Appendix

A1 Estimation of natural history disability progression matrix

Placebo arm of EXPAND trial only report transition probabilities from EDSS 1 to EDSS 7 (Table A1-2). A clubbed non-normalized TP matrix obtained from EXPAND (EDSS 1 to 7) and London Ontario database (EDSS 0 and EDSS 8 to 10) is reported in Table A1-3.

Normalization was done to club TP matrix obtained from EXPAND and London Ontario database. For example, Table A1-4 represents non-normalized natural history transition from EDSS 3 to other EDSS states. Table A1-5 represents intermediate calculations representing normalization of transition probabilities from EDSS 3 to other EDSS states, and Table A1-6 represents the results of these calculations. Similar to Table A1-6, all other probabilities are normalised and presented in Table A1-7.

Table A1-1: Natural history TP matrix from London Ontario database (Mauskopf et al. 2015 (1))

EDSS: From/To	0	1	2	3	4	5	6	7	8	9	10	Row sum
0	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000
1	0.0000	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000
2	0.0000	0.0000	0.4550	0.3750	0.0991	0.0412	0.0270	0.0020	0.0007	0.0000	0.0000	1.0000
3	0.0000	0.0000	0.0000	0.5630	0.2803	0.0885	0.0610	0.0053	0.0019	0.0000	0.0000	1.0000
4	0.0000	0.0000	0.0000	0.0000	0.4821	0.2808	0.2178	0.0131	0.0061	0.0000	0.0000	1.0000
5	0.0000	0.0000	0.0000	0.0000	0.0000	0.3396	0.5966	0.0408	0.0228	0.0002	0.0000	1.0000
6	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.8701	0.0810	0.0484	0.0005	0.0000	1.0000
7	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.6446	0.3490	0.0064	0.0000	1.0000
8	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.9916	0.0084	0.0000	1.0000
9	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000	0.0000	1.0000
10	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000	1.0000

EDSS = expanded disability status scale; TP= transition probabilities

Table A1-2: Natural history TP matrix from EXPAND placebo arm

EDSS: From/To	0	1	2	3	4	5	6	7	8	9	10	Row sum
0												
1	0.0000	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000				1.0000
2	0.0000	0.0000	0.5759	0.2793	0.1108	0.0271	0.0067	0.0002				1.0000
3	0.0000	0.0000	0.0784	0.4294	0.3297	0.1186	0.0424	0.0015				1.0000

4	0.0000	0.0000	0.0155	0.1641	0.4152	0.2521	0.1465	0.0066				1.0000
5	0.0000	0.0000	0.0029	0.0459	0.1959	0.3172	0.4119	0.0263				1.0000
6	0.0000	0.0000	0.0001	0.0028	0.0196	0.0711	0.8251	0.0813				1.0000
7	0.0000	0.0000	0.0000	0.0006	0.0056	0.0287	0.5148	0.4503				1.0000
8												
9												
10												

EDSS = expanded disability status scale; TP= transition probabilities

Table A1-3: Clubbed non-normalized natural history TP matrix

EDSS: From/To	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Row sum**
0	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	≠1
1	0.0000	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	≠1
2	0.0000	0.0000	0.5759	0.2793	0.1108	0.0271	0.0067	0.0002	0.0007	0.0000	0.0000	≠1
3	0.0000	0.0000	0.0784	0.4294	0.3297	0.1186	0.0424	0.0015	0.0019	0.0000	0.0000	≠1
4	0.0000	0.0000	0.0155	0.1641	0.4152	0.2521	0.1465	0.0066	0.0061	0.0000	0.0000	≠1
5	0.0000	0.0000	0.0029	0.0459	0.1959	0.3172	0.4119	0.0263	0.0228	0.0002	0.0000	≠1
6	0.0000	0.0000	0.0001	0.0028	0.0196	0.0711	0.8251	0.0813	0.0484	0.0005	0.0000	≠1
7	0.0000	0.0000	0.0000	0.0006	0.0056	0.0287	0.5148	0.4503	0.3490	0.0064	0.0000	≠1
8	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.9916	0.0084	0.0000	≠1
9	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000	0.0000	≠1
10	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000	≠1

