

*In February 2013, GlaxoSmithKline (GSK) announced a commitment to further clinical transparency through the public disclosure of GSK Clinical Study Reports (CSRs) on the GSK Clinical Study Register.*

*The following guiding principles have been applied to the disclosure:*

- Information will be excluded in order to protect the privacy of patients and all named persons associated with the study*
- Patient data listings will be completely removed\* to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the **GSK Clinical Study Register**.*

- Aggregate data will be included; with any direct reference to individual patients excluded*

*\*Complete removal of patient data listings may mean that page numbers are no longer consecutively numbered*

**PASS information**

<b>Title</b>	An observational cohort study to assess the risk of autoimmune diseases in adolescent and young adult women aged 9 to 25 years exposed to Cervarix® in the United Kingdom
<b>Version identifier of the final study report</b>	Study Report - Final
<b>Date of last version of the final study report</b>	17 March 2015
<b>EU PAS Register Number</b>	ENCEPP/SDPP/4584
<b>Active substance</b>	J07BM02-Papillomavirus (human types 16, 18)
<b>Medicinal product</b>	Cervarix®, Human Papillomavirus vaccine (Types 16, 18)
<b>Product reference</b>	EU/1/07/419
<b>Procedure number</b>	NA
<b>Marketing Authorisation Holder(s)</b>	GlaxoSmithKline Biologicals Rue de l'Institut 89 1330 Rixensart, Belgium
<b>Joint PASS</b>	No
<b>Research question and objectives</b>	To assess the risk of neuroinflammatory/ophthalmic autoimmune diseases and other pre-specified autoimmune diseases within 12 months following the administration of the first dose of <i>Cervarix</i>
<b>Country(-ies) of study</b>	United Kingdom
<b>Author</b>	Coordinating author: <ul style="list-style-type: none"> <li>• [REDACTED], Project Manager – Science Writing</li> </ul> GSK contributors: <ul style="list-style-type: none"> <li>• [REDACTED], Director, Head of Global Epidemiology</li> <li>• [REDACTED], Project Statistician</li> <li>• [REDACTED], Epidemiological Scientist/Statistician, [REDACTED], for GSK Biologicals</li> </ul>

	<ul style="list-style-type: none"> <li>• [REDACTED], Therapeutic Area Head (<i>Cervarix</i>), Safety Evaluation &amp; Risk Management (SERM), VCSP</li> <li>• [REDACTED], Safety Physician, VCSP</li> <li>• [REDACTED], Global Regulatory Affairs, [REDACTED] for GSK Biologicals</li> <li>• [REDACTED], Global Regulatory Lead</li> <li>• [REDACTED], Study Delivery Lead (SDL)</li> </ul> <p>Non GSK contributing authors (external experts):</p> <ul style="list-style-type: none"> <li>• [REDACTED] (previously known as [REDACTED]), Senior Researcher, CPRD Research Team</li> <li>• [REDACTED], Director Epidemiology at [REDACTED]</li> <li>• [REDACTED], [REDACTED]</li> <li>• [REDACTED], [REDACTED]</li> </ul>
--	---

**Marketing authorisation holder(s)**

<b>Marketing authorisation holder(s)</b>	GlaxoSmithKline Biologicals Rue de l'Institut 89, 1330 Rixensart, Belgium
<b>MAH contact person</b>	[REDACTED], Director, Head of Global Epidemiology, GSK Biologicals

Copyright 2015 of the GlaxoSmithKline group of companies. All rights reserved.  
Unauthorised copying or use of this information is prohibited.

## TABLE OF CONTENTS

	<b>PAGE</b>
1. ABSTRACT .....	49
2. LIST OF ABBREVIATIONS .....	51
3. ETHICS .....	52
3.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB) .....	52
3.2. Ethical conduct of the study .....	52
3.3. Subject information and consent .....	52
4. INVESTIGATORS .....	52
5. OTHER RESPONSIBLE PARTIES .....	52
6. MILESTONES .....	54
7. RATIONALE AND BACKGROUND .....	54
8. RESEARCH QUESTION AND OBJECTIVES .....	57
8.1. Primary objective .....	57
8.2. Secondary objectives .....	58
8.3. Exploratory objective .....	58
9. AMENDMENTS AND UPDATES .....	58
10. RESEARCH METHODS .....	59
10.1. Study design .....	59
10.1.1. Overview .....	59
10.2. Setting .....	60
10.2.1. The UK HPV National Immunization Programme and Cervarix coverage .....	60
10.2.2. The UK Clinical Practice Research Datalink General Practitioner OnLine database (CPRD GOLD) .....	61
10.2.3. Autoimmune diseases incidence rates for UK, USA, and recorded in the CPRD GOLD .....	62
10.2.3.1. Background Tables .....	62
10.2.4. Study Period .....	68
10.3. Subjects .....	68
10.3.1. Number of subjects .....	68
10.3.2. Inclusion criteria .....	68
10.3.2.1. Inclusion criteria for the exposed female cohort .....	68
10.3.2.2. Inclusion criteria for the unexposed historical female cohort .....	68
10.3.2.3. Inclusion criteria for the unexposed concurrent male cohort .....	69
10.3.2.4. Inclusion criteria for the unexposed historical male cohort .....	69
10.3.3. Exclusion criteria .....	69

10.3.3.1.	Exclusion criteria for all cohorts .....	69
10.3.3.2.	Exclusion criteria for the non-exposed cohorts .....	69
10.3.4.	Generation of the four cohorts .....	69
10.4.	Variables.....	71
10.4.1.	Primary endpoint.....	71
10.4.2.	Secondary endpoints .....	72
10.5.	Data sources and measurement .....	72
10.5.1.	Data source for case ascertainment.....	72
10.5.2.	Collected data.....	73
10.5.2.1.	Subjects characteristics .....	73
10.5.2.2.	Clinical outcomes .....	74
10.5.2.3.	Date of first symptom.....	74
10.5.2.4.	Other derived variables .....	75
10.5.3.	Final case ascertainment step .....	75
10.6.	Bias .....	76
10.7.	Study size .....	76
10.7.1.	Sample size for cohort design.....	76
10.7.2.	Sample size for self-controlled case-series .....	77
10.8.	Data transformation .....	77
10.9.	Statistical methods.....	78
10.9.1.	Main summary measures.....	78
10.9.1.1.	Subject disposition.....	78
10.9.1.2.	Case definitions.....	78
10.9.1.3.	Demographic and baseline characteristics .....	79
10.9.1.4.	Analysis of autoimmune diseases - co-primary endpoints and individual diseases .....	79
10.9.2.	Main statistical methods.....	80
10.9.2.1.	Hypotheses .....	80
10.9.2.1.1.	Hypotheses for the cohort analysis .....	80
10.9.2.1.2.	Hypotheses for the self-controlled case-series analysis .....	80
10.9.2.2.	Statistical calculations .....	81
10.9.2.3.	Statistical models .....	81
10.9.3.	Missing values .....	83
10.9.4.	Amendments to the statistical analysis plan.....	83
10.10.	Quality control.....	84
10.10.1.	Remote Data Entry instructions .....	84
10.10.2.	Final study database.....	84
11.	RESULTS .....	85
11.1.	Participants.....	85
11.2.	Descriptive data .....	85
11.2.1.	Demographic characteristics of the overall study population for Main analysis .....	85
11.2.1.1.	Demographic characteristics .....	86
11.2.1.2.	Exposure to other vaccines (One year prior to reference date up to end of follow-up period).....	87
11.2.1.3.	Exposure to <i>Cervarix</i> vaccines .....	87
11.3.	Outcome data .....	88
11.3.1.	Demographic characteristics of the Confirmed Cases in the Main Analysis population .....	92
11.4.	Main results .....	93

11.4.1.	Primary Objective .....	93
11.4.1.1.	Frequency of AD – Main Analysis.....	94
11.4.1.2.	Time disease-specific analysis .....	101
11.4.1.3.	Cohort comparison .....	101
11.4.1.4.	Analysis by age groups .....	105
11.4.1.5.	Analysis by dose .....	105
11.4.1.6.	Self-controlled case-series (SCCS) analysis.....	106
11.4.2.	Secondary objectives.....	107
11.5.	Other analyses .....	108
11.5.1.	Exploratory objectives.....	108
11.5.2.	Post-hoc analyses .....	109
11.5.2.1.	Time to onset analysis.....	109
11.5.2.2.	Geographical distribution.....	111
11.5.2.3.	Autoimmune thyroiditis or hypothyroiditis/hyperthyroiditis analysis.....	114
11.5.2.4.	Exclusion of the Northern Ireland-Scotland- Wales region analysis.....	115
11.6.	Adverse events/adverse reactions .....	117
12.	DISCUSSION.....	117
12.1.	Key results.....	117
12.2.	Limitations .....	118
12.3.	Interpretation .....	120
12.4.	Generalisability .....	122
13.	OTHER INFORMATION.....	122
14.	CONCLUSION .....	122
15.	REFERENCES.....	123
16.	APPENDICES .....	129

## MODULAR APPENDICES

## LIST OF TABLES

		PAGE
Table 1	Incidence rates in CPRD GOLD for the study co-primary endpoints .....	62
Table 2	Incidence rates in CPRD GOLD for selected autoimmune disease by sex and age classes.....	62
Table 3	Background incidence rates and prevalence rates of neuroinflammatory/ophthalmic AD in the UK and US .....	64
Table 4	Background incidence rates and prevalence rates of Other AD in the UK and US .....	65
Table 5	Sample size for a SCCS analysis - Number of cases in vaccinated subjects versus the incidence rate ratio that could be detected <sup>a</sup> .....	77
Table 6	Subject dispositions for the four cohorts.....	85
Table 7	Demographic characteristics for overall study population .....	86
Table 8	Demographic characteristics for confirmed cases in the main analysis population.....	92
Table 9	Incidence rate of new onset of autoimmune diseases – Known date of first symptom.....	95
Table 10	Incidence rate of new onset of autoimmune diseases – Imputed date of first symptom sensitivity analysis.....	96
Table 11	Incidence rate of new onset of autoimmune diseases – Date of onset=Date of disease diagnosis sensitivity analysis.....	97
Table 12	Incidence rate of new onset of autoimmune thyroiditis cases after additional patient profile review – Known date of first symptom.....	115
Table 13	Incidence Rate Ratio (95%CI) after exclusion of Northern Ireland-Scotland-Wales region for female cohorts.....	116
Table 14	Incidence rate of Other autoimmune diseases (confirmed cases) by regions for female cohorts .....	116
Table 15	Subject dispositions from CPRD GOLD – Exposed Female Cohort.....	129
Table 16	Subject dispositions from CPRD GOLD – Historical Female Cohort.....	130

Table 17	Subject dispositions from CPRD GOLD – Concurrent Male Cohort .....	131
Table 18	Subject dispositions from CPRD GOLD – Historical Male Cohort.....	132
Table 19	Number of autoimmune disease cases after patient profile review by exposed/non-exposed status (Total cohort).....	132
Table 20	Classification of AD , Date of first symptom , Date of diagnosis by exposed/non-exposed status (N=AD) (Total cohort).....	133
Table 21	Imputation of date of first symptom by exposed/non-exposed status (N=AD) (Total cohort) .....	133
Table 22	Classification of date of first symptom among known dates by exposed/non-exposed status (N=AD) (Total cohort).....	133
Table 23	Details on autoimmune disease cases by exposed/non-exposed status (Total cohort) .....	134
Table 24	Details on autoimmune disease cases by exposed/non-exposed status for subjects with known date of symptom (Total cohort).....	135
Table 25	Time between date of diagnosis and date of symptom by autoimmune disease (N=AD) (Total cohort) .....	136
Table 26	Number of subjects included in sensitivity analysis - Imputed dates of symptom (Total cohort).....	141
Table 27	Number of subjects included in the main analysis (Total cohort) .....	142
Table 28	Number of subjects included in sensitivity analysis - Onset = date of diagnosis (Total cohort).....	143
Table 29	Number of subjects included in sensitivity analysis - Imputed dates of symptom (Total cohort).....	144
Table 30	Number of subjects included in sensitivity analysis - Imputed dates of symptom (Total cohort).....	145
Table 31	Number of subjects included in the SCCS (Total cohort).....	146
Table 32	Summary of demographic characteristics by exposed/non-exposed status - Overall population - All cases (Total cohort) .....	147
Table 33	Data availability by exposed/non-exposed status - Overall population - All cases (Total cohort) .....	148
Table 34	Healthcare resources utilization by exposed/non-exposed status - Overall population - All cases (Total cohort).....	149
Table 35	Exposure to other vaccines by exposed/non-exposed status - Overall population - All cases (Total cohort) .....	150



Table 36	Exposure to other vaccines in the risk and control follow-up period for Exposed Female Cohort - Overall population - All cases (Total cohort) .....	151
Table 37	Exposure to Cervarix vaccine - Overall population - All cases (Total cohort).....	152
Table 38	Drugs prescription by exposed/non-exposed status - Overall population - All cases (Total cohort) .....	154
Table 39	P-Values comparing exposed female and unexposed female cohorts - Overall population - All cases (Total cohort) .....	154
Table 40	P-Values comparing unexposed concurrent male and historical male cohorts - Overall population - All cases (Total cohort).....	155
Table 41	Summary of demographic characteristics by exposed/non-exposed status - Main Analysis - Confirmed cases (Total cohort) .....	156
Table 42	Data availability by exposed/non-exposed status - Main Analysis - Confirmed cases (Total cohort) .....	157
Table 43	Healthcare resources utilization by exposed/non-exposed status - Main Analysis - Confirmed cases (Total cohort) .....	158
Table 44	Exposure to other vaccines by exposed/non-exposed status - Main Analysis - Confirmed cases (Total cohort) .....	159
Table 45	Exposure to other vaccines in the risk and control follow-up period for Exposed Female Cohort - Main Analysis - Confirmed cases (Total cohort) .....	160
Table 46	Exposure to Cervarix vaccine - Main Analysis - Confirmed cases (Total cohort).....	161
Table 47	Drugs prescription by exposed/non-exposed status - Main Analysis - Confirmed cases (Total cohort) .....	163
Table 48	P-Values comparing exposed female and unexposed female cohorts - Main Analysis - Confirmed cases (Total cohort).....	163
Table 49	P-Values comparing unexposed concurrent male and historical male cohorts - Main Analysis - Confirmed cases (Total cohort) .....	164
Table 50	Summary of demographic characteristics by exposed/non-exposed status - Main Analysis - All cases (Total cohort).....	165
Table 51	Data availability by exposed/non-exposed status - Main Analysis - All cases (Total cohort) .....	166
Table 52	Healthcare resources utilization by exposed/non-exposed status - Main Analysis - All cases (Total cohort).....	167

Table 53	Exposure to other vaccines by exposed/non-exposed status - Main Analysis - All cases (Total cohort).....	168
Table 54	Exposure to other vaccines in the risk and control follow-up period for Exposed Female Cohort - Main Analysis - All cases (Total cohort).....	169
Table 55	Exposure to Cervarix vaccine - Main Analysis - All cases (Total cohort).....	170
Table 56	Drugs prescription by exposed/non-exposed status - Main Analysis - All cases (Total cohort) .....	172
Table 57	P-Values comparing Exposed female and Non-Exposed female cohorts - Main Analysis - All cases (Total cohort).....	172
Table 58	P-Values comparing Non-Exposed concurrent male and historical male cohorts - Main Analysis - All cases (Total cohort) .....	173
Table 59	Summary of demographic characteristics by exposed/non-exposed status - Imputed date - Confirmed cases (Total cohort).....	174
Table 60	Data availability by exposed/non-exposed status - Imputed date - Confirmed cases (Total cohort) .....	175
Table 61	Healthcare resources utilization by exposed/non-exposed status - Imputed date - Confirmed cases (Total cohort) .....	176
Table 62	Exposure to other vaccines by exposed/non-exposed status - Imputed date - Confirmed cases (Total cohort) .....	177
Table 63	Exposure to other vaccines in the risk and control follow-up period for Exposed Female Cohort - Imputed date - Confirmed cases (Total cohort) .....	178
Table 64	Exposure to Cervarix vaccine - Imputed date - Confirmed cases (Total cohort).....	179
Table 65	Drugs prescription by exposed/non-exposed status - Imputed date - Confirmed cases (Total cohort) .....	181
Table 66	P-Values comparing exposed female and unexposed female cohorts - Imputed date - Confirmed cases (Total cohort).....	181
Table 67	P-Values comparing unexposed concurrent male and historical male cohorts - Imputed date - Confirmed cases (Total cohort) .....	182
Table 68	Summary of demographic characteristics by exposed/non-exposed status - Imputed date - All cases (Total cohort).....	183
Table 69	Data availability by exposed/non-exposed status - Imputed date - All cases (Total cohort).....	184

Table 70	Healthcare resources utilization by exposed/non-exposed status - Imputed date - All cases (Total cohort).....	185
Table 71	Exposure to other vaccines by exposed/non-exposed status - Imputed date - All cases (Total cohort).....	186
Table 72	Exposure to other vaccines in the risk and control follow-up period for Exposed Female Cohort - Imputed date - All cases (Total cohort).....	187
Table 73	Exposure to Cervarix vaccine - Imputed date - All cases (Total cohort).....	188
Table 74	Drugs prescription by exposed/non-exposed status - Imputed date - All cases (Total cohort).....	190
Table 75	P-Values comparing exposed female and unexposed female cohorts - Imputed date - All cases (Total cohort) .....	190
Table 76	P-Values comparing unexposed concurrent male and historical male cohorts - Imputed date - All cases (Total cohort) .....	191
Table 77	Summary of demographic characteristics by exposed/non- exposed status - Diagnosis date - Confirmed cases (Total cohort).....	192
Table 78	Data availability by exposed/non-exposed status - Diagnosis date - Confirmed cases (Total cohort) .....	193
Table 79	Healthcare resources utilization by exposed/non-exposed status - Diagnosis date - Confirmed cases (Total cohort).....	194
Table 80	Exposure to other vaccines by exposed/non-exposed status - Diagnosis date - Confirmed cases (Total cohort).....	195
Table 81	Exposure to other vaccines in the risk and control follow-up period for Exposed Female Cohort - Diagnosis date - Confirmed cases (Total cohort) .....	196
Table 82	Exposure to Cervarix vaccine - Diagnosis date - Confirmed cases (Total cohort) .....	197
Table 83	Drugs prescription by exposed/non-exposed status - Diagnosis date - Confirmed cases (Total cohort) .....	199
Table 84	P-Values comparing exposed female and unexposed female cohorts - Diagnosis date - Confirmed cases (Total cohort) .....	199
Table 85	P-Values comparing unexposed concurrent male and historical male cohorts - Diagnosis date - Confirmed cases (Total cohort) .....	200
Table 86	Summary of demographic characteristics by exposed/non- exposed status - Diagnosis date - All cases (Total cohort) .....	201

Table 87	Data availability by exposed/non-exposed status - Diagnosis date - All cases (Total cohort).....	202
Table 88	Healthcare resources utilization by exposed/non-exposed status - Diagnosis date - All cases (Total cohort).....	203
Table 89	Exposure to other vaccines by exposed/non-exposed status - Diagnosis date - All cases (Total cohort) .....	204
Table 90	Exposure to other vaccines in the risk and control follow-up period for Exposed Female Cohort - Diagnosis date - All cases (Total cohort).....	205
Table 91	Exposure to Cervarix vaccine - Diagnosis date - All cases (Total cohort).....	206
Table 92	Drugs prescription by exposed/non-exposed status - Diagnosis date - All cases (Total cohort).....	208
Table 93	P-Values comparing exposed female and unexposed female cohorts - Diagnosis date - All cases (Total cohort) .....	208
Table 94	P-Values comparing unexposed concurrent male and historical male cohorts - Diagnosis date - All cases (Total cohort).....	209
Table 95	Frequency of autoimmune diseases during the one year follow-up period by exposed/non-exposed status - Main Analysis - Confirmed and Non-Confirmed cases (Total cohort) .....	210
Table 96	Frequency of autoimmune diseases during the one year follow-up period by exposed/non-exposed status - Main Analysis - Confirmed cases (Total cohort) .....	210
Table 97	Frequency of autoimmune diseases during the one year follow-up period by exposed/non-exposed status - Main Analysis - Confirmed and Non-Confirmed cases (N=AD) (Total cohort).....	211
Table 98	Frequency of autoimmune diseases during the one year follow-up period by exposed/non-exposed status - Main Analysis - Confirmed cases (N=AD) (Total cohort) .....	212
Table 99	Frequency of autoimmune disease during the specific time period by exposed/non-exposed status - Main Analysis - Confirmed and Non-Confirmed cases (Total cohort) .....	213
Table 100	Frequency of autoimmune disease during the specific time period by exposed/non-exposed status - Main Analysis - Confirmed cases (Total cohort) .....	213
Table 101	Frequency of autoimmune disease during the specific time period by exposed/non-exposed status - Main Analysis - Confirmed and Non-Confirmed cases (Total cohort) .....	214

Table 102	Frequency of autoimmune disease during the specific time period by exposed/non-exposed status - Main Analysis - Confirmed cases (Total cohort) .....	214
Table 103	Frequency of autoimmune disease during the specific time period by exposed/non-exposed status - Main Analysis - Confirmed and Non-Confirmed cases (N=AD) (Total cohort).....	215
Table 104	Frequency of autoimmune disease during the specific time period by exposed/non-exposed status - Main Analysis - Confirmed cases (N=AD) (Total cohort) .....	216
Table 105	Incidence rate of Neuroinflammatory/Ophthalmic autoimmune diseases in Female Cohorts - Main Analysis - Confirmed cases (Total cohort).....	217
Table 106	Incidence rate difference of Neuroinflammatory/Ophthalmic autoimmune diseases in Female Cohorts - Main Analysis - Confirmed cases (Total cohort) .....	217
Table 107	Incidence rate of Other autoimmune diseases in Female Cohorts - Main Analysis - Confirmed cases (Total cohort) .....	217
Table 108	Incidence rate ratios of Other autoimmune diseases in Female Cohorts - Main Analysis - Confirmed cases (Total cohort).....	217
Table 109	Incidence rate difference of Other autoimmune diseases in Female Cohorts - Main Analysis - Confirmed cases (Total cohort) .....	218
Table 110	Incidence rate ratios of Other autoimmune diseases in Female Cohorts (covariates adjusted) - Main Analysis - Confirmed cases (Total cohort).....	218
Table 111	Incidence rate of Neuroinflammatory/Ophthalmic autoimmune diseases in Female Cohorts - Main Analysis - All cases (Total cohort).....	218
Table 112	Incidence rate ratios of Neuroinflammatory/Ophthalmic diseases in Female Cohorts - Main Analysis - All cases (Total cohort).....	218
Table 113	Incidence rate difference of Neuroinflammatory/Ophthalmic autoimmune diseases in Female Cohorts - Main Analysis - All cases (Total cohort) .....	219
Table 114	Incidence rate ratios of Neuroinflammatory/Ophthalmic diseases in Female Cohorts (covariates adjusted) - Main Analysis - All cases (Total cohort) .....	219
Table 115	Incidence rate of Other autoimmune diseases in Female Cohorts - Main Analysis - All cases (Total cohort).....	219
Table 116	Incidence rate ratios of Other autoimmune diseases in Female Cohorts - Main Analysis - All cases (Total cohort) .....	219

