Overview of GSK's MMR Vaccine

Remon Abu-Elyazeed MD, PhD

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GSK MMR Vaccine Development for the US

GSK's MMR vaccine (*PRIORIX*)

- First licensed in Germany in 1997; approved in > 100 countries outside US and over 400 million doses distributed worldwide

The goal of GSK's MMR development program is to bring a vaccine to the US market that:

1. fulfills the ACIP recommendations for measles, mumps and rubella vaccination [CDC, 2013]
2. demonstrates immunologic non-inferiority and comparable safety to the currently licensed US vaccine, *M-M-R II* (Merck & Co., Inc)
3. can be administered interchangeably to individuals who received a previous vaccination with *M-M-R II* or *ProQUAD*

PRIORIX Proposed Indication, Dose and Schedule

Indication:

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

Dose and Schedule:

- *PRIORIX* is administered as an approximately 0.5-mL dose by subcutaneous injection according to the following schedule.
  - The first dose is administered at 12 to 15 months of age. A second dose is administered at 4 to 6 years of age.
    - The second dose may be administered prior to 4 years of age, provided there is a minimum interval of 4 weeks between the doses of live measles, mumps, and rubella vaccine.
    - The second dose may also be administered at 7 years and older.

PRIORIX Phase III US Studies

Study	Age Group	Participants (GSK's MMR)
MMR-158* Immuno and safety of GSK's MMR vaccine compared to *M-M-R II* given as a 2nd dose at 4-6 years (co-ad with VV and DTaP-IPV)	4-6 years	4007 (2917)
MMR-159* Immuno and safety of GSK's MMR vaccine compared to *M-M-R II* given as a 2nd dose in children, adolescents and adults	≥7 years	911 (454)
MMR-160 Lot-to-lot consistency of GSK's MMR vaccine and immuno and safety compared to *M-M-R II* given as a1st dose at 12-15 months (co-ad with VV, HAV and PCV-13 vaccines)	12-15 months	5003 (3714)
MMR-161 Immuno and safety at an end of shelf-life potency of GSK's MMR vaccine compared to *M-M-R II* given as a 1st dose at 12-15 months (co-ad with VV, HAV and PCV-13 vaccines); 2nd dose in 2nd year of life	12-15 months	4516 (2990)
MMR-162 Safety and immuno at maximum potency of GSK's MMR vaccine compared to *M-M-R II* given as a 1st dose at 12-15 months (co-ad with VV, HAV and PCV-13)	12-15 months	1686 (1163)

* These studies demonstrate interchangeable administration of the MMR vaccines as the second dose

Demographic Characteristics For All Aggregated Studies (Total Vaccinated Cohort)

	Overall Study Population				US Study Population			
Ethnicity Geographic Ancestry	*PRIORIX* N = 11499		*MMR-II* N = 5242		*PRIORIX* N = 5752		*MMR-II* N = 2689	
	n	%	n	%	n	%	n	%
American Hispanic	**1641**	**14.3**	**752**	**14.3**	**1329**	**23.1**	**641**	**23.8**
Not American Hispanic	**9858**	**85.7**	**4490**	**85.7**	**4423**	**76.9**	**2048**	**76.2**
African Heritage / African American	**703**	**6.1**	**391**	**7.5**	**699**	**12.2**	**390**	**14.5**
American Indian / Alaskan Native	**278**	**2.4**	**94**	**1.8**	**276**	**4.8**	**93**	**3.5**
Asian Heritage	**2112**	**18.4**	**905**	**17.3**	**298**	**5.2**	**115**	**4.3**
Native Hawaiian / Other Pacific Islander	**23**	**0.2**	**8**	**0.2**	**23**	**0.4**	**8**	**0.3**
White - Caucasian / European Heritage	**7478**	**65.1**	**3474**	**66.2**	**3896**	**67.7**	**1828**	**67.9**
Other / Missed race	**905**	**7.9**	**370**	**7.1**	**560**	**9.7**	**255**	**9.5**

The demographic profile of the study participants represents the ethnically diverse US population and was similar between those who received *Priorix* and *M-M-R II*

