

Appendix
to
Report
Exposure to ENBREL® (etanercept) during Pregnancy
Non-Interventional Study

Sensitivity analyses

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Enbrel (etanercept)

B1801396 NON-INTERVENTIONAL STUDY REPORT

June 2018 Final version 3.0

Appendix figure 1. Flowchart of participants in each group of analyses. 45

Section 1 Sensitivity analyses as predefined

Appendix table 1 Subgroups of major birth defects according to EUROCAT classification									
Outcome	Enbrel			Non-bio Systemic			General population		
	N	Events	Rate (%)	N	Events	Rate (%)	N	Events	Rate (%)
Nervous system	425	*	*	3497	8	0.23	1670082	2340	0.14
Eye, Ear, face and neck	425	*	*	3497	9	0.26	1670082	4149	0.25
Congenital heart defects	425	7	1.65	3497	61	1.74	1670082	25886	1.55
Respiratory	425	*	*	3497	8	0.23	1670082	3720	0.22
Oro-facial clefts	425	*	*	3497	6	0.17	1670082	3073	0.18
Digestive system	425	*	*	3497	11	0.31	1670082	3924	0.23
Urinary	425	*	*	3497	21	0.60	1670082	6811	0.41
Genital organs	425	*	*	3497	10	0.29	1670082	6381	0.38
Limb	425	*	*	3497	33	0.94	1670082	15119	0.91
Musculoskeletal system	425	*	*	3497	9	0.26	1670082	3315	0.20
Chromosomal abnormalities	425	*	*	3497	*	*	1670082	2724	0.16
Others	425	*	*	3497	7	0.20	1670082	4125	0.25

*Only categories exceeding 5 cases are presented to maintain individual integrity.

Appendix table 2 Any major birth defect, excluding those exposed to teratogens in pregnancy

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	3400	158	4.65	1.00	.	.	.
	Etanercept	407	22	5.41	1.17	0.74	1.85	0.4961
OR2	Non-biologic systemic therapy	3400	158	4.65	1.00	.	.	.
	Etanercept	407	22	5.41	1.16	0.73	1.85	0.5380
OR3	Non-biologic systemic therapy	3400	158	4.65	1.00	.	.	.
	Etanercept	407	22	5.41	1.14	0.71	1.82	0.5971
OR4	Non-biologic systemic therapy	3400	158	4.65	1.00	.	.	.
	Etanercept	407	22	5.41	0.88	0.51	1.49	0.6271
OR5	Non-biologic systemic therapy	3400	158	4.65	1.00	.	.	.
	Etanercept	407	22	5.41	0.82	0.48	1.42	0.4803

Exposure windows: Etanercept – LMP to 90 days after LMP; Non-biologic systemic therapy – 90 days before LMP to birth.

Appendix table 3 All birth defects, excluding those exposed to teratogens in pregnancy

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	1927	161	8.35	1.00	.	.	.
	Etanercept	317	31	9.78	1.19	0.79	1.78	0.4013
OR2	Non-biologic systemic therapy	1927	161	8.35	1.00	.	.	.
	Etanercept	317	31	9.78	1.20	0.80	1.81	0.3808
OR3	Non-biologic systemic therapy	1927	161	8.35	1.00	.	.	.
	Etanercept	317	31	9.78	1.18	0.78	1.78	0.4415
OR4	Non-biologic systemic therapy	1927	161	8.35	1.00	.	.	.
	Etanercept	317	31	9.78	1.03	0.65	1.62	0.9004
OR5	Non-biologic systemic therapy	1927	161	8.35	1.00	.	.	.
	Etanercept	317	31	9.78	0.96	0.61	1.53	0.8752

Only data from Sweden and Denmark are included, since no information about minor birth defects were available from Finland.

Exposure windows: Etanercept – LMP to 90 days after LMP; Non-biologic systemic therapy – 90 days before LMP to birth.

Appendix table 4 Any minor birth defect, excluding those exposed to teratogens in pregnancy								
Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	1927	88	4.57	1.00	.	.	.
	Etanercept	317	13	4.10	0.89	0.49	1.62	0.7111
OR2	Non-biologic systemic therapy	1927	88	4.57	1.00	.	.	.
	Etanercept	317	13	4.10	0.91	0.50	1.66	0.7541
OR3	Non-biologic systemic therapy	1927	88	4.57	1.0	.	.	.
	Etanercept	317	13	4.10	0.88	0.48	1.63	0.6922
OR4	Non-biologic systemic therapy	1927	88	4.57	1.00	.	.	.
	Etanercept	317	13	4.10	0.87	0.46	1.66	0.6785
OR5	Non-biologic systemic therapy	1927	88	4.57	1.00	.	.	.
	Etanercept	317	13	4.10	0.86	0.45	1.64	0.6407

Only data from Sweden and Denmark are included, since no information about minor birth defects were available from Finland.

Exposure windows: Etanercept – LMP to 90 days after LMP; Non-biologic systemic therapy – 90 days before LMP to birth.

Appendix table 5 Any major birth defect, excluding those exposed to teratogens in pregnancy, not counting chromosomal anomalies

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	3400	157	4.62	1.00	.	.	.
	Etanercept	407	21	5.16	1.12	0.70	1.79	0.6246
OR2	Non-biologic systemic therapy	3400	157	4.62	1.00	.	.	.
	Etanercept	407	21	5.16	1.10	0.68	1.77	0.6920
OR3	Non-biologic systemic therapy	3400	157	4.62	1.00	.	.	.
	Etanercept	407	21	5.16	1.08	0.67	1.75	0.7606
OR4	Non-biologic systemic therapy	3400	157	4.62	1.00	.	.	.
	Etanercept	407	21	5.16	0.82	0.48	1.42	0.4783
OR5	Non-biologic systemic therapy	3400	157	4.62	1.00	.	.	.
	Etanercept	407	21	5.16	0.77	0.44	1.34	0.3531

Exposure windows: Etanercept – LMP to 90 days after LMP; Non-biologic systemic therapy – 90 days before LMP to birth.

Appendix table 6 All birth defects, excluding those exposed to teratogens in pregnancy, not counting chromosomal anomalies

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	1927	161	8.35	1.00	.	.	.
	Etanercept	317	31	9.78	1.19	0.79	1.78	0.4013
OR2	Non-biologic systemic therapy	1927	161	8.35	1.00	.	.	.
	Etanercept	317	31	9.78	1.20	0.80	1.81	0.3808
OR3	Non-biologic systemic therapy	1927	161	8.35	1.00	.	.	.
	Etanercept	317	31	9.78	1.18	0.78	1.78	0.4415
OR4	Non-biologic systemic therapy	1927	161	8.35	1.00	.	.	.
	Etanercept	317	31	9.78	1.03	0.65	1.62	0.9004
OR5	Non-biologic systemic therapy	1927	161	8.35	1.00	.	.	.
	Etanercept	317	31	9.78	0.96	0.61	1.53	0.8752

Only data from Sweden and Denmark are included, since no information about minor birth defects were available from Finland.

Exposure windows: Etanercept – LMP to 90 days after LMP; Non-biologic systemic therapy – 90 days before LMP to birth.

Appendix table 7 Any major birth defect, different time windows

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
90 days before LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	3497	163	4.66	1.00	.	.	.
	Etanercept	517	32	6.19	1.35	0.91	2.00	0.1321
OR2	Non-biologic systemic therapy	3497	163	4.66	1.00	.	.	.
	Etanercept	517	32	6.19	1.33	0.89	1.99	0.1600
OR3	Non-biologic systemic therapy	3497	163	4.66	1.00	.	.	.
	Etanercept	517	32	6.19	1.32	0.88	1.99	0.1747
OR4	Non-biologic systemic therapy	3497	163	4.66	1.00	.	.	.
	Etanercept	517	32	6.19	1.12	0.72	1.76	0.6162
OR5	Non-biologic systemic therapy	3497	163	4.66	1.00	.	.	.
	Etanercept	517	32	6.19	1.08	0.69	1.70	0.7356
30 days before LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	3497	163	4.66	1.00	.	.	.
	Etanercept	475	27	5.68	1.23	0.81	1.87	0.3275
OR2	Non-biologic systemic therapy	3497	163	4.66	1.00	.	.	.
	Etanercept	475	27	5.68	1.23	0.80	1.88	0.3477
OR3	Non-biologic systemic therapy	3497	163	4.66	1.00	.	.	.
	Etanercept	475	27	5.68	1.22	0.79	1.88	0.3657
OR4	Non-biologic systemic therapy	3497	163	4.66	1.00	.	.	.
	Etanercept	475	27	5.68	0.98	0.60	1.60	0.9443
OR5	Non-biologic systemic therapy	3497	163	4.66	1.00	.	.	.
	Etanercept	475	27	5.68	0.94	0.57	1.54	0.8021

Exposure windows for Non-biologic systemic therapy – 90 days before LMP to birth.

Appendix table 8 All birth defects, different time windows								
Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
90 days before LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	1997	167	8.36	1.00	.	.	.
	Etanercept	416	42	10.10	1.23	0.86	1.76	0.2534
OR2	Non-biologic systemic therapy	1997	167	8.36	1.00	.	.	.
	Etanercept	416	42	10.10	1.24	0.87	1.78	0.2351
OR3	Non-biologic systemic therapy	1997	167	8.36	1.00	.	.	.
	Etanercept	416	42	10.10	1.23	0.86	1.78	0.2582
OR4	Non-biologic systemic therapy	1997	167	8.36	1.00	.	.	.
	Etanercept	416	42	10.10	1.11	0.74	1.67	0.6033
OR5	Non-biologic systemic therapy	1997	167	8.36	1.00	.	.	.
	Etanercept	416	42	10.10	1.06	0.71	1.60	0.7694
30 days before LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	1997	167	8.36	1.00	.	.	.
	Etanercept	375	37	9.87	1.20	0.83	1.75	0.3409
OR2	Non-biologic systemic therapy	1997	167	8.36	1.00	.	.	.
	Etanercept	375	37	9.87	1.22	0.83	1.78	0.3088
OR3	Non-biologic systemic therapy	1997	167	8.36	1.00	.	.	.
	Etanercept	375	37	9.87	1.21	0.82	1.78	0.3308
OR4	Non-biologic systemic therapy	1997	167	8.36	1.00	.	.	.
	Etanercept	375	37	9.87	1.05	0.68	1.61	0.8293
OR5	Non-biologic systemic therapy	1997	167	8.36	1.00	.	.	.
	Etanercept	375	37	9.87	0.99	0.64	1.53	0.9767

Only data from Sweden and Denmark are included, since no information about minor birth defects were available from Finland.
Exposure windows for Non-biologic systemic therapy – 90 days before LMP to birth.

