.11**
anti-Mumps	Lot 2	Lot 3	0.61%	**-0.53%**	**1.79%**	1.11	**1.04**	**1.19**
anti-Rubella	Lot 1	Lot 2	0.14%	**-1.30%**	**1.58%**	1.08	**1.01**	**1.15**
anti-Rubella	Lot 1	Lot 3	-0.49%	**-1.86%**	**0.86%**	1.00	**0.94**	**1.07**
anti-Rubella	Lot 2	Lot 3	-0.62%	**-2.02%**	**0.74%**	0.93	**0.87**	**0.99**

INV_MMR_1 = *Priorix* lot 1; INV_MMR_2 = *Priorix* lot 2; INV_MMR_3 = *Priorix* lot 3
Source: Table 12 in m2.5 Clinical Overview

The co-primary objectives were sequentially tested. Because lot-to-lot consistency objectives were met, non-inferiority of Priorix (pooled lots) to MMR-II was assessed. The LL of the 95% CI of the difference in SRRs (Priorix minus MMR-II) was ≥ -5%, and

the LL of the 95% CI for the GMC ratio (Priorix over the MMR-II) was ≥ 0.67. See Table 57.

Table 57: Non-inferiority of *Priorix* versus *MMR-II* in terms of SRR rate and GMC ratios at Day 42 (ATP cohort for immunogenicity)

Antibody	*Priorix* SRR	*MMR-II* SRR	Diff	95% LL	95% UL	*Priorix* Adjusted GMC	*MMR-II* Adjusted GMC	Ratio	95% LL	95% UL
Anti-measles	98.2	98.0	0.18%	**-0.68%**	1.25%	3165.2	3215.4	0.98	**0.93**	1.05
Anti-mumps (PPD)	98.4	97.6	0.81%	**-0.10%**	1.96%	76.4	73.0	1.05	**0.99**	1.11
Anti-rubella	97.3	98.5	-1.15%	**-2.00%**	-0.15%	52.5	60.0	0.87	**0.83**	0.92

Source: Table 6 in m2.5 Clinical Overview

The final co-primary objective was to demonstrate an acceptable immune response of Inv_MMR in terms of SRRs for anti-MMR virus antibodies at Day 42. The LLs of the two-sided 95% CIs for the SRRs for the pooled Inv_MMR lots were ≥ 90% for anti-measles, anti-mumps and anti-rubella antibodies, meeting the criterion (see Table 58).

Table 58: Percentage of subjects with antibody concentration equal to or above particular values and GMCs - pooled INV_MMR groups (ATP cohort for immunogenicity)

Antibody	**Group**	**N**	**%≥ 200 mIU/mL**	**95%LL**	**95%UL**	**GMC**	**95%LL**	**95%UL**
anti-Measles antibody	INV_MMR	3248	98.2	97.6%	98.6%	3017.4	2923.9	3113.8
anti-Measles	COM_MMR	1137	98.0	97.0%	98.7%	3074.4	2911.0	3246.9
Antibody	**Group**	**N**	**%≥ 100 EU/mL**	**95%LL**	**95%UL**	**GMC**	**95%LL**	**95%UL**
anti-Mumps (PPD)	INV_MMR	3187	98.4	97.9%	98.8%	72.4	70.4	74.5
anti-Mumps (PPD)	COM_MMR	1107	97.6	96.5%	98.4%	69.1	65.7	72.7
Antibody	**Group**	**N**	**%≥ 10 IU/ml**	**95%LL**	**95%UL**	**GMC**	**95%LL**	**95%UL**
anti-Rubella antibody	INV_MMR	3245	97.3	96.7%	97.9%	55.7	54.2	57.3
anti-Rubella antibody	COM_MMR	1135	98.5	97.6%	99.1%	64.0	61.1	67.0

Source: Tables 30, 31, and 32 in Clinical Study Report MMR-160

6.5.9.2 Analyses of Secondary Endpoints

Since co-primary objectives 1 to 5 were met, the confirmatory secondary objectives were assessed. Secondary objective 1 was to demonstrate non-inferiority of Inv_MMR to Com_MMR in terms of the SRRs and GMC of anti-VZV antibodies in subsets A and B of the first 2500 children enrolled in the U.S. The LL of the two-sided 95% CI for the group difference (Inv_MMR minus Com_MMR) in SRRs for anti-VZV antibodies was ≥-10% (See Table 59).

Table 59: Difference between groups (INV_MMR minus COM_MMR) in SRR (ATP cohort for immunogenicity, VZV subset – evaluable subjects)

Antibody	**Type**	**INV_MMR**	**SRR**	**COM_MMR**	**SRR**	**Diff**	**95% CI LL**	**95% CI UL**
anti-VZV antibody	75 mIU/mL	N=1492	92.2%	N=540	90.9%	1.30%	-1.31%	4.29%

Source: Adapted from Table 34 in Clinical Study Report MMR-160

Also, the LL of the two-sided 95% CI on the GMC ratio (Inv_MMR over Com_MMR) was ≥0.67 for anti-VZV antibodies (see Table 61).

Secondary objective 2 was to demonstrate non-inferiority of Inv_MMR compared to Com_MMR in terms of GMC for antibodies to HAV at Day 42 (in evaluable subjects in subset A). The LL of the two-sided 95% CI for the GMC ratio was >0.5 (see Table 60).

Table 60: Ratios of Anti-HAV GMCs at Day 42 - pooled INV_MMR groups (ATP cohort for immunogenicity, HAV subset)

INV_MMR (N=748)	**COM_MMR (**N=271)	**Ratio**	**95% CI LL**	**95% CI UL**
GMC = 41.8	GMC = 42.8	0.98	0.86	1.11

Source: Adapted from Table 37 in Clinical Study Report MMR-160

Secondary objective 3 was to demonstrate non-inferiority of Inv_MMR compared to Com_MMR in terms of GMCs for antibodies to PS (13 serotypes), at Day 42 (in evaluable subjects in subset B). The LL of the two-sided 95% CI for the group GMC ratio (Inv_MMR over Com_MMR) was ≥0.5 for each of the 13 PS serotypes (Table 61).

Table 61: Non-inferiority of Priorix versus MMR-II in terms of GMC ratios for anti-VZV, anti-hepatitis A virus and anti-PS antibodies (ATP cohort for immunogenicity, VZV subset, HAV subset, and PCV subset)