Table 117	Incidence rate difference of Other autoimmune diseases in Female Cohorts - Main Analysis - All cases (Total cohort) .....	220
Table 118	Incidence rate ratios of Other autoimmune diseases in Female Cohorts (covariates adjusted) - Main Analysis - All cases (Total cohort).....	220
Table 119	Incidence rate of Neuroinflammatory/Ophthalmic autoimmune diseases in Male Cohorts - Main Analysis - Confirmed cases (Total cohort).....	220
Table 120	Incidence rate ratios of Neuroinflammatory/Ophthalmic diseases in Male Cohorts - Main Analysis - Confirmed cases (Total cohort) .....	220
Table 121	Incidence rate difference of Neuroinflammatory/Ophthalmic autoimmune diseases in Male Cohorts - Main Analysis - Confirmed cases (Total cohort) .....	221
Table 122	Incidence rate of Other autoimmune diseases in Male Cohorts - Main Analysis - Confirmed cases (Total cohort) .....	221
Table 123	Incidence rate ratios of Other autoimmune diseases in Male Cohorts - Main Analysis - Confirmed cases (Total cohort).....	221
Table 124	Incidence rate difference of Other autoimmune diseases in Male Cohorts - Main Analysis - Confirmed cases (Total cohort).....	221
Table 125	Incidence rate ratios of Other autoimmune diseases in Male Cohorts (covariates adjusted) - Main Analysis - Confirmed cases (Total cohort).....	222
Table 126	Incidence rate of Neuroinflammatory/Ophthalmic autoimmune diseases in Male Cohorts - Main Analysis - All cases (Total cohort).....	222
Table 127	Incidence rate ratios of Neuroinflammatory/Ophthalmic diseases in Male Cohorts - Main Analysis - All cases (Total cohort).....	222
Table 128	Incidence rate difference of Neuroinflammatory/Ophthalmic autoimmune diseases in Male Cohorts - Main Analysis - All cases (Total cohort) .....	222
Table 129	Incidence rate of Other autoimmune diseases in Male Cohorts - Main Analysis - All cases (Total cohort).....	223
Table 130	Incidence rate ratios of Other autoimmune diseases in Male Cohorts - Main Analysis - All cases (Total cohort) .....	223
Table 131	Incidence rate difference of Other autoimmune diseases in Male Cohorts - Main Analysis - All cases (Total cohort) .....	223
Table 132	Incidence rate of Acute Disseminated Encephalomyelitis in Female Cohorts - Main Analysis - All cases (Total cohort) .....	223

Table 133	Incidence rate of Autoimmune Hepatitis in Female Cohorts - Main Analysis - Confirmed cases (Total cohort) .....	223
Table 134	Incidence rate of Autoimmune Hepatitis in Female Cohorts - Main Analysis - All cases (Total cohort).....	224
Table 135	Incidence rate of Autoimmune Thyroiditis in Female Cohorts - Main Analysis - Confirmed cases (Total cohort) .....	224
Table 136	Incidence rate ratios of Autoimmune Thyroiditis in Female Cohorts - Main Analysis - Confirmed cases (Total cohort).....	224
Table 137	Incidence rate difference of Autoimmune Thyroiditis diseases in Female Cohorts - Main Analysis - Confirmed cases (Total cohort) .....	224
Table 138	Incidence rate ratios of Autoimmune Thyroiditis in Female Cohorts (covariates adjusted) - Main Analysis - Confirmed cases (Total cohort).....	225
Table 139	Incidence rate of Autoimmune Thyroiditis in Female Cohorts - Main Analysis - All cases (Total cohort).....	225
Table 140	Incidence rate ratios of Autoimmune Thyroiditis in Female Cohorts - Main Analysis - All cases (Total cohort) .....	225
Table 141	Incidence rate difference of Autoimmune Thyroiditis diseases in Female Cohorts - Main Analysis - All cases (Total cohort) .....	225
Table 142	Incidence rate ratios of Autoimmune Thyroiditis in Female Cohorts (covariates adjusted) - Main Analysis - All cases (Total cohort).....	226
Table 143	Incidence rate of Autoimmune Thyroiditis in Male Cohorts - Main Analysis - All cases (Total cohort) .....	226
Table 144	Incidence rate ratios of Autoimmune Thyroiditis in Male Cohorts - Main Analysis - All cases (Total cohort).....	226
Table 145	Incidence rate difference of Autoimmune Thyroiditis diseases in Male Cohorts - Main Analysis - All cases (Total cohort).....	226
Table 146	Incidence rate ratios of Autoimmune Thyroiditis in Male Cohorts (covariates adjusted) - Main Analysis - All cases (Total cohort).....	227
Table 147	Incidence rate of Autoimmune Uveitis in Female Cohorts - Main Analysis - All cases (Total cohort) .....	227
Table 148	Incidence rate of Autoimmune Uveitis in Male Cohorts - Main Analysis - All cases (Total cohort) .....	227
Table 149	Incidence rate of Autoimmune Crohn diseases in Female Cohorts - Main Analysis - Confirmed cases (Total cohort).....	227



Table 150	Incidence rate ratios of Crohn diseases in Female Cohorts - Main Analysis - Confirmed cases (Total cohort).....	227
Table 151	Incidence rate difference of Autoimmune Crohn diseases in Female Cohorts - Main Analysis - Confirmed cases (Total cohort) .....	228
Table 152	Incidence rate ratios of Crohn diseases in Female Cohorts (covariates adjusted) - Main Analysis - Confirmed cases (Total cohort).....	228
Table 153	Incidence rate of Crohn diseases in Male Cohorts - Main Analysis - Confirmed cases (Total cohort).....	228
Table 154	Incidence rate ratios of Crohn diseases in Male Cohorts - Main Analysis - Confirmed cases (Total cohort).....	228
Table 155	Incidence rate difference of Crohn diseases in Male Cohorts - Main Analysis - Confirmed cases (Total cohort) .....	229
Table 156	Incidence rate of Crohn diseases in Female Cohorts - Main Analysis - All cases (Total cohort) .....	229
Table 157	Incidence rate ratios of Crohn diseases in Female Cohorts - Main Analysis - All cases (Total cohort) .....	229
Table 158	Incidence rate difference of Crohn diseases in Female Cohorts - Main Analysis - All cases (Total cohort).....	229
Table 159	Incidence rate ratios of Crohn diseases in Female Cohorts (covariates adjusted) - Main Analysis - All cases (Total cohort).....	230
Table 160	Incidence rate of Crohn diseases in Male Cohorts - Main Analysis - All cases (Total cohort) .....	230
Table 161	Incidence rate ratios of Crohn diseases in Male Cohorts - Main Analysis - All cases (Total cohort) .....	230
Table 162	Incidence rate difference of Crohn diseases in Male Cohorts - Main Analysis - All cases (Total cohort).....	230
Table 163	Incidence rate of Inflammatory bowel diseases in Male Cohorts - Main Analysis - Confirmed cases (Total cohort) .....	231
Table 164	Incidence rate of Inflammatory bowel diseases in Female Cohorts - Main Analysis - All cases (Total cohort) .....	231
Table 165	Incidence rate of Inflammatory bowel diseases in Male Cohorts - Main Analysis - All cases (Total cohort).....	231
Table 166	Incidence rate of Juvenile Rheumatoid Arthritis in Female Cohorts - Main Analysis - Confirmed cases (Total cohort).....	231



Table 167	Incidence rate of Juvenile Rheumatoid Arthritis in Male Cohorts - Main Analysis - Confirmed cases (Total cohort) .....	231
Table 168	Incidence rate of Juvenile Rheumatoid Arthritis in Female Cohorts - Main Analysis - All cases (Total cohort) .....	231
Table 169	Incidence rate of Juvenile Rheumatoid Arthritis in Male Cohorts - Main Analysis - All cases (Total cohort).....	232
Table 170	Incidence rate of Multiple Sclerosis in Female Cohorts - Main Analysis - Confirmed cases (Total cohort).....	232
Table 171	Incidence rate of Multiple Sclerosis in Female Cohorts - Main Analysis - All cases (Total cohort) .....	232
Table 172	Incidence rate of Optic Neuritis in Female Cohorts - Main Analysis - All cases (Total cohort) .....	232
Table 173	Incidence rate of Psoriatic Arthritis in Female Cohorts - Main Analysis - Confirmed cases (Total cohort).....	232
Table 174	Incidence rate of Psoriatic Arthritis in Female Cohorts - Main Analysis - All cases (Total cohort) .....	232
Table 175	Incidence rate of Rheumatoid Arthritis in Female Cohorts - Main Analysis - Confirmed cases (Total cohort).....	233
Table 176	Incidence rate of Rheumatoid Arthritis in Female Cohorts - Main Analysis - All cases (Total cohort) .....	233
Table 177	Incidence rate of Systemic Lupus Erythematosus in Female Cohorts - Main Analysis - Confirmed cases (Total cohort).....	233
Table 178	Incidence rate of Systemic Lupus Erythematosus in Female Cohorts - Main Analysis - All cases (Total cohort) .....	233
Table 179	Incidence rate of Autoimmune Type 1 Diabetes Mellitus in Female Cohorts - Main Analysis - Confirmed cases (Total cohort) .....	233
Table 180	Incidence rate ratios of Type 1 Diabetes Mellitus in Female Cohorts - Main Analysis - Confirmed cases (Total cohort).....	234
Table 181	Incidence rate difference of Autoimmune Type 1 Diabetes Mellitus in Female Cohorts - Main Analysis - Confirmed cases (Total cohort).....	234
Table 182	Incidence rate ratios of Type 1 Diabetes Mellitus in Female Cohorts (covariates adjusted) - Main Analysis - Confirmed cases (Total cohort).....	234
Table 183	Incidence rate of Type 1 Diabetes Mellitus in Male Cohorts - Main Analysis - Confirmed cases (Total cohort) .....	234

Table 184	Incidence rate ratios of Type 1 Diabetes Mellitus in Male Cohorts - Main Analysis - Main Analysis - Confirmed cases (Total cohort) .....	235
Table 185	Incidence rate difference of Autoimmune Type 1 Diabetes Mellitus in Male Cohorts - Main Analysis - Confirmed cases (Total cohort).....	235
Table 186	Incidence rate of Type 1 Diabetes Mellitus in Female Cohorts - Main Analysis - All cases (Total cohort).....	235
Table 187	Incidence rate ratios of Type 1 Diabetes Mellitus in Female Cohorts - Main Analysis - All cases (Total cohort) .....	235
Table 188	Incidence rate difference of Autoimmune Type 1 Diabetes Mellitus in Female Cohorts - Main Analysis - All cases (Total cohort).....	236
Table 189	Incidence rate ratios of Type 1 Diabetes Mellitus in Female Cohorts (covariates adjusted) - Main Analysis - All cases (Total cohort).....	236
Table 190	Incidence rate of Type 1 Diabetes Mellitus in Male Cohorts - Main Analysis - All cases (Total cohort).....	236
Table 191	Incidence rate ratios of Type 1 Diabetes Mellitus in Male Cohorts - Main Analysis - All cases (Total cohort).....	236
Table 192	Incidence rate difference of Autoimmune Type 1 Diabetes Mellitus in Male Cohorts - Main Analysis - All cases (Total cohort).....	237
Table 193	Incidence rate of Autoimmune Ulcerative Colitis in Female Cohorts - Main Analysis - Confirmed cases (Total cohort).....	237
Table 194	Incidence rate of Ulcerative Colitis in Male Cohorts - Main Analysis - Confirmed cases (Total cohort).....	237
Table 195	Incidence rate of Ulcerative Colitis in Female Cohorts - Main Analysis - All cases (Total cohort) .....	237
Table 196	Incidence rate of Ulcerative Colitis in Male Cohorts - Main Analysis - All cases (Total cohort) .....	237
Table 197	Incidence rate of Idiopathic Thrombocytopenia Purpura in Female Cohorts - Main Analysis - Confirmed cases (Total cohort) .....	238
Table 198	Incidence rate of Idiopathic Thrombocytopenia Purpura in Male Cohorts - Main Analysis - Confirmed cases (Total cohort).....	238
Table 199	Incidence rate of Idiopathic Thrombocytopenia Purpura in Female Cohorts - Main Analysis - All cases (Total cohort) .....	238
Table 200	Incidence rate of Idiopathic Thrombocytopenia Purpura in Male Cohorts - Main Analysis - All cases (Total cohort) .....	238

Table 201	Frequency of autoimmune diseases during the one year follow-up period by exposed/non-exposed status - Sensitivity Analysis - Imputed date - Confirmed and Non-Confirmed cases (Total cohort).....	239
Table 202	Frequency of autoimmune diseases during the one year follow-up period by exposed/non-exposed status - Sensitivity Analysis - Imputed date - Confirmed cases (Total cohort) .....	239
Table 203	Frequency of autoimmune diseases during the one year follow-up period by exposed/non-exposed status - Sensitivity Analysis - Imputed date - Confirmed and Non-Confirmed cases (N=AD) (Total cohort).....	240
Table 204	Frequency of autoimmune diseases during the one year follow-up period by exposed/non-exposed status - Sensitivity Analysis - Imputed date - Confirmed cases (N=AD) (Total cohort).....	241
Table 205	Frequency of autoimmune disease during the specific time period by exposed/non-exposed status - Imputed date - Confirmed and Non-Confirmed cases (Total cohort) .....	242
Table 206	Frequency of autoimmune disease during the specific time period by exposed/non-exposed status - Imputed date - Confirmed cases (Total cohort) .....	242
Table 207	Frequency of autoimmune disease during the specific time period by exposed/non-exposed status - Imputed date - Confirmed and Non-Confirmed cases (Total cohort) .....	243
Table 208	Frequency of autoimmune disease during the specific time period by exposed/non-exposed status - Imputed date - Confirmed cases (Total cohort) .....	243
Table 209	Frequency of autoimmune disease during the specific time period by exposed/non-exposed status - Imputed date - Confirmed and Non-Confirmed cases (N=AD) (Total cohort).....	244
Table 210	Frequency of autoimmune disease during the specific time period by exposed/non-exposed status - Imputed date - Confirmed cases (N=AD) (Total cohort) .....	245
Table 211	Incidence rate of Neuroinflammatory/Ophthalmic autoimmune diseases in Female Cohorts - Imputed date - Confirmed cases (Total cohort).....	246
Table 212	Incidence rate ratios of Neuroinflammatory/Ophthalmic diseases in Female Cohorts - Imputed date - Confirmed cases (Total cohort).....	246
Table 213	Incidence rate difference of Neuroinflammatory/Ophthalmic autoimmune diseases in Female Cohorts - Imputed date - Confirmed cases (Total cohort) .....	246

Table 214	Incidence rate ratios of Neuroinflammatory/Ophthalmic diseases in Female Cohorts (covariates adjusted) - Imputed date - Confirmed cases (Total cohort) .....	246
Table 215	Incidence rate of Other autoimmune diseases in Female Cohorts - Imputed date - Confirmed cases (Total cohort) .....	247
Table 216	Incidence rate ratios of Other autoimmune diseases in Female Cohorts - Imputed date - Confirmed cases (Total cohort) .....	247
Table 217	Incidence rate difference of Other autoimmune diseases in Female Cohorts - Imputed date - Confirmed cases (Total cohort) .....	247
Table 218	Incidence rate ratios of Other autoimmune diseases in Female Cohorts (covariates adjusted) - Imputed date - Confirmed cases (Total cohort).....	247
Table 219	Incidence rate of Neuroinflammatory/Ophthalmic autoimmune diseases in Female Cohorts - Imputed date - All cases (Total cohort).....	248
Table 220	Incidence rate ratios of Neuroinflammatory/Ophthalmic diseases in Female Cohorts - Imputed date - All cases (Total cohort).....	248
Table 221	Incidence rate difference of Neuroinflammatory/Ophthalmic autoimmune diseases in Female Cohorts - Imputed date - All cases (Total cohort) .....	248
Table 222	Incidence rate ratios of Neuroinflammatory/Ophthalmic diseases in Female Cohorts (covariates adjusted) - Imputed date - All cases (Total cohort) .....	248
Table 223	Incidence rate of Other autoimmune diseases in Female Cohorts - Imputed date - All cases (Total cohort).....	249
Table 224	Incidence rate ratios of Other autoimmune diseases in Female Cohorts - Imputed date - All cases (Total cohort) .....	249
Table 225	Incidence rate difference of Other autoimmune diseases in Female Cohorts - Imputed date - All cases (Total cohort).....	249
Table 226	Incidence rate ratios of Other autoimmune diseases in Female Cohorts (covariates adjusted) - Imputed date - All cases (Total cohort).....	249
Table 227	Incidence rate of Neuroinflammatory/Ophthalmic autoimmune diseases in Male Cohorts - Imputed date - Confirmed cases (Total cohort).....	250
Table 228	Incidence rate ratios of Neuroinflammatory/Ophthalmic diseases in Male Cohorts - Imputed date - Confirmed cases (Total cohort).....	250

Table 229	Incidence rate difference of Neuroinflammatory/Ophthalmic autoimmune diseases in Male Cohorts - Imputed date - Confirmed cases (Total cohort) .....	250
Table 230	Incidence rate of Other autoimmune diseases in Male Cohorts - Imputed date - Confirmed cases (Total cohort) .....	250
Table 231	Incidence rate ratios of Other autoimmune diseases in Male Cohorts - Imputed date - Confirmed cases (Total cohort) .....	251
Table 232	Incidence rate difference of Other autoimmune diseases in Male Cohorts - Imputed date - Confirmed cases (Total cohort) .....	251
Table 233	Incidence rate ratios of Other autoimmune diseases in Male Cohorts (covariates adjusted) - Imputed date - Confirmed cases (Total cohort) .....	251
Table 234	Incidence rate of Neuroinflammatory/Ophthalmic autoimmune diseases in Male Cohorts - Imputed date - All cases (Total cohort) .....	251
Table 235	Incidence rate ratios of Neuroinflammatory/Ophthalmic diseases in Male Cohorts - Imputed date - All cases (Total cohort) .....	252
Table 236	Incidence rate difference of Neuroinflammatory/Ophthalmic autoimmune diseases in Male Cohorts - Imputed date - All cases (Total cohort) .....	252
Table 237	Incidence rate ratios of Neuroinflammatory/Ophthalmic diseases in Male Cohorts (covariates adjusted) - Imputed date - All cases (Total cohort) .....	252
Table 238	Incidence rate of Other autoimmune diseases in Male Cohorts - Imputed date - All cases (Total cohort) .....	252
Table 239	Incidence rate ratios of Other autoimmune diseases in Male Cohorts - Imputed date - All cases (Total cohort) .....	253
Table 240	Incidence rate difference of Other autoimmune diseases in Male Cohorts - Imputed date - All cases (Total cohort) .....	253
Table 241	Incidence rate ratios of Other autoimmune diseases in Male Cohorts (covariates adjusted) - Imputed date - All cases (Total cohort) .....	253
Table 242	Incidence rate of Acute Disseminated Encephalomyelitis in Female Cohorts - Imputed date - All cases (Total cohort) .....	253
Table 243	Incidence rate of Autoimmune Hepatitis in Female Cohorts - Imputed date - Confirmed cases (Total cohort) .....	254
Table 244	Incidence rate of Autoimmune Hepatitis in Female Cohorts - Imputed date - All cases (Total cohort) .....	254

Table 245	Incidence rate of Autoimmune Thyroiditis in Female Cohorts - Imputed date - Confirmed cases (Total cohort) .....	254
Table 246	Incidence rate ratios of Autoimmune Thyroiditis in Female Cohorts - Imputed date - Confirmed cases (Total cohort) .....	254
Table 247	Incidence rate difference of Autoimmune Thyroiditis diseases in Female Cohorts - Imputed date - Confirmed cases (Total cohort) .....	254
Table 248	Incidence rate ratios of Autoimmune Thyroiditis in Female Cohorts (covariates adjusted) - Imputed date - Confirmed cases (Total cohort).....	255
Table 249	Incidence rate of Autoimmune Thyroiditis in Male Cohorts - Imputed date - Confirmed cases (Total cohort) .....	255
Table 250	Incidence rate difference of Autoimmune Thyroiditis diseases in Male Cohorts - Imputed date - Confirmed cases (Total cohort) .....	255
Table 251	Incidence rate of Autoimmune Thyroiditis in Female Cohorts - Imputed date - All cases (Total cohort).....	255
Table 252	Incidence rate ratios of Autoimmune Thyroiditis in Female Cohorts - Imputed date - All cases (Total cohort) .....	256
Table 253	Incidence rate difference of Autoimmune Thyroiditis diseases in Female Cohorts - Imputed date - All cases (Total cohort).....	256
Table 254	Incidence rate ratios of Autoimmune Thyroiditis in Female Cohorts (covariates adjusted) - Imputed date - All cases (Total cohort).....	256
Table 255	Incidence rate of Autoimmune Thyroiditis in Male Cohorts - Imputed date - All cases (Total cohort).....	256
Table 256	Incidence rate ratios of Autoimmune Thyroiditis in Male Cohorts - Imputed date - All cases (Total cohort).....	257
Table 257	Incidence rate difference of Autoimmune Thyroiditis diseases in Male Cohorts - Imputed date - All cases (Total cohort).....	257
Table 258	Incidence rate ratios of Autoimmune Thyroiditis in Male Cohorts (covariates adjusted) - Imputed date - All cases (Total cohort).....	257
Table 259	Incidence rate of Autoimmune Uveitis in Female Cohorts - Imputed date - All cases (Total cohort).....	257
Table 260	Incidence rate ratios of Autoimmune Uveitis in Female Cohorts - Imputed date - All cases (Total cohort).....	258
Table 261	Incidence rate difference of Autoimmune Uveitis in Female Cohorts - Imputed date - All cases (Total cohort) .....	258

