GSK Medicine: GSK Biologicals' candidate measles-mumps-rubella-varicella (MMRV) vaccine

Study No.: MMRV (208136) – Meta-analysis - 201103

Title: Integrated Summary Output (ISO) on febrile convulsions

Rationale: The aim of this study was to assess the possible risk of febrile convulsions and to present the risk benefit analysis based on the assumption that there is a class effect of MMRV vaccines with regard to febrile convulsions
Priorix: GSK Biologicals' measles-mumps-rubella (MMR) vaccine
Varilrix: GSK Biologicals' varicella (V) vaccine

Objectives: To generate an ISO on febrile convulsions

Indication: Measles, Mumps, Rubella, Varicella disease

Study Investigators/Centres: Not applicable

Research Methods:

Data Source: Meta analysis data for all subjects reporting febrile convulsions based on all clinical studies using either the first Human Serum Albumin (HSA) free formulation of MMRV or the final commercial formulation (secondary meta analysis**) or only studies using the final commercial formulation carried out in subjects aged 3 years or younger (primary meta analysis*).

* Primary meta analysis was based on the following studies: 208136-038, 103388 & 104690, 104020, 104389, 105908, 105909, 106670, 100388, 110058 and 110876
** Secondary meta analysis was based on the studies used for primary meta analysis and the additional following studies: 208136-007, 208136-013, 208136-014, 208136-016, 208136-017, 208136-018, 208136-019 and 208136-022
For data concerning those individual studies, please refer to the individual CTRS.

Study Design: Prospective cohort for Meta analysis of Febrile convulsions in MMRV vaccinated subjects

Study Population: All interventional GSK sponsored studies within the MMRV clinical development plan that were completed as of March2011. Subjects who had received either MMRV vaccine (MMRV Group), MMR or MMR+V vaccines (Control Group)

Study Exposures, Outcomes:
For each meta-analysis, the outcomes below were considered.
Primary Outcomes:

- Percentage of subjects reporting the occurrence of febrile convulsion as per Brighton level 1-4* between Day 5 and Day 12 (inclusive) post-vaccination regardless of the study dose

* Brighton levels are defined as follows:

- Level 1 of diagnostic certainty: witnessed sudden loss of consciousness AND generalized, tonic, clonic, tonic-clonic, or atonic motor manifestations
- Level 2 of diagnostic certainty: history of unconsciousness AND generalized, tonic, clonic, tonic-clonic, or atonic motor manifestations
- Level 3 of diagnostic certainty: history of unconsciousness AND other generalized motor manifestations
- Level 4 of diagnostic certainty: reported generalized convulsive seizure with insufficient evidence to meet the case definitions for Level 1, 2 or 3 of diagnostic certainty above
- Level 5 of diagnostic certainty: Not a case of generalized convulsive seizure

Secondary Outcomes:

- Percentage of subjects reporting the occurrence of febrile convulsion as per Brighton level 1-3 between Day 5 and Day 12 (inclusive) post-vaccination regardless of the study dose
- Percentage of subjects reporting the occurrence of febrile convulsion as per Brighton level 1-3 between Day 7 and Day 10 (inclusive) post-vaccination regardless of the study dose
- Percentage of subjects reporting the occurrence of febrile convulsion as per Brighton level 1-4 between Day 7 and Day 10 (inclusive) post-vaccination regardless of the study dose
- Percentage of subjects reporting the occurrence of febrile convulsion as per Brighton level 1-3 within the 31-day (Days 0-30) post vaccination period regardless of the study dose
- Percentage of subjects reporting the occurrence of febrile convulsion as per Brighton level 1-4 within the 31-day (Days 0-30) post vaccination period regardless of the study dose
- Percentage of subjects reporting the occurrence of febrile convulsion as per Brighton level 1-3 within the 43-day (Days 0-42) post vaccination period regardless of the study dose
- Percentage of subjects reporting the occurrence of febrile convulsion as per Brighton level 1-4 within the 43-day (Days 0-42) post vaccination period regardless of the study dose

Data Analysis Methods:
Analysis was primarily performed on the Total vaccinated Cohort – primary meta-analysis and secondarily on the Total