Antibody	***Priorix*** **N**	***Priorix*** **GMC**	***MMR-II*** **N**	***MMR-II*** **GMC**	**Ratio**	**95% CI LL**	**95% CI UL**
Anti VZV	1492	169.6	540	167.2	1.01	**0.95**	1.08
Anti hepatitis A virus	748	41.8	271	42.8	0.98	**0.86**	1.11
anti-PnPS 1 antibody [(b) (4)] (µg/mL)	740	2.258	256	2.392	0.94	**0.85**	1.05
anti-PnPS 3 antibody [(b) (4)] (µg/mL)	739	0.499	255	0.503	0.99	**0.91**	1.08
anti-PnPS 4 antibody [(b) (4)] (µg/mL)	732	1.620	255	1.844	0.88	**0.79**	0.98
anti-PnPS 5 antibody [(b) (4)] (µg/mL)	738	2.092	256	2.280	0.92	**0.83**	1.01
anti-PnPS 6A antibody [(b) (4)] (µg/mL)	740	5.815	256	5.761	1.01	**0.92**	1.11
anti-PnPS 6B antibody [(b) (4)] (µg/mL)	739	5.812	256	5.924	0.98	**0.89**	1.09
anti-PnPS 7F antibody [(b) (4)] (µg/mL)	739	3.658	256	3.887	0.94	**0.86**	1.03
anti-PnPS 9V antibody [(b) (4)] (µg/mL)	740	2.295	256	2.324	0.99	**0.90**	1.08
anti-PnPS 14 antibody [(b) (4)] (µg/mL)	738	6.512	256	7.151	0.91	**0.81**	1.02
anti-PnPS 18C antibody [(b) (4)] (µg/mL)	740	2.082	255	2.255	0.92	**0.84**	1.02
anti-PnPS 19A antibody [(b) (4)] (µg/mL)	739	4.708	255	4.876	0.97	**0.87**	1.07
anti-PnPS 19F antibody [(b) (4)] (µg/mL)	740	4.186	256	4.367	0.96	**0.87**	1.06
anti-PnPS 23F antibody [(b) (4)] (µg/mL)	701	2.178	240	2.301	0.95	**0.85**	1.06

Adjusted GMC = geometric mean antibody concentration adjusted for baseline concentration
Source: Adapted from Table 11 in m2.5 Clinical Overview

6.5.9.3 Subpopulation Analyses

Primary analyses (non-inferiority between Priorix and MMR-II) were repeated by country, gender and geographic ancestry. Only the GMC ratio results are presented here.

Table 62: NI of INV_MMR vs COM_MMR in terms of adjusted GMC ratios for antibodies to MMR viruses at Day 42 (ATP cohort for immunogenicity)

Antibody	Sub-group	INV_MMR N	INV_MMR Adjusted GMC	COM_MMR N	COM_MMR Adjusted GMC	Ratio	95% CI LL	95% CI UL
anti-Measles (mIU/mL)	Sex: Male	1676	3024.9	586	3043.7	0.99	0.91	1.08
anti-Measles (mIU/mL)	Sex: Female	1572	3316.4	551	3404.3	0.97	0.89	1.06
anti-Measles (mIU/mL)	Race: White Caucasian/European	2481	2849.9	866	2887.7	0.99	0.92	1.06
anti-Measles (mIU/mL)	Race: American Hispanic or Latino	327	4582.2	114	4764.8	0.96	0.8	1.15
anti-Measles (mIU/mL)	Race: African Heritage/ African American	123	3591.8	54	3957.9	0.91	0.68	1.21
anti-Measles (mIU/mL)	Country: United States	1520	3260.8	546	3404.5	0.96	0.88	1.05
anti-Measles (mIU/mL)	Country: Mexico	272	4475.7	93	4358.5	1.03	0.84	1.25
anti-Measles (mIU/mL)	Country: Finland	971	2410.9	329	2414.2	1	0.89	1.12
anti-Measles (mIU/mL)	Country: Spain	158	3181.9	59	3412	0.93	0.69	1.26
anti-Measles (mIU/mL)	Country: Estonia	327	2875.9	110	2688.1	1.07	0.89	1.29
anti-Mumps (EU/m)	Sex: Male	1645	75	573	69.8	1.07	1	1.16
anti-Mumps (EU/m)	Sex: Female	1542	77.8	534	76.4	1.02	0.94	1.11
anti-Mumps (EU/m)	Race: White Caucasian/	2450	70.2	850	66.8	1.05	0.99	1.12
anti-Mumps (EU/m)	Race: American Hispanic or Latino	313	91.2	105	94.9	0.96	0.8	1.16
anti-Mumps (EU/m)	Race: African Heritage / African	121	90	54	103.9	0.87	0.65	1.16
anti-Mumps (EU/m)	Country: United States	1488	75.9	524	69.8	1.09	1	1.18
anti-Mumps (EU/m)	Country: Mexico	258	101.7	85	104.1	0.98	0.79	1.2
anti-Mumps (EU/m)	Country: Finland	947	62.4	327	61.6	1.01	0.91	1.12
anti-Mumps (EU/m)	Country: Spain	159	78.6	57	80.5	0.98	0.78	1.23
anti-Mumps (EU/m)	Country: Estonia	335	66.5	114	63	1.06	0.88	1.26
anti-Rubella (IU/mL)	Sex: Male	1674	48.5	585	56.6	0.86	0.8	0.92
anti-Rubella (IU/mL)	Sex: Female	1571	57.2	550	63.8	0.9	0.83	0.97
anti-Rubella (IU/mL)	Race: White Caucasian/ European	2479	49.6	865	56.7	0.88	0.82	0.93
anti-Rubella (IU/mL)	Race: American Hispanic or Latino	326	61.2	114	67.3	0.91	0.76	1.08
anti-Rubella (IU/mL)	Race: African Heritage / African	123	93.9	54	112.9	0.83	0.69	1
anti-Rubella (IU/mL)	Country: United States	1517	66.5	545	75.9	0.88	0.81	0.94
anti-Rubella (IU/mL)	Country: Mexico	271	61.1	93	67.7	0.9	0.74	1.1
anti-Rubella (IU/mL)	Country: Finland	971	45.6	328	56	0.81	0.74	0.9
anti-Rubella (IU/mL)	Country: Spain	159	54.7	59	55.1	0.99	0.74	1.33
anti-Rubella (IU/mL)	Country: Estonia	327	41.7	110	42.3	0.99	0.82	1.19

Source: Table 2 in 1.11.3 Clinical Information Amendment – Response to CBER Request 10Nov2021 (MMR-160 – Analysis 8)

***Reviewer comment**: Although there were differences in point estimates across subgroups (e.g., the Race: African Heritage/African American subgroup had relatively lower GMC ratios for anti-mumps and anti-Rubella antibodies), after taking into account sample sizes, CIs did not reflect reliable differences. Observed results were generally consistent with the overall results. It should be noted that the prespecified hypotheses in the primary*

objectives were non-inferiority and the LLs of many CIs on the GMC ratios exceeded the non-inferiority margin of 0.67.

6.5.9.4 Dropouts and/or Discontinuations

See Section 6.5.8 Study Population and Disposition for information on discontinuations.

6.5.9.5 Exploratory and Post Hoc Analyses

The confirmatory objectives were re-analyzed accounting for the randomization process. The p-value for each confirmatory objective was recomputed accounting for center as minimization factor and country as stratification factor. A total of 5000 rerandomizations were used to compute the p-value as the proportion of rerandomizations leading to a re-estimated value greater than the observed one. All p-values are below the one-sided nominal significance level.

6.5.10 Safety Analyses

The analysis of safety was performed on the TVC.

6.5.10.1 Overall incidence of AEs

The incidence of solicited and unsolicited symptoms reported by subjects from Day 0 to Day 42 following study vaccination is presented in Table 63. At least one solicited or unsolicited symptom was reported by 87.1% of subjects in the Inv_MMR group and by 88.3% in the Com_MMR group.