Appendix table 9 Any minor birth defect, different time windows

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
90 days before LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	1997	90	4.51	1.00	.	.	.
	Etanercept	416	17	4.09	0.90	0.53	1.53	0.7050
OR2	Non-biologic systemic therapy	1997	90	4.51	1.00	.	.	.
	Etanercept	416	17	4.09	0.91	0.54	1.56	0.7392
OR3	Non-biologic systemic therapy	1997	90	4.51	1.00	.	.	.
	Etanercept	416	17	4.09	0.90	0.52	1.54	0.6865
OR4	Non-biologic systemic therapy	1997	90	4.51	1.00	.	.	.
	Etanercept	416	17	4.09	0.86	0.48	1.55	0.6200
OR5	Non-biologic systemic therapy	1997	90	4.51	1.00	.	.	.
	Etanercept	416	17	4.09	0.85	0.47	1.54	0.5975
30 days before LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	1997	90	4.51	1.00	.	.	.
	Etanercept	375	16	4.27	0.94	0.55	1.63	0.8364
OR2	Non-biologic systemic therapy	1997	90	4.51	1.00	.	.	.
	Etanercept	375	16	4.27	0.96	0.55	1.66	0.8755
OR3	Non-biologic systemic therapy	1997	90	4.51	1.00	.	.	.
	Etanercept	375	16	4.27	0.94	0.54	1.64	0.8227
OR4	Non-biologic systemic therapy	1997	90	4.51	1.00	.	.	.
	Etanercept	375	16	4.27	0.89	0.49	1.63	0.7134
OR5	Non-biologic systemic therapy	1997	90	4.51	1.00	.	.	.
	Etanercept	375	16	4.27	0.88	0.48	1.62	0.6871

Only data from Sweden and Denmark are included, since no information about minor birth defects were available from Finland.

Exposure windows for Non-biologic systemic therapy – 90 days before LMP to birth.

Appendix table 10 Preterm birth (<37 weeks), excluding those exposed to teratogens in pregnancy

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	3411	338	9.91	1.00	.	.	.
	Etanercept	500	55	11.00	1.12	0.83	1.52	0.4488
OR2	Non-biologic systemic therapy	3411	338	9.91	1.00	.	.	.
	Etanercept	500	55	11.00	1.08	0.79	1.47	0.6216
OR3	Non-biologic systemic therapy	3411	338	9.91	1.00	.	.	.
	Etanercept	500	55	11.00	1.06	0.77	1.45	0.7245
OR4	Non-biologic systemic therapy	3411	338	9.91	1.00	.	.	.
	Etanercept	500	55	11.00	1.11	0.80	1.56	0.5285
OR5	Non-biologic systemic therapy	3411	338	9.91	1.00	.	.	.
	Etanercept	500	55	11.00	1.11	0.79	1.55	0.5610

Exposure windows for Etanercept and Non-biologic systemic therapy – 90 days before LMP to birth.

Appendix table 11 Very preterm birth (<32 weeks), excluding those exposed to teratogens in pregnancy

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	3411	48	1.41	1.00	.	.	.
	Etanercept	500	5	1.00	0.71	0.28	1.79	0.4642
OR2	Non-biologic systemic therapy	3411	48	1.41	1.00	.	.	.
	Etanercept	500	5	1.00	0.66	0.26	1.69	0.3867
OR3	Non-biologic systemic therapy	3411	48	1.41	1.00	.	.	.
	Etanercept	500	5	1.00	0.66	0.25	1.70	0.3888
OR4	Non-biologic systemic therapy	3411	48	1.41	1.00	.	.	.
	Etanercept	500	5	1.00	0.72	0.27	1.90	0.5070
OR5	Non-biologic systemic therapy	3411	48	1.41	1.00	.	.	.
	Etanercept	500	5	1.00	0.74	0.28	1.98	0.5540

Exposure windows for Etanercept and Non-biologic systemic therapy – 90 days before LMP to birth.

Appendix table 12 Small for gestational age, excluding those exposed to teratogens in pregnancy

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	3411	112	3.28	1.00	.	.	.
	Etanercept	500	23	4.60	1.42	0.90	2.25	0.1340
OR2	Non-biologic systemic therapy	3411	112	3.28	1.00	.	.	.
	Etanercept	500	23	4.60	1.49	0.93	2.38	0.1008
OR3	Non-biologic systemic therapy	3411	112	3.28	1.00	.	.	.
	Etanercept	500	23	4.60	1.45	0.90	2.33	0.1311
OR4	Non-biologic systemic therapy	3411	112	3.28	1.00	.	.	.
	Etanercept	500	23	4.60	1.23	0.73	2.09	0.4424
OR5	Non-biologic systemic therapy	3411	112	3.28	1.00	.	.	.
	Etanercept	500	23	4.60	1.17	0.69	1.99	0.5598

Exposure windows for Etanercept and Non-biologic systemic therapy – 90 days before LMP to birth.

Appendix table 13 Low birth weight (≤ 2500 g), excluding those exposed to teratogens in pregnancy

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	3411	273	8.00	1.00	.	.	.
	Etanercept	500	51	10.20	1.31	0.95	1.79	0.0967
OR2	Non-biologic systemic therapy	3411	273	8.00	1.00	.	.	.
	Etanercept	500	51	10.20	1.27	0.92	1.75	0.1480
OR3	Non-biologic systemic therapy	3411	273	8.00	1.00	.	.	.
	Etanercept	500	51	10.20	1.27	0.91	1.76	0.1557
OR4	Non-biologic systemic therapy	3411	273	8.00	1.00	.	.	.
	Etanercept	500	51	10.20	1.38	0.97	1.96	0.0714
OR5	Non-biologic systemic therapy	3411	273	8.00	1.00	.	.	.
	Etanercept	500	51	10.20	1.35	0.95	1.92	0.0933

Exposure windows for Etanercept and Non-biologic systemic therapy – 90 days before LMP to birth.

Appendix table 14 Very low birth weight (≤ 1500 g), excluding those exposed to teratogens in pregnancy								
Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	3411	45	1.32	1.00	.	.	.
	Etanercept	500	6	1.20	0.91	0.39	2.14	0.8263
OR2	Non-biologic systemic therapy	3411	45	1.32	1.00	.	.	.
	Etanercept	500	6	1.20	0.85	0.36	2.05	0.7238
OR3	Non-biologic systemic therapy	3411	45	1.32	1.00	.	.	.
	Etanercept	500	6	1.20	0.86	0.35	2.08	0.7352
OR4	Non-biologic systemic therapy	3411	45	1.32	1.00	.	.	.
	Etanercept	500	6	1.20	0.94	0.38	2.33	0.8904
OR5	Non-biologic systemic therapy	3411	45	1.32	1.00	.	.	.
	Etanercept	500	6	1.20	0.96	0.39	2.41	0.9369

Exposure windows for Etanercept and Non-biologic systemic therapy – 90 days before LMP to birth.

Appendix table 15 Preterm birth (<37 weeks), different time windows								
Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
90 days before LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	3508	347	9.89	1.00	.	.	.
	Etanercept	517	60	11.61	1.20	0.89	1.60	0.2280
OR2	Non-biologic systemic therapy	3508	347	9.89	1.00	.	.	.
	Etanercept	517	60	11.61	1.16	0.86	1.56	0.3422
OR3	Non-biologic systemic therapy	3508	347	9.89	1.00	.	.	.
	Etanercept	517	60	11.61	1.13	0.83	1.53	0.4336
OR4	Non-biologic systemic therapy	3508	347	9.89	1.00	.	.	.
	Etanercept	517	60	11.61	1.17	0.85	1.62	0.3449
OR5	Non-biologic systemic therapy	3508	347	9.89	1.00	.	.	.
	Etanercept	517	60	11.61	1.15	0.83	1.60	0.3965
LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	3508	347	9.89	1.00	.	.	.
	Etanercept	425	53	12.47	1.30	0.95	1.77	0.0973
OR2	Non-biologic systemic therapy	3508	347	9.89	1.00	.	.	.
	Etanercept	425	53	12.47	1.27	0.92	1.74	0.1413
OR3	Non-biologic systemic therapy	3508	347	9.89	1.00	.	.	.
	Etanercept	425	53	12.47	1.23	0.89	1.70	0.2080
OR4	Non-biologic systemic therapy	3508	347	9.89	1.00	.	.	.
	Etanercept	425	53	12.47	1.33	0.95	1.85	0.0987
OR5	Non-biologic systemic therapy	3508	347	9.89	1.00	.	.	.

Appendix table 15 Preterm birth (<37 weeks), different time windows								
Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
	Etanercept	425	53	12.47	1.30	0.93	1.82	0.1232
91 days after LMP to 180 days after LMP (2nd trimester)								
OR1	Non-biologic systemic therapy	3508	347	9.89	1.00	.	.	.
	Etanercept	98	11	11.22	1.15	0.61	2.18	0.6636
OR2	Non-biologic systemic therapy	3508	347	9.89	1.00	.	.	.
	Etanercept	98	11	11.22	1.16	0.61	2.20	0.6510
OR3	Non-biologic systemic therapy	3508	347	9.89	1.00	.	.	.
	Etanercept	98	11	11.22	1.14	0.60	2.17	0.6872
OR4	Non-biologic systemic therapy	3508	347	9.89	1.00	.	.	.
	Etanercept	98	11	11.22	1.30	0.68	2.50	0.4287
OR5	Non-biologic systemic therapy	3508	347	9.89	1.00	.	.	.
	Etanercept	98	11	11.22	1.28	0.66	2.46	0.4659
181 days after LMP to delivery (3rd trimester)								
OR1	Non-biologic systemic therapy	3508	347	9.89	1.00	.	.	.
	Etanercept	69	4	5.80	0.56	0.20	1.55	0.2641
OR2	Non-biologic systemic therapy	3508	347	9.89	1.00	.	.	.
	Etanercept	69	4	5.80	0.56	0.20	1.56	0.2675
OR3	Non-biologic systemic therapy	3508	347	9.89	1.00	.	.	.
	Etanercept	69	4	5.80	0.57	0.21	1.57	0.2759
OR4	Non-biologic systemic therapy	3508	347	9.89	1.00	.	.	.
	Etanercept	69	4	5.80	0.51	0.16	1.66	0.2660
OR5	Non-biologic systemic therapy	3508	347	9.89	1.00	.	.	.
	Etanercept	69	4	5.80	0.50	0.15	1.61	0.2451

Exposure windows for Non-biologic systemic therapy – 90 days before LMP to birth.

Appendix table 16 Very preterm birth (<32 weeks), different time windows								
Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
90 days before LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	3508	48	1.37	1.00	.	.	.
	Etanercept	517	5	0.97	0.70	0.28	1.78	0.4573
OR2	Non-biologic systemic therapy	3508	48	1.37	1.00	.	.	.
	Etanercept	517	5	0.97	0.66	0.26	1.69	0.3880
OR3	Non-biologic systemic therapy	3508	48	1.37	1.00	.	.	.
	Etanercept	517	5	0.97	0.66	0.26	1.72	0.3970
OR4	Non-biologic systemic therapy	3508	48	1.37	1.00	.	.	.
	Etanercept	517	5	0.97	0.73	0.28	1.92	0.5184
OR5	Non-biologic systemic therapy	3508	48	1.37	1.00	.	.	.
	Etanercept	517	5	0.97	0.76	0.28	2.01	0.5763
LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	3508	48	1.37	1.00	.	.	.
	Etanercept	425	5	1.18	0.86	0.34	2.17	0.7463
OR2	Non-biologic systemic therapy	3508	48	1.37	1.00	.	.	.
	Etanercept	425	5	1.18	0.81	0.32	2.07	0.6591
OR3	Non-biologic systemic therapy	3508	48	1.37	1.00	.	.	.
	Etanercept	425	5	1.18	0.81	0.31	2.09	0.6583
OR4	Non-biologic systemic therapy	3508	48	1.37	1.00	.	.	.
	Etanercept	425	5	1.18	0.87	0.33	2.30	0.7800
OR5	Non-biologic systemic therapy	3508	48	1.37	1.00	.	.	.
	Etanercept	425	5	1.18	0.92	0.34	2.44	0.8617
91 days after LMP to 180 days after LMP (2nd trimester)								
OR1	Non-biologic systemic therapy	3508	48	1.37	1.00	.	.	.
	Etanercept	98	3	3.06	2.28	0.70	7.44	0.1733
OR2	Non-biologic systemic therapy	3508	48	1.37	1.00	.	.	.
	Etanercept	98	3	3.06	2.21	0.67	7.25	0.1912
OR3	Non-biologic systemic therapy	3508	48	1.37	1.00	.	.	.
	Etanercept	98	3	3.06	2.10	0.64	6.93	0.2221
OR4	Non-biologic systemic therapy	3508	48	1.37	1.00	.	.	.
	Etanercept	98	3	3.06	2.58	0.77	8.69	0.1264
OR5	Non-biologic systemic therapy	3508	48	1.37	1.00	.	.	.
	Etanercept	98	3	3.06	2.47	0.73	8.38	0.1472
181 days after LMP to delivery (3rd trimester)								
*	Non-biologic systemic therapy	3508	48	1.37	1.00	.	.	.
	Etanercept	69	0	0.00	*	*	*	*

*No cases. Not possible to estimate a logistic regression model.