EDSS = expanded disability status scale: TP= transition probabilities

Table A1-4: Non-normalized natural history transition from EDSS 3 to other EDSS states

EDSS: From/To	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Row sum**
3	0.0000	0.0000	0.0784	0.4294	0.3297	0.1186	0.0424	0.0015	0.0019	0.0000	0.0000	≠1

EDSS = expanded disability status scale

Table A1-5: Intermediate calculations representing normalization of transition probabilities from EDSS 3 to other EDSS states

EDSS: From/ To	0	1	2	3	4	5	6	7	8	9	10
EDSS: 3	=0.0000*(1-SUM(0.0019 + 0.0000 + 0.0000))	=0.0000*(1-SUM(0.0019 + 0.0000 + 0.0000))	=0.0784*(1-SUM(0.0019 + 0.0000 + 0.0000))	=0.4294*(1-SUM(0.0019 + 0.0000 + 0.0000))	=0.3297*(1-SUM(0.0019 + 0.0000 + 0.0000))	=0.1186*(1-SUM(0.0019 + 0.0000 + 0.0000))	=0.0424*(1-SUM(0.0019 + 0.0000 + 0.0000))	=0.0015*(1-SUM(0.0019 + 0.0000 + 0.0000))	0.0019	0.0000	0.0000

EDSS = expanded disability status scale

Table A1-6: Normalized transition probabilities from EDSS 3 to other EDSS states

EDSS: From/To	0	1	2	3	4	5	6	7	8	9	10	Row sum
3	**0.0000**	**0.0000**	**0.0782**	**0.4286**	**0.3291**	**0.1184**	**0.0423**	**0.0015**	0.0019	0.0000	0.0000	1.0000

EDSS = expanded disability status scale

Table *A1-7*: Normalized natural history transition probabilities matrices from EXPAND and London Ontario database used in the CE model

EDSS: From/ To	0	1	2	3	4	5	6	7	8	9	10
0	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
1	**0.0000**	**1.0000**	**0.0000**	**0.0000**	**0.0000**	**0.0000**	**0.0000**	**0.0000**	0.0000	0.0000	0.0000
2	**0.0000**	**0.0000**	**0.5755**	**0.2791**	**0.1107**	**0.0271**	**0.0067**	**0.0002**	0.0007	0.0000	0.0000
3	**0.0000**	**0.0000**	**0.0782**	**0.4286**	**0.3291**	**0.1184**	**0.0423**	**0.0015**	0.0019	0.0000	0.0000
4	**0.0000**	**0.0000**	**0.0154**	**0.1631**	**0.4127**	**0.2506**	**0.1456**	**0.0066**	0.0061	0.0000	0.0000
5	**0.0000**	**0.0000**	**0.0028**	**0.0448**	**0.1914**	**0.3099**	**0.4024**	**0.0257**	0.0228	0.0002	0.0000
6	**0.0000**	**0.0000**	**0.0001**	**0.0027**	**0.0186**	**0.0676**	**0.7847**	**0.0773**	0.0484	0.0005	0.0000
7	**0.0000**	**0.0000**	**0.0000**	**0.0004**	**0.0036**	**0.0185**	**0.3318**	**0.2903**	0.3490	0.0064	0.0000
8	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.9916	0.0084	0.0000
9	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000	0.0000
10	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000

EDSS = expanded disability status scale * All bold and underlined transition probabilities are obtained from EXPAND trial placebo arm data using multi-state model approach. All other transition probabilities are taken from London Ontario database SPMS-SPMS transition data (1, 2).

A2: Application of treatment effect on transition probabilities

Competing risk approach was used to derive treatment adjusted TP matrix. Following steps are considered in applying competing risk approach:

- All transitions are categorized to disability progression (transitions to a higher EDSS health state) and no-disability progression (transitions to same or lower EDSS health state)
- All EDSS forward transition probabilities are converted to transition rates
- Treatment effect is applied as hazard ratio to rate of progression (all EDSS forward progression states together)
  Treatment adjusted disability progression=1-(1-sum of all disability progression transition probabilities)^hazard rate of 6-month CDP for treatment versus placebo
  Treatment adjusted no-disability progression=1-Treatment adjusted disability progression
- Adjusted rate of progression converted back to adjusted probability of progression. Redistribute the treatment adjusted disability progression probability based on the EDSS wise unadjusted disability progression probabilities
- Adjusted probability of progression is used to adjust no-progression transition probabilities. Redistribute the calculated treatment adjusted no-disability progression probability based on the EDSS wise unadjusted no-disability progression probabilities
- Although no direct treatment effect is applied to EDSS backward transitions, there is chance of increase in EDSS backward transition probabilities
- Treatment adjusted TP matrix for siponimod (when interferon beta-1a is selected as comparator for CE model) is reported in Table A2-1 below:

Table A2-1: Treatment adjusted TP matrix for siponimod (when interferon beta-1a is selected as comparator for CE model)

EDSS: From/To	0	1	2	3	4	5	6	7	8	9	10	Row sum
0	1.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.000
1	0.000	1.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.000
2	0.000	0.000	0.767	0.153	0.061	0.015	0.004	0.000	0.000	0.000	0.000	1.000
3	0.000	0.000	0.111	0.610	0.186	0.067	0.024	0.001	0.001	0.000	0.000	1.000
4	0.000	0.000	0.020	0.214	0.542	0.137	0.079	0.004	0.003	0.000	0.000	1.000
5	0.000	0.000	0.004	0.061	0.261	0.423	0.223	0.014	0.013	0.000	0.000	1.000

6	0.000	0.000	0.000	0.003	0.020	0.073	0.842	0.038	0.024	0.000	0.000	1.000
7	0.000	0.000	0.000	0.000	0.005	0.023	0.417	0.365	0.187	0.003	0.000	1.000
8	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.996	0.004	0.000	1.000
9	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.000	0.000	1.000
10	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.000	1.000

EDSS = expanded disability status scale; TP= transition probabilities

Application of treatment effect on natural history disability progression is showed in example below:

Application of treatment effect for EDSS 4 to other states

1. Natural history EDSS 4 progression (Table A2-2) is as follows:

Table A2-2: Natural history EDSS 4 transitions to other EDSS states

	0	1	2	3	4	5	6	7	8	9	10
EDSS 4	0.000	0.000	0.015	0.163	0.413	0.251	0.146	0.007	0.006	0.000	0.000

2. Classify and sum together as progression and no progression:
    a. Progression (EDSS 5 to 10): 0.591
    b. No-progression (EDSS 0 to 4): 0.409
3. Assess treatment adjusted disability progression and no-disability progression probability for siponimod vs BSC (when Extavia is selected as comparator for CE model) as follows:
   Treatment adjusted disability progression probability =1-(1-0.409)^0.48 =0.223
   Treatment adjusted no-disability progression probability =1-0.223 =0.777
4. Redistribute the calculated treatment adjusted disability progression probability based on the EDSS wise unadjusted disability progression probabilities (Table A2-3 and Table A2-4)

Table A2-3: Intermediate calculations to estimate treatment adjusted disability progression probabilities

	5	6	7	8	9	10
EDSS 4	=(0.251/0.591)*0.223	=(0.146/0.591)*0.223	=(0.007/0.591)*0.223	=(0.006/0.591)*0.223	=(0.000/0.591)*0.223	=(0.000/0.591)*0.223

EDSS = expanded disability status scale

Table A2-4: Treatment adjusted disability progression probabilities from EDSS 4 to EDSS 5 to 10

	5	6	7	8	9	10
EDSS 4	0.137	0.079	0.004	0.003	0.000	0.000

EDSS = expanded disability status scale

5. Similarly redistribute the calculated treatment adjusted no-disability progression probability based on the EDSS wise unadjusted no-disability progression probabilities (Table A2-5)

Table A2-5: Intermediate calculations to estimate treatment adjusted no-disability progression probabilities

	0	1	2	3	4
EDSS 4	=(0.000/0.409)*0.777	=(0.000/0.409)*0.777	=(0.015/0.409)*0.777	=(0.163/0.409)*0.777	=(0.413/0.409)*0.777

Table A2-6: Treatment adjusted no-disability progression probabilities from EDSS 4 to EDSS 0 to 4