Table 63: Incidence of symptoms (solicited and unsolicited) reported during the 43-day (Days 0-42) post-vaccination period (TVC)

Group	N	Any Symptom	95%LL	95%UL	General symptoms	95%LL	95%UL	Local symptoms	95%LL	95%UL
INV_MMR_1	1239	88.0%	86.0%	89.7%	85.6%	83.5%	87.5%	41.4%	38.6%	44.2%
INV_MMR_2	1232	85.6%	83.5%	87.5%	83.6%	81.4%	85.6%	39.5%	36.8%	42.3%
INV_MMR_3	1243	87.7%	85.7%	89.5%	85.1%	83.0%	87.1%	39.7%	36.9%	42.4%
INV_MMR	3714	87.1%	86.0%	88.1%	84.8%	83.6%	85.9%	40.2%	38.6%	41.8%
COM_MMR	1289	88.3%	86.4%	90.0%	86.1%	84.1%	88.0%	41.9%	39.2%	44.6%

Source: Table 43 in Clinical Study Report MMR-160

Compliance in returning symptom sheets for collection of local and general solicited AEs is provided in Table 64.

Table 64: Compliance in returning symptom information (TVC)

Group	Number of doses	Doses NOT according to protocol	Number of general SS	Compliance % general SS	Number of local SS	Compliance % local SS
INV_MMR_1	1239	5	1190	96.0	1186	95.7
INV_MMR_2	1232	5	1176	95.5	1175	95.4
INV_MMR_3	1243	6	1200	96.5	1194	96.1
INV_MMR	3714	16	3566	96.0	3555	95.7
COM_MMR	1289	5	1243	96.4	1242	96.4

SS = Symptom screens/sheets used for the collection of local and general solicited AEs
Compliance % = (number of doses with symptom screen/sheet return / number of administered doses) X 100
Source: Table 42 in Clinical Study Report MMR-160

Over the 4-day post-vaccination period, the most frequently reported solicited local symptoms in the Inv_MMR and Com_MMR groups were pain and redness. Overall, 25.9% of subjects in the Inv_MMR group reported pain compared to 28.1% in the Com_MMR group, and 24.5% of the Inv_MMR group reported redness compared to the 25.2% of subjects in the Com_MMR group.

Over the 15-day post-vaccination period, the most frequently reported general symptom was irritability or fussiness, reported in 63.3% in the Inv_MMR group compared to 65.9% in Com_MMR group. Drowsiness (44.9% and 47.1%) and loss of appetite (45.1% and 44.1%) were also frequently reported general symptoms, respectively.

During the period ranging from Day 5 to Day 12 post-vaccination, 24.3% and 22.8% of subjects in the Inv_MMR and Com_MMR groups, respectively, reported fever. Fever along with rash was reported in 9.7% and 8.4% of subjects in the Inv_MMR and Com_MMR groups. A severe (grade 3) rash was reported in 3.0% of subjects in the Inv_MMR group and 2.0% in the Com_MMR group.

A total of 10 subjects (0.3%) in the Inv_MMR group and 3 (0.2%) in the Com_MMR group reported febrile convulsions within the 43-day reporting period post-vaccination. Four of the 10 in the Inv_MMR group were grade 3, whereas none were grade 3 in the Com_MMR group. Nine out of 10 in the Inv_MMR group and 1 out of 3 in the Com_MMR group sought medical advice. Four of the 10 events in the Inv_MMR group and 2 of the 3 events in the Com_MMR group were considered related to vaccination.

Overall, 50.0% of subjects in the Inv_MMR group and 47.9% in the Com_MMR group in the TVC reported at least one unsolicited AE over the 43-day post-vaccination period.

6.5.10.3 Deaths

No deaths were reported in this study.

6.5.10.4 Nonfatal Serious Adverse Events

A total of 98 SAEs were reported by 77 subjects (2.1%) in the Inv_MMR group and 40 were reported in 25 subjects (1.9%) in the Com_MMR group. Two of the SAEs in the Inv_MMR group were considered related to the study vaccination. The most frequent SAE during the study period was bronchitis reported by 8 subjects (0.2%) in the Inv_MMR group and by 2 subjects (0.2%) in the Com_MMR group.

6.5.10.5 Adverse Events of Special Interest (AESI)

See the clinical reviewer's memo for discussions of AESIs.

6.5.10.6 Dropouts and/or Discontinuations

Two AEs occurred that led to subjects prematurely discontinuing the study. Both subjects were in the Inv_MMR_1 group, and their cases were reported as non-serious adverse events.

6.6 MMR-161

MMR-161 assessed non-inferiority of the immunogenicity of Priorix at an end of shelf-life (EOSL) potency compared to MMR-II, when given as a first dose and co-administered with VV, HAV and PCV-13 (in U.S. subjects only) in healthy children 12-15 months old. Two lots of Priorix, one at minimum potency (referred to as MIN lot) and another at medium potency (referred to as MED lot), were evaluated to establish an EOSL potency. Children received a second dose of either MMR vaccine 6 weeks after the first dose. Priorix groups received a second dose of the investigational MMR release potency (Inv_MMR_Release) lot, while MMR-II groups received a second dose from either of the two MMR-II lots. Immune responses following the second dose of Priorix were evaluated in subjects enrolled in the U.S. only.

6.6.1 Objectives

Primary Objectives (MIN lot) Day 42, post dose 1

1. Demonstrate non-inferiority of Priorix at MIN potency compared to pooled MMR-II in terms of SRR for antibodies to MMR viruses
2. Demonstrate non-inferiority of Priorix at MIN potency compared to pooled MMR-II in terms of GMC for antibodies to MMR viruses.
3. Demonstrate an acceptable immune response of Priorix at MIN potency in terms of SRR for antibodies to MMR viruses.
4. Demonstrate non-inferiority of Priorix at MIN potency compared to pooled MMR-II in terms of SRR for antibodies to mumps virus (by (b) (4)).
5. Demonstrate non-inferiority of Priorix at MIN potency compared to pooled MMR-II in terms of GMT for antibodies to mumps virus (by (b) (4)).

Primary Objectives (MED lot)

Primary objectives for the MED lot were the same as for the MIN lot, except that the objectives were labeled 6 through 10.

Secondary Immunogencity Objectives (Day 84, post dose 2, U.S. subjects only)

- Assess immunogenicity of Priorix at MIN potency followed by Priorix at release potency and pooled MMR-II in terms of SRR and GMC for antibodies to MMR viruses.
- Assess immunogenicity of Priorix at MED potency followed by Priorix at release potency and pooled MMR-II in terms of SRR and GMC for antibodies to MMR viruses.

6.6.2 Design Overview

This study was a Phase 3, observer-blind, randomized, controlled, multi-country study designed to evaluate non-inferiority of immune response and safety of a first dose of Priorix at EOSL potency as compared to a first dose of MMR-II when both vaccines were co-administered with VV, HAV and PCV-13 (subset of children in U.S. only) in subjects 12-15 months old at first dose.

A total of 4,535 subjects were randomized in a 2:2:1:1 ratio to 4 groups (2 different lots of Priorix and 2 different lots of MMR-II, which were pooled for analyses), and 4,516 subjects were vaccinated, of whom 1,000 subjects were from the U.S. The MIN lot was formulated to have measles and rubella potencies close to the EOSL potencies of Priorix marketed outside the U.S., whereas a higher potency was targeted for mumps based on the results obtained in the Phase 2 study MMR-157. The MED lot was formulated with higher targeted potencies for all 3 antigens.

The randomization algorithm used a minimization procedure accounting for center and country. Minimization factors had equal weights in the algorithm.

The thresholds for seroresponse were the same as those used for study MMR-162.