Table 262	Incidence rate ratios of Autoimmune Uveitis in Female Cohorts (covariates adjusted) - Imputed date - All cases (Total cohort).....	258
Table 263	Incidence rate of Autoimmune Uveitis in Male Cohorts - Imputed date - All cases (Total cohort).....	258
Table 264	Incidence rate ratios of Autoimmune Uveitis in Male Cohorts - Imputed date - All cases (Total cohort).....	259
Table 265	Incidence rate difference of Autoimmune Uveitis in Male Cohorts - Imputed date - All cases (Total cohort).....	259
Table 266	Incidence rate ratios of Autoimmune Uveitis in Male Cohorts (covariates adjusted) - Imputed date - All cases (Total cohort).....	259
Table 267	Incidence rate of Autoimmune Crohn diseases in Female Cohorts - Imputed date - Confirmed cases (Total cohort).....	259
Table 268	Incidence rate ratios of Crohn diseases in Female Cohorts - Imputed date - Confirmed cases (Total cohort) .....	260
Table 269	Incidence rate difference of Autoimmune Crohn diseases in Female Cohorts - Imputed date - Confirmed cases (Total cohort) .....	260
Table 270	Incidence rate ratios of Crohn diseases in Female Cohorts (covariates adjusted) - Imputed date - Confirmed cases (Total cohort).....	260
Table 271	Incidence rate of Crohn diseases in Male Cohorts - Imputed date - Confirmed cases (Total cohort).....	260
Table 272	Incidence rate ratios of Crohn diseases in Male Cohorts - Imputed date - Confirmed cases (Total cohort) .....	261
Table 273	Incidence rate difference of Crohn diseases in Male Cohorts - Imputed date - Confirmed cases (Total cohort) .....	261
Table 274	Incidence rate of Crohn diseases in Female Cohorts - Imputed date - All cases (Total cohort).....	261
Table 275	Incidence rate ratios of Crohn diseases in Female Cohorts - Imputed date - All cases (Total cohort).....	261
Table 276	Incidence rate difference of Crohn diseases in Female Cohorts - Imputed date - All cases (Total cohort).....	262
Table 277	Incidence rate ratios of Crohn diseases in Female Cohorts (covariates adjusted) - Imputed date - All cases (Total cohort).....	262
Table 278	Incidence rate of Crohn diseases in Male Cohorts - Imputed date - All cases (Total cohort) .....	262



Table 279	Incidence rate ratios of Crohn diseases in Male Cohorts - Imputed date - All cases (Total cohort).....	262
Table 280	Incidence rate difference of Crohn diseases in Male Cohorts - Imputed date - All cases (Total cohort).....	263
Table 281	Incidence rate of Inflammatory bowel diseases in Male Cohorts - Imputed date - Confirmed cases (Total cohort) .....	263
Table 282	Incidence rate of Inflammatory bowel diseases in Female Cohorts - Imputed date - All cases (Total cohort) .....	263
Table 283	Incidence rate of Inflammatory bowel diseases in Male Cohorts - Imputed date - All cases (Total cohort).....	263
Table 284	Incidence rate of Juvenile Rheumatoid Arthritis in Female Cohorts - Imputed date - Confirmed cases (Total cohort) .....	263
Table 285	Incidence rate of Juvenile Rheumatoid Arthritis in Male Cohorts - Imputed date - Confirmed cases (Total cohort) .....	264
Table 286	Incidence rate of Juvenile Rheumatoid Arthritis in Female Cohorts - Imputed date - All cases (Total cohort) .....	264
Table 287	Incidence rate of Juvenile Rheumatoid Arthritis in Male Cohorts - Imputed date - All cases (Total cohort).....	264
Table 288	Incidence rate of Multiple Sclerosis in Female Cohorts - Imputed date - Confirmed cases (Total cohort) .....	264
Table 289	Incidence rate ratios of Multiple Sclerosis in Female Cohorts - Imputed date - Confirmed cases (Total cohort) .....	264
Table 290	Incidence rate of Multiple Sclerosis in Female Cohorts - Imputed date - All cases (Total cohort).....	265
Table 291	Incidence rate ratios of Multiple Sclerosis in Female Cohorts - Imputed date - All cases (Total cohort).....	265
Table 292	Incidence rate of Optic Neuritis in Male Cohorts - Imputed date - Confirmed cases (Total cohort) .....	265
Table 293	Incidence rate of Optic Neuritis in Female Cohorts - Imputed date - All cases (Total cohort) .....	265
Table 294	Incidence rate ratios of Optic Neuritis in Female Cohorts - Imputed date - All cases (Total cohort).....	265
Table 295	Incidence rate of Optic Neuritis in Male Cohorts - Imputed date - All cases (Total cohort).....	266
Table 296	Incidence rate of Psoriatic Arthritis in Female Cohorts - Imputed date - Confirmed cases (Total cohort) .....	266



Table 297	Incidence rate ratios of Psoriatic Arthritis in Female Cohorts - Imputed date - Confirmed cases (Total cohort) .....	266
Table 298	Incidence rate of Psoriatic Arthritis in Female Cohorts - Imputed date - All cases (Total cohort).....	266
Table 299	Incidence rate ratios of Psoriatic Arthritis in Female Cohorts - Imputed date - All cases (Total cohort).....	266
Table 300	Incidence rate of Rheumatoid Arthritis in Female Cohorts - Imputed date - Confirmed cases (Total cohort) .....	267
Table 301	Incidence rate of Rheumatoid Arthritis in Female Cohorts - Imputed date - All cases (Total cohort).....	267
Table 302	Incidence rate of Systemic Lupus Erythematosus in Female Cohorts - Imputed date - Confirmed cases (Total cohort) .....	267
Table 303	Incidence rate of Systemic Lupus Erythematosus in Female Cohorts - Imputed date - All cases (Total cohort) .....	267
Table 304	Incidence rate of Autoimmune Type 1 Diabetes Mellitus in Female Cohorts - Imputed date - Confirmed cases (Total cohort) .....	267
Table 305	Incidence rate ratios of Type 1 Diabetes Mellitus in Female Cohorts - Imputed date - Confirmed cases (Total cohort) .....	268
Table 306	Incidence rate difference of Autoimmune Type 1 Diabetes Mellitus in Female Cohorts - Imputed date - Confirmed cases (Total cohort).....	268
Table 307	Incidence rate ratios of Type 1 Diabetes Mellitus in Female Cohorts (covariates adjusted) - Imputed date - Confirmed cases (Total cohort).....	268
Table 308	Incidence rate of Type 1 Diabetes Mellitus in Male Cohorts - Imputed date - Confirmed cases (Total cohort) .....	268
Table 309	Incidence rate ratios of Type 1 Diabetes Mellitus in Male Cohorts - Imputed date - Confirmed cases (Total cohort) .....	269
Table 310	Incidence rate difference of Autoimmune Type 1 Diabetes Mellitus in Male Cohorts - Imputed date - Confirmed cases (Total cohort).....	269
Table 311	Incidence rate ratios of Type 1 Diabetes Mellitus in Male Cohorts (covariates adjusted) - Imputed date - Confirmed cases (Total cohort).....	269
Table 312	Incidence rate of Type 1 Diabetes Mellitus in Female Cohorts - Imputed date - All cases (Total cohort).....	269

Table 313	Incidence rate ratios of Type 1 Diabetes Mellitus in Female Cohorts - Imputed date -All cases (Total cohort) .....	270
Table 314	Incidence rate difference of Autoimmune Type 1 Diabetes Mellitus in Female Cohorts - Imputed date - All cases (Total cohort).....	270
Table 315	Incidence rate ratios of Type 1 Diabetes Mellitus in Female Cohorts (covariates adjusted) - Imputed date - All cases (Total cohort).....	270
Table 316	Incidence rate of Type 1 Diabetes Mellitus in Male Cohorts - Imputed date - All cases (Total cohort).....	270
Table 317	Incidence rate ratios of Type 1 Diabetes Mellitus in Male Cohorts - Imputed date - All cases (Total cohort).....	271
Table 318	Incidence rate difference of Autoimmune Type 1 Diabetes Mellitus in Male Cohorts - Imputed date - All cases (Total cohort) .....	271
Table 319	Incidence rate ratios of Type 1 Diabetes Mellitus in Male Cohorts (covariates adjusted) - Imputed date - All cases (Total cohort) .....	271
Table 320	Incidence rate of Autoimmune Ulcerative Colitis in Female Cohorts - Imputed date - Confirmed cases (Total cohort).....	271
Table 321	Incidence rate of Ulcerative Colitis in Male Cohorts - Imputed date - Confirmed cases (Total cohort) .....	272
Table 322	Incidence rate ratios of Ulcerative Colitis in Male Cohorts - Imputed date - Confirmed cases (Total cohort) .....	272
Table 323	Incidence rate of Ulcerative Colitis in Female Cohorts - Imputed date - All cases (Total cohort).....	272
Table 324	Incidence rate ratios of Ulcerative Colitis in Female Cohorts - Imputed date - All cases (Total cohort).....	272
Table 325	Incidence rate of Ulcerative Colitis in Male Cohorts - Imputed date - All cases (Total cohort).....	272
Table 326	Incidence rate ratios of Ulcerative Colitis in Male Cohorts - Imputed date - All cases (Total cohort).....	273
Table 327	Incidence rate of Idiopathic Thrombocytopenia Purpura in Female Cohorts - Imputed date - Confirmed cases (Total cohort) .....	273
Table 328	Incidence rate ratios of Idiopathic Thrombocytopenia Purpura in Female Cohorts - Imputed date - Confirmed cases (Total cohort) .....	273
Table 329	Incidence rate of Idiopathic Thrombocytopenia Purpura in Male Cohorts - Imputed date - Confirmed cases (Total cohort) .....	273

Table 330	Incidence rate of Idiopathic Thrombocytopenia Purpura in Female Cohorts - Imputed date - All cases (Total cohort).....	273
Table 331	Incidence rate ratios of Idiopathic Thrombocytopenia Purpura in Female Cohorts - Imputed date - All cases (Total cohort).....	274
Table 332	Incidence rate of Idiopathic Thrombocytopenia Purpura in Male Cohorts - Imputed date - All cases (Total cohort) .....	274
Table 333	Frequency of autoimmune diseases during the one year follow-up period by exposed/non-exposed status - Sensitivity Analysis - Onset diagnosis - Confirmed and Non-Confirmed cases (Total cohort).....	274
Table 334	Frequency of autoimmune diseases during the one year follow-up period by exposed/non-exposed status - Sensitivity Analysis - Onset diagnosis - Confirmed cases (Total cohort).....	275
Table 335	Frequency of autoimmune diseases during the one year follow-up period by exposed/non-exposed status - Sensitivity Analysis - Onset diagnosis - Confirmed and Non-Confirmed cases (N=AD) (Total cohort).....	276
Table 336	Frequency of autoimmune diseases during the one year follow-up period by exposed/non-exposed status - Sensitivity Analysis - Onset diagnosis - Confirmed cases (N=AD) (Total cohort) .....	277
Table 337	Frequency of autoimmune disease during the specific time period by exposed/non-exposed status - Sensitivity Analysis - Onset diagnosis - Confirmed and Non-Confirmed cases (Total cohort).....	278
Table 338	Frequency of autoimmune disease during the specific time period by exposed/non-exposed status - Sensitivity Analysis - Onset diagnosis - Confirmed cases (Total cohort).....	278
Table 339	Frequency of autoimmune disease during the specific time period by exposed/non-exposed status - Sensitivity Analysis - Onset diagnosis - Confirmed and Non-Confirmed cases (Total cohort).....	279
Table 340	Frequency of autoimmune disease during the specific time period by exposed/non-exposed status - Sensitivity Analysis - Onset diagnosis - Confirmed cases (Total cohort).....	279
Table 341	Frequency of autoimmune disease during the specific time period by exposed/non-exposed status - Onset Analysis - Confirmed and Non-Confirmed cases (N=AD) (Total cohort).....	280
Table 342	Frequency of autoimmune disease during the specific time period by exposed/non-exposed status - Onset Analysis - Confirmed cases (N=AD) (Total cohort) .....	281

Table 343	Incidence rate of Neuroinflammatory/Ophthalmic autoimmune diseases in Female Cohorts - Onset Diagnosis - Confirmed cases (Total cohort) .....	282
Table 344	Incidence rate ratios of Neuroinflammatory/Ophthalmic diseases in Female Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	282
Table 345	Incidence rate difference of Neuroinflammatory/Ophthalmic autoimmune diseases in Female Cohorts - Onset Diagnosis - Confirmed cases (Total cohort) .....	282
Table 346	Incidence rate of Other autoimmune diseases in Female Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	282
Table 347	Incidence rate ratios of Other autoimmune diseases in Female Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	283
Table 348	Incidence rate difference of Other autoimmune diseases in Female Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	283
Table 349	Incidence rate ratios of Other autoimmune diseases in Female Cohorts (covariates adjusted) - Onset Diagnosis - Confirmed cases (Total cohort) .....	283
Table 350	Incidence rate of Neuroinflammatory/Ophthalmic autoimmune diseases in Female Cohorts - Onset Diagnosis - All cases (Total cohort).....	283
Table 351	Incidence rate ratios of Neuroinflammatory/Ophthalmic diseases in Female Cohorts - Onset Diagnosis - All cases (Total cohort).....	284
Table 352	Incidence rate difference of Neuroinflammatory/Ophthalmic autoimmune diseases in Female Cohorts - Onset Diagnosis - All cases (Total cohort) .....	284
Table 353	Incidence rate ratios of Neuroinflammatory/Ophthalmic diseases in Female Cohorts (covariates adjusted) - Onset Diagnosis - All cases (Total cohort) .....	284
Table 354	Incidence rate of Other autoimmune diseases in Female Cohorts - Onset Diagnosis - All cases (Total cohort) .....	284
Table 355	Incidence rate ratios of Other autoimmune diseases in Female Cohorts - Onset Diagnosis - All cases (Total cohort).....	285
Table 356	Incidence rate difference of Other autoimmune diseases in Female Cohorts - Onset Diagnosis - All cases (Total cohort) .....	285
Table 357	Incidence rate ratios of Other autoimmune diseases in Female Cohorts (covariates adjusted) - Onset Diagnosis - All cases (Total cohort).....	285

Table 358	Incidence rate of Neuroinflammatory/Ophthalmic autoimmune diseases in Male Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	285
Table 359	Incidence rate ratios of Neuroinflammatory/Ophthalmic diseases in Male Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	286
Table 360	Incidence rate difference of Neuroinflammatory/Ophthalmic autoimmune diseases in Male Cohorts - Onset Diagnosis - Confirmed cases (Total cohort) .....	286
Table 361	Incidence rate of Other autoimmune diseases in Male Cohorts - Onset Diagnosis - Confirmed cases (Total cohort) .....	286
Table 362	Incidence rate ratios of Other autoimmune diseases in Male Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	286
Table 363	Incidence rate difference of Other autoimmune diseases in Male Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	287
Table 364	Incidence rate ratios of Other autoimmune diseases in Male Cohorts (covariates adjusted) - Onset Diagnosis - Confirmed cases (Total cohort) .....	287
Table 365	Incidence rate of Neuroinflammatory/Ophthalmic autoimmune diseases in Male Cohorts - Onset Diagnosis - All cases (Total cohort).....	287
Table 366	Incidence rate ratios of Neuroinflammatory/Ophthalmic diseases in Male Cohorts - Onset Diagnosis - All cases (Total cohort).....	287
Table 367	Incidence rate difference of Neuroinflammatory/Ophthalmic autoimmune diseases in Male Cohorts - Onset Diagnosis - All cases (Total cohort) .....	288
Table 368	Incidence rate ratios of Neuroinflammatory/Ophthalmic diseases in Male Cohorts (covariates adjusted) - Onset Diagnosis - All cases (Total cohort) .....	288
Table 369	Incidence rate of Other autoimmune diseases in Male Cohorts - Onset Diagnosis - All cases (Total cohort).....	288
Table 370	Incidence rate ratios of Other autoimmune diseases in Male Cohorts - Onset Diagnosis - All cases (Total cohort) .....	288
Table 371	Incidence rate difference of Other autoimmune diseases in Male Cohorts - Onset Diagnosis - All cases (Total cohort).....	289
Table 372	Incidence rate ratios of Other autoimmune diseases in Male Cohorts (covariates adjusted) - Onset Diagnosis - All cases (Total cohort).....	289

Table 373	Incidence rate of Acute Disseminated Encephalomyelitis in Female Cohorts - Onset Diagnosis - All cases (Total cohort) .....	289
Table 374	Incidence rate of Ankylosing Spondylitis in Male Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	289
Table 375	Incidence rate of Ankylosing Spondylitis in Female Cohorts - Onset Diagnosis - All cases (Total cohort).....	289
Table 376	Incidence rate of Ankylosing Spondylitis in Male Cohorts - Onset Diagnosis - All cases (Total cohort).....	290
Table 377	Incidence rate of Peripheral neuropathies and plexopathies in Female Cohorts - Onset Diagnosis - All cases (Total cohort) .....	290
Table 378	Incidence rate of Autoimmune Thyroiditis in Female Cohorts - Onset Diagnosis - Confirmed cases (Total cohort) .....	290
Table 379	Incidence rate ratios of Autoimmune Thyroiditis in Female Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	290
Table 380	Incidence rate difference of Autoimmune Thyroiditis diseases in Female Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	290
Table 381	Incidence rate ratios of Autoimmune Thyroiditis in Female Cohorts (covariates adjusted) - Onset Diagnosis - Confirmed cases (Total cohort) .....	291
Table 382	Incidence rate of Autoimmune Thyroiditis in Male Cohorts - Onset Diagnosis - Confirmed cases (Total cohort) .....	291
Table 383	Incidence rate difference of Autoimmune Thyroiditis diseases in Male Cohorts - Onset Diagnosis - Confirmed cases (Total cohort) .....	291
Table 384	Incidence rate of Autoimmune Thyroiditis in Female Cohorts - Onset Diagnosis - All cases (Total cohort).....	291
Table 385	Incidence rate ratios of Autoimmune Thyroiditis in Female Cohorts - Onset Diagnosis - All cases (Total cohort) .....	292
Table 386	Incidence rate difference of Autoimmune Thyroiditis diseases in Female Cohorts - Onset Diagnosis - All cases (Total cohort) .....	292
Table 387	Incidence rate ratios of Autoimmune Thyroiditis in Female Cohorts (covariates adjusted) - Onset Diagnosis - All cases (Total cohort).....	292
Table 388	Incidence rate of Autoimmune Thyroiditis in Male Cohorts - Onset Diagnosis - All cases (Total cohort).....	292
Table 389	Incidence rate ratios of Autoimmune Thyroiditis in Male Cohorts - Onset Diagnosis - All cases (Total cohort).....	293

Table 390	Incidence rate difference of Autoimmune Thyroiditis diseases in Male Cohorts - Onset Diagnosis - All cases (Total cohort) .....	293
Table 391	Incidence rate ratios of Autoimmune Thyroiditis in Male Cohorts (covariates adjusted) - Onset Diagnosis - All cases (Total cohort).....	293
Table 392	Incidence rate of Autoimmune Uveitis in Female Cohorts - Onset Diagnosis - All cases (Total cohort).....	293
Table 393	Incidence rate ratios of Autoimmune Uveitis in Female Cohorts - Onset Diagnosis - All cases (Total cohort).....	294
Table 394	Incidence rate difference of Autoimmune Uveitis in Female Cohorts - Onset Diagnosis - All cases (Total cohort).....	294
Table 395	Incidence rate ratios of Autoimmune Uveitis in Female Cohorts (covariates adjusted) - Onset Diagnosis - All cases (Total cohort).....	294
Table 396	Incidence rate of Autoimmune Uveitis in Male Cohorts - Onset Diagnosis - All cases (Total cohort).....	294
Table 397	Incidence rate ratios of Autoimmune Uveitis in Male Cohorts - Onset Diagnosis - All cases (Total cohort).....	295
Table 398	Incidence rate difference of Autoimmune Uveitis in Male Cohorts - Onset Diagnosis - All cases (Total cohort) .....	295
Table 399	Incidence rate ratios of Autoimmune Uveitis in Male Cohorts (covariates adjusted) - Onset Diagnosis - All cases (Total cohort).....	295
Table 400	Incidence rate of Autoimmune Crohn diseases in Female Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	295
Table 401	Incidence rate ratios of Crohn diseases in Female Cohorts - Onset Diagnosis - Confirmed cases (Total cohort) .....	296
Table 402	Incidence rate difference of Autoimmune Crohn diseases in Female Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	296
Table 403	Incidence rate ratios of Crohn diseases in Female Cohorts (covariates adjusted) - Onset Diagnosis - Confirmed cases (Total cohort).....	296
Table 404	Incidence rate of Crohn diseases in Male Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	296
Table 405	Incidence rate ratios of Crohn diseases in Male Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	297
Table 406	Incidence rate difference of Crohn diseases in Male Cohorts - Onset Diagnosis - Confirmed cases (Total cohort) .....	297



Table 407	Incidence rate of Crohn diseases in Female Cohorts - Onset Diagnosis - All cases (Total cohort).....	297
Table 408	Incidence rate ratios of Crohn diseases in Female Cohorts - Onset Diagnosis - All cases (Total cohort).....	297
Table 409	Incidence rate difference of Crohn diseases in Female Cohorts - Onset Diagnosis - All cases (Total cohort).....	298
Table 410	Incidence rate ratios of Crohn diseases in Female Cohorts (covariates adjusted) - Onset Diagnosis - All cases (Total cohort).....	298
Table 411	Incidence rate of Crohn diseases in Male Cohorts - Onset Diagnosis - All cases (Total cohort).....	298
Table 412	Incidence rate ratios of Crohn diseases in Male Cohorts - Onset Diagnosis - All cases (Total cohort).....	298
Table 413	Incidence rate difference of Crohn diseases in Male Cohorts - Onset Diagnosis - All cases (Total cohort).....	299
Table 414	Incidence rate of Inflammatory bowel diseases in Female Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	299
Table 415	Incidence rate of Inflammatory bowel diseases in Male Cohorts - Onset Diagnosis - Confirmed cases (Total cohort) .....	299
Table 416	Incidence rate of Inflammatory bowel diseases in Female Cohorts - Onset Diagnosis - All cases (Total cohort) .....	299
Table 417	Incidence rate difference of Inflammatory bowel diseases in Female Cohorts - Onset Diagnosis - All cases (Total cohort) .....	299
Table 418	Incidence rate of Inflammatory bowel diseases in Male Cohorts - Onset Diagnosis - All cases (Total cohort).....	300
Table 419	Incidence rate of Juvenile Rheumatoid Arthritis in Female Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	300
Table 420	Incidence rate difference of Juvenile Rheumatoid Arthritis in Female Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	300
Table 421	Incidence rate of Juvenile Rheumatoid Arthritis in Male Cohorts - Onset Diagnosis - Confirmed cases (Total cohort) .....	300
Table 422	Incidence rate difference of Juvenile Rheumatoid Arthritis in Male Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	300
Table 423	Incidence rate of Juvenile Rheumatoid Arthritis in Female Cohorts - Onset Diagnosis - All cases (Total cohort).....	301