	0	1	2	3	4
EDSS 4	0.000	0.000	0.020	0.214	0.542

EDSS = expanded disability status scale

6. Together the treatment adjusted probabilities (Table A2-7) is as follows:

Table A2-7: Treatment adjusted transition probabilities from EDSS 4 to other EDSS states

	0	1	2	3	4	5	6	7	8	9	10
EDSS 4	0.000	0.000	0.020	0.214	0.542	0.137	0.079	0.004	0.003	0.000	0.000

EDSS = expanded disability status scale

A3

Adverse event data presented in this section only details parameter values for the base-case analysis (not for the scenario analyses which explored natalizumab and interferon beta-1b as comparators)

Table A3-1: Proportion of patients in each treatment strategy affected by adverse event

Adverse event	Siponimod*	Interferon beta-1a**
Alanine aminotransferase level increased	2.01%	0.00%
Arthralgia	1.51%	6.20%
Back pain	2.07%	4.50%
Bronchitis	0.00%	3.50%
Depression	1.51%	6.50%
Diarrhoea	2.17%	0.00%
Dizziness	2.33%	0.00%
Fall	4.04%	0.00%
Fatigue	3.13%	7.70%
Headache	5.08%	15.00%
Hypertension	3.62%	0.00%
Influenza	2.27%	0.00%
Influenza-like illness	0.00%	21.40%
Infusion related reaction	0.00%	9.70%
Injection site pain	0.00%	20.80%
Insomnia	0.00%	4.60%
Nasopharyngitis	4.74%	10.20%
Nausea	2.30%	0.00%
Pain in extremity	1.85%	0.00%
PML	0.00%	0.00%
Sinusitis	0.00%	5.40%

Upper respiratory tract infection	2.84%	10.50%
Urinary tract infection	4.21%	12.10%

*Sourced from EXPAND trial; only siponimod-treated patients during the first 18 months of trial. **Sourced from NICE ocrelizumab technology appraisal; https://www.nice.org.uk/guidance/ta533/

Table A3-2: Disutility and duration (number of days) of adverse events

Adverse event	Non-serious		Serious		Source
	Disutility	Duration	Disutility	Duration	
Alanine aminotransferase level increased	0	28	0	28	Daclizumab RRMS NICE submission
Arthralgia	0.25	10.5	0.25	24.5	Ocrelizumab RRMS NICE submission
Back pain	0.25	10.5	0.5	24.5	Ocrelizumab RRMS NICE submission
Bronchitis	0.01	14	0.01	14	Ocrelizumab RRMS NICE submission
Depression	0.165	75	0.56	365	Ocrelizumab RRMS NICE submission
Diarrhoea	0	10.5	0	24.5	Dimethyl fumarate RRMS NICE submission
Dizziness	0	7	0	14	Daclizumab RRMS NICE submission
Fall	0	7	0	14	Assumed same as dizziness - Daclizumab RRMS NICE submission
Fatigue	0	182.5	0	182.5	Ocrelizumab RRMS NICE submission
Headache	0.14	10.5	0.493	24.5	Ocrelizumab RRMS NICE submission
Hypertension	0	1	0	1	Assumption
Influenza	0.63	8.75	0.67	8.75	Dimethyl fumarate RRMS NICE submission
Influenza-like illness	0.08	1	0.08	1	Ocrelizumab RRMS NICE submission
Infusion related reaction	0.0002	1	0.0002	1	Ocrelizumab RRMS NICE submission
Injection site pain	0	7	0	7	Ocrelizumab RRMS NICE submission
Insomnia	0.0002	1	0.0002	1	Ocrelizumab RRMS NICE submission
Nasopharyngitis	0	7	0	14	Ocrelizumab RRMS NICE submission
Nausea	0	10.5	0	24.5	Dimethyl fumarate RRMS NICE submission
Pain in extremity	0.25	7	0.25	28	Daclizumab RRMS NICE submission
PML	0.3	365	0.3	365	Ocrelizumab RRMS NICE submission
Sinusitis	0	1	0	1	Ocrelizumab RRMS NICE submission
Upper respiratory tract infection	0.2	7	0.2	14	Ocrelizumab RRMS NICE submission
Urinary tract infection	0.1	5	0.1	5	Ocrelizumab RRMS NICE submission