6.6.3 Population

Healthy children 12-15 months old, with all routine vaccinations (U.S. only).

6.6.4 Study Treatments or Agents Mandated by the Protocol

4 parallel groups:

- INV_MMR_MIN: two doses of Priorix, 6 weeks apart (first dose at minimum potency and second dose at release potency: Inv_MMR_Release)
- INV_MMR_MED: two doses of Priorix, 6 weeks apart (first dose at medium potency and second dose at release potency)
- MMRII_1: two doses of MMR-II, the first from Lot 1, the second from either Lot 1 or Lot 2, 6 weeks apart
- MMRII_2: two doses of MMR-II, the first from Lot 2, the second from either Lot 1 or Lot 2, 6 weeks apart

All subjects were to receive HAV and VV as study vaccines, concomitantly with the MMR vaccine at the first dose. PCV-13 was only administered to subjects in the U.S.

Table 65: Study groups

Study groups	Number of subjects Planned
Inv_MMR_Min	1500
Inv_MMR_Med	1500
Com_MMR_L1	750
Com_MMR_L2	750

Source: Adapted from Table 2 in Clinical Study Report MMR-161

6.6.5 Sites and Centers

81 centers (44 in the U.S., 12 in Czech Republic, 11 in Spain, 6 in Finland, 5 in Thailand, and 3 in Malaysia)

6.6.6 Endpoints and Criteria for Study Success

Primary Endpoints

- Immunogenicity of the MMR vaccines at post Dose 1
  - Seroresponse to MMR viruses (by ELISA) and to mumps virus (by (b) (4))
  - MMR virus antibody concentrations (by ELISA) and mumps virus antibody titers (by (b) (4))

Criteria for Minimum potency vaccine:

- The LL of the 2-sided 97.5% CI for difference in SRRs (INV_MMR_MIN minus MMR-II) as measured by ELISA is ≥-5%.
- The LL of the 2-sided 97.5% CI on the ratio of GMCs (INV_MMR_MIN over MMR-II) is ≥ 0.67 for antibodies to MMR viruses.
- The LL of the 2-sided 97.5% CI for the SRR of INV_MMR_MIN is ≥ 90% for antibodies to MMR viruses.
- The LL of the 2-sided 97.5% CI on the group difference (INV_MMR_MIN minus MMR-II) in SRRs is ≥ -10% for antibodies to mumps virus (using (b) (4).
- The LL of the 2-sided 97.5% CI on the GMT ratio (INV_MMR_MIN over MMR-II) is ≥ 0.67 for antibodies to mumps virus (using (b) (4)).

Success criteria for Medium potency vaccine are the same as those for Minimum potency vaccine.

Secondary Immunogencity Endpoints (post dose 2, subjects in the U.S.)

- Immunogenicity of Inv_MMR_Min followed by Inv_MMR_Release or pooled Com_MMR vaccine in terms of SRRs and GMCs for antibodies to MMR viruses
- Immunogenicity of Inv_MMR_Med followed by Inv_MMR_Release or pooled Com_MMR vaccine in terms of SRR and GMCs for antibodies to MMR viruses

6.6.7 Statistical Considerations & Statistical Analysis Plan

Between-group comparisons used asymptotic standardized 97.5% CIs for the difference between vaccine groups. The 97.5% CI for the GMC ratio (Inv_MMR vaccine over pooled Com_MMR vaccine) was computed using an ANOVA model on the log-transformed concentrations/ titers with vaccine group and country as fixed effects.

To control the familywise type I error rate below 2.5%, a Bonferroni adjustment was used to compare Priorix to MMR-II independently for either MIN or MED lots. Each group comparison within MIN or MED lot used a one-sided 1.25% nominal type I error. To control the type I error within each set of objectives (#1-5 and #6-10) within lot type (MIN or MED), a hierarchical procedure was used. A primary objective could only be tested if the previous primary objectives had been reached. Within a single objective, non-inferiority could be demonstrated if the criteria specific to each MMR antigen were met simultaneously (p-value <1.25%).

The MED lot objectives (#6-10) were assessed only if one or more of the MIN lot objectives 1-5 related to the minimum potency vaccine were *not* met.

Reviewer comment*: As there was no pre-specified testing procedure for secondary objectives (as well as no pre-defined criteria) to control type I error rate, these were interpreted as non-confirmatory objectives, and analyses were not reviewed in detail.*

6.6.8 Study Population and Disposition

6.6.8.1 Populations Enrolled/Analyzed

The TVC cohort was the same as that used in study MMR-157.

The ATP cohort for analysis of safety was the same as for study MMR-157 except it excluded eligible subjects who had received a prohibited vaccine up to Visit 2 (day 42) for non-U.S. subjects and up to Visit 3 (day 84) for U.S. subjects.

The ATP cohort for analysis of immunogenicity post Dose 1 included all eligible subjects from the ATP cohort for safety:

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

ATP cohort for analysis of immunogenicity post Dose 2 included all eligible U.S. subjects in the ATP cohort for safety:

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

Results after two doses of Priorix were based on an adapted ATP cohort for immunogenicity that included Day 42 results from the ATP cohort for immunogenicity post-dose 1 and Day 84 results from the ATP cohort for immunogenicity post-dose 2.

6.6.8.1.1 Demographics

Overall, the mean age (± SD) of subjects in the TVC at time of first vaccination was 12.6 months ±0.9 months; the cohort was 68.4% White/Caucasian and 51.7% male. The mean age of subjects in the ATP cohort for immunogenicity at time of first vaccination was 12.7 months ±0.9 months; the cohort was 69.0% White/Caucasian and 52.0% male. Demographics were similar across groups.

6.6.8.1.2 Subject Disposition

A total of 4,516 subjects were enrolled and vaccinated, of whom 1,493 were in the INV_MMR_MIN group, 1,497 in the INV_MMR_MED group and 1,526 in the MMR-II control group. Of these, 95.5%, 95.3%, and 94.6%, completed the study in the three groups, respectively. See Table 66 and Table 67 for reasons for exclusion from analysis cohorts.

Table 66: Number of subjects enrolled and excluded from ATP analyses with reasons for exclusion – Post-dose 1 (All subjects enrolled except those excluded from all stat analysis)

Cohort/Reason for exclusion	Total	%	INV_MMR_Min n	INV_MMR_Med n	COM_MMR n	NOGRP n
Total cohort	4538		1497	1501	1530	10
Subjects excluded from all stat analysis	3		2	0	1	0
All subjects enrolled except subjects excluded from all stat analysis	4535		1495	1501	1529	10
Vaccine dose not administrated but subject number allocated	19		2	4	3	10
Total Vaccinated cohort	4516	100	1493	1497	1526	0
Administration of vaccine(s) forbidden in the protocol	24		5	9	10	0
Randomization code broken at the investigator site	2		1	0	1	0
Study vaccine dose not administered according to protocol	3		2	0	1	0
Vaccine temperature deviation	28		8	11	9	0
Expired vaccine administered	14		5	5	4	0
Others	7		2	2	3	0
ATP cohort for safety	4438	98.3	1470	1470	1498	0
Protocol violation (eligibility criteria)	8		5	2	1	0
Initially seropositive or initially unknown antibody status	59		21	17	21	0
Administration of any medication forbidden by the protocol	4		1	1	2	0
Underlying medical condition forbidden by the protocol	0		0	0	0	0
Non-compliance with blood sampling schedule	51		14	15	22	0
Essential serological data missing	199		66	62	71	0
ATP cohort for immunogenicity post dose 1	4117	91.2	1363	1373	1381	0