Exposure windows for Non-biologic systemic therapy – 90 days before LMP to birth.

Appendix table 17 Small for gestational age, different time windows

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
90 days before LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	3508	118	3.36	1.00	.	.	.
	Etanercept	517	26	5.03	1.52	0.99	2.35	0.0587
OR2	Non-biologic systemic therapy	3508	118	3.36	1.00	.	.	.
	Etanercept	517	26	5.03	1.59	1.02	2.49	0.0430
OR3	Non-biologic systemic therapy	3508	118	3.36	1.00	.	.	.
	Etanercept	517	26	5.03	1.53	0.97	2.40	0.0686
OR4	Non-biologic systemic therapy	3508	118	3.36	1.00	.	.	.
	Etanercept	517	26	5.03	1.33	0.81	2.18	0.2662
OR5	Non-biologic systemic therapy	3508	118	3.36	1.00	.	.	.
	Etanercept	517	26	5.03	1.27	0.77	2.10	0.3408
LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	3508	118	3.36	1.00	.	.	.
	Etanercept	425	17	4.00	1.20	0.71	2.01	0.4966
OR2	Non-biologic systemic therapy	3508	118	3.36	1.00	.	.	.
	Etanercept	425	17	4.00	1.22	0.72	2.08	0.4547
OR3	Non-biologic systemic therapy	3508	118	3.36	1.00	.	.	.
	Etanercept	425	17	4.00	1.17	0.68	2.00	0.5666
OR4	Non-biologic systemic therapy	3508	118	3.36	1.00	.	.	.
	Etanercept	425	17	4.00	1.19	0.69	2.06	0.5303
OR5	Non-biologic systemic therapy	3508	118	3.36	1.00	.	.	.
	Etanercept	425	17	4.00	1.14	0.65	1.97	0.6515
91 days after LMP to 180 days after LMP (2nd trimester)								
OR1	Non-biologic systemic therapy	3508	118	3.36	1.00	.	.	.
	Etanercept	98	8	8.16	2.55	1.21	5.39	0.0138
OR2	Non-biologic systemic therapy	3508	118	3.36	1.00	.	.	.
	Etanercept	98	8	8.16	2.55	1.20	5.38	0.0145
OR3	Non-biologic systemic therapy	3508	118	3.36	1.00	.	.	.
	Etanercept	98	8	8.16	2.40	1.13	5.10	0.0222
OR4	Non-biologic systemic therapy	3508	118	3.36	1.00	.	.	.
	Etanercept	98	8	8.16	2.40	1.11	5.18	0.0256
OR5	Non-biologic systemic therapy	3508	118	3.36	1.00	.	.	.
	Etanercept	98	8	8.16	2.31	1.07	4.98	0.0333
181 days after LMP to delivery (3rd trimester)								
OR1	Non-biologic systemic therapy	3508	118	3.36	1.00	.	.	.
	Etanercept	69	7	10.14	3.24	1.45	7.24	0.0041
OR2	Non-biologic systemic therapy	3508	118	3.36	1.00	.	.	.
	Etanercept	69	7	10.14	3.26	1.46	7.30	0.0039
OR3	Non-biologic systemic therapy	3508	118	3.36	1.00	.	.	.
	Etanercept	69	7	10.14	3.15	1.40	7.09	0.0055

Appendix table 17 Small for gestational age, different time windows

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR4	Non-biologic systemic therapy	3508	118	3.36	1.000	.	.	.
	Etanercept	69	7	10.14	2.96	1.23	7.17	0.0159
OR5	Non-biologic systemic therapy	3508	118	3.36	1.00	.	.	.
	Etanercept	69	7	10.14	2.79	1.15	6.78	0.0231

Exposure windows for Non-biologic systemic therapy – 90 days before LMP to birth.

Appendix table 18 Low birth weight, different time windows

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
90 days before LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	3508	286	8.15	1.00	.	.	.
	Etanercept	517	55	10.64	1.34	0.99	1.82	0.0586
OR2	Non-biologic systemic therapy	3508	286	8.15	1.00	.	.	.
	Etanercept	517	55	10.64	1.31	0.96	1.79	0.0937
OR3	Non-biologic systemic therapy	3508	286	8.15	1.00	.	.	.
	Etanercept	517	55	10.64	1.30	0.95	1.79	0.1006
OR4	Non-biologic systemic therapy	3508	286	8.15	1.00	.	.	.
	Etanercept	517	55	10.64	1.38	0.98	1.94	0.0617
OR5	Non-biologic systemic therapy	3508	286	8.15	1.00	.	.	.
	Etanercept	517	55	10.64	1.36	0.97	1.92	0.0763
LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	3508	286	8.15	1.00	.	.	.
	Etanercept	425	47	11.06	1.40	1.01	1.94	0.0430
OR2	Non-biologic systemic therapy	3508	286	8.15	1.00	.	.	.
	Etanercept	425	47	11.06	1.38	0.99	1.93	0.0592
OR3	Non-biologic systemic therapy	3508	286	8.15	1.00	.	.	.
	Etanercept	425	47	11.06	1.37	0.98	1.92	0.0678
OR4	Non-biologic systemic therapy	3508	286	8.15	1.00	.	.	.
	Etanercept	425	47	11.06	1.53	1.08	2.18	0.0175
OR5	Non-biologic systemic therapy	3508	286	8.15	1.00	.	.	.
	Etanercept	425	47	11.06	1.50	1.06	2.14	0.0237
91 days after LMP to 180 days after LMP (2nd trimester)								
OR1	Non-biologic systemic therapy	3508	286	8.15	1.00	.	.	.
	Etanercept	98	11	11.22	1.42	0.75	2.70	0.2777
OR2	Non-biologic systemic therapy	3508	286	8.15	1.00	.	.	.
	Etanercept	98	11	11.22	1.45	0.76	2.75	0.2596
OR3	Non-biologic systemic therapy	3508	286	8.15	1.00	.	.	.
	Etanercept	98	11	11.22	1.39	0.73	2.63	0.3210
OR4	Non-biologic systemic therapy	3508	286	8.15	1.00	.	.	.

Appendix table 18 Low birth weight, different time windows								
Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
	Etanercept	98	11	11.22	1.63	0.85	3.13	0.1445
OR5	Non-biologic systemic therapy	3508	286	8.15	1.00	.	.	.
	Etanercept	98	11	11.22	1.56	0.81	3.01	0.1825
181 days after LMP to delivery (3rd trimester)								
OR1	Non-biologic systemic therapy	3508	286	8.15	1.00	.	.	.
	Etanercept	69	7	10.14	1.27	0.58	2.81	0.5506
OR2	Non-biologic systemic therapy	3508	286	8.15	1.00	.	.	.
	Etanercept	69	7	10.14	1.29	0.58	2.84	0.5334
OR3	Non-biologic systemic therapy	3508	286	8.15	1.00	.	.	.
	Etanercept	69	7	10.14	1.26	0.57	2.79	0.5694
OR4	Non-biologic systemic therapy	3508	286	8.15	1.00	.	.	.
	Etanercept	69	7	10.14	1.34	0.57	3.18	0.4997
OR5	Non-biologic systemic therapy	3508	286	8.15	1.00	.	.	.
	Etanercept	69	7	10.14	1.26	0.53	2.99	0.5945

Exposure windows for Non-biologic systemic therapy – 90 days before LMP to birth.

Appendix table 19 Very low birth weight, different time windows								
Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
90 days before LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	3508	45	1.28	1.00	.	.	.
	Etanercept	517	6	1.16	0.90	0.38	2.13	0.8166
OR2	Non-biologic systemic therapy	3508	45	1.28	1.00	.	.	.
	Etanercept	517	6	1.16	0.86	0.36	2.05	0.7260
OR3	Non-biologic systemic therapy	3508	45	1.28	1.00	.	.	.
	Etanercept	517	6	1.16	0.87	0.36	2.11	0.7563
OR4	Non-biologic systemic therapy	3508	45	1.28	1.00	.	.	.
	Etanercept	517	6	1.16	0.95	0.38	2.35	0.9080
OR5	Non-biologic systemic therapy	3508	45	1.28	1.00	.	.	.
	Etanercept	517	6	1.16	0.98	0.39	2.46	0.9741
LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	3508	45	1.28	1.00	.	.	.
	Etanercept	425	6	1.41	1.10	0.47	2.60	0.8244
OR2	Non-biologic systemic therapy	3508	45	1.28	1.00	.	.	.
	Etanercept	425	6	1.41	1.05	0.44	2.51	0.9140
OR3	Non-biologic systemic therapy	3508	45	1.28	1.00	.	.	.
	Etanercept	425	6	1.41	1.06	0.44	2.58	0.8979
OR4	Non-biologic systemic therapy	3508	45	1.28	1.00	.	.	.
	Etanercept	425	6	1.41	1.16	0.47	2.87	0.7547

Appendix table 19 Very low birth weight, different time windows								
Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR5	Non-biologic systemic therapy	3508	45	1.28	1.00	.	.	.
	Etanercept	425	6	1.41	1.21	0.48	3.04	0.6802
91 days after LMP to 180 days after LMP (2nd trimester)								
OR1	Non-biologic systemic therapy	3508	45	1.28	1.00	.	.	.
	Etanercept	98	3	3.06	2.43	0.74	7.96	0.1424
OR2	Non-biologic systemic therapy	3508	45	1.28	1.00	.	.	.
	Etanercept	98	3	3.06	2.39	0.73	7.86	0.1519
OR3	Non-biologic systemic therapy	3508	45	1.28	1.00	.	.	.
	Etanercept	98	3	3.06	2.32	0.70	7.68	0.1676
OR4	Non-biologic systemic therapy	3508	45	1.28	1.00	.	.	.
	Etanercept	98	3	3.06	2.95	0.87	9.99	0.0818
OR5	Non-biologic systemic therapy	3508	45	1.28	1.00	.	.	.
	Etanercept	98	3	3.06	2.76	0.81	9.45	0.1060
181 days after LMP to delivery (3rd trimester)								
*	Non-biologic systemic therapy	3508	45	1.28	1.00	.	.	.
	Etanercept	69	0	*	*	*	*	*

*No cases. Not possible to estimate a logistic regression model.