*NICE= National Institute for Health and Care Excellence; RRMS= relapse remitting multiple sclerosis. NICE guidance documents available from https://www.nice.org.uk/guidance . Assumed 93% of events non-serious; 7% of events serious; based on NICE ocrelizumab submission

Table A3-3: Adverse event unit costs

AE	Non-serious	Serious	Source
Alanine aminotransferase level increased	0.00	89.05	Tarmed (00.0010,00.0020,00.0030), 30min
Arthralgia	0.95	232.96	SL und Tarmed (05.0010 und 00.0445*15min)
Back pain	0.00	604.45	Tarmed (05.0010) und Physiotherapietarife (7301+7350)
Bronchitis	88.35	88.35	Tarmed (00.0010,00.0020,00.0030), SL
Depression	2136.76	8445.86	Tarmed (00.0010,00.0020,00.0030; 02.0010,02.0020 *50min), SL
Diarrhoea	0.00	0.00	Assumption
Dizziness	0.00	327.00	https://datenspiegel60.swissdrg.org/drgs/57dfab352dbf0fedbf0001a9?locale=en [Minimum; 15.02.2019] D61 B - Schwindel und Taumel
Fall	0.00	327.00	https://datenspiegel60.swissdrg.org/drgs/57dfab352dbf0fedbf0001a9?locale=en [Minimum; 15.02.2019] D61 B - Schwindel und Taumel
Fatigue	0.00	441.78	Tarmed (00.0010,00.0020,00.0030), SL
Headache	0.00	221.87	Tarmed (00.0010,00.0020,00.0030,05.0010)
Hypertension	0.00	0.00	Assumption
Influenza	34.22	74.71	Tarmed (00.0010,00.0020,00.0030); https://www.adlershop.ch/p/6885/tamiflu-kapseln-75mg-10-stueck [14.02.2019], https://www.adlershop.ch/p/22644/relenza-disk-5mg-20-dos[14.02.2019]
Influenza-like illness	0.00	0.00	Assumption
Infusion related reaction	0.00	0.00	Assumption
Injection site pain	0.00	40.48	Tarmed (00.0010,00.0020,00.0030)
Insomnia	0.00	0.00	Assumption
Nasopharyngitis	0.00	40.48	Tarmed (00.0010,00.0020,00.0030)
Nausea	0.00	40.48	Tarmed (00.0010,00.0020,00.0030)
Pain in extremity	0.00	0.00	Assumption
PML	14735.95	14735.95	https://datenspiegel60.swissdrg.org/drgs/57dfab352dbf0fedbf000119?locale=en [oberes Quartil; 15.02.20198] B85D - Degenerative Krankheiten des Nervensystems

Sinusitis	0.00	0.00	Assumption
Upper respiratory tract infection	40.48	40.48	Tarmed (00.0010,00.0020,00.0030)
Urinary tract infection	10.28	5504.40	SL (250mg), https://datenspiegel60.swissdrg.org/drgs/57dfab382dbf0fedbf0005ac?locale=en [13.02.2019]

*SL=Spezialitaetenliste. Tarmed costs obtained from https://www.tarmed-browser.ch/de in February 2019. SL costs obtained from http://www.spezialitaetenliste.ch/ in February 2019. **Assumed 93% of events non-serious; 7% of events serious; based on National Institute for Health and Care Excellence (NICE) ocrelizumab submission available from https://www.nice.org.uk/guidance/ta585 .

A4.