Table 424	Incidence rate difference of Juvenile Rheumatoid Arthritis in Female Cohorts - Onset Diagnosis - All cases (Total cohort) .....	301
Table 425	Incidence rate of Juvenile Rheumatoid Arthritis in Male Cohorts - Onset Diagnosis - All cases (Total cohort).....	301
Table 426	Incidence rate difference of Juvenile Rheumatoid Arthritis in Male Cohorts - Onset Diagnosis - All cases (Total cohort) .....	301
Table 427	Incidence rate of Multiple Sclerosis in Female Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	301
Table 428	Incidence rate difference of Multiple Sclerosis in Female Cohorts - Onset Diagnosis - Confirmed cases (Total cohort) .....	302
Table 429	Incidence rate of Multiple Sclerosis in Female Cohorts - Onset Diagnosis - All cases (Total cohort).....	302
Table 430	Incidence rate difference of Multiple Sclerosis in Female Cohorts - Onset Diagnosis - All cases (Total cohort) .....	302
Table 431	Incidence rate of Optic Neuritis in Male Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	302
Table 432	Incidence rate of Optic Neuritis in Female Cohorts - Onset Diagnosis - All cases (Total cohort).....	302
Table 433	Incidence rate difference of Optic Neuritis in Female Cohorts - Onset Diagnosis - All cases (Total cohort).....	303
Table 434	Incidence rate of Optic Neuritis in Male Cohorts - Onset Diagnosis - All cases (Total cohort).....	303
Table 435	Incidence rate of Psoriatic Arthritis in Female Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	303
Table 436	Incidence rate difference of Psoriatic Arthritis in Female Cohorts - Onset Diagnosis - Confirmed cases (Total cohort) .....	303
Table 437	Incidence rate of Psoriatic Arthritis in Female Cohorts - Onset Diagnosis - All cases (Total cohort).....	303
Table 438	Incidence rate difference of Psoriatic Arthritis in Female Cohorts - Onset Diagnosis - All cases (Total cohort) .....	304
Table 439	Incidence rate of Rheumatoid Arthritis in Female Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	304
Table 440	Incidence rate difference of Autoimmune Type 1 Diabetes Mellitus in Female Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	304

Table 441	Incidence rate of Rheumatoid Arthritis in Female Cohorts - Onset Diagnosis - All cases (Total cohort).....	304
Table 442	Incidence rate difference of Rheumatoid Arthritis in Female Cohorts - Onset Diagnosis - All cases (Total cohort).....	304
Table 443	Incidence rate of Rheumatoid Arthritis in Male Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	305
Table 444	Incidence rate difference of Rheumatoid Arthritis in Male Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	305
Table 445	Incidence rate of Autoimmune Type 1 Diabetes Mellitus in Female Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	305
Table 446	Incidence rate ratios of Type 1 Diabetes Mellitus in Female Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	305
Table 447	Incidence rate difference of Autoimmune Type 1 Diabetes Mellitus in Female Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	305
Table 448	Incidence rate ratios of Type 1 Diabetes Mellitus in Female Cohorts (covariates adjusted) - Onset Diagnosis - Confirmed cases (Total cohort) .....	306
Table 449	Incidence rate of Type 1 Diabetes Mellitus in Male Cohorts - Onset Diagnosis - Confirmed cases (Total cohort) .....	306
Table 450	Incidence rate ratios of Type 1 Diabetes Mellitus in Male Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	306
Table 451	Incidence rate difference of Autoimmune Type 1 Diabetes Mellitus in Male Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	306
Table 452	Incidence rate ratios of Type 1 Diabetes Mellitus in Male Cohorts (covariates adjusted) - Onset Diagnosis - Confirmed cases (Total cohort).....	307
Table 453	Incidence rate of Type 1 Diabetes Mellitus in Female Cohorts - Onset Diagnosis - All cases (Total cohort).....	307
Table 454	Incidence rate ratios of Type 1 Diabetes Mellitus in Female Cohorts - Onset Diagnosis - All cases (Total cohort).....	307
Table 455	Incidence rate difference of Autoimmune Type 1 Diabetes Mellitus in Female Cohorts - Onset Diagnosis - All cases (Total cohort).....	307

Table 456	Incidence rate ratios of Type 1 Diabetes Mellitus in Female Cohorts (covariates adjusted) - Onset Diagnosis - All cases (Total cohort).....	308
Table 457	Incidence rate of Type 1 Diabetes Mellitus in Male Cohorts - Onset Diagnosis - All cases (Total cohort).....	308
Table 458	Incidence rate ratios of Type 1 Diabetes Mellitus in Male Cohorts - Onset Diagnosis - All cases (Total cohort) .....	308
Table 459	Incidence rate difference of Autoimmune Type 1 Diabetes Mellitus in Male Cohorts - Onset Diagnosis - All cases (Total cohort).....	308
Table 460	Incidence rate ratios of Type 1 Diabetes Mellitus in Male Cohorts (covariates adjusted) - Onset Diagnosis - All cases (Total cohort).....	309
Table 461	Incidence rate of Autoimmune Ulcerative Colitis in Female Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	309
Table 462	Incidence rate of Ulcerative Colitis in Male Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	309
Table 463	Incidence rate difference of Ulcerative Colitis in Male Cohorts - Onset Diagnosis - Confirmed cases (Total cohort) .....	309
Table 464	Incidence rate of Ulcerative Colitis in Female Cohorts - Onset Diagnosis - All cases (Total cohort).....	309
Table 465	Incidence rate difference of Ulcerative Colitis in Female Cohorts - Onset Diagnosis - All cases (Total cohort).....	310
Table 466	Incidence rate of Ulcerative Colitis in Male Cohorts - Onset Diagnosis - All cases (Total cohort).....	310
Table 467	Incidence rate difference of Ulcerative Colitis in Male Cohorts - Onset Diagnosis - All cases (Total cohort).....	310
Table 468	Incidence rate of Idiopathic Thrombocytopenia Purpura in Female Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	310
Table 469	Incidence rate difference of Idiopathic Thrombocytopenia Purpura in Female Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	310
Table 470	Incidence rate of Idiopathic Thrombocytopenia Purpura in Male Cohorts - Onset Diagnosis - Confirmed cases (Total cohort).....	311
Table 471	Incidence rate of Idiopathic Thrombocytopenia Purpura in Female Cohorts - Onset Diagnosis - All cases (Total cohort) .....	311

Table 472	Incidence rate difference of Idiopathic Thrombocytopenia Purpura in Female Cohorts - Onset Diagnosis - All cases (Total cohort).....	311
Table 473	Incidence rate of Idiopathic Thrombocytopenia Purpura in Male Cohorts - Onset Diagnosis - All cases (Total cohort).....	311
Table 474	Frequency of autoimmune diseases during the one year follow-up period by exposed/non-exposed status - in 9-17 years old - Main Analysis - Confirmed and Non-Confirmed cases (Total cohort).....	312
Table 475	Frequency of autoimmune diseases during the one year follow-up period by exposed/non-exposed status - in 18-25 years old - Main Analysis - Confirmed and Non-Confirmed cases (Total cohort).....	313
Table 476	Frequency of autoimmune diseases during the one year follow-up period by exposed/non-exposed status - in 9-17 years old - Main Analysis - Confirmed cases (Total cohort) .....	314
Table 477	Frequency of autoimmune diseases during the one year follow-up period by exposed/non-exposed status - in 18-25 years old - Main Analysis - Confirmed cases (Total cohort) .....	315
Table 478	Incidence rate of Neuroinflammatory/Ophthalmic autoimmune diseases in Female Cohorts in [9-17] years old - Confirmed cases (Total cohort) .....	316
Table 479	Incidence rate of Neuroinflammatory/Ophthalmic autoimmune diseases in Male Cohorts in [9-17] years old - Confirmed cases (Total cohort).....	316
Table 480	Incidence rate ratios of Neuroinflammatory/Ophthalmic diseases in Male Cohorts in [9-17] years old - Confirmed cases (Total cohort).....	316
Table 481	Incidence rate of Other autoimmune diseases in Female Cohorts in [9-17] years old - Confirmed cases (Total cohort).....	316
Table 482	Incidence rate ratios of Other autoimmune diseases in Female Cohorts in [9-17] years old - Confirmed cases (Total cohort).....	317
Table 483	Incidence rate of Other autoimmune diseases in Male Cohorts in [9-17] years old - Confirmed cases (Total cohort).....	317
Table 484	Incidence rate ratios of Other autoimmune diseases in Male Cohorts in [9-17] years old - Confirmed cases (Total cohort).....	317
Table 485	Incidence rate of Neuroinflammatory/Ophthalmic autoimmune diseases in Female Cohorts in [18-25] years old - Confirmed cases (Total cohort) .....	317

Table 486	Incidence rate of Neuroinflammatory/Ophthalmic autoimmune diseases in Male Cohorts in [18-25] years old - Confirmed cases (Total cohort).....	318
Table 487	Incidence rate of Other autoimmune diseases in Female Cohorts in [18-25] years old - Confirmed cases (Total cohort).....	318
Table 488	Incidence rate ratios of Other autoimmune diseases in Female Cohorts in [18-25] years old - Confirmed cases (Total cohort).....	318
Table 489	Incidence rate of Other autoimmune diseases in Male Cohorts in [18-25] years old - Confirmed cases (Total cohort).....	318
Table 490	Incidence rate ratios of Other autoimmune diseases in Male Cohorts in [18-25] years old - Confirmed cases (Total cohort).....	319
Table 491	Incidence rate of Neuroinflammatory/Ophthalmic autoimmune diseases in Female Cohorts in [9-17] years old - All cases (Total cohort).....	319
Table 492	Incidence rate ratios of Neuroinflammatory/Ophthalmic diseases in Female Cohorts in [9-17] years old - All cases (Total cohort).....	319
Table 493	Incidence rate of Neuroinflammatory/Ophthalmic autoimmune diseases in Male Cohorts in [18-25] years old - All cases (Total cohort).....	319
Table 494	Incidence rate ratios of Neuroinflammatory/Ophthalmic autoimmune diseases in Male Cohorts in [18-25] years old - All cases (Total cohort) .....	320
Table 495	Incidence rate of Other autoimmune diseases in Female Cohorts in [9-17] years old - All cases (Total cohort) .....	320
Table 496	Incidence rate ratios of Other autoimmune diseases in Female Cohorts in [9-17] years old - All cases (Total cohort).....	320
Table 497	Incidence rate of Other autoimmune diseases in Male Cohorts in [18-25] years old - All cases (Total cohort) .....	320
Table 498	Incidence rate ratios of Other autoimmune diseases in Male Cohorts in [18-25] years old - All cases (Total cohort).....	321
Table 499	Incidence rate of Neuroinflammatory/Ophthalmic autoimmune diseases in Female Cohorts in [18-25] years old - Confirmed cases (Total cohort) .....	321
Table 500	Incidence rate of Neuroinflammatory/Ophthalmic autoimmune diseases in Male Cohorts in [18-25] years old - All cases (Total cohort).....	321
Table 501	Incidence rate ratios of Neuroinflammatory/Ophthalmic diseases in Male Cohorts in [18-25] years old - All cases (Total cohort).....	321

Table 502	Incidence rate of Other autoimmune diseases in Female Cohorts in [18-25] years old - Confirmed cases (Total cohort).....	<a href="#">322</a>
Table 503	Incidence rate ratios of Other autoimmune diseases in Female Cohorts in [18-25] years old - Confirmed cases (Total cohort).....	<a href="#">322</a>
Table 504	Incidence rate of Other autoimmune diseases in Male Cohorts in [18-25] years old - All cases (Total cohort) .....	<a href="#">322</a>
Table 505	Incidence rate ratios of Other autoimmune diseases in Male Cohorts in [18-25] years old - All cases (Total cohort).....	<a href="#">322</a>
Table 506	Incidence rate of Autoimmune Thyroiditis in Female Cohorts in [9-17] years old - Confirmed cases (Total cohort).....	<a href="#">323</a>
Table 507	Incidence rate ratios of Autoimmune Thyroiditis in Female Cohorts in [9-17] years old - Confirmed cases (Total cohort).....	<a href="#">323</a>
Table 508	Incidence rate of Crohn diseases in Female Cohorts in [9-17] years old - Confirmed cases (Total cohort).....	<a href="#">323</a>
Table 509	Incidence rate ratios of Crohn diseases in Female Cohorts in [9-17] years old - Confirmed cases (Total cohort).....	<a href="#">323</a>
Table 510	Incidence rate of Type 1 Diabetes Mellitus in Female Cohorts in [9-17] years old - Confirmed cases (Total cohort).....	<a href="#">324</a>
Table 511	Incidence rate ratios of Type 1 Diabetes Mellitus in Female Cohorts in [9-17] years old - Confirmed cases (Total cohort).....	<a href="#">324</a>
Table 512	Incidence rate of Type 1 Diabetes Mellitus in Male Cohorts in [9-17] years old - Confirmed cases (Total cohort).....	<a href="#">324</a>
Table 513	Incidence rate ratios of Type 1 Diabetes Mellitus in Male Cohorts in [9-17] years old - Confirmed cases (Total cohort).....	<a href="#">324</a>
Table 514	Incidence rate of Autoimmune Thyroiditis in Female Cohorts in [9-17] years old - All cases (Total cohort) .....	<a href="#">325</a>
Table 515	Incidence rate ratios of Autoimmune Thyroiditis in Female Cohorts in [9-17] years old - All cases (Total cohort) .....	<a href="#">325</a>
Table 516	Incidence rate of Crohn diseases in Female Cohorts in [9-17] years old - All cases (Total cohort) .....	<a href="#">325</a>
Table 517	Incidence rate ratios of Crohn diseases in Female Cohorts in [9-17] years old - All cases (Total cohort) .....	<a href="#">325</a>
Table 518	Incidence rate of Type 1 Diabetes Mellitus in Female Cohorts in [9-17] years old - All cases (Total cohort) .....	<a href="#">326</a>
Table 519	Incidence rate ratios of Type 1 Diabetes Mellitus in Female Cohorts in [9-17] years old - All cases (Total cohort).....	<a href="#">326</a>

Table 520	Incidence rate of Type 1 Diabetes Mellitus in Male Cohorts in [9-17] years old - All cases (Total cohort) .....	326
Table 521	Incidence rate ratios of Type 1 Diabetes Mellitus in Male Cohorts in [9-17] years old - All cases (Total cohort) .....	326
Table 522	Incidence rate of Autoimmune Thyroiditis in Female Cohorts in [18-25] years old - Confirmed cases (Total cohort).....	327
Table 523	Incidence rate of Autoimmune Thyroiditis in Male Cohorts in [18-25] years old - Confirmed cases (Total cohort).....	327
Table 524	Incidence rate of Crohn diseases in Female Cohorts in [18-25] years old - Confirmed cases (Total cohort).....	327
Table 525	Incidence rate of Type 1 Diabetes Mellitus in Male Cohorts in [18-25] years old - Confirmed cases (Total cohort).....	327
Table 526	Incidence rate of Autoimmune Thyroiditis in Female Cohorts in [18-25] years old - All cases (Total cohort) .....	328
Table 527	Incidence rate of Autoimmune Thyroiditis in Male Cohorts in [18-25] years old - All cases (Total cohort) .....	328
Table 528	Incidence rate of Crohn diseases in Female Cohorts in [18-25] years old - All cases (Total cohort) .....	328
Table 529	Incidence rate of Crohn diseases in Male Cohorts in [18-25] years old - All cases (Total cohort) .....	328
Table 530	Incidence rate of Type 1 Diabetes Mellitus in Female Cohorts in [18-25] years old - All cases (Total cohort) .....	329
Table 531	Incidence rate of Type 1 Diabetes Mellitus in Male Cohorts in [18-25] years old - All cases (Total cohort) .....	329
Table 532	Incidence rate of Other autoimmune diseases after Cervarix dose 1 in Exposed cohort- Confirmed and Non-Confirmed cases (Total cohort).....	329
Table 533	Incidence rate of Other autoimmune diseases after Cervarix dose 1 in Exposed cohort- Confirmed cases (Total cohort) .....	329
Table 534	Incidence rate of Other autoimmune diseases after Cervarix dose 2 in Exposed cohort- Confirmed and Non-Confirmed cases (Total cohort).....	330
Table 535	Incidence rate of Other autoimmune diseases after Cervarix dose 2 in Exposed cohort- Confirmed cases (Total cohort) .....	330
Table 536	Incidence rate of Other autoimmune diseases after Cervarix dose 3 in Exposed cohort- Confirmed and Non-Confirmed cases (Total cohort).....	330



Table 537	Incidence rate of Other autoimmune diseases after Cervarix dose 3 in Exposed cohort- Confirmed cases (Total cohort) .....	330
Table 538	Incidence rate of Other autoimmune diseases after Cervarix dose 4 in Exposed cohort- Confirmed and Non-Confirmed cases (Total cohort).....	331
Table 539	Incidence rate of Other autoimmune diseases after Cervarix dose 4 in Exposed cohort- Confirmed cases (Total cohort) .....	331
Table 540	Incidence rate of Neuroinflammatory/Ophthalmic autoimmune diseases after Cervarix dose 1 in Exposed cohort - Confirmed and Non-Confirmed cases (Total cohort).....	331
Table 541	Incidence rate of Neuroinflammatory/Ophthalmic autoimmune diseases after Cervarix dose 1 in Exposed cohort- Confirmed cases (Total cohort) .....	331
Table 542	Incidence rate of Neuroinflammatory/Ophthalmic autoimmune diseases after Cervarix dose 2 in Exposed cohort- Confirmed and Non-Confirmed cases (Total cohort).....	332
Table 543	Incidence rate of Neuroinflammatory/Ophthalmic autoimmune diseases after Cervarix dose 2 in Exposed cohort- Confirmed cases (Total cohort) .....	332
Table 544	Incidence rate of Neuroinflammatory/Ophthalmic autoimmune diseases after Cervarix dose 3 in Exposed cohort- Confirmed and Non-Confirmed cases (Total cohort).....	332
Table 545	Incidence rate of Neuroinflammatory/Ophthalmic autoimmune diseases after Cervarix dose 3 in Exposed cohort- Confirmed cases (Total cohort) .....	332
Table 546	Incidence rate of Neuroinflammatory/Ophthalmic autoimmune diseases after Cervarix dose 4 in Exposed cohort- Confirmed and Non-Confirmed cases (Total cohort).....	333
Table 547	Incidence rate of Neuroinflammatory/Ophthalmic autoimmune diseases after Cervarix dose 4 in Exposed cohort- Confirmed cases (Total cohort) .....	333
Table 548	Incidence rate of Autoimmune thyroiditis after Cervarix dose 1 in Exposed cohort- Confirmed and Non-Confirmed cases (Total cohort).....	333
Table 549	Incidence rate of Autoimmune thyroiditis after Cervarix dose 1 in Exposed cohort- Confirmed cases (Total cohort).....	333
Table 550	Incidence rate of Autoimmune thyroiditis after Cervarix dose 2 in Exposed cohort- Confirmed and Non-Confirmed cases (Total cohort).....	334



Table 551	Incidence rate of Autoimmune thyroiditis after Cervarix dose 2 in Exposed cohort- Confirmed cases (Total cohort).....	334
Table 552	Incidence rate of Autoimmune thyroiditis after Cervarix dose 3 in Exposed cohort- Confirmed and Non-Confirmed cases (Total cohort).....	334
Table 553	Incidence rate of Autoimmune thyroiditis after Cervarix dose 3 in Exposed cohort- Confirmed cases (Total cohort).....	334
Table 554	Incidence rate of Autoimmune thyroiditis after Cervarix dose 4 in Exposed cohort- Confirmed and Non-Confirmed cases (Total cohort).....	335
Table 555	Incidence rate of Autoimmune thyroiditis after Cervarix dose 4 in Exposed cohort- Confirmed cases (Total cohort).....	335
Table 556	Incidence rate of Crohn diseases after Cervarix dose 1 in Exposed cohort- Confirmed and Non-Confirmed cases (Total cohort).....	335
Table 557	Incidence rate of Crohn diseases after Cervarix dose 1 in Exposed cohort- Confirmed cases (Total cohort).....	335
Table 558	Incidence rate of Crohn diseases after Cervarix dose 2 in Exposed cohort- Confirmed and Non-Confirmed cases (Total cohort).....	336
Table 559	Incidence rate of Crohn diseases after Cervarix dose 2 in Exposed cohort- Confirmed cases (Total cohort).....	336
Table 560	Incidence rate of Crohn diseases after Cervarix dose 3 in Exposed cohort- Confirmed and Non-Confirmed cases (Total cohort).....	336
Table 561	Incidence rate of Crohn diseases after Cervarix dose 3 in Exposed cohort- Confirmed cases (Total cohort).....	336
Table 562	Incidence rate of Crohn diseases after Cervarix dose 4 in Exposed cohort- Confirmed and Non-Confirmed cases (Total cohort).....	337
Table 563	Incidence rate of Crohn diseases after Cervarix dose 4 in Exposed cohort- Confirmed cases (Total cohort).....	337
Table 564	Incidence rate of Type 1 Diabetes Mellitus after Cervarix dose 1 in Exposed cohort- Confirmed and Non-Confirmed cases (Total cohort).....	337
Table 565	Incidence rate of Type 1 Diabetes Mellitus after Cervarix dose 1 in Exposed cohort- Confirmed cases (Total cohort).....	337