% = percentage of subjects in the considered ATP cohort relative to the Total vaccinated cohort
Source: Table 23 in Clinical Study Report MMR-161

Table 67: Number of subjects enrolled and excluded from ATP analyses with reasons for exclusion – Post-dose 2 (All subjects enrolled except those excluded from all stat analysis)

Cohort/Reason for exclusion	Total	%	INV_MMR_Min n	INV_MMR_Med n	COM_MMR n	NOGRP n
Total cohort	4538		1497	1501	1530	10
Subjects excluded from all stat analysis	3		2	0	1	0
All subjects enrolled except subjects excluded from all stat analysis	4535		1495	1501	1529	10
Vaccine dose not administrated but subject number allocated	19		2	4	3	10
Total Vaccinated cohort	4516	100	1493	1497	1526	0

Cohort/Reason for exclusion	Total	%	INV_MMR_Min n	INV_MMR_Med n	COM_MMR n	NOGRP n
Administration of vaccine(s) forbidden in the protocol	41		12	13	16	0
Randomization code broken at the investigator site	2		1	0	1	0
Study vaccine dose not administered according to protocol	21		7	5	9	0
Vaccine temperature deviation	24		7	9	8	0
Expired vaccine administered	13		5	5	3	0
Others	7		2	2	3	0
ATP cohort for safety	4408	97.6	1459	1463	1486	0
Protocol violation (eligibility criteria)	8		5	2	1	0
Initially seropositive or initially unknown antibody status	57		21	15	21	0
Administration of any medication forbidden by the protocol	6		2	2	2	0
Underlying medical condition forbidden by the protocol	0		0	0	0	0
Non compliance with vaccination schedule	51		12	15	24	0
Non-compliance with blood sampling schedule	7		4	2	1	0
Essential serological data missing	114		38	34	42	0
Subject not planned to be bled for all blood	3401		1132	1132	1137	0
ATP cohort for immunogenicity post dose 2	764	16.9	245	261	258	0

% = percentage of subjects in the considered ATP cohort relative to the Total vaccinated cohort
Source: Table 24 in Clinical Study Report MMR-161

***Reviewer comment**: There is a slightly higher non-compliance rate with blood sampling (post-dose 1) and vaccination schedule (post-dose 2) in the Com_MMR group. However, there was no pattern of this in other studies. That is, one group was not consistently higher or lower than another across studies.*

6.6.9 Immunogenicity Analyses

The analysis of immunogenicity was based on the ATP cohort for immunogenicity. Post vaccination 1 and 2 analyses were based on subjects who were seronegative for that assay prior to first vaccination. With the exception of the mumps assays, relatively few subjects (< 3%) were seropositive pre-vaccination. For mumps, 6.9% (89/1363), 8.9% (115/1373), and 7.4% (300/4117) were seropositive at baseline for the MIN, MED, and MMR-II groups, respectively.

6.6.9.1 Analyses of Primary Endpoints

Non-inferiority of the MIN lot of Priorix to MMR-II

The first primary objective to demonstrate non-inferiority of the Priorix MIN lot to MMR-II in terms of SRR difference (Priorix minus MMR-II) for all vaccine antigens was met for mumps (PPD ELISA) and rubella, but not met for measles. The LL of the two-sided 97.5% CI for the difference in SRR was ≥-5% for mumps and rubella (-1.91% and -3.11%, respectively), but was < -5% for measles (-7.65%). See Table 68, below.

With the failure of the primary objective, according to the hierarchical testing procedure, no hypotheses on the MIN lot could be tested for any subsequent co-primary objective (co-primary objectives 2 to 5).

Table 68: Non-inferiority of Inv_MMR_Min vs Com_MMR in terms of SRR at Day 42 (ATP cohort for immunogenicity post Dose 1, without subjects excluded from all stat analysis) [Objective 1]

Antibody	Inv_MMR_Min SRR (%)	Com_MMR SRR (%)	Difference	97.5% CI LL (%)	97.5% CI UL (%)
anti-Measles antibody	90.8	96.3	-5.48%	**-7.65**	-3.43
anti-Mumps (PPD) antibody	97.4	97.8	-0.42%	-1.91	1.04
anti-Mumps (b) (4)) antibody	71.2	80.6	-9.41%	**-13.20**	-5.62
anti-Rubella antibody	96.8	98.5	-1.71%	-3.11	-0.42

Source: Table 27 in Clinical Study Report MMR-161

***Reviewer comment**: The mumps antibody measured using (b) (4) was included as a primary endpoint for objectives #4 and #5. The difference in SRR between Priorix MIN lot and Com_MMR was relatively large, at -9.41%. The GMC ratio result (objective #5) was also low (0.60) with 97.5% CI (0.53, 0.68).*

Non-inferiority of the MED lot of Priorix to MMR-II

The subsequent 5 primary objectives (#6 to #10) for Inv_MMR_Med were evaluated according to the method for type I error rate control.

The co-primary objectives to demonstrate non-inferiority of the Priorix MED lot to MMR-II in terms of SRR difference (Priorix minus MMR-II) and GMC ratio (Priorix over MMR-II) as measured by ELISA were met for measles, mumps, and rubella (co-primary objectives 6 and 7):

- The LL of the two-sided 97.5% CI for the difference in SRR was ≥ -5% (-3.96%, -2.11% and -2.50%, respectively).
- The LL of the two-sided 97.5% CI for the GMC ratio was ≥ 0.67 (0.83, 0.78, and 0.80, respectively). See Table 69, below.

Table 69: Summary of the immunogenicity results post-dose 1 for the MED potency lot of Priorix (defined as the EOSL potency)

Antibody (readout)	Priorix SRR	MMR-II SRR	Difference (95% CI)	Priorix Adjusted GMC	MMR-II Adjusted GMC	GMC Ratio (95% CI)
Anti-measles (ELISA)	94.2%	96.3%	-2.08% (-3.96, -0.27)	2553.8	2798.9	0.91 (0.83, 1.01)
Anti-mumps (ELISA)	97.3%	97.8%	-0.58% (-2.11, 0.91)	59.4	70.6	0.84 (0.78, 0.91)
Anti-rubella (ELISA)	97.3%	98.5%	-1.18% (-2.50, 0.05)	55.6	63.0	0.88 (0.83, 0.95)
Anti-mumps (b) (4)	73.4%	80.6%	-7.22% **(-10.94**, -3.49)	*10.2*	*15.6*	*0.65 (**0.57**, 0.74)*

Source: Table 10 in m2.5 Clinical Overview

The co-primary objective 8 was also met:

- The LL of the two-sided 97.5% CI for the SRR for Inv_MMR_Med was above 90% for anti-measles, anti-mumps, and anti-rubella antibodies tested with ELISA (at percentages of 92.6%, 96.0% and 96.1%, respectively).

However, objective 9 (non-inferiority measured for mumps by (b) (4)) was not met:

- The LL of the two-sided 97.5% CI for the difference in SRRs with respect to anti-mumps anti-body measured using (b) (4) was < -10% (-10.94%). See Table 69.

Because co-primary objective 9 was not met, hypothesis testing did not proceed to co-primary objective 10.