Table A4-1: Administration and monitoring costs for siponimod

Siponimod			**Annual Resource Use (Units)**		**Annual costs (CHF)**	
Resource	Unit Cost (CHF)	Unit cost source	First Year	Subsequent Year	First Year	Subsequent Year
Oral administration	0.00	Assumption	0.00	0.00	0.00	0.00
CYP2C9 genotype testing	227.05	Tarmed and Analysenliste	1.00	0.00	227.05	0.00
Neurology visit	270.44	Tarmed (00.0010,00.0020,00.0030), 30min, Tarmed (05.0010)	1.00	0.00	270.44	0.00
Neurology visit (follow-up)	97.14	Tarmed (00.0515), 15min	2.00	2.00	194.29	194.29
Cardiology visit	89.05	Tarmed (00.0010, 00.0020,00.0030), 30min	1.00	0.00	89.05	0.00
Ophthalmology visit	89.05	Tarmed (00.0010,00.0020,00.0030), 30min [treatment initiation]	1.00	0.00	89.05	0.00
Varicella zoster antibodies test	29.00	Analysenliste 3177.00	1.00	0.00	29.00	0.00
Full blood count	9.00	Analysenliste 1371.00	4.00	4.00	36.00	36.00
Electrocardiogram	138.25	Tarmed 17.0090 Belastungs EKG	1.00	0.00	138.25	0.00
Liver Function	29.74	Tarmed 19.0170 Atemtest mit Harnstoff zum Nachweis von Heliobacter pylori durch nichtärztliches Personal	1.00	1.00	29.74	29.74
Pregnancy test	17.50	Analysenliste 1425.00	1.00	0.00	17.50	0.00
Total Cost					1237.37	260.03

*Tarmed costs obtained from https://www.tarmed-browser.ch/de in February 2019.

Table A4-2: Administration and monitoring costs for interferon beta-1a

Interferon beta-1a			**Annual Resource Use (Units)**		**Annual costs (CHF)**	
Resource	Unit Cost (CHF)	Unit cost source	First Year	Subsequent Year	First Year	Subsequent Year
Assisted administration	119.11	Tarmed (00.0750, 00.1370) for 60 min	1.00	0.00	119.11	0.00
Neurology Visit	270.44	Tarmed (00.0010,00.0020,00.0030), 30min, Tarmed (05.0010)	1.00	0.00	270.44	0.00
Neurology visit (follow-up)	97.14	Tarmed (00.0515), 15min	2.00	1.00	194.29	97.14
Full Blood Count	9.00	AL 1371.00	4.00	2.00	36.00	18.00
Liver Function	29.74	Tarmed 19.0170 Atemtest mit Harnstoff zum Nachweis von Heliobacter pylori durch nichtärztliches Personal	4.00	2.00	118.95	59.47
Thyroid function test	18.00	AL 1718.10, 1721.00	1.00	0.00	18.00	0.00
Renal function test	7.50	AL 1509.00, 1406.00, 1634.00	4.00	2.00	30.00	15.00
Total Cost					903.79	189.62

*AL=Analysenliste. **Tarmed costs obtained from https://www.tarmed-browser.ch/de in February 2019. Analysenliste costs obtained from https://www.bag.admin.ch/bag/de/home/versicherungen/krankenversicherung/krankenversicherung-leistungen-tarife/Analysenliste.html in February 2019.

A5: Budget impact analysis

The role of cost-effectiveness analysis is to assess the value for money of an intervention. However, it does not indicate to a funder the actual costs of adopting a new intervention that will impact his or her current and future budget projections. In order to generate such estimates, we performed a budget impact analysis (BIA).

Methods

We undertook a budget impact analysis to estimate the impact of introducing siponimod into the Swiss health care market, for the years 2021, 2022 and 2023. In the analysis, we included the costs of drug acquisition, administration and monitoring, and adverse events management. Unlike the cost-effectiveness analysis described in this paper, the BIA did not consider disease management and relapse costs. Apart from this restriction, a Swiss health insurance system perspective was adopted. This perspective aims to include the costs of all services principally reimbursable by the Swiss compulsory health insurance, irrespective of the actual payer.

As presented in Table A5-1, we estimated the current distribution of treatments for active SPMS in Switzerland using a combination of market research with 41 Swiss neurologists on DMT use in RRMS patients demonstrating a transition to SPMS (and considered to be a reasonable proxy for active SPMS subtype) conducted by Novartis, and IQVIA sales data. We were able to ascertain the distribution for 99.1% of patients across ten treatments or no treatment (those recorded as receiving "no treatment" were assumed to still be receiving best supportive care in clinical practice). In addition, 0.9% of patients were reported to receive a treatment in the "other" category; we equally assigned these patients to further treatment options available in Switzerland, namely cladribine and mitoxantrone. For the world with siponimod, we assumed 90% of siponimod patients would be on a dose of 2 mg per day and 10% on a dose of 1 mg per day, and also assumed in each year that market share for alternative treatments to siponimod would be reduced from their estimates in the world without siponimod by the estimate percentage uptake of siponimod for that year.