PRIORIX: Safety Evaluation

1. Post-dose 1 in children aged 12 to 15 months
2. Post-dose 2 in children aged 12 to 15 Months
   - who received a Second Dose of *PRIORIX* 6 weeks after the First Dose
3. Post-dose 2 in children aged 4 to 6 years
4. Post-dose 2 in individuals aged 7 years or older

Safety Endpoints

In children and adults receiving 1 or 2 doses of *PRIORIX*

Event	Time Period
Injection Site Redness, Swelling, Pain	Day 0-3
Drowsiness, irritability, loss of appetite*	Day 0-14
Fever, Rash (including separate categories for measles-rubella like rash and varicella-like rash), parotid gland swelling, any signs of meningism including febrile seizure**, joint pain (arthralgia/arthritis)***	Day 0-42
Unsolicited Adverse Events	Day 0-42
New Onset Chronic Disease	Day 0-180
Adverse Events Prompting a medical visit	Day 0-180
Adverse Events Prompting an ER Visit	Day 0-180
Serious Adverse Events	Day 0- Study End

*drowsiness, irritability and loss of appetite are solicited symptoms in 12–15-month-old children; drowsiness and loss of appetite are solicited symptoms in 4–6-year-olds for only 4 days post-vaccination
** febrile seizures are only solicited in 12–15-month-old and 4–6-year-old children
*** joint pain (arthralgia / arthritis) is only solicited in adults / children 7 years and older

Incidence of Solicited Local and General Adverse Reactions after the First Dose Coadministered with *HAVRIX*, Varicella, and PCV13 Vaccines in Children Aged 12 to 15 Months (Study MMR-160 [NCT01702428], TVC)

Adverse Reaction	*PRIORIX* % (Grade 3*)	*M-M-R II* % (Grade 3*)
Local (within 4 Days)	**n = 3,555**	**n = 1,242**
Pain	25.9 (0.7)	28.1 (1.0)
Redness	24.5 (0.4)	25.2 (0.6)
Swelling	8.9 (0.3)	10.7 (0.4)
General (within 15 Days)	**n = 3,566**	**n = 1,243**
Drowsiness	44.9 (2.4)	47.1 (1.8)
Irritability	63.3 (4.9)	65.9 (4.7)
Loss of appetite	45.1 (2.0)	44.1 (2.5)
General (within 43 Days)	**n = 3,566**	**n = 1,243**
Measles/rubella-like rash	6.6 (3.0)	6.2 (2.0)
Fever (defined as temperature ≥38°C/100.4°F)	34.7 (2.9)	33.1 (2.6)
Parotid/ salivary gland swelling	0	0
Meningism including febrile convulsions	0.3	0.2

*Grade 3 was defined as: limb spontaneously painful or child cried when limb was moved (pain); diameter >20 mm (redness, swelling); temperature >39.5°C (fever); adverse event preventing normal, everyday activities (drowsiness); not eating at all (loss of appetite); crying inconsolably (irritability/fussiness).

Incidence of Solicited Local and General Adverse Reactions after the second Dose* administered 6 Weeks after the First Dose (MMR-161 [NCT01681992], TVC)

Adverse Reaction	*PRIORIX* % (Grade 3*)	*M-M-R II* % (Grade 3*)
Local (within 4 Days)	**n =2867**	**n = 1456**
Pain	12.7 (0.3)	13.5 (0.2)
Redness	13.6 (0.2)	14.9 (0.9)
Swelling	6.3 (0.0)	6.6 (0.5)
General (within 43 Days)	**n = 2869**	**n = 1455**
Measles/rubella-like rash	1.0 (0.6)	1.0 (0.8)
Fever (defined as temperature ≥38◦C/100.4◦F)	32.5 (3.5)	34.3 (3.2)
Parotid/ salivary gland swelling	0.1	0
Meningism including febrile convulsions	0.3	0.3

*following previous administration of the same vaccine

There were no co-administration vaccines with the second dose, so drowsiness, irritability, or loss of appetite were not solicited.

*Grade 3 defined as crying when limb was moved or limb was spontaneously painful (pain), diameter >20 mm (redness and swelling), temperature >39.5 °C (fever), preventing normal activity (drowsiness and irritability), crying inconsolably (irritability), and not eating at all (loss of appetite).