6.6.9.2 Analyses of Secondary Endpoints

The secondary immunogenicity endpoints evaluated immunogenicity of Priorix as a second dose of MMR vaccine at release potency or MMR-II at Day 84, both administered within 6 weeks after the first dose. The analysis was performed in a sub-cohort of children enrolled in the U.S. A total of 764 U.S. children were included in the ATP cohort for immunogenicity post-dose 2 (N=506 for Priorix and N=258 for MMR-II). Table 70, Table 71, and Table 72, below, provide the Day 84 SRRs and GMCs by group, for each antibody. Results are largely consistent across groups for each antibody.

Table 70: Percentage of subjects with an anti-measles antibody concentration ≥ 200 mIU/ML and GMCs in initially seronegative subjects at Day 84 (ATP cohort for immunogenicity post dose 2, without subjects excluded from all stat analysis

Group	N	≥ 200 mIU/ml	95%LL	95%UL	GMC	95%LL	95%UL
Inv_MMR_Min	245	99.6%	97.7%	100%	4803.5	4290.4	5378.0
Inv_MMR_Med	258	98.4%	96.1%	99.6%	4557.7	4061.5	5114.4
Com_MMR	257	98.4%	96.1%	99.6%	4453.9	3951.9	5019.8

Source: Table 35 in Clinical Study Report MMR-161

Table 71: Percentage of subjects with an anti-rubella antibody concentration ≥ 10 IU/ML and GMCs in initially seronegative subjects at Day 84 (ATP cohort for immunogenicity post dose 2, without subjects excluded from all stat analysis

Group	N	≥ 10 IU/ml	95%LL	95%UL	GMC	95%LL	95%UL
Inv_MMR_Min	245	99.6%	97.7%	100%	112.7	104.1	122.0
Inv_MMR_Med	259	99.6%	97.9%	100%	110.7	102.9	119.1
Com_MMR	255	99.6%	97.8%	100%	110.9	101.8	120.8

Source: Table 37 in Clinical Study Report MMR-161

Table 72: Percentage of subjects with an anti-Mumps antibody concentration ≥ 10 EU/ML and GMCs in initially seronegative subjects at Day 84 (ATP cohort for immunogenicity post dose 2, without subjects excluded from all stat analysis

Group	N	≥ 10 EU/ml	95%LL	95%UL	GMC	95%LL	95%UL
Inv_MMR_Min	216	99.1%	96.7%	99.9%	88.9	80.4	98.3
Inv_MMR_Med	199	100%	98.2%	100%	94.1	85.3	103.8
Com_MMR	212	98.6%	95.9%	99.7%	86.4	77.4	96.5

Source: Table 36 in Clinical Study Report MMR-161

6.6.9.3 Subpopulation Analyses

The analyses of immunogenicity were also repeated for subjects in each country, by gender and by geographic ancestry. This section presents results for objectives using the MED lot.

Table 73 and Table 74, below, show that many subgroups have 97.5% CIs for the difference in SRRs that are consistent with the primary objective results.

Table 73: Non-inferiority of Inv_MMR_Med vs Com_MMR in terms of SRR at Day 42 (ATP cohort for immunogenicity post Dose 1, without Subjects excluded from all stat analysis) – Objectives 6 and 9

Antibody	Sub-group	Inv_MMR_Med	SRR (%)	COM_MMR	SRR (%)	Diff (%)	97.5% LL (%)	97.5% UL (%)
anti-Measles	Sex: Male	N=720	94.2	N=695	96.3	-2.09	-4.75	0.47
anti-Measles	Sex: Female	N=646	94.3	N=683	96.3	-2.07	-4.83	0.54
anti-Measles	Race: White Caucasian/ European Heritage	N=936	93.2	N=957	95.9	-2.76	-5.2	-0.43
anti-Measles	Race: South East Asian Heritage	N=339	96.2	N=340	97.1	-0.89	-4.35	2.43
anti-Measles	Country: Spain	N=403	93.1	N=402	93.8	-0.73	-4.8	3.3
anti-Measles	Country: Czech Republic	N=218	95.9	N=230	98.3	-2.39	-6.8	1.37
anti-Measles	Country: United States	N=271	93	N=278	96.8	-3.77	-8.47	0.47
anti-Measles	Country: Thailand	N=309	95.8	N=309	97.7	-1.94	-5.6	1.4
anti-Measles	Country: Finland	N=135	92.6	N=128	97.7	-5.06	-12.13	1.13
anti-Measles	Country: Malaysia	N=30	100	N=31	90.3	9.68	-5.58	27.88
anti-Mumps (PPD)	Sex: Male	N=604	97.4	N=577	98.1	-0.74	-2.87	1.32
anti-Mumps (PPD)	Sex: Female	N=527	97.2	N=578	97.6	-0.42	-2.81	1.83
anti-Mumps (PPD)	Race: White Caucasian/ European Heritage	N=778	97.7	N=800	98.6	-0.94	-2.64	0.62
anti-Mumps (PPD)	Race: South East Asian Heritage	N=288	95.5	N=291	95.9	-0.39	-4.51	3.66
anti-Mumps (PPD)	Country: Spain	N=335	97.9	N=323	98.5	-0.54	-3.32	2.15
anti-Mumps (PPD)	Country: Czech Republic	N=184	96.7	N=202	98.5	-1.78	-6.35	2.05
anti-Mumps (PPD)	Country: United States	N=201	100	N=217	98.2	1.84	-0.62	5.24
anti-Mumps (PPD)	Country: Thailand	N=263	95.4	N=265	96.6	-1.17	-5.43	2.91
anti-Mumps (PPD)	Country: Finland	N=123	95.9	N=122	99.2	-3.25	-9.48	1.75
anti-Mumps (PPD)	Country: Malaysia	N=25	96	N=26	88.5	7.54	-13.28	29.09
anti-Mumps (b) (4)	Sex: Male	N=667	75	N=645	82	-7.05	-12.12	-1.97
anti-Mumps (b) (4)	Sex: Female	N=598	71.6	N=642	79.1	-7.56	-13.04	-2.08
anti-Mumps (b) (4)	Race: White Caucasian/ European Heritage	N=864	75.6	N=891	82.4	-6.8	-11.16	-2.45
anti-Mumps (b) (4)	Race: South East Asian Heritage	N=318	65.7	N=323	75.5	-9.82	-17.8	-1.76
anti-Mumps (b) (4)	Country: Spain	N=363	77.4	N=373	84.5	-7.04	-13.57	-0.55
anti-Mumps (b) (4)	Country: Czech Republic	N=205	77.6	N=218	83.5	-5.93	-14.67	2.72
anti-Mumps (b) (4)	Country: United States	N=249	75.9	N=250	82	-6.1	-14.3	2.11