Table A5-1: Projected distribution of treatments in worlds with and without (w/o) siponimod

	World w/o siponimod	World with siponimod		
Treatment year	**2021/2022/2023**	**2021**	**2022**	**2023**
Siponimod	Not applicable	8.0%	17.0%	25.0%
Siponimod (1 mg/day)	Not applicable	0.8%	1.7%	2.5%
Siponimod (2 mg/day)	Not applicable	7.2%	15.3%	22.5%
Alemtuzumab	0.1%	0.1%	0.1%	0.1%
Cladribine	0.5%	0.4%	0.4%	0.3%
Dimethyl fumarate	10.9%	10.0%	9.0%	8.2%
Fingolimod	21.0%	19.3%	17.4%	15.8%
Glatiramer acetate	6.6%	6.1%	5.5%	5.0%
Interferon beta-1a (Avonex®)	7.0%	6.4%	5.8%	5.3%
Interferon beta-1a (Rebif®)	4.9%	4.5%	4.1%	3.7%
Interferon beta-1b	5.0%	4.6%	4.2%	3.8%
Mitoxantrone	0.5%	0.4%	0.4%	0.3%
Natalizumab	8.7%	8.0%	7.2%	6.5%
Ocrelizumab	17.3%	15.9%	14.4%	13.0%
Peginterferon beta-1a	2.1%	1.9%	1.7%	1.6%
Teriflunomide	4.1%	3.8%	3.4%	3.1%
Best supportive care	11.4%	10.5%	9.5%	8.6%
Total	100.0%	100.0%	100.0%	100.0%

We estimated the active SPMS population eligible for siponimod treatment using demographic and epidemiological data for the current and projected future Swiss adult population, a MS prevalence estimate of 180.5 per 100,000 general population(3), an annual MS incidence of 9.43 per 100,000 population(4), an annual MS-related death incidence of 2.17 per 100,000 population(5), a proportion of 30% of MS patients having SPMS based on an unpublished market research survey among 41 Swiss neurologists commissioned by Novartis, and a proportion of 36% of SPMS patients having active SPMS based on the distribution of patients in the EXPAND trial(6). It was assumed that the siponimod uptake rate would be 8% of active SPMS patients treated in clinical practice in 2021, 17% in 2022 and 25% in 2023. Resulting predicted numbers of siponimod-treated patients are presented in Table A5-2.

Table A5-2: Number of predicted patients in Switzerland used for the budget impact analysis

	2021	2022	2023
Number of MS patients	18,444	19,082	19,724
Number of active SPMS patients	1,984	2,053	2,122
Number of siponimod treated patients	159	349	530

We used the list prices (public prices) of siponimod of CHF 62.69 for 1 mg dose and CHF 62.83 for 2 mg dose. Drug acquisition unit costs of the other DMTs and best supportive care were obtained from Spezialitätenliste in April 2020.(7) Dosage and administration frequencies of DMTs were based on their treatment indications for MS in Switzerland (8). Resource use for administration and monitoring in the first year and every subsequent year were estimated using the recent NICE manufacturer submissions for the relevant DMTs (available from https://www.nice.org.uk/guidance website) and summary of product characteristics of each included DMT, and are specified in full in the Novartis internal report for the UK budget impact analysis (9). However, some subsequent adjustments were made based on Swiss clinical expert feedback we obtained. These adjustments were three neurologist visits (as opposed to two visits) in the first year and two visits in subsequent years, the inclusion of HIV, tuberculosis und hepatitis screening at the onset of treatment for each DMT, and the exclusion of MS nurse visits as this is uncommon in Switzerland. Associated unit costs of each resource item were obtained from Swiss data sources used for the cost-effectiveness model and are specified in appendix A4.