Vaccinated Cohort – secondary meta-analysis.
- The Total vaccinated Cohort – primary meta-analysis included all subjects less than 3 years of age and who had received at least one dose of the final commercial formulation of MMRV vaccine (MMRV Group) or a dose of MMR or MMR+V vaccines (Control Group).
- The Total vaccinated Cohort – secondary meta-analysis included all subjects who had received at least one dose of either the HSA-free formulation of MMRV or the final commercial formulation (MMRV Group), or a dose of MMR or MMR+V vaccines (Control Group).
For both cohorts and for each group, the percentages of subjects reporting the occurrence of febrile convulsion as per Brighton levels 1-3 and 1-4 were tabulated for each follow-up period: between Day 5 and Day 12, between Day 7 and Day 10, within the 31-day (Days 0-30) and within the 43-day (Days 0-42) post vaccination period, regardless of the study doseDifferences between MMRV and the control Group (MMR or MMR+V) were evaluated in terms of relative risks (RR). The RR and its 95 % Confidence Intervals (CI's) were based on the exact conditional likelihood approach adjusted for the study effect.

Limitations: Studies without febrile convulsion or without control group did not contribute to the computation of the relative risk

Study Results: The secondary meta analysis showed that the RR of MMRV over the control was 2.84 at Day 5-12 as per Brighton level 1-4 while the primary meta analysis showed the RR of MMRV over the control to be 3.96, for the same time period and same Brighton level.

Demographic/Baseline Characteristics:	**MMRV Group**	**Control Group**
Total N (secondary meta-analysis)	10426	6660
Age	From 11 months to 6 years	From 11 months to 6 years
Total N (primary meta-analysis)	7317	4455
Age	From 11 months to less than 3 years	From 11 months to less than 3 years

Primary Outcome: Percentage of subjects reporting the occurrence of febrile convulsion and relative risk (Total Vaccinated cohort - primary meta-analysis)

		MMRV Group N = 7317				**Control Group N = 4455**				**Relative Risk (MMRV over Control)**		
				95% CI				**95% CI**			**95% CI**	
Time window	**Brighton Collaboration Criteria Level**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**RR**	**LL**	
Day 5-12	Level 1 to 3	1	0.01	0.00	0.08	0	0.00	0.00	0.08	ND	ND	IND
	Level 1 to 4**	10	0.14	0.07	0.25	2	0.04	0.01	0.16	3.96	0.78	38.87
Day 7-10	Level 1 to 3	1	0.01	0.00	0.08	0	0.00	0.00	0.08	ND	ND	ND
	Level 1 to 4	10	0.14	0.07	0.25	1	0.02	0.00	0.13	7.71	1.01	347.4
Day 0-30	Level 1 to 3	3	0.04	0.01	0.12	0	0.00	0.00	0.08	INF	0.00	INF
	Level 1 to 4	18	0.25	0.15	0.39	8	0.18	0.08	0.35	1.53	0.57	4.34
Day 0-42	Level 1 to 3	4	0.05	0.01	0.14	0	0.00	0.00	0.08	INF	0.03	INF
	Level 1 to 4	22	0.30	0.19	0.45	8	0.18	0.08	0.35	1.61	0.62	4.53

N = number of subjects with least one administered dose
n/% = number/percentage of subjects reporting febrile convulsion
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
*95% CI = 95% confidence interval for relative risk
NA = Not Applicable as all events were in one stratum
ND = the event did not contribute to the evaluation of the relative risk as the study included the MMRV Group only (see also Limitations section). ** Primary Outcome measure

Primary Outcome: Percentage of subjects reporting the occurrence of febrile convulsion **post dose 1** and relative risk (Total Vaccinated cohort - primary meta-analysis)

		MMRV Group N = 7102				Control Group N = 4236				Relative Risk (MMRV over Control)		
				95% CI				95% CI			95% CI*	
Time window	**Brighton Collaboration Criteria Level**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**RR**	**LL**	**UL**
Day 5-12	Level 1 to 3	1	0.01	0.00	0.08	0	0.00	0.00	0.09	ND	ND	ND
	Level 1 to 4	9	0.13	0.06	0.24	1	0.02	0.00	0.13	7.18	0.91	327.9
Day 7-10	Level 1 to 3	1	0.01	0.00	0.08	0	0.00	0.00	0.09	ND	ND	ND
	Level 1 to 4	9	0.13	0.06	0.24	1	0.02	0.00	0.13	7.18	0.91	327.9
Day 0-30	Level 1 to 3	3	0.04	0.01	0.12	0	0.00	0.00	0.09	INF	0.00	INF
	Level 1 to 4	15	0.21	0.12	0.35	3	0.07	0.01	0.21	2.97	0.74	17.25
Day 0-42	Level 1 to 3	3	0.04	0.01	0.12	0	0.00	0.00	0.09	INF	0.00	INF
	Level 1 to 4	16	0.23	0.13	0.37	3	0.07	0.01	0.21	2.97	0.74	17.25