Exposure windows for Non-biologic systemic therapy – 90 days before LMP to birth.

Appendix table 20 Infections in the first year of life, excluding those exposed to teratogens in pregnancy								
Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	3400	885	26.03	1.00	.	.	.
	Etanercept	500	156	31.20	1.29	1.05	1.58	0.0149
OR2	Non-biologic systemic therapy	3400	885	26.03	1.00	.	.	.
	Etanercept	500	156	31.20	1.06	0.86	1.31	0.5960
OR3	Non-biologic systemic therapy	3400	885	26.03	1.00	.	.	.
	Etanercept	500	156	31.20	1.06	0.86	1.32	0.5652
OR4	Non-biologic systemic therapy	3400	885	26.03	1.00	.	.	.
	Etanercept	500	156	31.20	1.00	0.80	1.25	0.9869
OR5	Non-biologic systemic therapy	3400	885	26.03	1.00	.	.	.
	Etanercept	500	156	31.20	0.99	0.79	1.25	0.9449

Exposure windows for Etanercept and Non-biologic systemic therapy – 90 days before LMP to birth.

Appendix table 21 Opportunistic infections in the first year of life, excluding those exposed to teratogens in pregnancy								
Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	3400	71	2.09	1.00	.	.	.
	Etanercept	500	13	2.60	1.25	0.69	2.28	0.4623
OR2	Non-biologic systemic therapy	3400	71	2.09	1.00	.	.	.
	Etanercept	500	13	2.60	1.66	0.89	3.07	0.1096
OR3	Non-biologic systemic therapy	3400	71	2.09	1.00	.	.	.
	Etanercept	500	13	2.60	1.53	0.82	2.86	0.1818
OR4	Non-biologic systemic therapy	3400	71	2.09	1.00	.	.	.
	Etanercept	500	13	2.60	1.30	0.62	2.75	0.4896
OR5	Non-biologic systemic therapy	3400	71	2.09	1.00	.	.	.
	Etanercept	500	13	2.60	1.22	0.57	2.58	0.6100

Exposure windows for Etanercept and Non-biologic systemic therapy – 90 days before LMP to birth.

Appendix table 22 Infections in the first year of life, different time windows								
Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
90 days before LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	3497	910	26.02	1.00	.	.	.
	Etanercept	517	161	31.14	1.29	1.05	1.57	0.0142
OR2	Non-biologic systemic therapy	3497	910	26.02	1.00	.	.	.
	Etanercept	517	161	31.14	1.05	0.86	1.29	0.6310
OR3	Non-biologic systemic therapy	3497	910	26.02	1.00	.	.	.

Appendix table 22 Infections in the first year of life, different time windows

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
	Etanercept	517	161	31.14	1.06	0.86	1.31	0.5869
OR4	Non-biologic systemic therapy	3497	910	26.02	1.00	.	.	.
	Etanercept	517	161	31.14	1.01	0.81	1.26	0.9268
OR5	Non-biologic systemic therapy	3497	910	26.02	1.00	.	.	.
	Etanercept	517	161	31.14	1.00	0.80	1.25	0.9988
LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	3497	910	26.02	1.00	.	.	.
	Etanercept	425	135	31.76	1.32	1.07	1.65	0.0116
OR2	Non-biologic systemic therapy	3497	910	26.02	1.00	.	.	.
	Etanercept	425	135	31.76	1.08	0.86	1.35	0.5030
OR3	Non-biologic systemic therapy	3497	910	26.02	1.00	.	.	.
	Etanercept	425	135	31.76	1.08	0.87	1.36	0.4842
OR4	Non-biologic systemic therapy	3497	910	26.02	1.00	.	.	.
	Etanercept	425	135	31.76	1.07	0.84	1.35	0.6007
OR5	Non-biologic systemic therapy	3497	910	26.02	1.00	.	.	.
	Etanercept	425	135	31.76	1.05	0.83	1.33	0.6892
91 days after LMP to 180 days after LMP (2nd trimester)								
OR1	Non-biologic systemic therapy	3497	910	26.02	1.00	.	.	.
	Etanercept	98	26	26.53	1.03	0.65	1.62	0.9094
OR2	Non-biologic systemic therapy	3497	910	26.02	1.00	.	.	.
	Etanercept	98	26	26.53	0.89	0.56	1.41	0.6266
OR3	Non-biologic systemic therapy	3497	910	26.02	1.00	.	.	.
	Etanercept	98	26	26.53	0.90	0.57	1.43	0.6574
OR4	Non-biologic systemic therapy	3497	910	26.02	1.00	.	.	.
	Etanercept	98	26	26.53	0.94	0.58	1.52	0.7961
OR5	Non-biologic systemic therapy	3497	910	26.02	1.00	.	.	.
	Etanercept	98	26	26.53	0.90	0.55	1.47	0.6771
181 days after LMP to delivery (3rd trimester)								
OR1	Non-biologic systemic therapy	3497	910	26.02	1.00	.	.	.
	Etanercept	69	19	27.54	1.08	0.63	1.84	0.7767
OR2	Non-biologic systemic therapy	3497	910	26.02	1.00	.	.	.
	Etanercept	69	19	27.54	0.97	0.56	1.66	0.8975
OR3	Non-biologic systemic therapy	3497	910	26.02	1.00	.	.	.
	Etanercept	69	19	27.54	0.97	0.57	1.67	0.9230
OR4	Non-biologic systemic therapy	3497	910	26.02	1.00	.	.	.
	Etanercept	69	19	27.54	0.99	0.56	1.75	0.9590
OR5	Non-biologic systemic therapy	3497	910	26.02	1.00	.	.	.
	Etanercept	69	19	27.54	0.95	0.53	1.69	0.8546

Exposure windows for Non-biologic systemic therapy – 90 days before LMP to birth.

Appendix table 23 Opportunistic infections in the first year of life, different time windows

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
90 days before LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	3497	72	2.06	1.00	.	.	.
	Etanercept	517	14	2.71	1.33	0.74	2.37	0.3422
OR2	Non-biologic systemic therapy	3497	72	2.06	1.00	.	.	.
	Etanercept	517	14	2.71	1.72	0.94	3.12	0.0773
OR3	Non-biologic systemic therapy	3497	72	2.06	1.00	.	.	.
	Etanercept	517	14	2.71	1.58	0.86	2.90	0.1386
OR4	Non-biologic systemic therapy	3497	72	2.06	1.00	.	.	.
	Etanercept	517	14	2.71	1.38	0.67	2.82	0.3815
OR5	Non-biologic systemic therapy	3497	72	2.06	1.00	.	.	.
	Etanercept	517	14	2.71	1.30	0.63	2.66	0.4750
LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	3497	72	2.06	1.00	.	.	.
	Etanercept	425	13	3.06	1.50	0.82	2.73	0.1842
OR2	Non-biologic systemic therapy	3497	72	2.06	1.00	.	.	.
	Etanercept	425	13	3.06	1.94	1.05	3.60	0.0359
OR3	Non-biologic systemic therapy	3497	72	2.06	1.00	.	.	.
	Etanercept	425	13	3.06	1.75	0.94	3.28	0.0798
OR4	Non-biologic systemic therapy	3497	72	2.06	1.00	.	.	.
	Etanercept	425	13	3.06	1.60	0.78	3.26	0.1990
OR5	Non-biologic systemic therapy	3497	72	2.06	1.00	.	.	.
	Etanercept	425	13	3.06	1.50	0.73	3.07	0.2652
91 days after LMP to 180 days after LMP (2nd trimester)								
OR1	Non-biologic systemic therapy	3497	72	2.06	1.00	.	.	.
	Etanercept	98	4	4.08	2.03	0.73	5.66	0.1782
OR2	Non-biologic systemic therapy	3497	72	2.06	1.00	.	.	.
	Etanercept	98	4	4.08	2.28	0.81	6.40	0.1187
OR3	Non-biologic systemic therapy	3497	72	2.06	1.00	.	.	.
	Etanercept	98	4	4.08	2.17	0.77	6.11	0.1447
OR4	Non-biologic systemic therapy	3497	72	2.06	1.00	.	.	.
	Etanercept	98	4	4.08	2.58	0.90	7.42	0.0779
OR5	Non-biologic systemic therapy	3497	72	2.06	1.00	.	.	.
	Etanercept	98	4	4.08	2.35	0.81	6.80	0.1145
181 days after LMP to delivery (3rd trimester)								
OR1	Non-biologic systemic therapy	3497	72	2.06	1.00	.	.	.
	Etanercept	69	2	2.90	1.42	0.34	5.91	0.6298
OR2	Non-biologic systemic therapy	3497	72	2.06	1.00	.	.	.
	Etanercept	69	2	2.90	1.58	0.38	6.58	0.5317
OR3	Non-biologic systemic therapy	3497	72	2.06	1.00	.	.	.
	Etanercept	69	2	2.90	1.44	0.34	6.05	0.6193

Appendix table 23 Opportunistic infections in the first year of life, different time windows

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR4	Non-biologic systemic therapy	3497	72	2.06	1.00	.	.	.
	Etanercept	69	2	2.90	0.92	0.12	6.89	0.9388
OR5	Non-biologic systemic therapy	3497	72	2.06	1.00	.	.	.
	Etanercept	69	2	2.90	0.79	0.11	5.98	0.8232

Exposure windows for Non-biologic systemic therapy – 90 days before LMP to birth.

Appendix table 24 Other treatment during pregnancy

Variable	Etanercept		Non-bio Systemic	
	n	(%)	n	(%)
Total	522	100.0	3508	100.0
Tocilizumab	2	0.4	.	.
Adalimumab	18	3.4	.	.
Certolizumab pegol	1	0.2	.	.
Golimumab	1	0.2	.	.
Azathioprine	18	3.4	161	4.6
Mercaptopurine	.	.	7	0.2
Corticosteroids for systemic use	348	66.7	2067	58.9
Ciclosporin	12	2.3	56	1.6
Tacrolimus	.	.	2	0.1
Tioguanin/Lanvis	.	.	1	0.0
Phototherapy, PUVA, oral	.	.	1	0.0
Chloroquine	1	0.2	19	0.5
Hydroxychloroquine	51	9.8	503	14.3
Sulfalsalazine	93	17.8	1852	52.8
Methotrexate	41	7.9	137	3.9
Leflunomide	.	.	3	0.1
Acitretin	.	.	1	0.0
Mycophenolic acid	.	.	3	0.1

Section 2 Changing the exposure window for both etanercept and non-biologic systemic Main analyses

Appendix table 25 Any major birth defect, exposure in the first trimester for both cohorts: Results of Logistic regression								
Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	2696	129	4.78	1.00	.	.	.
	Etanercept	425	24	5.65	1.19	0.76	1.86	0.4446
OR2	Non-biologic systemic therapy	2696	129	4.78	1.00	.	.	.
	Etanercept	425	24	5.65	1.22	0.77	1.93	0.4058
OR3	Non-biologic systemic therapy	2696	129	4.78	1.00	.	.	.
	Etanercept	425	24	5.65	1.20	0.75	1.92	0.4398
OR4	Non-biologic systemic therapy	2696	129	4.78	1.00	.	.	.
	Etanercept	425	24	5.65	0.97	0.58	1.64	0.9139
OR5	Non-biologic systemic therapy	2696	129	4.78	1.00	.	.	.
	Etanercept	425	24	5.65	0.94	0.55	1.59	0.8161

Compare to Table 8 in report. Exposure windows: Etanercept – LMP to 90 days after LMP; Non-biologic systemic therapy – LMP to 90 days after LMP.