For the unit costs of adverse events, we used resource use data from the NICE ocrelizumab submission (2) and unit costs of resource items derived from Tarmed.(10) A Swiss unit cost was not available for the adverse event cost of plegridy. Here, we converted the British cost in GBP obtained from NICE technology appraisal 527 (11), to CHF by multiplying by 2.04 (based on the purchasing power parity factor between the two countries).(12) Incidence of adverse events in the first year and every subsequent year were obtained from a range of studies (further details are provided in the UK budget impact model report (9)).

Results

We projected that 159 active SPMS patients would be on siponimod treatment in 2021, 349 patients in 2022 and 530 patients in 2023. The analysis found higher drug acquisition costs in a world with siponimod caused by siponimod drug acquisition costs of CHF 23,817,856 (CHF 3,641,660 in 2021, CHF 8,006,144 in 2022 and CHF 12,170,050 in 2023; Table A5-3) The majority of these costs would be offset by the reduction in drug acquisition costs of currently used DMTs in this population. To an extent, costs would be offset by lower drug administration and monitoring costs and lower adverse event management costs. Over the first three years, siponimod was predicted to generate a net budget impact (higher overall costs) of CHF 2,177,021 (CHF 308,342 in 2021, CHF 697,246 in 2022, and CHF 1,171,434 in 2023).

Table A5-3: Costs over first three years in worlds with and without siponimod

	World without siponimod - Budget			World with siponimod - Budget			Incremental difference for world with versus world without siponimod		
Costs (CHF)	**2021**	**2022**	**2023**	**2021**	**2022**	**2023**	**2021**	**2022**	**2023**
Siponimod acquisition costs	n/a	n/a	n/a	3,641,660	8,006,144	12,170,050	3,641,660	8,006,144	12,170,050
Other drug acquisition costs	36,865,038	38,134,824	38,991,155	33,915,835	31,651,904	29,243,366	-2,949,203	-6,482,920	-9,747,789
Drug administration and monitoring costs	6,906,343	5,097,607	5,255,623	6,534,816	4,299,251	4,044,997	-371,527	-798,356	-1,210,626
AE monitoring costs	279,955	289,332	291,922	267,367	261,708	251,719	-12,588	-27,623	-40,202
Total costs	44,051,337	43,521,763	44,538,699	44,359,678	44,219,008	45,710,133	308,342	697,246	1,171,434

*AE= adverse event; n/a= not applicable

A6

Table A6: Base-case and lower/upper limits of the most influential parameters of the deterministic sensitivity analysis

Parameter	Base case	Lower limit	Upper limit
Siponimod - hazard ratio progression efficacy	0.48	0.22	0.91
Siponimod - cost per dose (CHF)	62.82	50.26	75.38
Interferon beta-1a - hazard ratio progression efficacy	1.13	0.81	1.54
Interferon beta-1a - cost per dose (CHF)	90.64	72.51	108.77
Disease management cost (EDSS 8)	19,403.26	15,878.35	23,475.91
Utility (EDSS 3)	0.639	0.511	0.758
Interferon beta-1a - discontinuation rate	0.092	0.074	0.110
Utility (EDSS 4)	0.597	0.479	0.710
Siponimod - hazard ratio relapse efficacy	0.50	0.28	0.83
Utility (EDSS 2)	0.714	0.567	0.841
Utility (EDSS 6)	0.497	0.400	0.593
Utility (EDSS 8)	0.114	0.093	0.137
Disease management cost in CHF (EDSS 6)	22,727.37	18,598.59	27,497.74
Disease management cost in CHF (EDSS 4)	15,306.23	12,525.62	18,518.94
DMT discontinuation cut-off	6.5	6.0	7.0
Utility (EDSS 5)	0.560	0.450	0.667
Mortality multiplier (EDSS 8)	4.45	3.64	5.38
Siponimod - proportion relapse not requiring hospitalization	0.66	0.45	0.84
Interferon beta-1a - proportion relapse not requiring hospitalization	0.66	0.45	0.84
Interferon beta-1a -hazard ratio relapse efficacy	0.69	0.56	0.84
Disease management cost (EDSS 5)	14,147	11,577	17,116
Disease management cost (EDSS 9)	21,413	17,523	25,908
Disease management cost (EDSS 3)	5,256	4,301	6,360

*KEY: EDSS= expanded disability status scale; CHF= Swiss francs

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