Table 566	Incidence rate of Type 1 Diabetes Mellitus after Cervarix dose 2 in Exposed cohort- Confirmed and Non-Confirmed cases (Total cohort).....	338
Table 567	Incidence rate of Type 1 Diabetes Mellitus after Cervarix dose 2 in Exposed cohort- Confirmed cases (Total cohort).....	338
Table 568	Incidence rate of Type 1 Diabetes Mellitus after Cervarix dose 3 in Exposed cohort- Confirmed and Non-Confirmed cases (Total cohort).....	338
Table 569	Incidence rate of Type 1 Diabetes Mellitus after Cervarix dose 3 in Exposed cohort- Confirmed cases (Total cohort).....	338
Table 570	Incidence rate of Type 1 Diabetes Mellitus after Cervarix dose 4 in Exposed cohort- Confirmed and Non-Confirmed cases (Total cohort).....	339
Table 571	Incidence rate of Type 1 Diabetes Mellitus after Cervarix dose 4 in Exposed cohort- Confirmed cases (Total cohort).....	339
Table 572	Number of Other Autoimmune diseases by CTRL/RISK period - Main Analysis - Main SCCS- All cases (Total cohort).....	339
Table 573	Number of Other Autoimmune diseases by CTRL/RISK period - Main Analysis - Main SCCS - All cases .....	339
Table 574	Number of Diabetes diseases by CTRL/RISK period - Main Analysis - All cases (Total cohort) .....	340
Table 575	Number of Diabetes diseases by CTRL/RISK period - Main Analysis - All cases .....	340
Table 576	Number of Thyroiditis diseases by CTRL/RISK period - Main Analysis - All cases (Total cohort) .....	340
Table 577	Number of Thyroiditis diseases by CTRL/RISK period - Main Analysis - All cases .....	341
Table 578	Number of Crohn diseases by CTRL/RISK period - Main Analysis - All cases (Total cohort) .....	341
Table 579	Number of Crohn diseases by CTRL/RISK period - Main Analysis - - Main SCCS - All cases.....	341
Table 580	Number of Neuroinflammatory/Ophthalmic diseases by CTRL/RISK period - Main Analysis - Main SCCS - All cases (Total cohort).....	342
Table 581	Number of Neuroinflammatory/Ophthalmic diseases by CTRL/RISK period - Main Analysis - Main SCCS - All cases.....	342

Table 582	Number of Other Autoimmune diseases by CTRL/RISK period - Main Analysis - Sensitivity SCCS - All cases (Total cohort).....	342
Table 583	Number of Other Autoimmune diseases by CTRL/RISK period - Main Analysis - Sensitivity SCCS - All cases.....	343
Table 584	Number of Neuroinflammatory/Ophthalmic diseases by CTRL/RISK period - Main Analysis - Sensitivity SCCS - All cases (Total cohort).....	343
Table 585	Number of Neuroinflammatory/Ophthalmic diseases by CTRL/RISK period - Main Analysis - Sensitivity Analysis - All cases .....	343
Table 586	Number of Other Autoimmune diseases by CTRL/RISK period - Main Analysis - Main SCCS- Confirmed cases (Total cohort).....	344
Table 587	Number of Other Autoimmune diseases by CTRL/RISK period - Main Analysis - Main SCCS - Confirmed cases.....	344
Table 588	Number of Diabetes diseases by CTRL/RISK period - Main Analysis - Confirmed cases (Total cohort).....	344
Table 589	Number of Diabetes diseases by CTRL/RISK period - Main Analysis - Confirmed cases .....	345
Table 590	Number of Thyroiditis diseases by CTRL/RISK period - Main Analysis - Confirmed cases (Total cohort).....	345
Table 591	Number of Thyroiditis diseases by CTRL/RISK period - Main Analysis - Confirmed cases .....	345
Table 592	Number of Neuroinflammatory/Ophthalmic diseases by CTRL/RISK period - Main Analysis - Main SCCS - Confirmed cases (Total cohort) .....	345
Table 593	Number of Neuroinflammatory/Ophthalmic diseases by CTRL/RISK period - Main Analysis - Main SCCS - Confirmed cases .....	346
Table 594	Number of Other Autoimmune diseases by CTRL/RISK period - Main Analysis - Sensitivity SCCS - Confirmed cases (Total cohort).....	346
Table 595	Number of Other Autoimmune diseases by CTRL/RISK period - Main Analysis - Sensitivity SCCS - Confirmed cases .....	346
Table 596	Number of Neuroinflammatory/Ophthalmic diseases by CTRL/RISK period - Main Analysis - Sensitivity SCCS - Confirmed cases (Total cohort) .....	347

Table 597	Number of Neuroinflammatory/Ophthalmic diseases by CTRL/RISK period - Main Analysis - Sensitivity Analysis - Confirmed cases .....	347
Table 598	Incidence Rate Ratio for diabetes adjusted for male effect (Total cohort).....	347
Table 599	Sat Scan Results-Main analysis: Exposed Female cohort – Temporal windows = 60 days .....	348
Table 600	Sat Scan Results-Main analysis Non-Exposed Female cohort – Temporal windows = 60 days .....	349
Table 601	Sat Scan Results-Main analysis Concurrent Male cohort – Temporal windows = 60 days .....	350
Table 602	Sat Scan Results-Main analysis Historical Male cohort – Time Aggregation = 60 days .....	351
Table 603	Sat Scan Results-Main analysis Exposed Female cohort – Temporal windows = 120 days .....	352
Table 604	Sat Scan Results-Main analysis Non-Exposed Female cohort – Temporal windows = 120 days .....	353
Table 605	Sat Scan Results-Main analysis Concurrent Male cohort – Temporal windows = 120 days .....	353
Table 606	Sat Scan Results-Main analysis Historical Male cohort – Temporal windows = 120 days .....	354
Table 607	Sat Scan Results Imputed date Exposed Female cohort – Temporal windows = 60 days .....	355
Table 608	Sat Scan Results Imputed date Non-Exposed Female cohort – Temporal windows = 60 days .....	356
Table 609	Sat Scan Results Imputed date Concurrent Male cohort – Temporal windows = 60 days .....	357
Table 610	Sat Scan Results Imputed date Historical Male cohort – Temporal windows = 60 days .....	357
Table 611	Sat Scan Results Imputed date Exposed Female cohort – Temporal windows = 120 days .....	358
Table 612	Sat Scan Results Imputed date Non-Exposed Female cohort – Temporal windows = 120 days .....	359
Table 613	Sat Scan Results Imputed date Concurrent Male cohort – Temporal windows = 120 days .....	359

Table 614	Sat Scan Results Imputed date Historical Male cohort – Temporal windows = 120 days .....	360
Table 615	Sat Scan Results Diagnosis date Exposed Female cohort – Temporal windows = 60 days .....	361
Table 616	Sat Scan Results Diagnosis date Non-Exposed Female cohort – Temporal windows = 60 days .....	362
Table 617	Sat Scan Results Diagnosis date Concurrent Male cohort – Temporal windows = 60 days .....	363
Table 618	Sat Scan Results Diagnosis date Historical Male cohort – Temporal windows = 60 days .....	364
Table 619	Sat Scan Results Diagnosis date Exposed Female cohort – Temporal windows = 120 days .....	365
Table 620	Sat Scan Results Diagnosis date Non-Exposed Female cohort – Temporal windows = 120 days .....	366
Table 621	Sat Scan Results Diagnosis date Concurrent Male cohort – Temporal windows = 120 days .....	367
Table 622	Sat Scan Results Diagnosis date Historical Male cohort – Temporal windows = 120 days .....	368
Table 623	Geographical distribution of the two co-primary endpoints - Confirmed cases (Total cohort) .....	369
Table 624	Geographical distribution of the two co-primary endpoints - All cases (Total cohort) .....	371
Table 625	Geographical distribution of thyroiditis cases - Confirmed cases (Total cohort).....	373
Table 626	Geographical distribution of thyroiditis cases - All cases (Total cohort).....	373
Table 627	Geographical distribution of Diabetes Type 1 cases - Confirmed cases (Total cohort) .....	374
Table 628	Geographical distribution of Diabetes Type 1 cases - All cases (Total cohort).....	374
Table 629	Geographical distribution of Crohn's disease - Confirmed cases (Total cohort).....	375
Table 630	Geographical distribution of Crohn's disease - All cases (Total cohort).....	375

Table 631	Frequency of autoimmune diseases during the one year follow-up period by exposed/non-exposed status - Main Analysis - Confirmed and Non-Confirmed cases (N=AD) (Total cohort).....	376
Table 632	Classification of thyroiditis cases - All cases (Total cohort).....	377
Table 633	HES linkage - All cases (Total cohort).....	377
Table 634	Incidence rate of Hypothyroiditis in Female Cohorts - Main Analysis - All cases (Total cohort) .....	377
Table 635	Incidence rate ratios of Hypothyroiditis in Female Cohorts - Main Analysis - All cases (Total cohort) .....	377
Table 636	Incidence rate difference of Hypothyroiditis diseases in Female Cohorts - Main Analysis - All cases (Total cohort) .....	378
Table 637	Incidence rate ratios of Hypothyroiditis in Female Cohorts (covariates adjusted) - Main Analysis - All cases (Total cohort).....	378
Table 638	Incidence rate of Hypothyroiditis in Male Cohorts - Main Analysis - All cases (Total cohort).....	378
Table 639	Incidence rate ratios of Hypothyroiditis in Male Cohorts - Main Analysis - All cases (Total cohort) .....	378
Table 640	Incidence rate difference of Hypothyroiditis diseases in Male Cohorts - Main Analysis - All cases (Total cohort) .....	379
Table 641	Incidence rate ratios of Hypothyroiditis in Male Cohorts (covariates adjusted) - Main Analysis - All cases (Total cohort).....	379
Table 642	Frequency of autoimmune diseases during the one year follow-up period by exposed/non-exposed status - Main Analysis - Confirmed cases (N=AD) (Total cohort) .....	380
Table 643	Classification of thyroiditis cases - Confirmed cases (Total cohort).....	381
Table 644	HES linkage - All cases (Total cohort).....	381
Table 645	Incidence rate of Hypothyroiditis in Female Cohorts - Main Analysis - Confirmed cases (Total cohort).....	381
Table 646	Incidence rate ratios of Hypothyroiditis in Female Cohorts - Main Analysis - Confirmed cases (Total cohort).....	382
Table 647	Incidence rate difference of Hypothyroiditis diseases in Female Cohorts - Main Analysis - Confirmed cases (Total cohort).....	382
Table 648	Incidence rate ratios of Hypothyroiditis in Female Cohorts (covariates adjusted) - Main Analysis - Confirmed cases (Total cohort).....	382

## LIST OF FIGURES

	<b>PAGE</b>
Figure 1 Cohort design.....	59
Figure 2 Self-control case-series analysis .....	60
Figure 3 Detectable relative risk and difference versus the incidence rate in the ( <i>Cervarix</i> ) unexposed cohort.....	76
Figure 4 Population size for a SCCS analysis versus the incidence rate ratio and the background incidence in the general population .....	77
Figure 5 Risk and control periods for the various endpoints .....	82
Figure 6 Summary of follow-up time for each of the four cohorts.....	87
Figure 7 Selection of subjects for the main and imputed date of first symptom sensitivity analysis .....	89
Figure 8 Selection of subjects for the date of disease diagnosis sensitivity analysis .....	90
Figure 9 Relationship between date of diagnosis and date of first symptom .....	91
Figure 10 Number of cases (confirmed and non-confirmed) in female cohorts .....	99
Figure 11 Number of cases (confirmed and non-confirmed) in male cohorts .....	100
Figure 12 Incidence Rate Ratio results summary for the two co-primary endpoints <sup>1</sup> .....	103
Figure 13 Incidence Rate Ratio results summary for the individual AD <sup>1</sup> .....	104
Figure 14 Confirmed cases in the 9-17 years age group .....	105
Figure 15 Incidence rates by dose in exposed female cohorts .....	106
Figure 16 Relative incidence (95% CI) between risk and control periods for confirmed cases .....	107
Figure 17 Time to onset of confirmed autoimmune diseases by cohort .....	109
Figure 18 Time to onset of autoimmune thyroiditis cases by cohort .....	110
Figure 19 Disease onset for the autoimmune thyroiditis cases according to <i>Cervarix</i> vaccination .....	111

Figure 20	Geographical distribution of confirmed cases for Other autoimmune diseases .....	112
Figure 21	Geographical distribution of Thyroiditis, Type 1 diabetes and Crohn's disease cases by cohort.....	113



## LIST OF ANNEXES

	<b>PAGE</b>
Annex 1	List of stand-alone documents..... 383
Annex 2	Glossary of Terms..... 383
Annex 3	Trademarks..... 385
Annex 4	Changes in the conduct of the study ..... 385
Annex 5	Pallas Methodology Report ..... 386
Annex 6	Additional information.....424
Annex 7	Report sign-off .....424

## 1. ABSTRACT

### Title

An observational cohort study to assess the risk of autoimmune diseases in adolescent and young adult women aged 9 to 25 years exposed to Cervarix® in the United Kingdom

### Keywords

*Cervarix*, cohort study, adolescent/young-adult women, autoimmune diseases

### Rationale and background

*Cervarix* is a bivalent recombinant vaccine against human papillomavirus (HPV, types 16 and 18). UK *Cervarix* vaccination was started in September 2008 for 12-13 year old girls, with a catch-up programme for girls/women aged 14-18 years, with more than 6 million doses currently administered. GSK Biologicals had a post-marketing regulatory commitment with the US FDA to investigate the incidence of autoimmune diseases (AD) in subjects receiving *Cervarix*. An earlier US database study was started (EPI-HPV-015), but low recruitment meant that the study objectives could not be assessed in a reasonable timeframe. This UK study investigating incidence of AD using the CPRD GOLD database (Clinical Practice Research Datalink General Practitioner OnLine Database) was planned, and hence was proposed as an alternative study for addressing the US FDA commitment.

### Research question and objectives

The primary objective was to assess whether *Cervarix* vaccination was associated with increased risk of 1) Neuroinflammatory/ophthalmic AD or 2) Other AD (co-primary objectives) within 12 months of first dose. The secondary objective was to investigate the incidence of pre-specified AD within 2, 6 or 12 months of first *Cervarix* dose.

### Study design

Observational cohort study using CPRD GOLD, and a self-controlled case-series (SCCS) analysis for confirmed AD in the exposed female cohort.

### Setting

CPRD GOLD containing coded records from UK general practices and its linked component of the Hospital Episode Statistics (HES).

### Subjects and study size, including dropouts

The main study population included 259,876 subjects, of which 64,964 subjects were exposed to *Cervarix*.

## Variables and data sources

The data sources were CPRD GOLD including “free-text” entries and HES. The endpoint for the primary objective was occurrence of one of the selected ADs within 12 months of the first *Cervarix* dose. Secondary endpoints were occurrence of selected ADs within 2, 6, or 12 months of first *Cervarix* dose. Algorithms were used to identify subjects with CPRD GOLD medcodes that corresponded to the selected ADs. After first patient profile review, individual data with doubt on the aetiology were reviewed by an expert.

## Results

For the neuroinflammatory/ophthalmic diseases (confirmed cases), the adjusted Incidence Rate Ratio (IRR) for male cohorts was 0.95 [95%CI: 0.06-15.18] and it was not done for females due to only one case in the non-exposed cohort.

For the other autoimmune diseases (confirmed cases), the adjusted IRRs were 1.41 [95%CI: 0.86-2.31] for the exposed and non-exposed female cohorts and 1.77 [95%CI: 0.94-3.35] for the concurrent and historical male cohorts.

For autoimmune (AI) thyroiditis, the IRR was 3.75 [95%CI: 1.25-11.31] for confirmed cases in the two female cohorts meaning that the risk is higher in exposed women and the difference between exposed and non-exposed women was statistically significant. When considering confirmed and non-confirmed cases the IRR was 1.45 [95%CI: 0.79-2.64] and became non-significant.

## Discussion

The present study did not show any evidence of increased risk for the two co-primary endpoints (neuroinflammatory/ophthalmic AD and other AD).

No cluster with regards to time to onset and *Cervarix* dosing was observed in the 49 cases of AI thyroiditis. The individual review of the cases concluded that it is not consistent with vaccination having caused the events, considering the known natural progression of AI thyroiditis, i.e. the cases observed could represent pre-existing conditions at the time of vaccination. Similar conclusions were published for the HPV4 vaccine.

## Marketing Authorisation Holder(s)

GlaxoSmithKline Biologicals, Rue de l'Institut 89, 1330 Rixensart, Belgium

## Names and affiliations of principal investigators

Not applicable

**2. LIST OF ABBREVIATIONS**

<b>AD</b>	Autoimmune disease(s)
<b>ADEM</b>	Acute Disseminated Encephalomyelitis
<b>AI</b>	Autoimmune
<b>ANOVA</b>	Analysis of Variance
<b>CARS</b>	Computer Aided Regulatory Submission
<b>CI</b>	Confidence interval
<b>CPRD GOLD</b>	Clinical Practice Research Datalink General Practitioner OnLine database
<b>DH</b>	Department of Health (UK)
<b>EU</b>	European Union
<b>EXP</b>	Exposed Cohort
<b>FDA</b>	Food and Drug Administration (US)
<b>FU</b>	Follow up
<b>GBS</b>	Guillain-Barré Syndrome
<b>GP</b>	General Practitioner
<b>GPP</b>	Good Pharmacoepidemiology Practices (Guidelines)
<b>GSK</b>	GlaxoSmithKline
<b>HES</b>	Hospital Episode Statistics
<b>HIST</b>	Non Exposed Historical Male Cohort
<b>HPV</b>	Human papillomavirus
<b>ICD</b>	International Classification of Diseases
<b>IEC</b>	Independent ethics committee
<b>IRB</b>	Institutional review board
<b>IRR</b>	Incidence rate ratio
<b>ISAC</b>	Independent Scientific Advisory Committee (for Medicines and Healthcare products Regulatory Agency database research)
<b>ISPE</b>	International Society for Pharmacoepidemiology
<b>ITP</b>	Idiopathic thrombocytopenic purpura
<b>JRA</b>	Juvenile rheumatoid arthritis
<b>LL</b>	95% Lower exact confidence limit
<b>MALE</b>	Non Exposed Concurrent Male Cohort
<b>MHRA</b>	Medicines and Healthcare products Regulatory Agency
<b>N</b>	Number of subjects
<b>NNEXP</b>	Non Exposed Historical Female Cohort
<b>NRES</b>	National Research Ethics Service Committee
<b>PASS</b>	Post Authorization Safety Study
<b>pIMD</b>	potential immune-mediated disorders
<b>QC</b>	quality control
<b>RA</b>	Rheumatoid arthritis
<b>RDE</b>	Remote Data Entry
<b>RR</b>	Relative Risk
<b>SCCS</b>	Self-controlled case-series
<b>SD</b>	Standard Deviation
<b>SDD</b>	SAS Drug Development

<b>SDL</b>	Study Delivery Lead
<b>SERM</b>	Safety Evaluation and Risk Management
<b>SLE</b>	Systemic Lupus Erythematosus
<b>UK</b>	United Kingdom
<b>UL</b>	95% Upper exact confidence limit
<b>US</b>	United States (of America)
<b>VCSP</b>	Vaccines Clinical Safety & Pharmacovigilance

### **3. ETHICS**

#### **3.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)**

The study protocol and other information that required pre-approval were reviewed and approved by the Independent Scientific Advisory Committee (ISAC) for Medicines and Healthcare products Regulatory Agency (MHRA) database research. ISAC protocol approval was given on 30 August 2012.

#### **3.2. Ethical conduct of the study**

The study was conducted in accordance with all applicable regulatory requirements, with the Guidelines for Good Pharmacoepidemiology Practices (GPP) [[ISPE](#), 2007], all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

#### **3.3. Subject information and consent**

No patient informed consent was needed, because the patient information in the Clinical Practice Research Datalink General Practice OnLine Database (CPRD GOLD) is fully coded and GlaxoSmithKline (GSK) Biologicals personnel were not able to make a link between the data and specific individuals.

The CPRD GOLD has obtained ethical approval from a National Research Ethics Service Committee (NRES) for purely observational research (i.e. studies that do not include patient involvement [[CPRD GOLD](#), 2014a]).

### **4. INVESTIGATORS**

Not applicable

### **5. OTHER RESPONSIBLE PARTIES**

GSK Biologicals had the overall responsibility for the conduct of the study.

[REDACTED] was the GSK Biologicals designated Director and Head of Global Epidemiology.

The ISAC of MHRA reviewed the protocol and other information requiring pre-approval. The key roles of this committee are to provide expert advice on the medical aspects, statistical/epidemiological aspects and methodological aspects of studies involving CPRD GOLD [CPRD GOLD, 2014b].

The ascertainment of the etiologic diagnosis and date of disease onset for all identified autoimmune diseases was performed by Pallas, Health Research and Consultancy B.V to ensure the correct classification of each case (see Section 10.5.1). Pallas reviewed all subject data retrieved from CPRD GOLD including clinical diagnosis, vaccines history, laboratory testing, and drug prescription, the relevant “free text” and Hospital Episode Statistics (HES; including specific ICD-10 diagnostic codes), when available. Pallas assessed whether the aetiology of the autoimmune disease was confirmed or not and whether the date of disease diagnosis fell within the observation period of the study, which was one year after the reference date. The GSK safety physician and a Physician/Director of Epidemiology at RTI Health Solutions reviewed all suspected cases of autoimmune disease for which Pallas had some doubts.

In the event that the (date of) diagnosis, first symptom and/or first abnormal laboratory test could not be confirmed, a second review step was conducted with an expert physician to reach an agreement. A panel of 5 physicians from different medical specialty were constituted including experts in internal medicine (2), neurology (1), ophthalmology (1) and rheumatology (1). The experts were blinded with regards to HPV vaccine exposure. Furthermore, the experts reviewed a random sample of 10% of the cases per autoimmune disease.

## 6. MILESTONES

Milestone	Planned date	Actual date	Comments
ISAC protocol approval	Protocol submitted on 12 July 2012	Approval: 30 August 2012	None
Final protocol submitted to Regulatory Authorities	31 July 2013	31 July 2013	None
Registration in the EU PAS register	16 September 2013	01 October 2013	Registry number: ENCEPP/SDPP/4584
Start of data collection	30 September 2013	28 October 2013	
End of data collection	31 May 2014	12 August 2014	This corresponded to the date when the final case ascertainment was entered into RDE. The timelines were updated due to an unexpected workload during the case ascertainment process (additional review of patient profiles and requests for further expert consultation).
Projected study completion (Statistical analysis complete; SAC)	30 September 2014	16-October-2014	The date on which the statistical analysis for the database results was completed (SAC).
Final report of study results	31 March 2015	17 March 2015	

## 7. RATIONALE AND BACKGROUND

*Cervarix* is a GlaxoSmithKline (GSK) Biologicals' bivalent recombinant vaccine against human papillomavirus (HPV, types 16 and 18). It is currently licensed in more than 130 countries worldwide, including the European Union (EU) via the Centralised Procedure. Cervarix was granted approval by the European Medicines Agency (EMA) in September 2007 and the US Centre for Biologics Evaluation and Research (CBER) in October 2009. In the US, Cervarix is indicated for the prevention of cervical cancer, cervical intraepithelial neoplasia (CIN) grade 2 or worse and adenocarcinoma in situ, and cervical intraepithelial neoplasia (CIN) grade 1, caused by oncogenic human papillomavirus (HPV) types 16 and 18, in females 9 through 25 years of age. In the EU, Cervarix is indicated in females from 9 years of age onwards for the prevention of persistent infection, premalignant genital (cervical, vulvar and vaginal) lesions and cervical, vulvar and vaginal cancers (squamous-cell carcinoma and adenocarcinoma) caused by oncogenic Human Papillomaviruses (HPV).