Appendix table 26 Any birth defect, major or minor, exposure in the first trimester for both cohorts: Results of Logistic regression								
Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	1483	131	8.83	1.00	.	.	.
	Etanercept	329	33	10.03	1.15	0.77	1.72	0.4939
OR2	Non-biologic systemic therapy	1483	131	8.83	1.00	.	.	.
	Etanercept	329	33	10.03	1.21	0.80	1.82	0.3663
OR3	Non-biologic systemic therapy	1483	131	8.83	1.00	.	.	.
	Etanercept	329	33	10.03	1.18	0.78	1.79	0.4338
OR4	Non-biologic systemic therapy	1483	131	8.83	1.00	.	.	.
	Etanercept	329	33	10.03	1.06	0.67	1.68	0.7936
OR5	Non-biologic systemic therapy	1483	131	8.83	1.00	.	.	.
	Etanercept	329	33	10.03	1.01	0.63	1.59	0.9798

Compare to Table 9 in report. Only data from Sweden and Denmark are included, since no information about minor birth defects were available from Finland. Exposure windows: Etanercept – LMP to 90 days after LMP; Non-biologic systemic therapy – LMP to 90 days after LMP.

Appendix table 27 Any minor birth defect, exposure in the first trimester for both cohorts: Results of Logistic regression

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	1483	70	4.72	1.00	.	.	.
	Etanercept	329	14	4.26	0.90	0.50	1.61	0.7169
OR2	Non-biologic systemic therapy	1483	70	4.72	1.00	.	.	.
	Etanercept	329	14	4.26	0.94	0.51	1.70	0.8295
OR3	Non-biologic systemic therapy	1483	70	4.72	1.00	.	.	.
	Etanercept	329	14	4.26	0.91	0.50	1.66	0.7513
OR4	Non-biologic systemic therapy	1483	70	4.72	1.00	.	.	.
	Etanercept	329	14	4.26	0.89	0.47	1.69	0.7242
OR5	Non-biologic systemic therapy	1483	70	4.72	1.00	.	.	.
	Etanercept	329	14	4.26	0.87	0.46	1.66	0.6819

Compare to Table 10 in report. Only data from Sweden and Denmark are included, since no information about minor birth defects were available from Finland. Exposure windows: Etanercept – LMP to 90 days after LMP; Non-biologic systemic therapy – LMP to 90 days after LMP.

Sensitivity analyses, compound table

Appendix table 28 Birth outcomes (Preterm birth, Low Birth Weight, Small for Gestational Age): Results of sensitivity analysis of different time windows. Changing time window for both groups. OR4.								
Time window	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
Preterm birth (<37 weeks)								
90 days before LMP to 90 days after LMP	Non-biologic systemic therapy	3148	308	9.78	1.00	.	.	.
	Etanercept	517	60	11.61	1.18	0.85	1.63	0.3341
LMP to 90 days after LMP	Non-biologic systemic therapy	2705	275	10.17	1.00	.	.	.
	Etanercept	425	53	12.47	1.29	0.92	1.82	0.1458
91 days after LMP to 180 days after LMP	Non-biologic systemic therapy	2238	231	10.32	1.00	.	.	.
	Etanercept	98	11	11.22	1.22	0.63	2.36	0.5564
181 days after LMP to birth	Non-biologic systemic therapy	2074	215	10.37	1.00	.	.	.
	Etanercept	69	4	5.80	0.50	0.15	1.63	0.2497
Low birth weight (≤ 2500 g)								
90 days before LMP to 90 days after LMP	Non-biologic systemic therapy	3148	260	8.26	1.00	.	.	.
	Etanercept	517	55	10.64	1.30	0.93	1.84	0.1285
LMP to 90 days after LMP	Non-biologic systemic therapy	2705	235	8.69	1.00	.	.	.
	Etanercept	425	47	11.06	1.39	0.97	1.99	0.0742
91 days after LMP to 180 days after LMP	Non-biologic systemic therapy	2238	197	8.80	1.00	.	.	.
	Etanercept	98	11	11.22	1.41	0.72	2.74	0.3124
181 days after LMP to birth	Non-biologic systemic therapy	2074	181	8.73	1.00	.	.	.
	Etanercept	69	7	10.14	1.23	0.52	2.94	0.6374
SGA								
90 days before LMP to 90 days after LMP	Non-biologic systemic therapy	3148	101	3.21	1.00	.	.	.
	Etanercept	517	26	5.03	1.29	0.78	2.14	0.3168
LMP to 90 days after LMP	Non-biologic systemic therapy	2705	96	3.55	1.00	.	.	.
	Etanercept	425	17	4.00	1.03	0.59	1.81	0.9133
91 days after LMP to 180 days after LMP	Non-biologic systemic therapy	2238	84	3.75	1.00	.	.	.
	Etanercept	98	8	8.16	2.06	0.94	4.54	0.0728
181 days after LMP to birth	Non-biologic systemic therapy	2074	75	3.62	1.00	.	.	.
	Etanercept	69	7	10.14	2.75	1.11	6.77	0.0281

Compare to Table 16 in report. SGA, 2nd and 3rd trimester is attenuated. Both exposure groups vary in size according to time window of exposure.

Sensitivity analyses, different time periods, changing period in both groups

Appendix table 29 Any major birth defect, time windows change for both groups								
Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
90 days before LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	3137	146	4.65	1.00	.	.	.
	Etanercept	517	32	6.19	1.35	0.91	2.01	0.1337
OR2	Non-biologic systemic therapy	3137	146	4.65	1.00	.	.	.
	Etanercept	517	32	6.19	1.35	0.90	2.02	0.1497
OR3	Non-biologic systemic therapy	3137	146	4.65	1.00	.	.	.
	Etanercept	517	32	6.19	1.29	0.86	1.95	0.2185
OR4	Non-biologic systemic therapy	3137	146	4.65	1.00	.	.	.
	Etanercept	517	32	6.19	1.09	0.69	1.71	0.7222
OR5	Non-biologic systemic therapy	3137	146	4.65	1.00	.	.	.
	Etanercept	517	32	6.19	1.07	0.67	1.69	0.7780
30 days before LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	2887	134	4.64	1.00	.	.	.
	Etanercept	475	27	5.68	1.24	0.81	1.89	0.3246
OR2	Non-biologic systemic therapy	2887	134	4.64	1.00	.	.	.
	Etanercept	475	27	5.68	1.26	0.81	1.95	0.3037
OR3	Non-biologic systemic therapy	2887	134	4.64	1.00	.	.	.
	Etanercept	475	27	5.68	1.24	0.79	1.92	0.3472
OR4	Non-biologic systemic therapy	2887	134	4.64	1.00	.	.	.
	Etanercept	475	27	5.68	1.00	0.61	1.65	0.9945
OR5	Non-biologic systemic therapy	2887	134	4.64	1.00	.	.	.
	Etanercept	475	27	5.68	0.97	0.59	1.61	0.9103

Compare to Appendix table 7. Both exposure groups vary in size according to time window of exposure.

Appendix table 30 All birth defects, time windows change for both groups								
Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
90 days before LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	1800	153	8.50	1.00	.	.	.
	Etanercept	416	42	10.10	1.21	0.84	1.73	0.3008
OR2	Non-biologic systemic therapy	1800	153	8.50	1.00	.	.	.
	Etanercept	416	42	10.10	1.23	0.86	1.78	0.2611
OR3	Non-biologic systemic therapy	1800	153	8.50	1.00	.	.	.
	Etanercept	416	42	10.10	1.20	0.83	1.74	0.3272
OR4	Non-biologic systemic therapy	1800	153	8.50	1.00	.	.	.
	Etanercept	416	42	10.10	1.08	0.72	1.63	0.7009
OR5	Non-biologic systemic therapy	1800	153	8.50	1.00	.	.	.
	Etanercept	416	42	10.10	1.04	0.69	1.57	0.8557
30 days before LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	1595	138	8.65	1.00	.	.	.
	Etanercept	375	37	9.87	1.16	0.79	1.69	0.4572
OR2	Non-biologic systemic therapy	1595	138	8.65	1.00	.	.	.
	Etanercept	375	37	9.87	1.20	0.81	1.77	0.3568
OR3	Non-biologic systemic therapy	1595	138	8.65	1.00	.	.	.
	Etanercept	375	37	9.87	1.19	0.80	1.76	0.3939
OR4	Non-biologic systemic therapy	1595	138	8.65	1.00	.	.	.
	Etanercept	375	37	9.87	1.04	0.67	1.61	0.8765
OR5	Non-biologic systemic therapy	1595	138	8.65	1.00	.	.	.
	Etanercept	375	37	9.87	0.98	0.63	1.52	0.9216

Compare to Appendix table 8. Both exposure groups vary in size according to time window of exposure.

Appendix table 31 Any minor birth defect, time windows change for both groups								
Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
90 days before LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	1800	85	4.72	1.00	.	.	.
	Etanercept	416	17	4.09	0.86	0.50	1.46	0.5775
OR2	Non-biologic systemic therapy	1800	85	4.72	1.00	.	.	.
	Etanercept	416	17	4.09	0.87	0.51	1.50	0.6267
OR3	Non-biologic systemic therapy	1800	85	4.72	1.00	.	.	.
	Etanercept	416	17	4.09	0.86	0.50	1.49	0.5994
OR4	Non-biologic systemic therapy	1800	85	4.72	1.00	.	.	.
	Etanercept	416	17	4.09	0.83	0.46	1.49	0.5306
OR5	Non-biologic systemic therapy	1800	85	4.72	1.00	.	.	.
	Etanercept	416	17	4.09	0.81	0.45	1.47	0.4891
30 days before LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	1595	75	4.70	1.00	.	.	.
	Etanercept	375	16	4.27	0.90	0.52	1.57	0.7178
OR2	Non-biologic systemic therapy	1595	75	4.70	1.00	.	.	.
	Etanercept	375	16	4.27	0.93	0.53	1.64	0.8126
OR3	Non-biologic systemic therapy	1595	75	4.70	1.00	.	.	.
	Etanercept	375	16	4.27	0.92	0.52	1.62	0.7746
OR4	Non-biologic systemic therapy	1595	75	4.70	1.00	.	.	.
	Etanercept	375	16	4.27	0.86	0.47	1.60	0.6362
OR5	Non-biologic systemic therapy	1595	75	4.70	1.00	.	.	.
	Etanercept	375	16	4.27	0.84	0.45	1.56	0.5820

Compare to Appendix table 9. Both exposure groups vary in size according to time window of exposure.