N = number of subjects with least one administered dose
n/% = number/percentage of subjects reporting febrile convulsion
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
*95% CI = 95% confidence interval for relative risk
NA = Not Applicable as all events were in one stratum
ND = the event did not contribute to the evaluation of the relative risk as the study included the MMRV Group only (see also Limitations section)

Primary Outcome: Percentage of subjects reporting the occurrence of febrile convulsion **post dose 2** and relative risk (Total Vaccinated cohort - primary meta-analysis)

		MMRV Group N = 5151				Control Group N = 1772				Relative Risk (MMRV over Control)		
				95% CI				95% CI			95% CI*	
Time window	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**RR**	**LL**	**UL**
Day 5-12	Level 1 to 4	1	0.02	0.00	0.11	0	0.00	0.00	0.21	INF	0.01	INF
	Level 1 to 3	0	0.00	0.00	0.07	0	0.00	0.00	0.21	ND	ND	ND
Day 7-10	Level 1 to 4	1	0.02	0.00	0.11	0	0.00	0.00	0.21	INF	0.01	INF
	Level 1 to 3	0	0.00	0.00	0.07	0	0.00	0.00	0.21	ND	ND	ND
Day 0-30	Level 1 to 4	3	0.06	0.01	0.17	1	0.06	0.00	0.31	1.26	0.10	66.96
	Level 1 to 3	0	0.00	0.00	0.07	0	0.00	0.00	0.21	ND	ND	ND
Day 0-42	Level 1 to 4	5	0.10	0.03	0.23	1	0.06	0.00	0.31	1.80	0.19	86.62
	Level 1 to 3	1	0.02	0.00	0.11	0	0.00	0.00	0.21	INF	0.00	INF

N = number of subjects with least one administered dose
n/% = number/percentage of subjects reporting febrile convulsion
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
*95% CI = 95% confidence interval for relative risk
NA = Not Applicable as all events were in one stratum
ND = the event did not contribute to the evaluation of the relative risk as the study included the MMRV Group only (see also Limitations section)

Primary Outcome: Percentage of subjects reporting the occurrence of febrile convulsion and relative risk (Total Vaccinated cohort - secondary meta-analysis)

		MMRV Group N = 10426				Control Group N = 6660				Relative Risk (MMRV over Control)		
				95% CI				**95% CI**			**95% CI**	
Time window	**Brighton Collaboration Criteria Level**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**RR**	**LL**	**UL**
Day 5-12	Level 1 to 3	1	0.01	0.00	0.05	0	0.00	0.00	0.06	ND	ND	ND
	Level 1 to 4	12	0.12	0.06	0.20	3	0.05	0.01	0.13	2.84	0.69	16.65
Day 7-10	Level 1 to 3	1	0.01	0.00	0.05	0	0.00	0.00	0.06	ND	ND	ND
	Level 1 to 4	12	0.12	0.06	0.20	2	0.03	0.00	0.11	4.16	0.84	40.36
Day 0-30	Level 1 to 3	3	0.03	0.01	0.08	0	0.00	0.00	0.06	INF	0.00	INF
	Level 1 to 4	20	0.19	0.12	0.30	10	0.15	0.07	0.28	1.28	0.52	3.30
Day 0-42	Level 1 to 3	4	0.04	0.01	0.10	0	0.00	0.00	0.06	INF	0.03	INF
	Level 1 to 4	25	0.24	0.16	0.35	10	0.15	0.07	0.28	1.46	0.61	3.66

N = number of subjects with least one administered dose
n/% = number/percentage of subjects reporting febrile convulsion
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
NA = Not Applicable as all events were in one stratum
ND = the event did not contribute to the evaluation of the relative risk as the study included the MMRV Group only (see also Limitations section).

Conclusion: The meta analysis showed that the relative risk of febrile convulsions (MMRV group over Control group) per Brighton level 1-4 at Day 5-12 was 3.96 (95% CI: 0.78-38.87) for the primary meta analysis.

Publications: None

Date updated: 20-Sep-2011