Pre-licensure clinical studies provided key vaccine safety data, but their power to detect rare outcomes such as new onset of autoimmune disease(s) (AD) is limited due to their sample size, since incidence rates of different AD vary roughly from 1 to 20/100,000 per year [Cooper, 2003]. A pooled analysis of AD data from 68,000 subjects exposed to AS04-adjuvanted HPV-16/18, herpes simplex virus and hepatitis B vaccines in the GSK development programs did not suggest any excess risk associated with the AS04-adjuvanted vaccines compared to control vaccines [Verstraeten, 2008]. A pooled

safety analysis of data from almost 30,000 adolescent and adult females aged 9 years and above, of whom 16,142 received at least one dose of HPV vaccine, showed the vaccine to be generally well tolerated in women of all ages [[Prophylactic HPV-16/18 L1 VLP Vaccine Formulated with AS04. Investigator Brochure Edition 11](#), March 2012; [Descamps](#), 2009]. Analysis of the end-of-study PATRICIA efficacy trial showed the vaccine to be generally well-tolerated, which included the recorded incidence of AD in a broad range of women, including those of different nationalities and ethnicities [[Lehtinen](#), 2012]. The percentage of subjects experiencing an AD as assessed by GSK or the investigators was low and comparable between the two groups (99 (1.1%) in the Cervarix group and 95 (1.0%) in the Hepatitis A (Havrix) group), and no imbalances between groups were observed for any event classified by the MedDRA Preferred Term. Another safety pooling was performed with a later data lock point of 30 April 2011. This last pooling included data from more than 42 completed or on-going controlled and uncontrolled studies conducted in 40 countries with more than 31,000 subjects in the HPV group and 24,000 subjects in Control groups (2,000 in the Coad group) [[Angelo](#), 2014a]. The analysis of potential Immune Mediated Diseases (new approach used by the company which includes autoimmune and other diseases for which immune mediated pathophysiology is suspected) did not show statistical evidence of an increased risk of any immune-mediated disease, or of any specific syndrome after HPV-16/18 vaccination compared with other vaccines used as controls during a 1 year follow-up period and the entire study period [[Angelo](#), 2014a].

Human papillomavirus universal immunisation using HPV-16/18 vaccine was initiated in the UK in September 2008 for 12–13 year old girls, with a catch-up programme that included girls/women 14–18 years of age, with more than 6 million doses administered. During the course of the four years that Cervarix was in use in the HPV immunisation programme, the UK Medicines and Healthcare products Regulatory Agency (MHRA) closely monitored safety. The ‘end of routine use’ review of safety data gathered to the end of July 2012 supports the conclusions that the balance of its benefits and risks remains clearly positive [[MHRA](#), 2012a]. As part of the MHRA’s enhanced pharmacovigilance strategy for Cervarix, certain events were evaluated via statistical Observed/Expected analyses, including Guillain-Barré Syndrome (GBS), encephalitis, Bell’s palsy (VIIth nerve paralysis/facial palsy), complex regional pain syndrome and chronic fatigue syndrome / post viral fatigue syndrome. The available evidence suggests that the number of reports received by the MHRA of these events was no greater than expected and therefore consistent with chance, given the number of girls vaccinated and the natural incidence of these conditions in adolescent girls [[MHRA](#), 2012a].

GSK was committed to develop a post-licensure study of AD as outlined in the 2009 approval letter for *Cervarix* in the US:

“To conduct an observational study in a US managed care organization to evaluate the incidence of new onset autoimmune disease among at least 50,000 *Cervarix* recipients. The final protocol will be submitted by March 2010. Projected completion of patient accrual, subject to vaccine uptake, will be completed by March 2013. Projected study completion, subject to vaccine uptake, will be completed by September 2014. The final study report is projected to be submitted by March 2015 (6 months after study completion)”.



In order to address this regulatory commitment, GSK initiated an observational cohort study to assess the risk of AD within 12 months following the administration of at least one dose of *Cervarix* (exposed) versus a non-*Cervarix* vaccinated cohort (unexposed). This study (e-track: 113522, EPI-HPV-015) planned to include 140,000 females, aged 9 to 25 years, enrolled in US health plans. Based on the low incidence of AD in this age group, composite endpoints were defined and agreed with the FDA.

In the US, the commercial distribution of *Cervarix* began in November 2009. During the time period of 16 October 2009 to 28 February 2013, 1061 females in the *Cervarix* exposed and 1079 females in the unexposed cohorts were accrued [Holick, 2014]. All women in the *Cervarix* exposed cohort received the first dose of *Cervarix*, while 594 (56.0%) received the second dose and 301 (28.4%) received the third dose. This was 1.5% of the target number of 70,000 females in the *Cervarix* exposed and unexposed cohorts, respectively, which meant that it would have taken significantly longer than the planned 3 years to complete accrual [Holick, 2014].

Due to the low uptake of *Cervarix* in US, accrual of subjects exposed to *Cervarix* was limited in the EPI-HPV-015 study. The resulting sample size was not sufficient to draw conclusions. Therefore, GSK was already planning to conduct an alternative study in the UK, since it is the first country in Europe that implemented the HPV mass immunization program nationwide with over 4 million doses of *Cervarix* being administered since the start of the program in 2008 [EPI-HPV-015 VS US DB study report, 2014].

Post-licensure safety surveillance after more than 4 years of HPV-16/18 vaccine use confirms the acceptable benefit–risk of vaccination in adolescent girls and adult women. An analysis of potentially immune-mediated diseases after vaccination showed no patterns or trends for concern. The observed incidences of VIIth nerve (facial) palsy and Guillain-Barré syndrome were within the overall range of expected background incidence rates in the general population. GSK continues to closely monitor pIMDs and pregnancy outcomes, with no specific safety concern identified from more than 4 years of HPV-16/18 vaccine use in routine clinical practice [Angelo, 2014a].

## 8. RESEARCH QUESTION AND OBJECTIVES

### 8.1. Primary objective

- To assess the risk of neuroinflammatory/ophthalmic new onset of autoimmune disease(s) (AD) and other pre-specified AD within 12 months following the administration of the first dose of *Cervarix*:

#### [1] Neuroinflammatory/ophthalmic autoimmune diseases:

- Multiple Sclerosis
- Transverse myelitis
- Optic neuritis
- Guillain-Barré syndrome, including Miller Fisher syndrome and other variants
- Other demyelinating diseases:
  - Acute disseminated encephalomyelitis, including site specific variants: e.g. non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculomyelitis
  - Autoimmune (AI) peripheral neuropathies and plexopathies (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy).
- Autoimmune uveitis

#### [2] Other autoimmune diseases:

- Systemic lupus erythematosus
- AI disease with rheumatologic conditions:
  - Rheumatoid arthritis (RA)
  - Juvenile rheumatoid arthritis (JRA)
  - Still's disease
  - Psoriatic arthritis
  - Ankylosing Spondylitis
- AI haematological conditions:
  - Idiopathic thrombocytopenic purpura (ITP)
  - AI haemolytic anaemia
- AI endocrine conditions:
  - Type 1 diabetes mellitus
  - AI thyroiditis including Hashimoto's disease, Graves' /Basedows' disease
- Inflammatory bowel / hepatic diseases:
  - Crohn's diseases
  - Ulcerative colitis
  - Autoimmune hepatitis

## 8.2. Secondary objectives

- To describe individually the incidence of the pre-specified AD considering different time periods following the administration of the first dose of *Cervarix*:
  - Incidence of Guillain Barré syndrome (including Miller Fisher syndrome and other variants), and autoimmune haemolytic anaemia within two months following the administration of the first dose of Cervarix;
  - Incidence of idiopathic thrombocytopenic purpura (ITP) within six months following the administration of the first dose of Cervarix;
  - Incidence of multiple sclerosis, transverse myelitis, optic neuritis, other demyelinating diseases <sup>1</sup>, autoimmune uveitis, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), juvenile rheumatoid arthritis (JRA), Still's disease, psoriatic arthritis, ankylosing spondylitis, type 1 diabetes mellitus, autoimmune thyroiditis (including Hashimoto's disease, Graves'/Basedows' disease), and inflammatory bowel / hepatic disease (Crohn's disease, ulcerative colitis and autoimmune hepatitis) within one year following the administration of the first dose of Cervarix.

Refer to Section 10.4 for the definition of the primary and secondary endpoints and the pre-specified list of AD.

## 8.3. Exploratory objective

- To evaluate if temporal clustering of the individual ADs comprising the primary endpoint and the secondary endpoints (i.e., those ADs on the pre-defined list) occurred following the administration of at least one dose of *Cervarix* within the 12-month follow-up period.

## 9. AMENDMENTS AND UPDATES

None.

---

<sup>1</sup> Other demyelinating diseases:

- Acute disseminated encephalomyelitis, including site specific variants: e.g. non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculomyelitis
- AI peripheral neuropathies and plexopathies (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy).

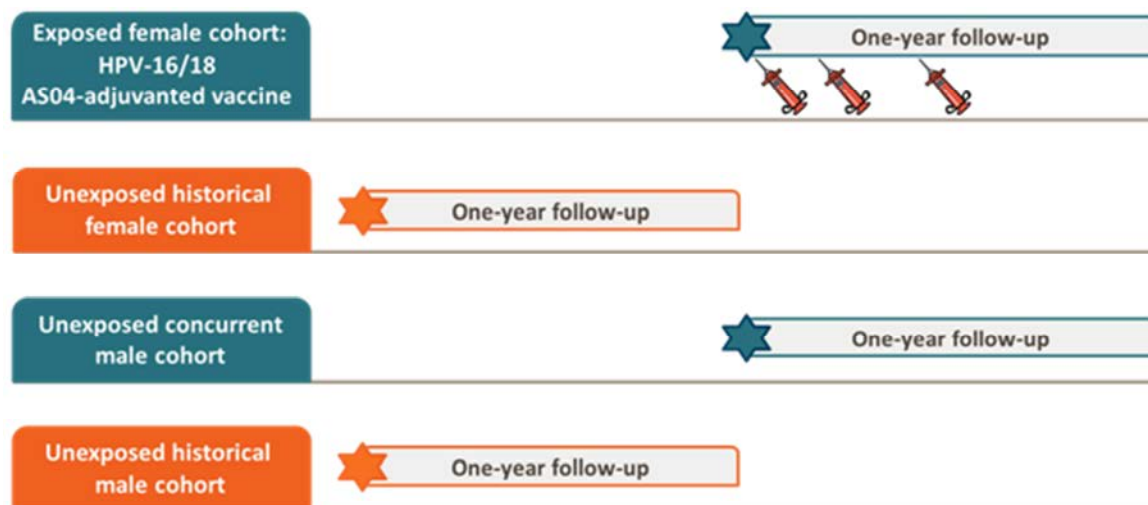
## 10. RESEARCH METHODS

### 10.1. Study design

#### 10.1.1. Overview

- This was an observational cohort study using the CPRD GOLD data source in the UK.
- Four cohorts were defined based on exposure to *Cervarix* and sex as recorded in the CPRD GOLD data source (See [Figure 1](#)):
  1. *Cervarix* vaccinated (exposed) female cohort
  2. Unexposed historical female cohort
  3. Unexposed concurrent male cohort
  4. Unexposed historical male cohort

**Figure 1 Cohort design**



- ★ Reference date between 1 SEPTEMBER 2005 and 31 AUGUST 2007: female and male subjects with  $\geq 1$  general practitioner consultation.
- ★ Reference date between 1 SEPTEMBER 2008 and 31 AUGUST 2010: female subjects vaccinated with a first dose of vaccine and male subjects with  $\geq 1$  general practitioner consultation. Not all female subjects who received one *Cervarix* vaccine completed all three planned *Cervarix* vaccinations.

- Study population:
  - Female population was composed of female subjects vaccinated with *Cervarix* between the ages of 9 to 25 years and unexposed female subjects identified from historical data.
  - Male population was composed of 9- to 25-year-old male subjects not vaccinated with *Cervarix*.

Female subjects included in the exposed cohort have received at least one dose of GSK's vaccine *Cervarix* administered according to local practice.

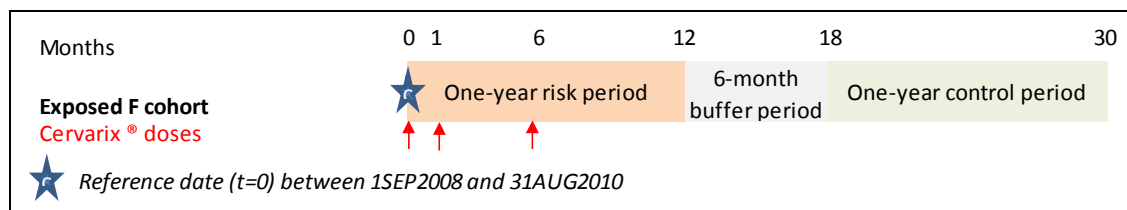
Female subjects in the unexposed historical cohort were frequency matched for age and practice region identifier to the subjects included in the vaccinated (exposed) cohort.

Study design:

Comparison of the unexposed concurrent male cohort with the unexposed historical male cohort was used as an internal control for changes over time in CPRD GOLD in reporting AD. The unexposed concurrent male cohort consisted of frequency age-matched and practice region-matched by one-year classes (15, 16, 17, etc.) male subjects from the period after the introduction of *Cervarix*. The unexposed historical male cohort consisted of frequency age-matched and practice region-matched male subjects from the period before the introduction of *Cervarix*.

A self-controlled case-series (SCCS) analysis for confirmed AD in the exposed female cohort was also conducted, using a risk period of one year after the first *Cervarix* dose, a six-month buffer period after the risk period and a one-year control period after the buffer period (See [Figure 2](#)).

**Figure 2 Self-control case-series analysis**



Note: all three doses may not have been administered

## 10.2. Setting

### 10.2.1. The UK HPV National Immunization Programme and Cervarix coverage

The UK had sufficient *Cervarix* vaccination coverage to enable data acquisition. A public immunisation programme targeting girls between 12-13 years of age including a catch-up programme for young women up to 18 years was undertaken during the academic year 2008/09. A phased catch-up programme for females born 1 September 1991 to 31 August 1995 during the 2008/09 academic year was completed by the end of the 2009/10 academic year. The programme was delivered largely through secondary schools [[Crawford, 2009](#); [Sheridan, 2009](#); [Sheridan, 2010](#)]. In the UK public HPV immunization program (12-13 year olds), HPV vaccination coverage in the UK for 2010/11 was 89.0%, 87.6% and 83.8% for the first, second and third dose respectively [[Health Protection Agency, 2012](#)]. The recommended age range for the UK programme matched the age range required by the FDA (9-25 years of age) for the post-licensure safety study. The bivalent vaccine was replaced in the programme by *Gardasil*® in September 2012.

### 10.2.2. The UK Clinical Practice Research Datalink General Practitioner OnLine database (CPRD GOLD)

The CPRD GOLD is one of the largest computerised databases of linked anonymised longitudinal medical records from primary care. The data were drawn from the computer systems used by general practitioners (GPs) to maintain the clinical records within their practices. As of March 2011, CPRD GOLD contained records from over 12 million patients contributing 64 million person-years of prospectively recorded high-quality primary healthcare data [Williams, 2012].

The CPRD GOLD is operated on a non-profit basis by the UK Medicines and Healthcare products Regulatory Agency (MHRA), containing coded longitudinal medical records from general practices and more recently has been linked to data sources from hospital-based care (e.g., Hospital Episode Statistics, HES). Data quality is monitored continuously by the MHRA and data quality markers are provided at both patient and practice level. The linkage between CPRD GOLD primary care data and HES data was around 50% as of Q1 2013. The CPRD GOLD database was licensed in-house by GSK.

During the feasibility assessment the CPRD GOLD database (release 2012Q3) identified 123,085 female subjects vaccinated with *Cervarix* between 01-Sep-2008 and 31-Aug-2010. The number of vaccinated women in the relevant age-range, 9 to 25 years old, included in the CPRD GOLD was equal to 121,881. The number of HPV-vaccinated females in the CPRD GOLD appeared to be sufficient for studying potential AD adverse events.

One of the key criteria for the feasibility assessment was:

- To estimate the incidence of new cases of autoimmune disease (AD) in female and male subjects aged 9-25 years for the two study periods (01-SEP-2005 to 31-AUG-2007 and 01-SEP-2008 to 31-AUG-2010).

Table 1 illustrates the incidence rate range estimates in CPRD for the study co-primary endpoints, which confirmed that there were sufficient neuroinflammatory/ophthalmic autoimmune diseases and other autoimmune diseases recorded in CPRD GOLD to assess the causal association between *Cervarix* vaccination and these autoimmune adverse events.

**Table 1 Incidence rates in CPRD GOLD for the study co-primary endpoints**

Endpoints	Incidence Rate 01-Sep-2005 to 31-Aug-2007 /100,000 person-years	Incidence Rate 01-Sep-2008 to 31-Aug-2010 /100,000 person-years
[1] Neuroinflammatory/Ophthalmic autoimmune disease*	6.42 - 27.13	5.76 - 21.72
[2] Other autoimmune diseases	81.51	77.87

\*6.42/100,000py and 5.76/100,000py are incidence rates including Multiple Sclerosis, Transverse Myelitis, Optic neuritis and Guillain Barre Syndrome. The incidence rates 27.13/100,000py and 21.72/100,000py are rates for Multiple Sclerosis, Transverse Myelitis, Optic neuritis, Guillain Barre Syndrome and Other demyelinating diseases (Acute disseminated encephalomyelitis, including site specific variants: e.g. non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculomyelitis; All peripheral neuropathies and plexopathies, including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy; and autoimmune uveitis). During the review and classification of the CPRD medical codes (medcodes), all the medcodes were classified as confirmed except for Other demyelinating diseases and uveitis where any medcodes were confirmed but classified as potential.

Table 2 illustrates the incidence rates for selected autoimmune diseases, which further confirms that CPRD GOLD is a suitable database to assess the association between certain autoimmune diseases and vaccination with *Cervarix*.

**Table 2 Incidence rates in CPRD GOLD for selected autoimmune disease by sex and age classes**

Autoimmune diseases	Ages Classes (years)	Incidence rate 01-Sep-2005 to 31-Aug-2007 (per 100,000 person-years)		Incidence rate 01-Sep-2008 to 31-Aug-2010 (per 100,000 person-years)	
		Males	Females	Males	Females
Type 1 Diabetes Mellitus	[9-18[	36.42	30.82	31.11	25.28
	[18-25]	26.05	16.46	15.71	13.37
Autoimmune Thyroiditis	[9-18[	1.79	5.53	1.22	5.52
	[18-25]	1.88	12.78	0.90	8.30
Crohn's disease	[9-18[	15.52	12.54	21.76	14.02
	[18-25]	26.52	31.21	27.16	29.05
Ulcerative colitis	[9-18[	7.56	4.68	9.76	6.59
	[18-25]	19.95	18.43	21.55	20.98

After the feasibility assessment, this study protocol to be conducted using CPRD GOLD was submitted to the US FDA as an alternative epidemiological study to the originally planned US database study to fulfil the post-marketing commitment.

### 10.2.3. Autoimmune diseases incidence rates for UK, USA, and recorded in the CPRD GOLD

#### 10.2.3.1. Background Tables

The background incidence rates of autoimmune diseases in the UK and USA for male and female subjects were derived from published literature and have been tabulated by Pallas in Table 3 and Table 4, showing no difference in magnitude between the two

countries for the age range from 9 to 25 years and for events for which data are available in both countries.

In the feasibility assessment for the study, the estimates for individual autoimmune disease incidence rates were close to those published in the literature, which means the algorithms for autoimmune disease diagnosis in CPRD GOLD were correctly defined for the studied age groups (see feasibility report assessment: Report modular appendices).