Antibody	Sub-group	Inv_MMR_Med	SRR (%)	COM_MMR	SRR (%)	Diff (%)	97.5% LL (%)	97.5% UL (%)
anti-Mumps (b) (4)	Country: Thailand	N=291	64.9	N=299	76.6	-11.64	-19.92	-3.26
anti-Mumps (b) (4)	Country: Finland	N=130	69.2	N=123	74	-4.75	-17.35	8.04
anti-Mumps (b) (4)	Country: Malaysia	N=27	74.1	N=24	62.5	11.57	-17.62	39.65
anti-Rubella	Sex: Male	N=718	97.1	N=694	98.1	-1.05	-3.04	0.84
anti-Rubella	Sex: Female	N=648	97.5	N=682	98.8	-1.3	-3.2	0.37
anti-Rubella	Race: White Caucasian/ European Heritage	N=937	96.8	N=956	97.9	-1.11	-2.88	0.57
anti-Rubella	Race: South East Asian Heritage	N=338	98.2	N=340	99.7	-1.48	-3.97	0.38
anti-Rubella	Country: Spain	N=402	97	N=401	97.8	-0.74	-3.57	1.97
anti-Rubella	Country: Czech Republic	N=218	96.3	N=230	98.3	-1.93	-6.2	1.76
anti-Rubella	Country: United States	N=273	98.5	N=277	98.6	-0.02	-2.91	2.83
anti-Rubella	Country: Thailand	N=308	98.1	N=310	99.7	-1.63	-4.35	0.41
anti-Rubella	Country: Finland	N=135	94.8	N=128	97.7	-2.84	-9.28	3.06
anti-Rubella	Country: Malaysia	N=30	100	N=30	100	0	-14.55	14.55

Source: Table 3 in 1.11.3 Clinical Information Amendment – Response to CBER Request 10Nov2021 (MMR-161 – Analysis 6)

Table 74: Non-inferiority of Inv_MMR_Med vs Com_MMR in terms of adjusted GMC ratios at Day 42 (ATP cohort for immunogenicity post Dose 1, without Subjects excluded from all stat analysis) – Objectives 7 and 10

Antibody	Sub-group	Inv_MMR_Med	Adjusted GMC	COM_MMR	Adjusted GMC	Ratio	97.5% LL	97.5% UL
anti-Measles	Sex: Male	n=720	2436.4	n=695	2613.8	0.93	0.81	1.08
anti-Measles	Sex: Female	n=646	2662.7	n=683	2976.5	0.89	0.78	1.03
anti-Measles	Race: White Caucasian/ European Heritage	n=936	2437.6	n=957	2747.2	0.89	0.78	1
anti-Measles	Race: South East Asian Heritage	n=339	2416.4	n=340	2618.1	0.92	0.77	1.11
anti-Measles	Country: Spain	n=403	2725	n=402	2759	0.99	0.81	1.21
anti-Measles	Country: Czech	n=218	2219.7	n=230	2747.7	0.81	0.66	0.99
anti-Measles	Country: United States	n=271	2970.9	n=278	3307.3	0.9	0.71	1.14
anti-Measles	Country: Thailand	n=309	2329.5	n=309	2697.2	0.86	0.71	1.05
anti-Measles	Country: Finland	n=135	2126.3	n=128	2408.9	0.88	0.65	1.2
anti-Measles	Country: Malaysia	n=30	3522.5	n=31	1946	1.81	0.99	3.32
anti-Mumps (PPD)	Sex: Male	n=604	60	n=577	70.1	0.86	0.77	0.96
anti-Mumps	Sex: Female	n=527	60.3	n=578	73.1	0.82	0.73	0.93
anti-Mumps (PPD)	Race: White Caucasian/ European Heritage	n=778	60.8	n=800	72.9	0.83	0.76	0.91
anti-Mumps (PPD)	Race: South East Asian Heritage	n=288	53.7	n=291	64	0.84	0.71	0.99
anti-Mumps (PPD)	Country: Spain	n=335	61.4	n=323	69.4	0.88	0.76	1.02
anti-Mumps (PPD)	Country: Czech Republic	n=184	60.3	n=202	73.9	0.82	0.67	0.99
anti-Mumps (PPD)	Country: United States	n=201	70.7	n=217	83.3	0.85	0.71	1.02

Antibody	Sub-group	Inv_MMR_Med	Adjusted GMC	COM_MMR	Adjusted GMC	Ratio	97.5% LL	97.5% UL
anti-Mumps (PPD)	Country: Thailand	n=263	52.8	n=265	66.1	0.8	0.67	0.95
anti-Mumps (PPD)	Country: Finland	n=123	56.8	n=122	73.7	0.77	0.61	0.97
anti-Mumps	Country: Malaysia	n=25	64.5	n=26	46.2	1.4	0.76	2.55
anti-Mumps	Sex: Male	n=667	11.6	n=645	16.9	0.69	0.57	0.82
anti-Mumps	Sex: Female	n=598	9.7	n=642	15.8	0.61	0.51	0.74
anti-Mumps	Race: White Caucasian/ European Heritage	n=864	11.4	n=891	18.3	0.62	0.53	0.72
anti-Mumps	Race: South East Asian Heritage	n=318	8.1	n=323	11.5	0.7	0.54	0.91
anti-Mumps	Country: Spain	n=363	13.1	n=373	19.2	0.68	0.54	0.86
anti-Mumps	Country: Czech Republic	n=205	11.4	n=218	19	0.6	0.44	0.81
anti-Mumps	Country: United States	n=249	11.6	n=250	19.1	0.61	0.45	0.82
anti-Mumps	Country: Thailand	n=291	7.8	n=299	11.8	0.66	0.51	0.87
anti-Mumps	Country: Finland	n=130	9.0	n=123	14.2	0.64	0.42	0.97
anti-Mumps	Country: Malaysia	n=27	11.1	n=24	8.1	1.38	0.48	3.99
anti-Rubella	Sex: Male	n=718	53.8	n=694	59.6	0.9	0.82	1
anti-Rubella	Sex: Female	n=648	60.6	n=682	69.7	0.87	0.79	0.96
anti-Rubella	Race: White Caucasian/ European Heritage	n=937	52.9	n=956	60	0.88	0.81	0.96
anti-Rubella	Race: South East Asian Heritage	n=338	61.6	n=340	71.8	0.86	0.75	0.98
anti-Rubella	Country: Spain	n=402	58.8	n=401	66.2	0.89	0.78	1.01
anti-Rubella	Country: Czech	n=218	41.6	n=230	46.1	0.9	0.75	1.08
anti-Rubella	Country: United States	n=273	76.7	n=277	77.3	0.99	0.86	1.14
anti-Rubella	Country: Thailand	n=308	60.6	n=310	72	0.84	0.73	0.97
anti-Rubella	Country: Finland	n=135	38.5	n=128	54.3	0.71	0.58	0.87
anti-Rubella	Country: Malaysia	n=30	73.1	n=30	70.6	1.04	0.66	1.62

Source: Table 4 in 1.11.3 Clinical Information Amendment – Response to CBER Request 10Nov2021 (MMR-161 – Analysis 6)

6.6.9.4 Dropouts and/or Discontinuations

See Section 6.6.8 Study Population and Disposition for description of discontinuations.

6.6.9.5 Exploratory and Post Hoc Analyses

The confirmatory objectives were re-analyzed accounting for the randomization process. The p-value for each confirmatory objective was recomputed accounting for center and countries as minimization factors, and accounting for the sub-cohort of children in the U.S. for immunogenicity post Dose 2 as stratification factor. A total of 5000 re-

randomizations were performed to compute the p-value as the proportion of rerandomizations leading to a re-estimated value greater than the observed one. All re-estimated p-values were consistent with initial p-values, including non-significant results for anti-mumps antigens.

6.6.10 Safety Analyses

The analysis of safety was based on the TVC.