Appendix table 32 Preterm birth (<37 weeks), time windows change for both groups

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
90 days before LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	3148	308	9.78	1.00	.	.	.
	Etanercept	517	60	11.61	1.21	0.90	1.62	0.2020
OR2	Non-biologic systemic therapy	3148	308	9.78	1.00	.	.	.
	Etanercept	517	60	11.61	1.17	0.86	1.58	0.3169
OR3	Non-biologic systemic therapy	3148	308	9.78	1.00	.	.	.
	Etanercept	517	60	11.61	1.15	0.85	1.57	0.3570
OR4	Non-biologic systemic therapy	3148	308	9.78	1.00	.	.	.
	Etanercept	517	60	11.61	1.18	0.85	1.63	0.3341
OR5	Non-biologic systemic therapy	3148	308	9.78	1.00	.	.	.
	Etanercept	517	60	11.61	1.18	0.85	1.64	0.3292
LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	2705	275	10.17	1.00	.	.	.
	Etanercept	425	53	12.47	1.26	0.92	1.72	0.1499
OR2	Non-biologic systemic therapy	2705	275	10.17	1.00	.	.	.
	Etanercept	425	53	12.47	1.22	0.88	1.69	0.2271
OR3	Non-biologic systemic therapy	2705	275	10.17	1.00	.	.	.
	Etanercept	425	53	12.47	1.19	0.85	1.64	0.3081
OR4	Non-biologic systemic therapy	2705	275	10.17	1.00	.	.	.
	Etanercept	425	53	12.47	1.29	0.92	1.82	0.1458
OR5	Non-biologic systemic therapy	2705	275	10.17	1.00	.	.	.
	Etanercept	425	53	12.47	1.29	0.92	1.83	0.1415
91 days after LMP to 180 days after LMP (2nd trimester)								
OR1	Non-biologic systemic therapy	2238	231	10.32	1.00	.	.	.
	Etanercept	98	11	11.22	1.10	0.58	2.09	0.7741
OR2	Non-biologic systemic therapy	2238	231	10.32	1.00	.	.	.
	Etanercept	98	11	11.22	1.08	0.57	2.06	0.8101
OR3	Non-biologic systemic therapy	2238	231	10.32	1.00	.	.	.
	Etanercept	98	11	11.22	1.06	0.55	2.03	0.8616
OR4	Non-biologic systemic therapy	2238	231	10.32	1.00	.	.	.
	Etanercept	98	11	11.22	1.22	0.63	2.36	0.5564
OR5	Non-biologic systemic therapy	2238	231	10.32	1.00	.	.	.
	Etanercept	98	11	11.22	1.21	0.62	2.34	0.5744
181 days after LMP to delivery (3rd trimester)								
OR1	Non-biologic systemic therapy	2074	215	10.37	1.00	.	.	.
	Etanercept	69	4	5.80	0.53	0.19	1.47	0.2252
OR2	Non-biologic systemic therapy	2074	215	10.37	1.00	.	.	.
	Etanercept	69	4	5.80	0.52	0.19	1.44	0.2051
OR3	Non-biologic systemic therapy	2074	215	10.37	1.00	.	.	.
	Etanercept	69	4	5.80	0.54	0.19	1.50	0.2348

Appendix table 32 Preterm birth (<37 weeks), time windows change for both groups

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR4	Non-biologic systemic therapy	2074	215	10.37	1.00	.	.	.
	Etanercept	69	4	5.80	0.50	0.15	1.63	0.2497
OR5	Non-biologic systemic therapy	2074	215	10.37	1.00	.	.	.
	Etanercept	69	4	5.80	0.50	0.15	1.62	0.2451

Compare to Appendix table 15. Both exposure groups vary in size according to time window of exposure.

Appendix table 33 Very preterm birth (<32 weeks), time windows change for both groups								
Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
90 days before LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	3148	44	1.40	1.00	.	.	.
	Etanercept	517	5	0.97	0.69	0.27	1.75	0.4321
OR2	Non-biologic systemic therapy	3148	44	1.40	1.00	.	.	.
	Etanercept	517	5	0.97	0.65	0.25	1.66	0.3645
OR3	Non-biologic systemic therapy	3148	44	1.40	1.00	.	.	.
	Etanercept	517	5	0.97	0.63	0.24	1.65	0.3504
OR4	Non-biologic systemic therapy	3148	44	1.40	1.00	.	.	.
	Etanercept	517	5	0.97	0.71	0.27	1.88	0.4851
OR5	Non-biologic systemic therapy	3148	44	1.40	1.00	.	.	.
	Etanercept	517	5	0.97	0.73	0.27	1.95	0.5278
LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	2705	36	1.33	1.00	.	.	.
	Etanercept	425	5	1.18	0.88	0.34	2.26	0.7948
OR2	Non-biologic systemic therapy	2705	36	1.33	1.00	.	.	.
	Etanercept	425	5	1.18	0.87	0.33	2.27	0.7714
OR3	Non-biologic systemic therapy	2705	36	1.33	1.00	.	.	.
	Etanercept	425	5	1.18	0.81	0.31	2.17	0.6813
OR4	Non-biologic systemic therapy	2705	36	1.33	1.00	.	.	.
	Etanercept	425	5	1.18	0.89	0.33	2.44	0.8229
OR5	Non-biologic systemic therapy	2705	36	1.33	1.00	.	.	.
	Etanercept	425	5	1.18	0.90	0.33	2.49	0.8439
91 days after LMP to 180 days after LMP (2nd trimester)								
OR1	Non-biologic systemic therapy	2238	33	1.47	1.00	.	.	.
	Etanercept	98	3	3.06	2.11	0.64	7.01	0.2219
OR2	Non-biologic systemic therapy	2238	33	1.47	1.00	.	.	.
	Etanercept	98	3	3.06	2.10	0.63	7.02	0.2292
OR3	Non-biologic systemic therapy	2238	33	1.47	1.00	.	.	.
	Etanercept	98	3	3.06	1.98	0.59	6.68	0.2716
OR4	Non-biologic systemic therapy	2238	33	1.47	1.00	.	.	.
	Etanercept	98	3	3.06	2.07	0.60	7.16	0.2502
OR5	Non-biologic systemic therapy	2238	33	1.47	1.00	.	.	.
	Etanercept	98	3	3.06	1.93	0.56	6.73	0.2998
181 days after LMP to delivery (3rd trimester)								
*	Non-biologic systemic therapy	3508	48	1.37	1.00	.	.	.
	Etanercept	69	0	0.00	*	*	*	*

*No cases. Not possible to estimate a logistic regression model.

Compare to Appendix table 16. Both exposure groups vary in size according to time window of exposure.

Appendix table 34 Small for gestational age, time windows change for both groups

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
90 days before LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	3148	101	3.21	1.00	.	.	.
	Etanercept	517	26	5.03	1.60	1.03	2.48	0.0375
OR2	Non-biologic systemic therapy	3148	101	3.21	1.00	.	.	.
	Etanercept	517	26	5.03	1.60	1.01	2.52	0.0443
OR3	Non-biologic systemic therapy	3148	101	3.21	1.00	.	.	.
	Etanercept	517	26	5.03	1.52	0.96	2.42	0.0743
OR4	Non-biologic systemic therapy	3148	101	3.21	1.00	.	.	.
	Etanercept	517	26	5.03	1.29	0.78	2.14	0.3168
OR5	Non-biologic systemic therapy	3148	101	3.21	1.00	.	.	.
	Etanercept	517	26	5.03	1.27	0.76	2.10	0.3601
LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	2705	96	3.55	1.00	.	.	.
	Etanercept	425	17	4.00	1.13	0.67	1.92	0.6433
OR2	Non-biologic systemic therapy	2705	96	3.55	1.00	.	.	.
	Etanercept	425	17	4.00	1.09	0.63	1.86	0.7667
OR3	Non-biologic systemic therapy	2705	96	3.55	1.00	.	.	.
	Etanercept	425	17	4.00	1.05	0.61	1.82	0.8573
OR4	Non-biologic systemic therapy	2705	96	3.55	1.00	.	.	.
	Etanercept	425	17	4.00	1.03	0.59	1.81	0.9133
OR5	Non-biologic systemic therapy	2705	96	3.55	1.00	.	.	.
	Etanercept	425	17	4.00	1.02	0.58	1.79	0.9514
91 days after LMP to 180 days after LMP (2nd trimester)								
OR1	Non-biologic systemic therapy	2238	84	3.75	1.00	.	.	.
	Etanercept	98	8	8.16	2.28	1.07	4.85	0.0325
OR2	Non-biologic systemic therapy	2238	84	3.75	1.00	.	.	.
	Etanercept	98	8	8.16	2.15	1.00	4.60	0.0486
OR3	Non-biologic systemic therapy	2238	84	3.75	1.00	.	.	.
	Etanercept	98	8	8.16	2.15	1.00	4.60	0.0497
OR4	Non-biologic systemic therapy	2238	84	3.75	1.00	.	.	.
	Etanercept	98	8	8.16	2.06	0.94	4.54	0.0728
OR5	Non-biologic systemic therapy	2238	84	3.75	1.00	.	.	.
	Etanercept	98	8	8.16	2.05	0.93	4.53	0.0744
181 days after LMP to delivery (3rd trimester)								
OR1	Non-biologic systemic therapy	2074	75	3.62	1.00	.	.	.
	Etanercept	69	7	10.14	3.01	1.33	6.80	0.0080
OR2	Non-biologic systemic therapy	2074	75	3.62	1.00	.	.	.
	Etanercept	69	7	10.14	2.99	1.32	6.76	0.0088
OR3	Non-biologic systemic therapy	2074	75	3.62	1.00	.	.	.
	Etanercept	69	7	10.14	3.12	1.36	7.13	0.0070

Appendix table 34 Small for gestational age, time windows change for both groups

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR4	Non-biologic systemic therapy	2074	75	3.62	1.00	.	.	.
	Etanercept	69	7	10.14	2.75	1.11	6.77	0.0281
OR5	Non-biologic systemic therapy	2074	75	3.62	1.00	.	.	.
	Etanercept	69	7	10.14	2.56	1.03	6.36	0.0425

Compare to Appendix table 17. Both exposure groups vary in size according to time window of exposure.

Appendix table 35 Low birth weight, time windows change for both groups

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
90 days before LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	3148	260	8.26	1.00	.	.	.
	Etanercept	517	55	10.64	1.32	0.97	1.80	0.0742
OR2	Non-biologic systemic therapy	3148	260	8.26	1.00	.	.	.
	Etanercept	517	55	10.64	1.26	0.92	1.73	0.1503
OR3	Non-biologic systemic therapy	3148	260	8.26	1.00	.	.	.
	Etanercept	517	55	10.64	1.26	0.91	1.73	0.1609
OR4	Non-biologic systemic therapy	3148	260	8.26	1.00	.	.	.
	Etanercept	517	55	10.64	1.30	0.93	1.84	0.1285
OR5	Non-biologic systemic therapy	3148	260	8.26	1.00	.	.	.
	Etanercept	517	55	10.64	1.29	0.91	1.82	0.1465
LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	2705	235	8.69	1.00	.	.	.
	Etanercept	425	47	11.06	1.31	0.94	1.82	0.1131
OR2	Non-biologic systemic therapy	2705	235	8.69	1.00	.	.	.
	Etanercept	425	47	11.06	1.26	0.89	1.77	0.1917
OR3	Non-biologic systemic therapy	2705	235	8.69	1.00	.	.	.
	Etanercept	425	47	11.06	1.25	0.88	1.77	0.2078
OR4	Non-biologic systemic therapy	2705	235	8.69	1.00	.	.	.
	Etanercept	425	47	11.06	1.39	0.97	1.99	0.0742
OR5	Non-biologic systemic therapy	2705	235	8.69	1.00	.	.	.
	Etanercept	425	47	11.06	1.39	0.97	2.00	0.0719
91 days after LMP to 180 days after LMP (2nd trimester)								
OR1	Non-biologic systemic therapy	2238	197	8.80	1.00	.	.	.
	Etanercept	98	11	11.22	1.31	0.69	2.49	0.4107
OR2	Non-biologic systemic therapy	2238	197	8.80	1.00	.	.	.
	Etanercept	98	11	11.22	1.29	0.68	2.47	0.4363
OR3	Non-biologic systemic therapy	2238	197	8.80	1.00	.	.	.