CONFIDENTIAL

116239 (EPI-HPV-040 VS UK)

Report Final

**Table 3 Background incidence rates and prevalence rates of neuroinflammatory/ophthalmic AD in the UK and US**

Disease	Age (years)	Incidence rate UK (per 100,000/year) Or Prevalence rate UK (bold italic text; per 100,000 population)			Age (years)	Incidence rate US (per 100,000/year) Or Prevalence rate US (bold italic text; per 100,000 population)			References
		Overall	Males	Females		Overall	Males	Females	
Multiple sclerosis: Incidence	10-19		0-0.4	0.9-1.4	10-17		0	0-2.3	UK: <a href="#">Alonso</a> , 2007 <sup>§</sup> ; <a href="#">Mackenzie</a> , 2014; US: <a href="#">Mayr</a> , 2003; <a href="#">Deussing</a> , 2012; NCKP <sup>\$\$</sup>
	20-29		1.7-3.9	5.9-11.6	18-25		5.3-6.7	7.5-8.6	UK: <a href="#">Alonso</a> , 2007 <sup>§</sup> ; <a href="#">Mackenzie</a> , 2014; US: <a href="#">Mayr</a> , 2003; <a href="#">Deussing</a> , 2012; NCKP <sup>\$\$</sup>
	0-29	9.64			0-29	12.9	9.6	2.5-32.0	US: <a href="#">Chao</a> , 2011
<b>Multiple sclerosis: Prevalence</b>	<b>0-14</b>		<b>0.0</b>	<b>0.0-2.6</b>					UK: <a href="#">Hirst</a> , 2009; <a href="#">Gray</a> , 2008
	<b>10-19</b>		<b>2.4</b>	<b>3.0</b>					UK: <a href="#">Mackenzie</a> , 2014
	<b>15-24</b>		<b>0.0-9.4</b>	<b>30.3-48.8</b>					UK: <a href="#">Hirst</a> , 2009; <a href="#">Gray</a> , 2008
	<b>20-29</b>		<b>19.6</b>	<b>58.4</b>					UK: <a href="#">Mackenzie</a> , 2014
Optic neuritis					9-26			3.9	US: <a href="#">Chao</a> , 2011
Guillain-Barré syndrome					10-17			0.8-1.8	UK: <a href="#">Hughes</a> , 2006
					5-17		1.1-1.9	0.8-1.2	US: <a href="#">Shui</a> , 2012; <a href="#">Beghi</a> , 1996; <a href="#">Koobatian</a> , 1991; <a href="#">Riggs</a> , 1989; NCKP <sup>\$\$</sup>
	15-24		0.6	1.1	18-25		1.4-2.2	0.4-2	
AI Uveitis					9-26			11.9	US: <a href="#">Chao</a> , 2011

<sup>§</sup> Used data from the beginning of the GPRD, likely to be incomplete;

<sup>\$\$</sup> Northern California Kaiser Permanente. Only female data available from the previous GSK review. See EPI-HPV-015 (e-track: 113522)

**Table 4 Background incidence rates and prevalence rates of Other AD in the UK and US**

Disease	Age (years)	Incidence rate UK (per 100,000/year) Or Prevalence rate UK (bold italic text; per 100,000 population)			Age (years)	Incidence rate US (per 100,000/year) Or Prevalence rate US (bold italic text; per 100,000 population)			References
		Overall	Males	Females		Overall	Males	Females	
Systemic lupus erythematosus: Incidence	10-19		0.1	2.3	9-17	1.9-6.4	0-1.8	1.5-11.0	UK: <a href="#">Nightingale</a> , 2006; US: <a href="#">Hochberg</a> , 1985; <a href="#">McCarty</a> , 1995; <a href="#">Naleway</a> , 2005; <a href="#">Hiraki</a> , 2012
	20-29		0.0	4.7	18-25		1.3-1.7	5.6-19.2	
					9-26			10.3	
<b>Systemic lupus erythematosus: Prevalence</b>					<b>3-18</b>	<b>9.7</b>	<b>3.1</b>	<b>16.4</b>	UK: <a href="#">Nightingale</a> , 2007 US: <a href="#">Hiraki</a> , 2012
	<b>0-9</b>		<b>0.9-1.4</b>	<b>0.0-0.5</b>					
					<b>9-11</b>	<b>4.9</b>	<b>1.7</b>	<b>8.2</b>	
					<b>12-14</b>	<b>11.2</b>	<b>3.7</b>	<b>19.0</b>	
					<b>15-17</b>	<b>18.9</b>	<b>5.7</b>	<b>31.0</b>	
	<b>10-19</b>		<b>0.0-1.8</b>	<b>5.4-10.6</b>					
	<b>20-29</b>		<b>2.5-4.3</b>	<b>26.1-39.3</b>					
Rheumatoid arthritis	15-24		0	18.6					UK: <a href="#">Humphreys</a> , 2013 US: <a href="#">Myasoedova</a> , 2010; <a href="#">Chao</a> , 2011
					9-34		3.6	7.0-13.8	
Juvenile idiopathic arthritis: Incidence					0-15	11.9	7.7	16.4	US: <a href="#">Harrold</a> , 2013
					11-15	15.4	9.2	21.7	
<b>Juvenile idiopathic arthritis: Prevalence</b>					<b>0-15</b>	<b>44.7</b>	<b>28.6</b>	<b>61.6</b>	US: <a href="#">Harrold</a> , 2013
					<b>11-15</b>	<b>67.3</b>	<b>45.7</b>	<b>89.7</b>	
Immune or idiopathic thrombocytopenic purpura (ITP)	0-18		4.7	3.7	9-26			5.9	UK: <a href="#">Yong</a> , 2010; US: <a href="#">Chao</a> , 2011 UK: <a href="#">Schoonen</a> , 2009; US: Simpson, 1989; NCKP\$\$ UK: <a href="#">Abrahamson</a> , 2009; US: Simpson, 1989, NCKP\$\$
	6-17		2.1-2.6	2.7-3.4	10-17			1.5-15	
	18-29		0.6-1.6	3.6-4.9	18-25			3.3-15	

CONFIDENTIAL

116239 (EPI-HPV-040 VS UK)

Report Final

Disease	Age (years)	Incidence rate UK (per 100,000/year) Or Prevalence rate UK (bold italic text; per 100,000 population)			Age (years)	Incidence rate US (per 100,000/year) Or Prevalence rate US (bold italic text; per 100,000 population)			References
		Overall	Males	Females		Overall	Males	Females	
Diabetes mellitus type 1: Incidence	0-14	25.0	15.4-26.8	15.3-25.9	0-14		14.1-19.1	15.1-16.4	UK: <a href="#">Diamond Project Group</a> , 2006**; <a href="#">Harron</a> , 2011; <a href="#">Imkampe</a> , 2011; <a href="#">Hodgson</a> , 2012 US: <a href="#">Diamond Project Group</a> , 2006**
	10-19	35.7	35.0	26.0	10-17		6.7-33.1	6-28.2	UK: <a href="#">Gonzalez</a> , 2009; <a href="#">Hodgson</a> , 2012; US: <a href="#">Kostraba</a> , 1992; <a href="#">Lipton</a> , 1995; <a href="#">MacDonald</a> , 1989; <a href="#">Allen</a> , 1986; NCKP\$
	15-34		20.0	10.1	18-25		10.0-15.2	7.9-19.2	UK: <a href="#">Imkampe</a> , 2011; US: <a href="#">Fishbein</a> , 1982; <a href="#">Allen</a> , 1986; NCKP\$
					9-26			18.0	US: <a href="#">Chao</a> , 2011
<b>Diabetes mellitus type 1: Prevalence</b>					<b>0-20</b>		<b>193<sup>#</sup></b>	<b>193<sup>#</sup></b>	US: <a href="#">Dabelea</a> , 2014
					<b>10-14</b>	<b>269<sup>#</sup></b>			
					<b>15-19</b>	<b>322<sup>#</sup></b>			
<b>Idiopathic thrombocytopenic purpura: Prevalence</b>					<b>6-11</b>	<b>7.3</b>			US: <a href="#">Segal</a> , 2006
					<b>11-14</b>	<b>4.1</b>			
					<b>15-18</b>	<b>5.6</b>			
					<b>19-24</b>	<b>4.1</b>			
Combined Hashimoto's and Graves' disease: Incidence	10-14		1.1-22.0	3.4-99.0 <sup>€</sup>	9-26			107.1	UK: <a href="#">Williamson</a> , 2010; <a href="#">Leese</a> , 2008 US: <a href="#">Chao</a> , 2011
Inflammatory bowel disease: Incidence ***	10-19		4.2-16.4	3.4-11.8					UK: <a href="#">Steed</a> , 2010; <a href="#">Henderson</a> , 2012
	20-29		15.5	21.9					UK: <a href="#">Steed</a> , 2010; <a href="#">Henderson</a> , 2012;
	0-18		2.2-8.8	1.9-6.8	0-18	5.7			UK: <a href="#">Henderson</a> , 2012; US: <a href="#">Deneau</a> , 2013
Inflammatory bowel disease: Prevalence					0-18	22.3*			US: <a href="#">Deneau</a> , 2013;

CONFIDENTIAL

116239 (EPI-HPV-040 VS UK)

Report Final

Disease	Age (years)	Incidence rate UK (per 100,000/year) Or Prevalence rate UK (bold italic text; per 100,000 population)			Age (years)	Incidence rate US (per 100,000/year) Or Prevalence rate US (bold italic text; per 100,000 population)			References
		Overall	Males	Females		Overall	Males	Females	
Crohn's disease: Incidence					5-9		1.1-1.5	1.0-1.4	US: <a href="#">Abramson</a> , 2010; <a href="#">Herrinton</a> , 2008
					10-14		4.5-5.7	3.5-5.2	
					15-19		3.9-6.8	6.1-7.4	
<b><i>Crohn's disease: Prevalence</i></b>					<b>5-9</b>		<b>2.0-7.3</b>	<b>5.6-6.2</b>	US: <a href="#">Abramson</a> , 2010; <a href="#">Herrinton</a> , 2008
					<b>10-14</b>		<b>21.1-24.7</b>	<b>14.8-19.7</b>	
					<b>15-19</b>		<b>34.0-45.2</b>	<b>28.5-79.2</b>	
Ulcerative colitis : Incidence					5-9		1.2-1.9	1.2-1.4	US: <a href="#">Abramson</a> , 2010; <a href="#">Herrinton</a> , 2008
					10-14		2.1-4.2	4.0-5.0	
					15-19		8.2-8.7	7.7-9.4	
<b><i>Ulcerative colitis : Prevalence</i></b>					<b>5-9</b>		<b>7.0-8.7</b>	<b>4.6-8.3</b>	US: <a href="#">Abramson</a> , 2010; <a href="#">Herrinton</a> , 2008
					<b>10-14</b>		<b>11.3-27.3</b>	<b>29.0-30.4</b>	
					<b>15-19</b>		<b>49.3-50.2</b>	<b>32.4-52.7</b>	
Autoimmune hepatitis: Incidence					0-18	0.4			US: <a href="#">Deneau</a> , 2013
<b><i>Autoimmune hepatitis: Prevalence</i></b>					<b>0-18</b>	<b>3.0*</b>			US: <a href="#">Deneau</a> , 2013

\*\* Study conducted in several parts of the UK and US. UK: the ranges represent data from Scotland (upper end), Leicestershire (lower end), Northern Ireland, Oxford, Plymouth and Yorkshire. US: The ranges represent data from Allegheny (upper end) and Jefferson (lower end);

\*\*\* Inflammatory bowel disease includes Crohn's disease, ulcerative colitis and non-Crohn's colitis (ulcerative colitis and unclassified inflammatory bowel disease combined);

\$ Used data from the beginning of the GPRD, likely to be incomplete;

\$\$ Northern California Kaiser Permanente. Only female data available from the previous GSK review. See EPI-HPV-015 (e-track: 113522)

\*# Crude prevalence – Prevalence rates were converted to per 100,000 population by Pallas.

€ For the [Leese](#), 2008 study, the incidence rate of 99.0 per 100,000 per year was a point estimate for hyperthyroidism from a Scottish population including adults and children. For the [Williamson](#), 2010 study, the incidence rate of 3.4 per 100,000 per year was for the UK and Ireland population and age range of 10-14 year old girls.

#### 10.2.4. Study Period

The cohort design for the study illustrating the different periods of subject selection is illustrated in [Figure 1](#). Subjects receiving *Cervarix* vaccinations were followed for a period of one year with the reference date for Cervarix vaccination being a date between 01-SEP-2008 and 31-AUG-2010. For subjects in the three unexposed cohorts, either unexposed historical female, unexposed concurrent male or unexposed historical male, the reference date was chosen as explained in [10.3.4](#). These subjects were also followed for one year, either over the same timeframe of 01-SEP-2008 and 31-AUG-2010, or 3 years earlier for the two historical cohorts: 01-SEP-2005 to 31-AUG-2007.

### 10.3. Subjects

#### 10.3.1. Number of subjects

For the cohort design, the target sample size was 65,000 subjects for each cohort. Refer to Section [10.7](#) for a detailed description of the estimation of the sample size.

#### 10.3.2. Inclusion criteria

Note: Other vaccines were allowed in this study regardless of the time of administration and the time interval between subsequent doses.

##### 10.3.2.1. Inclusion criteria for the exposed female cohort

Exposed females must have satisfied ALL the following criteria at study entry:

- Female aged from 9 to 25 years at the reference date (*Cervarix* vaccination date between 01 September 2008 through 31 August 2010)
- Recorded in the CPRD GOLD for at least 12 months before the reference date
- The first dose of *Cervarix* received between 01 September 2008 through 31 August 2010, Full date (day/month/year) of *Cervarix* vaccination(s) available (reference date)
- Subject defined as acceptable in CPRD GOLD

##### 10.3.2.2. Inclusion criteria for the unexposed historical female cohort

Unexposed females must have satisfied ALL the following criteria at study entry:

- Female aged 9 to 25 years at the reference date (GP consultation between 01 September 2005 through 31 August 2007; refer to Section [10.3.4](#) for selection procedure)
- Recorded in the CPRD GOLD for at least 12 months before the reference date
- Subject defined as acceptable in CPRD GOLD

**10.3.2.3. Inclusion criteria for the unexposed concurrent male cohort**

Unexposed concurrent males must have satisfied ALL the following criteria at study entry:

- Male aged 9 to 25 years at the reference date (GP consultation between 01 September 2008 through 31 August 2010; refer to Section 10.3.4 for selection procedure)
- Recorded in the CPRD GOLD for at least 12 months before the reference date
- Subject defined as acceptable in CPRD GOLD

**10.3.2.4. Inclusion criteria for the unexposed historical male cohort**

Unexposed historical males must have satisfied ALL the following criteria at study entry:

- Male aged 9 to 25 years at the reference date (GP consultation between 01 September 2005 through 31 August 2007; refer to Section 10.3.4 for selection procedure)
- Recorded in the CPRD GOLD for at least 12 months before the reference date
- Subject defined as acceptable in CPRD GOLD

**10.3.3. Exclusion criteria****10.3.3.1. Exclusion criteria for all cohorts**

- Subjects with a diagnostic code of any autoimmune disease during the year prior to the reference date
- Subjects who received at least one dose of unspecified HPV vaccine or *Gardasil* at any time before the reference date
- Subjects who have been included in any other cohort

**10.3.3.2. Exclusion criteria for the non-exposed cohorts**

- Subjects who received any dose of *Cervarix* at any time before the reference date.

**10.3.4. Generation of the four cohorts**

The exposed eligible cohort was identified based on the stepwise approach defined in Annex 5 of the Protocol. Amongst the eligible exposed subjects, 65,000 subjects were randomly selected using the RANUNI function of SAS. The RANUNI function generated streams of random numbers from an initial starting point (called *seed*) and returned numbers that were generated from the uniform distribution on the interval (0, 1). A random subject number was computed for each subject as

*random\_subj\_number=ranuni(seed)*. The subjects were ordered according the *random\_subj\_number* and the first 65,000 subjects were included in the exposed cohort.

The unexposed eligible cohorts were identified based on the stepwise approach defined in the Protocol (Annex 5 of the Protocol).

All the unexposed subjects who matched to exposed subjects for age (birth cohort) and region (frequency matching) were identified. This represented 72 combinations of birth cohort-region (18 birth cohorts and 13 regions categorised in 4 groups in CPRD GOLD). In each combination, the subjects were randomly selected based on the distribution in the exposed cohort.

The reference date was the first *Cervarix* vaccination date for subjects in the exposed cohort between 01-SEP-2008 and 31-AUG-2010. For the three unexposed cohorts, one reference date was selected per subject. The reference date for the subjects in the three unexposed cohorts was a random date selected among the reference dates of the matched exposed subjects, but the random selection was conducted so that there was an even distribution of reference dates across the time period within each of the four cohorts. For the concurrent male cohort, the reference date was between 01-SEP-2008 and 31-AUG-2010. For the historical non-exposed female and male cohorts, the reference date was between 01-SEP-2005 and 31-AUG-2007 (reference dates for exposed cohort minus 3 years).

The random reference dates in each ‘birth cohort-region’ combination was attributed randomly using the RANUNI function of SAS.

The age at reference date was calculated for the unexposed cohorts. After applying the exclusion criteria, the eligible subjects (65,000 subjects in each cohort) were randomly selected in each of the combinations ‘birth cohort-region’ taking into account the distribution in the exposed cohort. The random selection was implemented using the RANUNI function of SAS.

## 10.4. Variables

### 10.4.1. Primary endpoint

- Occurrence of new onset of confirmed<sup>2</sup> autoimmune disease during the period of one year following administration of the first dose of *Cervarix* (risk period) among an exposed cohort and during an equivalent time period in the unexposed cohorts for the following two co-primary composite endpoints:

#### [1] Neuroinflammatory/ophthalmic autoimmune diseases:

- Multiple Sclerosis
- Transverse myelitis
- Optic neuritis
- Guillain-Barré syndrome, including Miller Fisher syndrome and other variants
- Other demyelinating diseases:
  - Acute disseminated encephalomyelitis, including site specific variants: e.g. non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculomyelitis
  - Autoimmune (AI) peripheral neuropathies and plexopathies (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy).
- AI uveitis

#### [2] Other autoimmune diseases:

- Systemic lupus erythematosus
- Rheumatologic AI disease:
  - Rheumatoid arthritis (RA)
  - Juvenile rheumatoid arthritis (JRA)
  - Still's disease
  - Psoriatic arthritis
  - Ankylosing spondylitis
- AI haematological disease:
  - Idiopathic thrombocytopenic purpura (ITP)
  - AI haemolytic anaemia
- AI endocrine disease:
  - Type 1 diabetes mellitus
  - AI thyroiditis including Hashimoto's disease, Graves' /Basedows' disease
- Inflammatory bowel / hepatic diseases:
  - Crohn's diseases
  - Ulcerative colitis

---

<sup>2</sup> Autoimmune disease diagnosis ascertainment by an expert physician panel (Section 10.5.1).



- AI hepatitis

#### 10.4.2. Secondary endpoints

Secondary endpoint was the occurrence of new onset of individual confirmed autoimmune disease during the following specific periods:

- Occurrence of Guillain Barré syndrome (including Miller Fisher syndrome and other variants), and autoimmune haemolytic anaemia within two months following the administration of the first dose of *Cervarix*;
- Occurrence of idiopathic thrombocytopenic purpura (ITP) within six months following the administration of the first dose of *Cervarix*;
- Occurrence of multiple sclerosis, transverse myelitis, optic neuritis, other demyelinating diseases (see the two sub-bullets for these diseases in Section 10.4.1), autoimmune uveitis, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), juvenile rheumatoid arthritis (JRA), Still's disease, psoriatic arthritis, ankylosing spondylitis, type 1 diabetes mellitus, autoimmune thyroiditis (including Hashimoto's disease, Graves'/Basedows' disease), and inflammatory bowel / hepatic disease (Crohn's disease, ulcerative colitis and autoimmune hepatitis) within one year following the administration of the first dose of *Cervarix*.

#### 10.5. Data sources and measurement

##### 10.5.1. Data source for case ascertainment

CPRD GOLD is based on data from GPs, while most autoimmune diseases are probably diagnosed in specialist settings. Consequently, the number of autoimmune diseases, the quality of the information, and the diagnostic certainty might be limited. In particular the specific information related to the onset of clinical symptoms, and radiological and biological data associated with the etiologic diagnosis of autoimmune diseases may not all be available in the CPRD GOLD database and associated resources. Besides, not all general practices participating to CPRD GOLD consented to the linkage between CPRD GOLD primary care data and HES data. Specific algorithms for each outcome of interest were developed (See the Protocol: Annex 5), individual subject profiles were produced, and available "free text" that related to autoimmune disease diagnoses were requested from CPRD GOLD when needed.

Expert case review of medical records has been proposed for autoimmune safety studies, and case identification could be expanded by use of laboratory test results and other relevant measures in addition to specific ICD-10 diagnosis codes [Chao, 2012]. In the current study, free text in CPRD GOLD was searched to gather information on clinical symptoms, medical diagnosis, suitable laboratory test results, other diagnostic test results and data on possible first symptoms to ascertain if the specific ICD-10 codes were correct. The case ascertainment process which is explained below was applied consistently to enable the maximum number of cases to be confirmed, although only a proportion of identified cases were eventually confirmed.

The ascertainment of the etiologic diagnosis and date of disease onset for all identified autoimmune diseases was performed by Pallas, a GSK identified reviewer (Pallas, health research and consultancy) to ensure the correct classification of each case. Pallas was asked to review all subject profiles and to collect relevant information from these profiles to import into the Remote Data Entry (RDE) computer application. The subject profile consisted of data retrieved from CPRD GOLD including clinical diagnosis, laboratory testing, drug prescription, and HES data (including specific ICD-10 diagnostic codes). The relevant free-text was identified by Pallas and requested when necessary for disease confirmation. The free-text request was sent by GSK to CPRD GOLD and extracted free-text was de-identified by the CPRD GOLD research group before sending to GSK. The free-text was reviewed by Pallas. Pallas assessed whether the aetiology of the autoimmune disease was confirmed or not and whether the date of disease diagnosis fell within the observation period of the study, which was one year<sup>3</sup> after the reference date. The GSK safety physician and a medical Epidemiologist at RTI Health Solutions reviewed all subjects for which Pallas had some doubts.

In the event that the (date of) diagnosis, first symptom and/or first abnormal laboratory test could not be confirmed, a second review step was to be conducted with an expert physician panel as described in Section 10.5.3.

A report was prepared by Pallas providing the decisions taken after reviewing the subject profiles, review of the requested free-text, describing how the expert review was conducted and how relevant data was imported in RDE – see Pallas Methodology Report (Report Annex 5).

The final study database consisted of data extracted from CPRD GOLD, HES and additional data from free-text review. The final study database was frozen on 26<sup>th</sup> August 2014 and stored by GSK Biologicals' data management.

## **10.5.2. Collected data**

### **10.5.2.1. Subjects characteristics**

The following data were extracted for the analysis population (study database population):

- Demographic characteristics: birth month and birth year, sex, region, practice region identifier, date of death (if applicable) and CPRD patient acceptability flag. Patients are labelled 'acceptable' if their data did not contain obvious errors such as first registration date being empty, year of birth labelled as missing, current registration date in CPRD GOLD being before first registration date, gender being listed as neither female, male or indeterminate etc. For a full explanation of this acceptability

---

<sup>3</sup> Note: for the purpose of the Self-Control Case-Series analysis the observation period was extended to 30 months after reference date for the cases exposed to Cervarix vaccination.

flag please refer to the Data Quality Section (pages 3-4) of the publication by [Williams, 2012].

- CPRD GOLD information: CPRD GOLD start date, first registration date, current registration date, registration gaps, registration status, transfer-out date, transfer-out reason.
- HES information: Linkage to HES data.
- Vaccines:  
Administration of any other vaccine from one year before the reference date until the end of follow-up was collected: date of vaccination, medcodes and immunization type were extracted from the immunisation file.
- Health care resource utilization: number of times a primary care resource was utilized during the year before the reference date (it refers to all available information for a patient in the database including GP visits, prescriptions, laboratory tests, etc.).

#### **10.5.2.2. Clinical outcomes**

Occurrence of autoimmune diseases defined as study endpoints were identified in CPRD GOLD by using defined algorithms (see the protocol: Annex 5).

For each case, the following data were extracted - from the reference date up to end of the follow-up period (12 months for non-exposed cohorts and 30 months for exposed female cohort)-:

- Medical code(s)
- Date of event

The algorithms were able to identify and extract free-text identifiers. A preliminary review step of the subject profiles (all records from one year before reference date to the end of the follow-up period) was performed by Pallas, which was the GSK-identified reviewer, in order to identify all relevant free-texts, which were additional to those pre-identified by the algorithm. For all the identified cases of autoimmune diseases, the subject profile and associated free-text were reviewed by GSK-identified reviewers for confirmation and determination of the aetiology and the date of first symptoms of AD.

#### **10.5.2.3. Date of first symptom**

The first clinical sign or symptom from the patient profiles or associated free text was considered as the onset of the disease.

The following rules were applied for the determination of the symptom date:

1. If there was no free text belonging to the event considered to be the first symptom, the event date of that first symptom was used;
2. If some free text was available with a time indication, the date of first symptom was derived according specific rules - see Pallas Methodology Report (Report [Annex 5](#)).

