Stick or Twist? Cost-Effectiveness of Siponimod in the Treatment of Active Secondary Progressive Multiple Sclerosis in the UK

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Objective

- To report the cost-effectiveness of oral siponimod, an active secondary progressive multiple sclerosis (SPMS) disease-modifying therapy (DMT), versus continued oral or infused relapsing-remitting multiple sclerosis (RRMS) DMTs for patients with active SPMS in the UK.

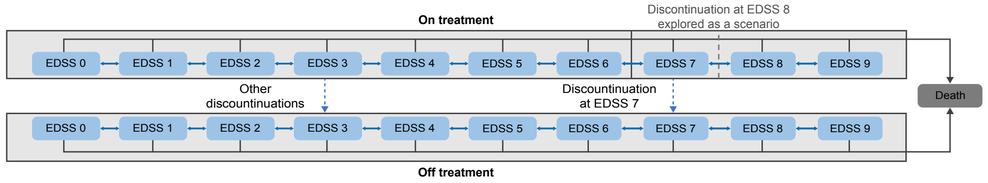
Background

- In the UK there are approximately 130,000 patients with MS, with around 7000 new diagnoses a year.[1] Within 15 years, approximately 50% of untreated patients with RRMS will transition to SPMS.[2]
- SPMS, characterised by cumulatively increasing disability with or without relapses, presents an increased disease burden for patients.
- Siponimod has been shown to slow confirmed disability progression (CDP), as measured on the Expanded Disability Status Scale (EDSS), and reduce the annualised relapse rate (ARR) in patients with active SPMS.[3]
- Siponimod was found to be cost-effective versus injectable interferon beta-1b and best supportive care during the National Institute for Health and Care Excellence (NICE) and Scottish Medicines Consortium appraisals. Despite being the only other licensed treatment option, clinical experts confirmed that the use of interferon beta-1b was negligible in patients with active SPMS.[4,5]
- Limited DMTs licensed and reimbursed for SPMS, and the insidious transition from RRMS, mean that the true scenario for many patients will be continuation of oral and infused RRMS DMTs during the early stages of SPMS.[4]

Methods

- A cohort Markov model, constructed in adherence to NICE guidelines and based on disease progression through EDSS health states, with annual cycles and lifetime time horizon, was employed to determine the cost-effectiveness of siponimod from an NHS perspective for patients with active SPMS **(Figure 1)**.
- In the base case, treatment discontinuation at EDSS health state 7 was modelled, in line with the NHS England algorithm for MS treatment.[6]
- Baseline characteristics, health state utility values, hazard ratio (HR) for 6-month CDP, ARR ratio, discontinuation rate and adverse events for siponimod were sourced from the EXPAND clinical trial.[3,7]
- Natural history probabilities for transitions between EDSS 3–6 were obtained from the placebo arm of the EXPAND clinical trial and those for EDSS 0–2 and 7–9 taken from the London Ontario database.

Figure 1. Structure of the cohort Markov model employed in this analysis.



EDSS: Expanded Disability Status Scale.

- Through systematic review, limited efficacy and safety data were found on comparator DMTs for patients with SPMS. Efficacy data used in the model are summarised in **Table 1** with the following assumptions:
  - Given the paucity of clinical trial data, HRs for 6-month CDP for RRMS DMTs (HR: 1.000) were assumed to be consistent with the results of the ASCEND trial of the high efficacy RRMS DMT, natalizumab, which showed no efficacy benefit versus placebo (odds ratio: 1.060) on the proportion of patients with SPMS and 6-month CDP at 96 weeks.[9]
  - RRMS DMTs were assumed to have positive effects on relapses in patients with active SPMS; data from a recent network meta analysis for relapsing forms of MS were used in the absence of SPMS clinical trial data.[10]
  - The HRs for efficacy on 6-month CDP of each DMT were applied to the probabilities of natural history of disease progression; efficacy on relapses was applied using the ARR ratios.

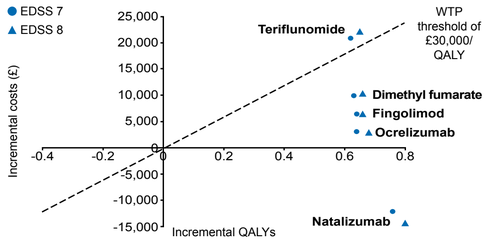
Table 1. Efficacy inputs for all DMTs, versus placebo

DMT	6-Month CDP HR (CI)	Source	ARR ratio (CI or CrI)	Source
Siponimod	0.630 (0.470–0.860)	EXPAND[3]	0.540 (0.390–0.770)	EXPAND[3]
Natalizumab	1.060[a] (0.740–1.530)	ASCEND[9]	0.453 (0.323–0.634)	ASCEND[9]
Ocrelizumab	1.000	Assumption	0.330 (0.250–0.440)	NMA[10]
Fingolimod	1.000	Assumption	0.460 (0.370–0.550)	NMA[10]
Dimethyl fumarate	1.000	Assumption	0.500 (0.400–0.620)	NMA[10]
Teriflunomide[b]	1.000	Assumption	0.660 (0.560–0.810)	NMA[10]

DMTs included were those used in clinical practice at study conception. ARR ratios were calculated from clinical trial data or obtained from an NMR (along with CrIs). [a]Odds ratio for the proportion of patients with 6-month CDP at 96 weeks. [b]ARR ratio for 14 mg teriflunomide. ARR: annualised relapse rate; CI: confidence interval; CrI: credible interval; DMT: disease-modifying therapy; NMA: network meta-analysis.