Appendix table 35 Low birth weight, time windows change for both groups								
Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
	Etanercept	98	11	11.22	1.25	0.65	2.39	0.5059
OR4	Non-biologic systemic therapy	2238	197	8.80	1.00	.	.	.
	Etanercept	98	11	11.22	1.41	0.72	2.74	0.3124
OR5	Non-biologic systemic therapy	2238	197	8.80	1.00	.	.	.
	Etanercept	98	11	11.22	1.41	0.72	2.74	0.3145
181 days after LMP to delivery (3rd trimester)								
OR1	Non-biologic systemic therapy	2074	181	8.73	1.00	.	.	.
	Etanercept	69	7	10.14	1.18	0.53	2.62	0.6824
OR2	Non-biologic systemic therapy	2074	181	8.73	1.00	.	.	.
	Etanercept	69	7	10.14	1.17	0.53	2.60	0.7011
OR3	Non-biologic systemic therapy	2074	181	8.73	1.00	.	.	.
	Etanercept	69	7	10.14	1.17	0.52	2.60	0.7075
OR4	Non-biologic systemic therapy	2074	181	8.73	1.00	.	.	.
	Etanercept	69	7	10.14	1.23	0.52	2.94	0.6374
OR5	Non-biologic systemic therapy	2074	181	8.73	1.00	.	.	.
	Etanercept	69	7	10.14	1.21	0.51	2.88	0.6676

Compare to Appendix table 18. Both exposure groups vary in size according to time window of exposure.

Appendix table 36 Very low birth weight, time windows change for both groups

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
90 days before LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	3148	40	1.27	1.00	.	.	.
	Etanercept	517	6	1.16	0.91	0.38	2.16	0.8350
OR2	Non-biologic systemic therapy	3148	40	1.27	1.00	.	.	.
	Etanercept	517	6	1.16	0.85	0.35	2.06	0.7219
OR3	Non-biologic systemic therapy	3148	40	1.27	1.00	.	.	.
	Etanercept	517	6	1.16	0.85	0.35	2.07	0.7163
OR4	Non-biologic systemic therapy	3148	40	1.27	1.00	.	.	.
	Etanercept	517	6	1.16	0.94	0.37	2.35	0.8923
OR5	Non-biologic systemic therapy	3148	40	1.27	1.00	.	.	.
	Etanercept	517	6	1.16	0.96	0.38	2.41	0.9247
LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	2705	35	1.29	1.00	.	.	.
	Etanercept	425	6	1.41	1.09	0.46	2.61	0.8426
OR2	Non-biologic systemic therapy	2705	35	1.29	1.00	.	.	.
	Etanercept	425	6	1.41	1.09	0.44	2.67	0.8512
OR3	Non-biologic systemic therapy	2705	35	1.29	1.00	.	.	.
	Etanercept	425	6	1.41	1.04	0.41	2.59	0.9391
OR4	Non-biologic systemic therapy	2705	35	1.29	1.00	.	.	.
	Etanercept	425	6	1.41	1.19	0.46	3.07	0.7182
OR5	Non-biologic systemic therapy	2705	35	1.29	1.00	.	.	.
	Etanercept	425	6	1.41	1.21	0.47	3.15	0.6907
91 days after LMP to 180 days after LMP (2nd trimester)								
OR1	Non-biologic systemic therapy	2238	29	1.30	1.00	.	.	.
	Etanercept	98	3	3.06	2.41	0.72	8.04	0.1538
OR2	Non-biologic systemic therapy	2238	29	1.30	1.00	.	.	.
	Etanercept	98	3	3.06	2.32	0.69	7.81	0.1746
OR3	Non-biologic systemic therapy	2238	29	1.30	1.00	.	.	.
	Etanercept	98	3	3.06	2.23	0.66	7.56	0.1997
OR4	Non-biologic systemic therapy	2238	29	1.30	1.00	.	.	.
	Etanercept	98	3	3.06	2.41	0.69	8.40	0.1659
OR5	Non-biologic systemic therapy	2238	29	1.30	1.00	.	.	.
	Etanercept	98	3	3.06	2.24	0.63	7.94	0.2101
181 days after LMP to delivery (3rd trimester)								
*	Non-biologic systemic therapy	3508	45	1.28	1.00	.	.	.
	Etanercept	69	0	*	*	*	*	*

*No cases. Not possible to estimate a logistic regression model.

Compare to Appendix table 19. Both exposure groups vary in size according to time window of exposure.

Appendix table 37 Infections in the first year of life, time windows change for both groups

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
90 days before LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	3137	806	25.69	1.00	.	.	.
	Etanercept	517	161	31.14	1.31	1.07	1.60	0.0094
OR2	Non-biologic systemic therapy	3137	806	25.69	1.00	.	.	.
	Etanercept	517	161	31.14	1.07	0.87	1.32	0.5183
OR3	Non-biologic systemic therapy	3137	806	25.69	1.00	.	.	.
	Etanercept	517	161	31.14	1.07	0.87	1.32	0.5389
OR4	Non-biologic systemic therapy	3137	806	25.69	1.00	.	.	.
	Etanercept	517	161	31.14	1.02	0.81	1.27	0.8958
OR5	Non-biologic systemic therapy	3137	806	25.69	1.00	.	.	.
	Etanercept	517	161	31.14	1.01	0.80	1.27	0.9347
LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	2696	672	24.93	1.00	.	.	.
	Etanercept	425	135	31.76	1.40	1.12	1.75	0.0029
OR2	Non-biologic systemic therapy	2696	672	24.93	1.00	.	.	.
	Etanercept	425	135	31.76	1.14	0.90	1.43	0.2725
OR3	Non-biologic systemic therapy	2696	672	24.93	1.00	.	.	.
	Etanercept	425	135	31.76	1.13	0.89	1.42	0.3122
OR4	Non-biologic systemic therapy	2696	672	24.93	1.00	.	.	.
	Etanercept	425	135	31.76	1.12	0.87	1.43	0.3801
OR5	Non-biologic systemic therapy	2696	672	24.93	1.00	.	.	.
	Etanercept	425	135	31.76	1.12	0.87	1.43	0.3784
91 days after LMP to 180 days after LMP (2nd trimester)								
OR1	Non-biologic systemic therapy	2232	560	25.09	1.00	.	.	.
	Etanercept	98	26	26.53	1.08	0.68	1.71	0.7477
OR2	Non-biologic systemic therapy	2232	560	25.09	1.00	.	.	.
	Etanercept	98	26	26.53	0.92	0.58	1.47	0.7307
OR3	Non-biologic systemic therapy	2232	560	25.09	1.00	.	.	.
	Etanercept	98	26	26.53	0.93	0.58	1.49	0.7617
OR4	Non-biologic systemic therapy	2232	560	25.09	1.00	.	.	.
	Etanercept	98	26	26.53	0.99	0.60	1.61	0.9596
OR5	Non-biologic systemic therapy	2232	560	25.09	1.00	.	.	.
	Etanercept	98	26	26.53	0.98	0.60	1.61	0.9399
181 days after LMP to delivery (3rd trimester)								
OR1	Non-biologic systemic therapy	2069	506	24.46	1.00	.	.	.
	Etanercept	69	19	27.54	1.17	0.69	2.01	0.5591
OR2	Non-biologic systemic therapy	2069	506	24.46	1.00	.	.	.
	Etanercept	69	19	27.54	1.01	0.58	1.75	0.9705
OR3	Non-biologic systemic therapy	2069	506	24.46	1.00	.	.	.
	Etanercept	69	19	27.54	1.04	0.60	1.80	0.8927

Appendix table 37 Infections in the first year of life, time windows change for both groups								
Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR4	Non-biologic systemic therapy	2069	506	24.46	1.00	.	.	.
	Etanercept	69	19	27.54	1.05	0.58	1.88	0.8818
OR5	Non-biologic systemic therapy	2069	506	24.46	1.00	.	.	.
	Etanercept	69	19	27.54	1.03	0.57	1.87	0.9134

Compare to Appendix table 22. Both exposure groups vary in size according to time window of exposure.

Appendix table 38 Opportunistic infections in the first year of life, time windows change for both groups

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
90 days before LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	3137	63	2.01	1.00	.	.	.
	Etanercept	517	14	2.71	1.36	0.76	2.44	0.3066
OR2	Non-biologic systemic therapy	3137	63	2.01	1.00	.	.	.
	Etanercept	517	14	2.71	1.80	0.98	3.30	0.0591
OR3	Non-biologic systemic therapy	3137	63	2.01	1.00	.	.	.
	Etanercept	517	14	2.71	1.64	0.89	3.04	0.1140
OR4	Non-biologic systemic therapy	3137	63	2.01	1.00	.	.	.
	Etanercept	517	14	2.71	1.41	0.69	2.92	0.3483
OR5	Non-biologic systemic therapy	3137	63	2.01	1.00	.	.	.
	Etanercept	517	14	2.71	1.32	0.63	2.75	0.4610
LMP to 90 days after LMP								
OR1	Non-biologic systemic therapy	2696	55	2.04	1.00	.	.	.
	Etanercept	425	13	3.06	1.52	0.82	2.80	0.1842
OR2	Non-biologic systemic therapy	2696	55	2.04	1.00	.	.	.
	Etanercept	425	13	3.06	2.04	1.08	3.87	0.0288
OR3	Non-biologic systemic therapy	2696	55	2.04	1.00	.	.	.
	Etanercept	425	13	3.06	1.86	0.97	3.57	0.0613
OR4	Non-biologic systemic therapy	2696	55	2.04	1.00	.	.	.
	Etanercept	425	13	3.06	1.77	0.84	3.71	0.1331
OR5	Non-biologic systemic therapy	2696	55	2.04	1.00	.	.	.
	Etanercept	425	13	3.06	1.66	0.79	3.52	0.1826
91 days after LMP to 180 days after LMP (2nd trimester)								
OR1	Non-biologic systemic therapy	2232	52	2.33	1.00	.	.	.
	Etanercept	98	4	4.08	1.78	0.63	5.04	0.2742
OR2	Non-biologic systemic therapy	2232	52	2.33	1.00	.	.	.
	Etanercept	98	4	4.08	1.97	0.69	5.62	0.2025
OR3	Non-biologic systemic therapy	2232	52	2.33	1.00	.	.	.
	Etanercept	98	4	4.08	2.00	0.70	5.74	0.1975
OR4	Non-biologic systemic therapy	2232	52	2.33	1.00	.	.	.
	Etanercept	98	4	4.08	2.53	0.86	7.45	0.0924
OR5	Non-biologic systemic therapy	2232	52	2.33	1.00	.	.	.
	Etanercept	98	4	4.08	2.52	0.85	7.47	0.0953
181 days after LMP to delivery (3rd trimester)								
OR1	Non-biologic systemic therapy	2069	39	1.88	1.00	.	.	.
	Etanercept	69	2	2.90	1.55	0.37	6.57	0.5491
OR2	Non-biologic systemic therapy	2069	39	1.88	1.00	.	.	.
	Etanercept	69	2	2.90	1.72	0.40	7.30	0.4649
OR3	Non-biologic systemic therapy	2069	39	1.88	1.00	.	.	.
	Etanercept	69	2	2.90	1.56	0.36	6.73	0.5506

Appendix table 38 Opportunistic infections in the first year of life, time windows change for both groups

Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR4	Non-biologic systemic therapy	2069	39	1.88	1.00	.	.	.
	Etanercept	69	2	2.90	1.06	0.14	8.08	0.9579
OR5	Non-biologic systemic therapy	2069	39	1.88	1.00	.	.	.
	Etanercept	69	2	2.90	1.03	0.13	7.96	0.9796

Compare to Appendix table 23. Both exposure groups vary in size according to time window of exposure.