#### **10.5.2.4. Other derived variables**

The following variables were derived from the CPRD GOLD data:

- If the birthdate day was missing, the Subject's date of birth was defined as the 15th of the birth month and birth year. If the birth day and month were missing, the birth date was defined as the 30th of June of the birth year.
- Incomplete dates (except for vaccination date which was the reference date) were substituted as follows for calculation of age and/or time to event; if the day was missing the date was defined as the 15th of the month, if both the day and the month were missing, the date was defined as 30th of June of the year.
- Age at a specific event was computed as the difference between the date of the event and the date of birth.

#### **10.5.3. Final case ascertainment step**

After the first patient profile review which was performed by Pallas, the GSK safety physician and a medical Epidemiologist from RTI, individual data with a doubt on the aetiology were reviewed by an expert. The panel of experts consisted of five physicians in the fields of rheumatology, neurology, ophthalmology and internal medicine. Each physician reviewed the case profiles according to their specialty, which included data of first symptom, date of diagnosis, date of first abnormal laboratory test and final classification of AD. Additionally among the autoimmune disease cases with no doubt on the aetiology, a random 10% sample from each of the categories of autoimmune disease were reviewed by the experts as a quality check. During this quality check, agreement on the date of first symptom, date of diagnosis and classification of AD existed for all rheumatology and neurology cases and for most of the ophthalmology and internal medicine cases. For autoimmune uveitis, however, the expert decided to include an additional symptom (i.e. conjunctivitis/episcleritis) that was not used by Pallas, GSK and RTI until then. For IBD, CD and UC, the expert suggested other criteria to determine the date of diagnosis and confirmation of the diagnosis. All uveitis, IBD, CD and UC cases were therefore reviewed again by Pallas, applying the new rules accordingly. Furthermore, after review by the expert of the SLE subjects, the expert proposed other criteria to determine the diagnosis and its confirmation. The expert reviewed all remaining cases and applied these criteria.

For further details of the expert review of cases, please refer to the Pallas Methodology Report – Section 5.1 (p19-21) which is located in Report [Annex 5](#). The experts were blinded with regards to HPV vaccine exposure, and their opinions were captured into RDE.

## 10.6. Bias

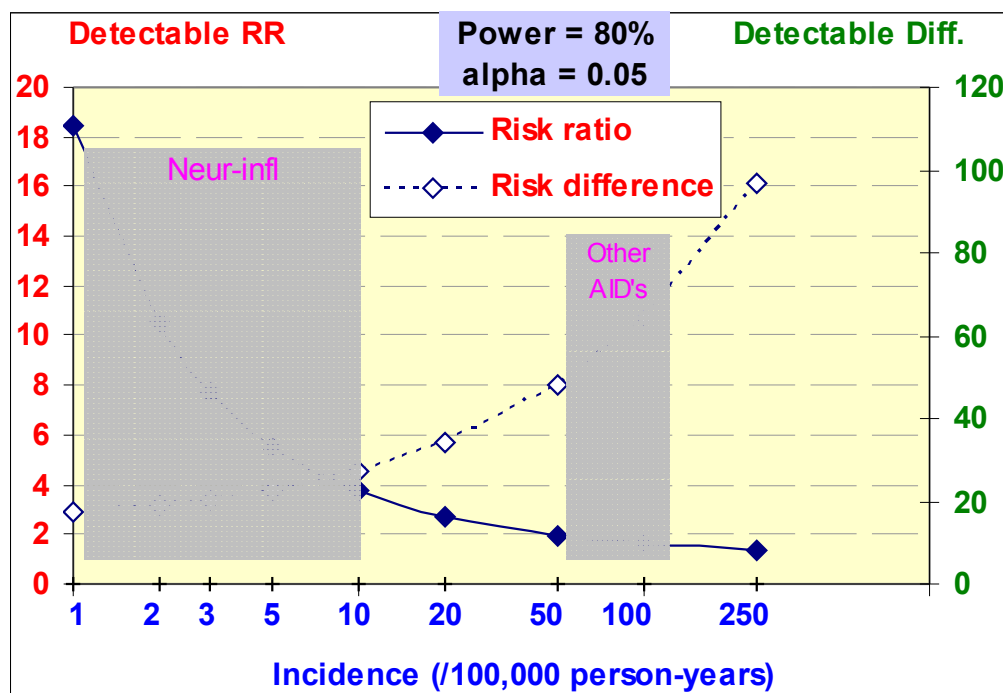
Please refer to Section 12.2 Study limitations.

## 10.7. Study size

### 10.7.1. Sample size for cohort design

The target sample size was 50,000 subjects in each cohort. The relative risk (RR) that would be detected with 80% power and  $\alpha = 0.05$  is given in Figure 3 versus the incidence rate in the (*Cervarix*) unexposed cohort. The detectable difference in incidence rate (= additional cases per 100,000 person-years) is also depicted.

**Figure 3 Detectable relative risk and difference versus the incidence rate in the (*Cervarix*) unexposed cohort**



(Method: Comparison of two independent proportions using a likelihood ratio test, PASS 2005)

Cohorts of 50,000 subjects each should allow detection, with 80% power, of a RR between 3.7 and 18.7 for the neuro-inflammatory AD (incidence rate between 10 and 1/100,000 person-years) and between 1.6 and 2.0 for other AD (incidence rate between 100 and 50/100,000 person-years).

Because of risk of lost to follow-up, the sample size was increased by approximately 30% in each cohort to approx. 65,000 subjects.

### 10.7.2. Sample size for self-controlled case-series

The power of the SCCS analysis depended on the number of cases and the ratio between the duration of the risk and the control periods. With a risk and a control period of 12 months each, the number of cases needed versus the detectable risk ratio (incidence rate ratio) is summarized in Table 5. Figure 4 shows the total number of vaccinated subjects needed to follow-up for 30 months after vaccination versus the number of cases and the background incidence.

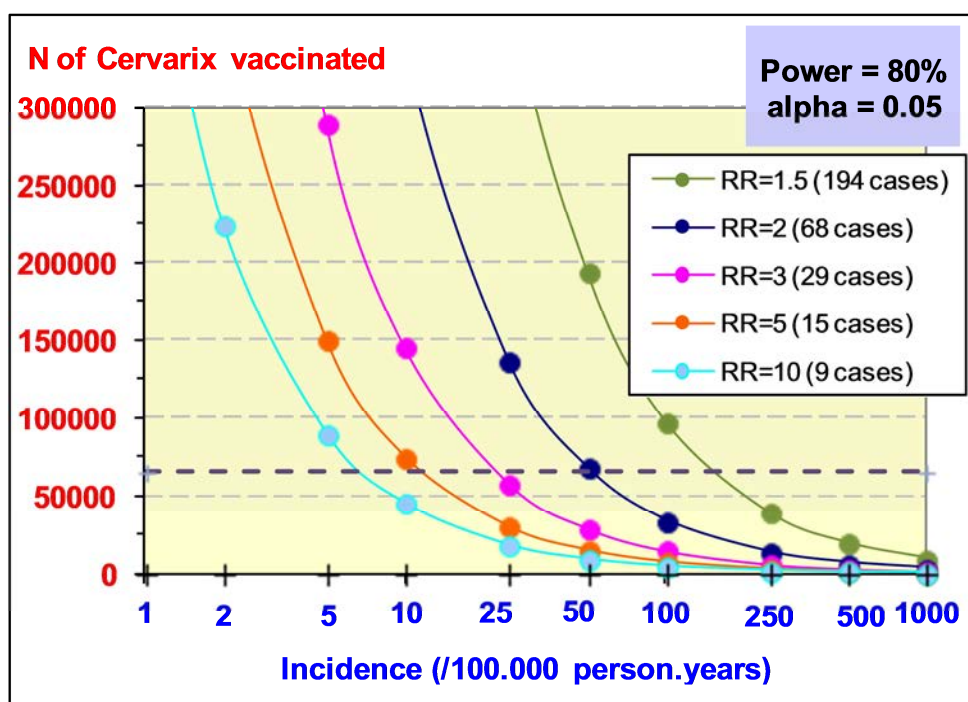
**Table 5 Sample size for a SCCS analysis - Number of cases in vaccinated subjects versus the incidence rate ratio that could be detected <sup>a</sup>**

Incidence rate ratio	Total number of cases
1.5	194
2	68
3	29
5	15

Method: sample for case-series analysis based on the signed root likelihood ratio [Musonda, 2006]

<sup>a</sup> 80% power using a two-sided test and alpha = 0.05

**Figure 4 Population size for a SCCS analysis versus the incidence rate ratio and the background incidence in the general population**



Dotted line: target sample size of the exposed cohort

### 10.8. Data transformation

The CPRD GOLD data source was used in order to create the final study database. Specific study variables (please refer to the study Case Report Form) were defined based on the original database using algorithms and manual data review.

## 10.9. Statistical methods

### 10.9.1. Main summary measures

#### 10.9.1.1. Subject disposition

Subject disposition was summarized for each cohort by computing:

- Number of screened subjects.
- Number (%) of non-eligible subjects for each of the following reasons of non-eligibility:
  - Diagnostic code of AD during the year prior to the reference date (for all cohorts);
  - Subject not actively registered with the practice during the study period (for all cohorts);
  - Subject not flagged as acceptable in CPRD GOLD (for all cohorts);
  - Subject not recorded for at least 12 months within CPRD GOLD at reference date;
  - At least one dose of unspecified HPV vaccine or *Gardasil* at any time before the reference date (for all cohorts);
  - At least one dose of *Cervarix* vaccine at any time before the reference date (for unexposed cohorts);
  - The first dose of *Cervarix* received before 01 September 2008 or after 31 August 2010 (for the exposed female cohort);
  - Subjects non-included after frequency matching for birth cohort and practice-region.
- Number of included subjects in each cohort.

A detailed, comprehensive list of reasons for elimination for the analyses was established at the time of data cleaning.

#### 10.9.1.2. Case definitions

Three case definitions were defined leading to three analyses:

1. Main analysis included all the autoimmune cases with a known date of first symptom;
2. Imputed dates analysis included all the autoimmune cases with a known date of symptom plus all the autoimmune cases with an unknown date of symptom. In case of missing/unknown date of onset (date of first symptom), a date was imputed. The imputed date was computed as the date of diagnosis minus the median number of days between the date of diagnosis and the known date of



disease onset. The imputation was performed specifically for each disease and used all the known symptom dates (confirmed and non-confirmed cases) for computation of the median number of days;

3. Analysis based on known date of diagnosis.

#### **10.9.1.3. Demographic and baseline characteristics**

Demographic and baseline characteristics of the overall study population and autoimmune disease cases (age at reference date, region [GP practice], availability of data in CPRD GOLD [follow-up time within CPRD GOLD at reference date, proportion of HES linkage] and healthcare resources utilization the year prior to the reference date) were summarized per cohort and overall, using descriptive statistics: n of subjects, mean, standard deviation (SD), median, minimum and maximum; or (n, %).

Exposure to other vaccines was summarised in frequency tables (n, %) per cohort and period (the year prior the reference date and during the follow-up period).

Number of cases with an autoimmune disease drug prescription was tabulated per cohort and overall (n, %).

The two female cohorts and the two male cohorts were compared for their demographic and baseline characteristics using a Chi-Square test or Student t-test.

The four cohorts were compared for the age at reference date using a one-way Analysis of Variance (ANOVA).

#### **10.9.1.4. Analysis of autoimmune diseases - co-primary endpoints and individual diseases**

The proportion of autoimmune diseases (co-primary endpoints and individual diseases) was calculated for the exposed female cohorts and the non-exposed cohorts, as the number of autoimmune cases divided by the total number of included subjects in each cohort.

The incidence rates of autoimmune diseases (co-primary endpoints and individual diseases) during the 1-year follow-up period were calculated by dividing the number of cases by the total person-time. The comparison of the incidence rates of autoimmune diseases was done using a Poisson regression model (see Section 10.9.2.3. The incidence difference was calculated as incidence of exposed cohort minus incidence of non-exposed cohort. These analyses were also performed for the two male cohorts (concurrent and historical cohorts).

The incidence of autoimmune diseases (co-primary endpoints and individual diseases) was calculated after each *Cervarix* dose for the exposed female cohort by dividing the number of cases by the total person-time. The person-time was defined as the period between the *Cervarix* dose and the end of risk period (6 months after each dose), date of the next *Cervarix* dose, subject's date of death, date of unspecified HPV vaccine or *Gardasil*, or date of autoimmune diseases onset whichever occurred first.



A Self-Controlled Case-Series (SCCS) analysis for both co-primary endpoints and individual diseases was performed for the exposed female cohort. The SCCS is only based on cases, and provides consistent estimates of the relative incidence. This method controls implicitly for potential confounders which do not vary with time. The relative incidence was calculated as the ratio of the incidence rate during the risk period and the incidence rate during the control period.

Sensitivity analyses were performed as described in Section [10.9.2.3](#).

An exploratory analysis was performed assessing the presence of a temporal clustering of the individual AD or the two co-primary endpoints during the follow-up period for each cohort (30 months for the exposed female cohort and 12 months for non-exposed cohorts). A variable time window was used with respectively, a maximal scan window of 60 days (2 months) and 120 days (4 months), and a time aggregation of 1 day was applied. Poisson-based likelihood was used to compare the expected number of cases and actual number of cases within the window. Significance was evaluated with 9999 replications. The analysis was performed by using the SatScan tool ([SaTScan](#) version 9.3.1, 2014).

All the analyses were performed for the two co-primary endpoints and for the individual disease if more than 10 cases were observed in both female cohorts.

The individual disease analyses (main and sensitivity) were performed according to a time schedule that was disease-specific: 2 months for GBS and Haemolytic anaemia, 6 months for ITP and 12 months for all the other autoimmune diseases.

## **10.9.2. Main statistical methods**

### **10.9.2.1. Hypotheses**

#### ***10.9.2.1.1. Hypotheses for the cohort analysis***

**Null hypothesis (H0):** the incidence of neuroinflammatory/ophthalmic autoimmune diseases (other autoimmune diseases) in the exposed female cohort is equal to the incidence in the historical non-exposed female cohort.

**Alternative hypothesis (H1):** the incidence of neuroinflammatory/ophthalmic autoimmune diseases (other autoimmune diseases) in the exposed female cohort is not equal to the incidence in the historical non-exposed female cohort.

#### ***10.9.2.1.2. Hypotheses for the self-controlled case-series analysis***

**Null hypothesis (H0):** the incidence rate of neuroinflammatory/ophthalmic autoimmune diseases and other autoimmune diseases in the exposed female cohort is the same during the risk period and the control period.

**Alternative hypothesis (H1):** the incidence rate of neuroinflammatory/ophthalmic autoimmune diseases and other autoimmune diseases in the exposed female cohort is different during the risk period and the control period.

These hypotheses were tested separately for each of the two co-primary endpoints. These hypotheses were also tested for individual diseases if more than 10 cases were recorded in both exposed and non-exposed cohorts.

#### 10.9.2.2. Statistical calculations

All the statistical calculations were done in SAS 9.2.

All the statistical tests were two-sided at alpha level of 0.05.

#### 10.9.2.3. Statistical models

##### Poisson regression

The dependent variable was the number of events. The log transformed person-time was included in the model as an offset. The end of the follow-up time was defined as the end of study period (12 months after reference date), date of death of the subjects, date of unspecified HPV vaccine or *Gardasil* or *Cervarix* vaccine (for non-exposed cohort) or the date of disease onset whichever occurred first.

The main model (Model 1) included the exposure status (exposed vs. non-exposed) as a binary independent variable and the age in groups ([9-17],[18-25]) as a covariate.

The incidence risk ratio (exposed/non-exposed) was derived as the exponential of the coefficient associated with the exposure status and its 95% Wald confidence interval (CI).

The same model was run for comparing the two male cohorts (concurrent vs. historical).

The following models were computed as sensitivity analyses:

Model 2: A Poisson regression model including, in addition to the exposure status and age-group, other covariates:

- Region (class variable);
- Vaccination during the year prior to reference date (binary variable);
- Use of healthcare resources during the year prior to reference date (4 classes according to quartile).

Model 3: A Poisson regression model adjusted for time effect was performed where a significant difference in incidence rates was observed between the two male cohorts. This model is identical to Model 1 with the inclusion of a contrast for the temporal effect.

Model 4: A Poisson regression model stratified by age group ([9-17] and [18-25]) was performed. The model included the event as dependent variable and the exposure status as binary independent variable plus log transformed person-time as an offset.

### Self-controlled case-series

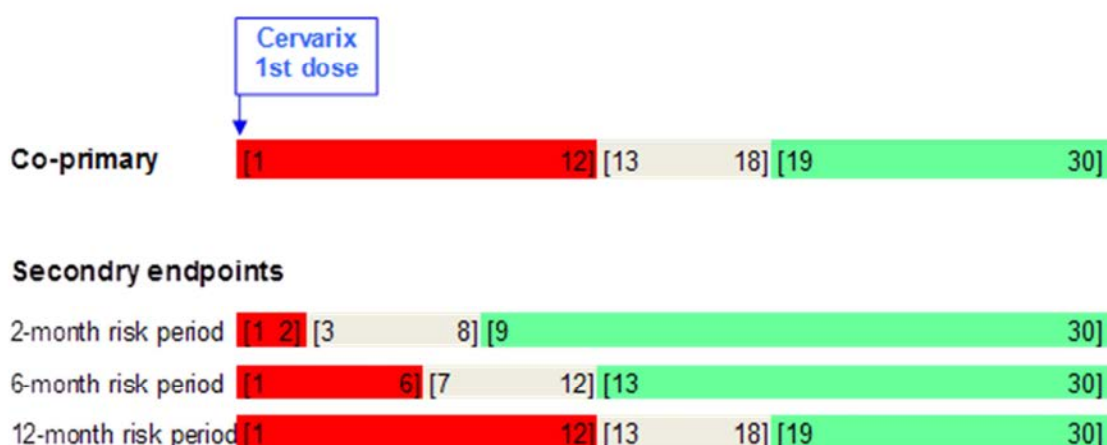
The statistical calculation was done by using the specific SAS macro developed by Whitaker et al. [Whitaker, 2006] and available online from <http://statistics.open.ac.uk/sccs>.

For the main SCCS the risk period was defined as (reference date +364 days), the buffer period was defined as (end of the risk period + 180 days) and the control period was defined as (end of the buffer period + 365 days). The relative risk was calculated for the co-primary endpoints and for the diseases with more than 10 cases in both risk and control periods as the ratio of the incidence in the risk period versus incidence in the control period.

For the sensitivity SCCS the risk period was defined as a period from the first dose of Cervarix until 6 months after the last dose. A buffer period covered a period of 6 months after the end of risk period, the control period starting after the buffer period until 30 months after the first dose of Cervarix (910 days). The relative risk was calculated between risk and control period.

An exclusion criterion was applied on the cases, if the disease onset was within the defined risk period but the date of diagnosis was after the risk period then the case was excluded from the SCCS analysis. A similar rule was applied for cases occurring in the control period. The reason of that rule was to avoid a bias in the number of cases occurring in the risk period. Indeed the exposed cohort was followed up to 30 months in the CPRD database, with this FU period we could expected to have more cases with a first symptom date in the risk period than in the control period.

**Figure 5 Risk and control periods for the various endpoints**



**10.9.3. Missing values**

Missing data was not substituted, except for the unknown date of first symptom where an imputation method was applied (see Section 10.9.1.2).

**10.9.4. Amendments to the statistical analysis plan**

- The formula for the incidence rate calculation adjusted for temporal effect was corrected as follows:

```
PROC GENMOD data=<filename> ;
  Class X (ref=' 1 ');
  MODEL Y= X Z / offset=Ln_PY dist=poisson link=log ;
  Contrast "vaccine adjusted effect in Females" X 1 -1 -1 +1 / estimate=exp;
RUN;
```

Note: X=1 for the exposed female cohort, 2 for the non-exposed female cohort, 3 for concurrent male cohort, and 4 for the historical male cohort.

- Categorization of variables:
  - Three regional categories were created for inferential statistics:
    1. North England (North East - North West - Yorkshire & The Humber);
    2. South England (East of England - South West - Central England - London - South Coast) and;
    3. Midlands (East Midlands - West Midlands) & Northern Ireland – Scotland – Wales.

Further to presentation of the results of the planned analyses at the GSK Safety Review Committee, a few additional analyses (post-hoc) were requested:

- Descriptive analysis of time-to-onset of all the confirmed cases and especially the autoimmune diseases cases;
- Descriptive analysis of the geographical distribution of the cases;
- An additional patient profile review was conducted for the confirmed autoimmune thyroiditis cases and included in the main analysis to clarify the diseases aetiology (hypo-or hyperthyroiditis). The incidence risk ratio for hypo-/hyperthyroiditis was calculated. The analysis based on the cases with a known date of onset was repeated for the cases of hypothyroiditis;
- The incidence rate ratios excluding the region Northern Ireland – Scotland - Wales were calculated;
- The analysis based on the cases with a known date of onset was repeated on the two co-primary endpoints and the three selected individual diseases after exclusion of subjects from Northern Ireland, Scotland and Wales.

## **10.10. Quality control**

Validation of clinical outcomes is described in Section 10.5.2 and Section 10.5.1.

Clinical data management was performed in accordance with applicable GSK standards and data cleaning procedures.

The final study dataset was archived and stored on a secured, access limited, computer platform SAS Drug Development (SDD) according to GSK Biologicals Standard Procedures. Specific statistical programs were to be written in SAS 9.2 (or higher) and validated according to the GSK standard procedures. The validation of the quality control (QC) of the statistical analysis was to be documented. All statistical programs, output files and QC documentation were to be saved as read-only files on SDD.

The final study protocol and possible amendments, the final statistical report and the QC document, and the final study report(s) were to be archived on a Document management system based on the Documentum platform: Computer Aided Regulatory Submission (CARS).

### **10.10.1. Remote Data Entry instructions**

Remote Data Entry (RDE) using a validated computer application was used by the GSK identified reviewer to enter the information obtained from different data sources, and conduct the final case ascertainment classification and validation by the experts (when necessary).

Subject data necessary for analysis and reporting were entered/transmitted into a validated database or data system. Clinical data management was performed in accordance with applicable GSK standards and data cleaning procedures.

No monitoring was done. The GSK identified reviewer remained accountable for the data entry.

### **10.10.2. Final study database**

The final study database consisted of data extracted from CPRD GOLD, HES and additional data from free-text review. The study database was locked and stored by GSK Biologicals' data management according to GSK Biologicals Standard Procedures.