- In the absence of treatment discontinuation data in SPMS patients for comparators other than natalizumab, assumptions were required. Given the lack of established efficacy on disability progression, combined with guidelines to discontinue such DMTs once SPMS is formally recognised, it was assumed that the discontinuation rate would be 30% higher for such comparators relative to siponimod; this assumption of higher discontinuation was found to be conservative in the model.
- Treatment and administration costs were obtained from the British National Formulary (list prices for all DMTs), most recent NHS reference (2019–20) and Personal Social Services Research Unit costs (2020). Monitoring and resource costs were sourced from the relevant NICE appraisals.

Figure 2. Cost-effectiveness of siponimod versus RRMS DMTs at a WTP threshold of £30,000/QALY for the base case (EDSS 7) and scenario analysis (EDSS 8) discontinuation thresholds.



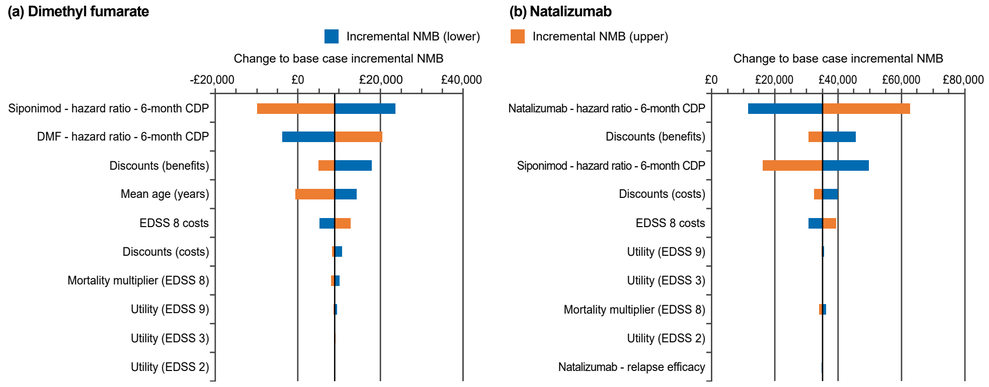
Labels indicate the comparator versus which siponimod was compared. DMT: disease-modifying therapy; EDSS: Expanded Disability Status Scale; QALY: quality-adjusted life year; RRMS: relapsing-remitting multiple sclerosis; WTP: willingness-to-pay.

Results

Base Case

- **Table 2** summarises the base case results obtained from the model with siponimod predicted to have greater quality-adjusted life years (QALYs) versus all comparators.
- Siponimod was predicted to be cost-effective against all comparators, except teriflunomide, at a willingness-to-pay threshold (WTP) of £30,000/QALY **(Figure 2)**.
  - Both siponimod and teriflunomide are known to have confidential discounts, thus the predicted ICER should be interpreted with caution given the uncertainty of the incremental costs.
- Incremental cost-effectiveness ratios (ICERs) are presented as cost (GBP) per QALY.

Figure 3. Tornado plots for deterministic sensitivity analyses versus dimethyl fumarate (a) and natalizumab (b).



CDP: confirmed disability progression; DMF: dimethyl fumarate; EDSS: Expanded Disability Status Scale; NMB: net monetary benefit.

Table 2. Base case results obtained from the model for siponimod versus each comparator.

				Siponimod vs comparator		
DMT	Total LYs	Total costs, £	Total QALYs	Incremental LYs	ICER, £/QALY	NMB at WTP of £30,000, £
Siponimod	16.39	335,714	3.45	-	-	-
Natalizumab	16.25	347,805	2.69	0.14	**Dominant**	35,000
Ocrelizumab	16.26	332,591	2.79	0.12	**4,760**	16,558
Fingolimod	16.26	329,334	2.81	0.12	**10,033**	12,697
Dimethyl fumarate	16.26	325,725	2.82	0.12	**15,837**	8,933
Teriflunomide	16.26	314,786	2.83	0.12	**33,689**	-2,291

These results are calculated using the non-discounted list prices of all DMTs. DMT: disease-modifying therapy; ICER: incremental cost-effectiveness ratio; LYs: life years; NMB: net monetary benefit; QALY: quality-adjusted life year; WTP: willingness-to-pay.

Scenario Analysis (EDSS 8)

- Discontinuation of treatment at EDSS health state 8 aligned with the base case results **(Figure 2)**.
- Incremental QALYs were slightly increased versus all comparators, driven by small improvements in the total QALYs predicted for siponimod.
- This scenario explored the extension of treatment eligibility within the NHS and the potential cost-effectiveness outcomes, were this to be implemented for patients with active SPMS.

Sensitivity Analyses

- Deterministic sensitivity analyses (DSAs) indicated that intervention and comparator efficacy with respect to 6-month CDP, discounts and mean age were the most influential model inputs on the net monetary benefit.
- Example tornado plots for the DSAs are shown in **Figure 3** for comparison versus dimethyl fumarate and natalizumab.

Conclusions

Recognition of active SPMS, and treatment with siponimod – a clinically effective DMT licensed for active SPMS evidenced by relapses or imaging features of inflammatory activity – offers a cost-effective treatment approach compared with continued use of oral or infused RRMS DMTs taking into account assumptions and limitations in the absence of SPMS data, as described in the poster.

References

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Disclosures

SM and **FW**: Employees of Costello Medical Consulting Ltd. **MK**: Employee of Novartis Pharmaceuticals UK Ltd; owner of shares in Novartis. **UV**: Employee of Novartis Ireland Limited. **KG**: Employee of Novartis Healthcare Private Limited.

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