Section 3 Generalized estimating Equation (GEE)

Appendix table 39 GEE - Any major birth defect								
Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	3497	163	4.66	1.00	.	.	.
	Etanercept	425	24	5.65	1.25	0.80	1.93	0.3263
OR2	Non-biologic systemic therapy	3497	163	4.66	1.00	.	.	.
	Etanercept	425	24	5.65	1.24	0.79	1.94	0.3553
OR3	Non-biologic systemic therapy	3497	163	4.66	1.00	.	.	.
	Etanercept	425	24	5.65	1.25	0.79	1.98	0.3401
OR4	Non-biologic systemic therapy	3497	163	4.66	1.00	.	.	.
	Etanercept	425	24	5.65	0.98	.	.	Model not working
OR5	Non-biologic systemic therapy	3497	163	4.66	1.00	.	.	.
	Etanercept	425	24	5.65	0.93	.	.	Model not working

Exposure windows: Etanercept – LMP to 90 days after LMP; Non-biologic systemic therapy – 90 days before LMP to birth.

Appendix table 40 GEE - All birth defects								
Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	1997	167	8.36	1.00	.	.	.
	Etanercept	329	33	10.03	1.26	0.85	1.86	0.2442
OR2	Non-biologic systemic therapy	1997	167	8.36	1.00	.	.	.
	Etanercept	329	33	10.03	1.28	0.85	1.91	0.2329
OR3	Non-biologic systemic therapy	1997	167	8.36	1.00	.	.	.
	Etanercept	329	33	10.03	1.26	0.84	1.89	0.2620
OR4	Non-biologic systemic therapy	1997	167	8.36	1.00	.	.	.
	Etanercept	329	33	10.03	1.08	.	.	Model not working
OR5	Non-biologic systemic therapy	1997	167	8.36	1.00	.	.	.
	Etanercept	329	33	10.03	1.03	.	.	Model not working

Only data from Sweden and Denmark are included, since no information about minor birth defects were available from Finland.

Exposure windows: Etanercept – LMP to 90 days after LMP; Non-biologic systemic therapy – 90 days before LMP to birth.

Appendix table 41 GEE - Minor birth defects								
Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	1997	90	4.51	1.00	.	.	.
	Etanercept	329	14	4.26	0.98	0.55	1.74	0.9448
OR2	Non-biologic systemic therapy	1997	90	4.51	1.00	.	.	.
	Etanercept	329	14	4.26	0.99	0.55	1.76	0.9598
OR3	Non-biologic systemic therapy	1997	90	4.51	1.00	.	.	.
	Etanercept	329	14	4.26	0.96	0.54	1.69	0.8785
OR4	Non-biologic systemic therapy	1997	90	4.51	1.00	.	.	.
	Etanercept	329	14	4.26	0.92	.	.	Model not working
OR5	Non-biologic systemic therapy	1997	90	4.51	1.00	.	.	.
	Etanercept	329	14	4.26	0.91	.	.	Model not working

Only data from Sweden and Denmark are included, since no information about minor birth defects were available from Finland.

Exposure windows: Etanercept – LMP to 90 days after LMP; Non-biologic systemic therapy – 90 days before LMP to birth.

Appendix table 42 GEE - Preterm birth (<37 weeks)								
Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	3508	347	9.89	1.00	.	.	.
	Etanercept	522	60	11.49	1.11	0.77	1.60	0.5711
OR2	Non-biologic systemic therapy	3508	347	9.89	1.00	.	.	.
	Etanercept	522	60	11.49	1.07	0.74	1.55	0.7297
OR3	Non-biologic systemic therapy	3508	347	9.89	1.00	.	.	.
	Etanercept	522	60	11.49	1.05	0.72	1.52	0.8073
OR4	Non-biologic systemic therapy	3508	347	9.89	1.00	.	.	.
	Etanercept	522	60	11.49	1.09	.	.	Model not working
OR5	Non-biologic systemic therapy	3508	347	9.89	1.00	.	.	.
	Etanercept	522	60	11.49	1.07	.	.	Model not working

Exposure windows: Etanercept – 90 days before LMP to birth; Non-biologic systemic therapy – 90 days before LMP to birth.

Appendix table 43 GEE - Very preterm birth (<32 weeks)								
Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	3508	48	1.37	1.00	.	.	.
	Etanercept	522	5	0.96	0.62	0.11	3.55	0.5924
OR2	Non-biologic systemic therapy	3508	48	1.37	1.00	.	.	.
	Etanercept	522	5	0.96	0.58	0.09	3.62	0.5594
OR3	Non-biologic systemic therapy	3508	48	1.37	1.00	.	.	.

Appendix table 43 GEE - Very preterm birth (<32 weeks)								
Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
	Etanercept	522	5	0.96	0.57	0.10	3.38	0.5331
OR4	Non-biologic systemic therapy	3508	48	1.37	1.00	.	.	.
	Etanercept	522	5	0.96	0.72	.	.	Model not working
OR5	Non-biologic systemic therapy	3508	48	1.37	1.00	.	.	.
	Etanercept	522	5	0.96	0.75	.	.	Model not working

Exposure windows: Etanercept – 90 days before LMP to birth; Non-biologic systemic therapy – 90 days before LMP to birth.

Appendix table 44 GEE - Small for gestational age								
Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	3508	118	3.36	1.00	.	.	.
	Etanercept	522	26	4.98	1.48	0.95	2.31	0.0838
OR2	Non-biologic systemic therapy	3508	118	3.36	1.00	.	.	.
	Etanercept	522	26	4.98	1.54	0.98	2.43	0.0605
OR3	Non-biologic systemic therapy	3508	118	3.36	1.00	.	.	.
	Etanercept	522	26	4.98	1.49	0.95	2.35	0.0838
OR4	Non-biologic systemic therapy	3508	118	3.36	1.00	.	.	.
	Etanercept	522	26	4.98	1.36	0.83	2.21	0.2229
OR5	Non-biologic systemic therapy	3508	118	3.36	1.00	.	.	.
	Etanercept	522	26	4.98	1.30	0.80	2.13	0.2860

Exposure windows: Etanercept – 90 days before LMP to birth; Non-biologic systemic therapy – 90 days before LMP to birth.

Appendix table 45 GEE - Low birth weight (<=2500 g)								
Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	3508	286	8.15	1.00	.	.	.
	Etanercept	522	55	10.54	1.26	0.87	1.84	0.2186
OR2	Non-biologic systemic therapy	3508	286	8.15	1.00	.	.	.
	Etanercept	522	55	10.54	1.25	0.86	1.82	0.2440
OR3	Non-biologic systemic therapy	3508	286	8.15	1.00	.	.	.
	Etanercept	522	55	10.54	1.22	0.83	1.79	0.3180
OR4	Non-biologic systemic therapy	3508	286	8.15	1.00	.	.	.
	Etanercept	522	55	10.54	1.29	0.86	1.95	0.2227
OR5	Non-biologic systemic therapy	3508	286	8.15	1.00	.	.	.
	Etanercept	522	55	10.54	1.27	0.85	1.92	0.2480

Exposure windows: Etanercept – 90 days before LMP to birth; Non-biologic systemic therapy – 90 days before LMP to birth.

Appendix table 46 GEE - Very low birth weight (<=1500 g)								
Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	3508	45	1.28	1.00	.	.	.
	Etanercept	522	6	1.15	1.01	0.39	2.62	0.9828
OR2	Non-biologic systemic therapy	3508	45	1.28	1.00	.	.	.
	Etanercept	522	6	1.15	0.97	0.37	2.54	0.9513
OR3	Non-biologic systemic therapy	3508	45	1.28	1.00	.	.	.
	Etanercept	522	6	1.15	0.94	0.36	2.48	0.9069
OR4	Non-biologic systemic therapy	3508	45	1.28	1.00	.	.	.
	Etanercept	522	6	1.15	0.95	.	.	Model not working
OR5	Non-biologic systemic therapy	3508	45	1.28	1.00	.	.	.
	Etanercept	522	6	1.15	0.98	.	.	Model not working

Exposure windows: Etanercept – 90 days before LMP to birth; Non-biologic systemic therapy – 90 days before LMP to birth.

Appendix table 47 GEE - Infectious pathogens in first year of life								
Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	3497	910	26.02	1.00	.	.	.
	Etanercept	522	162	31.03	1.28	1.03	1.57	0.0227
OR2	Non-biologic systemic therapy	3497	910	26.02	1.00	.	.	.
	Etanercept	522	162	31.03	1.06	0.85	1.32	0.6130
OR3	Non-biologic systemic therapy	3497	910	26.02	1.00	.	.	.
	Etanercept	522	162	31.03	1.06	0.85	1.32	0.5871
OR4	Non-biologic systemic therapy	3497	910	26.02	1.00	.	.	.
	Etanercept	522	162	31.03	1.00	0.79	1.26	0.9838
OR5	Non-biologic systemic therapy	3497	910	26.02	1.00	.	.	.
	Etanercept	522	162	31.03	0.99	0.79	1.26	0.9624

Exposure windows: Etanercept – 90 days before LMP to birth; Non-biologic systemic therapy – 90 days before LMP to birth.

Appendix table 48 GEE - opportunistic infections pathogens in first year of life								
Statistic Model	Group	N	Events	(%)	OR	95% CI lower limit	95% CI upper limit	P-value
OR1	Non-biologic systemic therapy	3497	72	2.06	1.00	.	.	.
	Etanercept	522	14	2.68	1.32	0.73	2.37	0.3582
OR2	Non-biologic systemic therapy	3497	72	2.06	1.00	.	.	.
	Etanercept	522	14	2.68	1.69	0.90	3.18	0.1017
OR3	Non-biologic systemic therapy	3497	72	2.06	1.00	.	.	.
	Etanercept	522	14	2.68	1.64	0.86	3.12	0.1341
OR4	Non-biologic systemic therapy	3497	72	2.06	1.00	.	.	.
	Etanercept	522	14	2.68	1.41	0.67	2.98	0.3694
OR5	Non-biologic systemic therapy	3497	72	2.06	1.00	.	.	.
	Etanercept	522	14	2.68	1.33	0.62	2.87	0.4699

Exposure windows: Etanercept – 90 days before LMP to birth; Non-biologic systemic therapy – 90 days before LMP to birth.

Appendix figure 1. Flowchart of participants in each group of analyses.

Compare to figure 1 in report