6.6.10.1 Overall incidence of AEs

The incidence and nature of solicited and unsolicited symptoms reported by subjects from Day 0 to Day 42 following study vaccination are presented in Table 75. At least one solicited or unsolicited symptom was reported by 85.1% of subjects in Inv_MMR_Min group, 86.3% in Inv_MMR_Med group and 84.8% in the Com_MMR groups post Dose 1; and in 63.9%, 67.4% and 67.0% post Dose 2, respectively.

Table 75: Incidence of symptoms (solicited and unsolicited) reported during the 43-day (Days 0-42) post-vaccination period following each dose (TVC, without Subjects excluded from all stat analysis)

Dose	Group	N	Any Symptom	95%LL	95%UL	General symptoms	95%LL	95%UL	Local symptoms	95%LL	95%UL
Dose 1	Inv_MMR_Min	1493	85.1%	83.2	86.8	83.1%	81.1	84.9	27.8%	25.5	30.1
Dose 1	Inv_MMR_Med	1497	86.3%	84.5	88.0	84.2%	82.3	86.0	28.9%	26.6	31.3
Dose 1	Com_MMR	1526	84.8%	82.9	86.6	81.8%	79.8	83.7	31.4%	29.1	33.8
Dose 2	Inv_MMR_Min	1449	63.9%	61.4	66.4	57.2%	54.6	59.8	18.2%	16.2	20.2
Dose 2	Inv_MMR_Med	1464	67.4%	64.9	69.8	59.8%	57.3	62.4	20.8%	18.8	23.0
Dose 2	Com_MMR	1483	67.0%	64.5	69.4	59.2%	56.7	61.7	22.3%	20.2	24.5

% =/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
Source: Table 40 in Clinical Study Report MMR-161

Compliance in returning symptom sheets for collection of local and general solicited AEs is given in Table 76.

Table 76: Compliance in returning symptom information (Total vaccinated cohort, without Subjects excluded from all stat analysis)

Dose	Group	Number of doses	Doses not according to protocol	Number of general SS	Compliance % general SS	Number of local SS	Compliance % local SS
1	Inv_MMR_Min	1493	7	1454	97.4	1453	97.3
1	Inv_MMR_Med	1497	7	1466	97.9	1464	97.8
1	Com_MMR	1526	4	1486	97.4	1482	97.1
2	Inv_MMR_Min	1449	2	1427	98.5	1428	98.6
2	Inv_MMR_Med	1464	2	1443	98.6	1440	98.4
2	Com_MMR	1483	3	1455	98.1	1456	98.2
Total	Inv_MMR_Min	2942	9	2881	97.9	2881	97.9
Total	Inv_MMR_Med	2961	9	2909	98.2	2904	98.1
Total	Com_MMR	3009	7	2941	97.7	2938	97.6

SS = Symptom screens/sheets used for the collection of local and general solicited AEs
Compliance % = (number of doses with symptom screen/sheet return / number of administered doses) X 100
Source: Table 39 in Clinical Study Report MMR-161

Table 77 provides the most frequently reported solicited local and general AEs, with respective sample sizes in Table 76. Local symptoms were solicited within the 4-day post-vaccination periods. General symptoms were solicited within the 15-day post-vaccination periods for post dose 1 and 2.

Table 77: Most frequently reported solicited local and general symptoms post-dose 1 (PD1) and post-dose 2 (PD2)

Symptom	Inv_MMR_Min	Inv_MMR_Med	Com_MMR
Local pain (PD1)	18.0%	17.9%	20.3%
Local redness (PD1)	16.0%	17.5%	19.3%
Local pain (PD2)	11.9%	12.7%	13.5%
Local redness (PD2)	11.1%	13.6%	14.9%
General irritability/ fussiness (PD1)	51.5%	54.0%	53.0%
Grade 3 irritability/ fussiness (PD1)	2.8%	3.5%	3.4%
General drowsiness (PD1)	37.9%	38.5%	39.2%
Grade 3 drowsiness (PD1)	1.8%	1.7%	1.6%
General loss of appetite (PD1)	39.2%	40.2%	39.8%
Grade 3 loss of appetite (PD1)	2.1%	1.4%	2.1%
fever >39.0°C (PD1)	4.3%	5.4%	4.4%
Fever related to vaccine	2.5%	2.9%	2.5%
Medical advice sought	6.5%	7.9%	6.2%
With rash	7.9%	9.1%	8.8%
fever >39.0°C (PD2)	2.0%	2.6%	1.8%
Fever related to vaccine	0.8%	0.8%	0.8%
Medical advice sought	4.3%	3.7%	3.3%
With rash	3.6%	4.4%	3.6%

Source: Reviewer-created table

In addition, 51.0% of subjects in Inv_MMR_Min, 53.0% in Inv_MMR_Med and 50.9% in Com_MMR groups reported at least one unsolicited AE post Dose 1; and 46.0%, 48.0% and 46.5% post Dose 2, respectively, during the 43-day reporting periods post vaccination.

6.6.10.3 Deaths

Three SAEs were fatal, one in each group. No fatalities were considered related to vaccination by investigator.

6.6.10.4 Nonfatal Serious Adverse Events

A total of 285 subjects reported one or more SAEs in this study. Specifically, 143 SAEs were reported in 91 subjects (6.1%) in Inv_MMR_Min, 174 SAEs were reported in 102 subjects (6.8%) in Inv_MMR_Med, and 147 SAEs were reported in 92 subjects (6.0%) in Com_MMR.

6.6.10.5 Adverse Events of Special Interest (AESI)

See the clinical reviewer's memo for discussion of AESIs.

6.6.10.6 Dropouts and/or Discontinuations

Eight subjects were withdrawn from the study due to an AE or an SAE (including the 3 fatal SAEs), 3 in the Inv_MMR_Min group, 2 in the Inv_MMR_Med group, and 3 in the Com_MMR group. See the clinical reviewer's memo for details.

7. INTEGRATED OVERVIEW OF EFFICACY/SAFETY

CBER agreed during pre-BLA review that no Integrated Summary of Safety nor Integrated Summary of Efficacy was required in the submission, and that an aggregated analysis of safety was not necessary because the Priorix used in each study contained a different potency, the concomitant vaccines administered varied by study population, and the study participants overall varied in age (12-15 months, 4-6 years, or older than 7 years of age).

8. CONCLUSIONS

Overall, the primary immunogenicity and safety endpoints were largely met in the five phase III studies. One exception is that in MMR-161, non-inferiority between Priorix and MMR-II in anti-mumps antibody concentration measured by (b) (4) was not met.

Two studies (MMR-160, MMR-161) showed slightly lower average anti-rubella antibody amount from Priorix over MMR-II, as measured by GMC ratio and SRR differences. In these studies, the associated non-inferiority objectives were still met, and the SRRs were high for both groups. In a third study (MMR-162) the difference in percentage of subjects above a cut-off threshold for anti-rubella measured with ELISA increased as the threshold increased. However, immunogenicity endpoints were not confirmatory in MMR-162, and the respective GMCs at day 42 were well above the pre-specified sero-response threshold. I defer to the clinical review team on the clinical significance of observed differences in anti-mumps and anti-rubella antibody concentrations in Priorix over MMR-II.

The safety profile of Priorix as compared to MMR-II appears to be satisfactory from a statistical perspective. Any observed differences in adverse event rates between groups has been considered acceptable by the clinical team.