Incidence of Solicited Local and General Adverse Reactions after the Second Dose* Coadministered with *KINRIX* and Varicella vaccines in Children Aged 4 to 6 Years (MMR-158 [NCT01621802], TVC)

Adverse Reaction	*PRIORIX* % (Grade 3*)	*M-M-R II* % (Grade 3*)
Local (within 4 Days)	**n = 727**	**n = 267**
Pain	40.6 (3.0)	40.8 (1.5)
Redness	21.6 (1.2)	25.8 (1.5)
Swelling	11.3 (0.4)	10.5 (1.1)
General (within 4 Days)	**n = 731**	**n = 268**
Drowsiness	27.2 (1.4)	26.9 (1.1)
Loss of appetite	21.1 (0.3)	22.0 (0.7)
General (within 43 Days)	**n = 731**	**n = 268**
Measles/rubella-like rash	1.9 (0.4)	1.9 (0.0)
Fever (defined as temperature ≥38°C/100.4°F)	24.1 (1.0)	24.6 (2.2)
Parotid/ salivary gland swelling	0	0
Meningism including febrile convulsions	0	0.7

*The initial dose was M-M-R II or ProQuad in the second year of life

*Grade 3 was defined as: limb spontaneously painful or child cried when limb was moved (pain); diameter >50 mm (redness, swelling); temperature >39.5°C (fever); adverse event preventing normal, everyday activities (drowsiness); not eating at all (loss of appetite).

Incidence of Solicited Local and General Adverse Reactions after the Second Dose* in Individuals Aged 7 Years and Older (MMR-159 [NCT02058563], TVC)

Adverse Reaction	*PRIORIX* % (Grade 3*)	*M-M-R II* % (Grade 3*)
Local (within 4 Days)	**n = 433**	**n = 445**
Pain	11.8 (0.2)	11.5 (0.0)
Redness	12.2 (0.0)	11.7 (0.0)
Swelling	5.3 (0.0)	6.5 (0.0)
General (within 43 Days)	**n = 431**	**n = 445**
Fever (defined as temperature ≥38°C/100.4°F)	3.0 (0.2)	5.2 (1.3)
Measles/rubella-like rash	0 (0.0)	0.4 (0.0)
Joint pain (arthralgia/arthritis)	1.9 (0.0)	0.9 (0.0)
Parotid/ salivary gland swelling	0.2 (0.2)	0.2 (0.0)
Meningism/seizure	0.2	0.2

*following previous administration of a combined measles-, mumps-, and rubella-containing vaccine

*Grade 3 was defined as: limb was painful at rest, which prevented normal everyday activities (pain); diameter >50 mm (redness and swelling); temperature >39.5 C (fever); adverse event preventing normal, everyday activities (joint pain, rash/exanthem, meningism/seizure); swelling with accompanying general symptoms (parotid/salivary gland swelling).

PRIORIX: Immunogenicity Evaluation

1. Post-dose 1 in children aged 12 to 15 months
2. Post-dose 2 in children aged 12 to 15 Months
   - who received a **Second Dose** of *PRIORIX* 6 weeks after the First Dose
3. Post-dose 2 in children aged 4 to 6 years
4. Post-dose 2 in individuals aged 7 years or older

Immune Responses in Children Aged 12 to 15 Months 42 days after the First Dose of *PRIORIX* Compared with *M-M-R II* Administered with *HAVRIX*, Varicella, and PCV13 Vaccines (MMR-160 [NCT01702428], ATP)

Antibody	*Priorix* N= 3187-3248 SR rate	*MMR-II* N=1107-1137 SR rate	Difference (*Priorix* minus *MMR-II*) %	95% CI LL	95% CI UL	*Priorix* N= 3187-3248 Adjusted GMC	*MMR-II* N=1107-1137 Adjusted GMC	Adjusted GMC ratio (*Priorix* over *MMR-II*) Value	95% CI LL	95% CI UL
Anti-measles antibody	98.2	98.0	0.18	-0.68	1.25	3165.2	3215.4	0.98	0.93	1.05
Anti-mumps antibody	98.4	97.6	0.81	-0.10	1.96	76.4	73.0	1.05	0.99	1.11
Anti-rubella antibody	97.3	98.5	-1.15	-2.00	-0.15	52.5	60.0	0.87	0.83	0.92

[a]SRR = Seroresponse rate - **Non-inferiority criterion met** for all antigens (lower limit of 2-sided 95% CI for the difference was ≥-5%)
[b]GMC = Geometric mean antibody concentration adjusted for country- **Non-inferiority criterion met** for all antigens (lower limit of 2-sided 95% CI for the ratio was ≥0.67).

Immune Responses in Children Aged 12 to 15 Months 42 Days after the Second Dose* of *PRIORIX* Compared with *M-M-R II* administered 6 Weeks after the First Dose (MMR-161, [NCT01681992], ATP)

Parameter	Antigen	*PRIORIX* n = 199-259	*M-M-R II* n = 212-257
SRR (%)	Measles	98.4	98.4
	Mumps	100	98.6
	Rubella	99.6	99.6
GMC	Measles (mIU/mL)	4,557.7	4,453.9
	Mumps (ELU/mL)	94.1	86.4
	Rubella (IU/mL)	110.7	110.9

*following previous administration of the same vaccine

SRR = Seroresponse rate
GMC = Geometric mean antibody concentration

Immune Responses in Children Aged 4 to 6 Years 42 Days after the Second Dose* of *PRIORIX* Compared with *M-M-R II* Administered with *KINRIX* and Varicella Vaccines (MMR-158, [NCT01621802], ATP)

Antibody	*Priorix* N=697-698 SRR (%)	*MMR-II* N=249-250 SRR (%)	Difference (*Priorix* minus *MMR-II*) %	97.5% CI LL	97.5% CI UL	*Priorix* N=697-698 Adjusted GMC	*MMR-II* N=249-250 Adjusted GMC	Adjusted GMC ratio (*Priorix* over *MMR-II*) Value	97.5% CI LL	97.5% CI UL
Anti-measles	100	100	0.00	-0.72	1.98	4285.0	4333.5	0.99	0.92	1.06
Anti-mumps	100	100	0.00	-0.72	1.97	171.3	188.5	0.91	0.83	1.00
Anti-rubella	99.9	100	-0.14	-0.98	1.84	97.1	94.5	1.03	0.97	1.09

*The initial dose was M-M-R II, or ProQuad in the second year of life.

[a]SRR = Seroresponse rate - **Non-inferiority criterion met** for all antigens (lower limit of 2-sided 97.5% CI for the difference was ≥-5%)
[b]GMC = Geometric mean antibody concentration adjusted for pre-vaccination concentration - **Non-inferiority criterion met** for all antigens (lower limit of 2-sided 97.5% CI for the ratio was ≥0.67).

Immune Responses in Individuals Aged 7 Years or Older 42 Days after the Second Dose* of *PRIORIX* Compared with *M-M-R II* (MMR-159 [NCT02058563], ATP)

Antibody	*Priorix* N=433	*MMR-II* N=436	Difference (*Priorix* minus *MMR-II*)			*Priorix* N=433	*MMR-II* N=436	Adjusted GMC ratio (*Priorix* over *MMR-II*)		
			%	95% CI				Value	95% CI	
	SRR (%)	SRR (%)		LL	UL	Adjusted GMC	Adjusted GMC		LL	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

*following previous administration of a combined measles-, mumps-, and rubella-containing vaccine

[a]SRR = Seroresponse rate - **Non-inferiority criterion met** for all antigens (lower limit of 2-sided 95% CI for the difference was ≥-5%)
[b]GMC = Geometric mean antibody concentration adjusted for pre-vaccination concentration, gender, age, and country - **Non-inferiority criterion met** for all antigens (lower limit of 2-sided 95% CI for the ratio was ≥0.67).

Interchangeable administration with other Measles-, Mumps-, and Rubella-Containing Vaccines

Based on the comparable immunogenicity data in primed subjects who received either MMR vaccine in studies MMR-158 and MMR-159, Priorix can be administered interchangeably with other MMR vaccines.

NCT01621802 & NCT02058563

Concomitant Administration

1. Concomitant Administration with *HAVRIX*, Varicella Vaccine, and PCV13

2. Concomitant Administration with *KINRIX* and Varicella Vaccine

No evidence that *PRIORIX* interfered with the antibody responses to the antigens in the above vaccines compared with the immune responses of *M-M-R II* co-administered with these vaccines (MMR-160 & MMR-158)

NCT01702428 & NCT01621802

Immunogenicity of Priorix in Infants Less than 12 Months of Age

Seroconversion rates at Day 42-43 Post-dose 1 and Post-dose 2 of Priorix (According-to-Protocol Immunogenicity Cohort)

Study/Age at each dose	Antigen	Seroconversion[a] Rate % (95% CI) in MMR+V group			
		N	Post-dose 1	N	Post-dose 2
Goh *et al*. 2007[1] 9–10 months at dose 1 (MMR+V) 12 months at dose 2 (MMR+V)	Measles	122	**92.6** (86.5–96.6)	123	100 (97–100)
	Mumps	118	**91.5** (85–95.9)	121	99.2 (95.5–100)
	Rubella	123	**100** (97–100)	123	100 (97–100)
Lalwani *et al*. 2015[2] 9–10 months at dose 1 (MMR) 15 months at dose 2 (MMR+V)	Measles	72	**87.5** (77.6–94.1)	72	100 (95–100)
	Mumps	72	**83.3** (72.7–91.9)	72	100 (95–100)
	Rubella	73	**100** (95.1–100)	73	100 (95.1–100)

1. Goh P, Lim FS, Han HH, et al. *Infection*. 2007;35(5):326-333. http://dx.doi.org/10.1007/s15010-007-6337-z.
2. Lalwani S, Chatterjee S, Balasubramanian S, et al. *BMJ Open*. 2015;5(9):e007202. http://dx.doi.org/10.1136/bmjopen-2014-007202.

Conclusion on *PRIORIX* Safety

PRIORIX safety profile:

- is acceptable, and comparable to that of *M-M-R II*
- is generally well tolerated in subjects 12-15 months of age, 4-6 YOA, and ≥ 7 YOA when given as a first dose or second dose
- second dose has a safety profile comparable to that of the first dose
- safety profile following co-administration of routine vaccines is comparable to *M-M-R II* co-administered with the same vaccines
- safety profile in subjects enrolled in the US is comparable to the overall global enrollment
- subset analysis (e.g. race, gender) showed that the safety profile is comparable to that of the overall study population.

Conclusion on *PRIORIX* Immunogenicity

- *PRIORIX* demonstrated non-inferiority of the immune response compared to *M-M-R II*
  - in subjects 12-15 months of age after a single dose of *PRIORIX*
  - in subjects 4-6 YOA and ≥7 YOA after *PRIORIX* given as a second dose of MMR vaccine.
- *PRIORIX* can be administered interchangeably to individuals who received a previous vaccination with *M-M-R II or ProQUAD*
- Immune response to any of the antigens contained in *PRIORIX* or the coadministered vaccines was similar to the immune responses obtained when *M-M-R II* was coadministered with the same routine US pediatric vaccines.

GSK's MMR Vaccine Development for the US meets all ambitions to bring PRIORIX to the US market

1. fulfills the ACIP recommendations for measles, mumps and rubella vaccination [CDC, 2013]

2. demonstrates immunologic non-inferiority and comparable safety to the currently licensed US vaccine, *M-M-R II* (Merck & Co., Inc)

3. can be administered interchangeably to individuals who received a previous vaccination with *M-M-R II* or *ProQUAD.*

Thank You

GSK *PRIORIX* Phase II & III Published Studies

Phase II

1. Mufson MA, Diaz C, Leonardi M, Harrison CJ, Grogg S, Carbayo A, Carlo-Torres S, JeanFreau R, Quintero-Del-Rio A, Bautista G, Povey M, Da Costa C, Nicholson O, Innis BL. Safety and Immunogenicity of Human Serum Albumin-Free MMR Vaccine in US Children Aged 12-15 Months. *J Pediatric Infect Dis Soc*. 2015 Dec;4(4):339-48. DOI: http://dx.doi.org/10.1093/jpids/piu081. Epub 2014 Aug 7. PMID: 26582873; PMCID: PMC4681379.
2. Berry AA, Abu-Elyazeed R, Diaz-Perez C, Mufson MA, Harrison CJ, Leonardi M, Twiggs JD, Peltier C, Grogg S, Carbayo A, Shapiro S, Povey M, Baccarini C, Innis BL, Henry O. Two-year antibody persistence in children vaccinated at 12-15 months with a measles-mumps-rubella virus vaccine without human serum albumin. *Hum Vaccin Immunother*. 2017 May 8:1. DOI: http://dx.doi.org/10.1080/21645515.2017.1309486.

Phase III

1. Abu-Elyazeed R, Jennings W, Severance R, Noss M, Caplanusi A, Povey M, Henry O. Immunogenicity and safety of a second dose of a measles-mumps-rubella vaccine administered to healthy participants 7 years of age or older: A phase III, randomized study. *Hum Vaccin Immunother*. 2018 Jun 14:1-8. DOI: http://dx.doi.org/10.1080/21645515.2018.1489186.
2. The MMR-162 Study Group (2018) Safety and immunogenicity of an upper-range release titer measles-mumps-rubella vaccine in children vaccinated at 12 to 15 months of age: a phase III, randomized study, *Hum Vaccin Immunother.* DOI: http://dx.doi.org/10.1080/21645515.2018.1502527.
3. Klein N, Abu-Elyazeed R, Povey M, Parra M, Diez-Domingo J, Ahonen A, Korhonen T, Tinoco J, Weiner L, Marshall G, Silas P, Sarpong K, Ramsey K, Fling J, Speicher D, Campos M, Munjal I, Peltier C, Vesikari T, Baccarini C, Caplanusi A, Gillard P, Carryn S, Henry O. Immunogenicity and safety of a measles-mumps-rubella vaccine administered as a first dose to children aged 12 to 15 months: a phase III, randomized, noninferiority, lot-to-lot consistency study. *J Pediatr Infect Dis Soc.* 2020;9(2):194-201. DOI: http://dx.doi.org/10.1093/jpids/piz010.
4. MMR-158 Study Group. A second dose of a measles-mumps-rubella vaccine administered to healthy four-to-six-year-old children: a phase III, observer-blind, randomized, safety and immunogenicity study comparing GSK MMR and *M-M-R II* with and without DTaP-IPV and varicella vaccines co-administration. *Hum Vaccin Immunother*. 2019;15(4):786-799. DOI: http://dx.doi.org/10.1080/21645515.2018.1554971. Epub 2019 Feb 20.
5. MMR-161 Study Group. Immunogenicity and safety of measles-mumps-rubella vaccine at two different potency levels administered to healthy children aged 12-15 months: A phase III, randomized, non-inferiority trial. *Vaccine*. 2018 Sep 11;36(38):5781-5788. DOI: http://dx.doi.org/10.1016/j.vaccine.2018.07.076. Epub 2018 Aug 10. PubMed PMID: 30104117.

How Supplied/Storage and Handling

How Supplied[1]

- PRIORIX is supplied as 2 components in 1 box (NDC 58160-824-15):
  - ➢10 single-dose vials of lyophilized vaccine (powder): NDC 58160-831-03
  - ➢10 single-dose prefilled syringes of sterile water diluent (packaged without needles): NDC 58160-833-02

Storage before Reconstitution[1]

- **Lyophilized vaccine vials**: Store refrigerated between 36°F and 46°F (2°C and 8°C) in the original packaging in order to protect vials from light.
- **Prefilled syringe of sterile water diluent**: Store refrigerated between 36°F and 46°F (2°C and 8°C) or at controlled room temperature up to 77°F (25°C).
- Do not freeze vaccine or diluent. Discard vaccine if frozen.

Storage after Reconstitution[1]

- Administer PRIORIX immediately or store refrigerated between 36°F and 46°F (2°C and 8°C) for up to 8 hours.

Shelf Life[2]

- 2 years

1. Prescribing Information for PRIORIX
2. Global Data Sheet for PRIORIX