National Institute for Health and Care Excellence

Draft

Multiple Sclerosis in adults: management (update)

Cost-utility analysis: Fampridine for the treatment of MS mobility

NICE guideline CGXX

Economic analysis report

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Contents

Cost-effectiveness analysis: What is the clinical and cost effectiveness of prolonged-release (PR)-fampridine plus best supportive care (BSC) versus BSC alone for the improvement of walking ability in patients with MS?

1 Introduction

Multiple sclerosis (MS) is a chronic, incurable, inflammatory condition, characterized by areas of demyelination (lesions) within the central nervous system[42]. Common symptoms that Individuals with MS experience include issues with gait pattern, balance and muscle stiffness which can result in walking difficulties[29]. Walking impairment for people with MS can mean a reduction in both walking speed[16] and endurance[9] resulting effects on physical function and quality of life[29]. Fampridine is a 10mg prolonged-release (PR) tablet, licensed for the improvement of walking in adults with MS with walking disability (Expanded Disability Status Scale [EDSS] 4 to 7)[17]. It is typically taken twice daily, once in the morning and evening. Treatment should also be discontinued if walking benefit is no longer observed during future assessments[17].

A de novo economic analysis had been conducted as part of the previous MS NICE Clinical Guidance 186[35] and concluded that fampridine was not cost-effective at a threshold of £20,000 per quality-adjusted life-year (QALY). This was in-part due to over half (57%) of participants not responding to fampridine in RCT data[25] alongside a marginal clinical benefit for those who did respond. As a result, fampridine was not recommended in England to treat lack of mobility in people with MS. The literature review identified a number health economic (HE) studies that were conducted with the purpose of aiding national funding/access decisions, for either UK countries or Sweden.[1,2,46] All three economic models found that fampridine was cost effective when the cost of fampridine was reduced. These models did not always employ NICE's preference EQ5D-3L measure and did not pool all the relevant clinical evidence (responder rate and EQ5D data). In December 2019, the Welsh Government's Health and Social Services advisory body, the All-Wales Medicines Strategy Group (AWMSG), recommended to make fampridine routinely available on the NHS conditional of a Wales Patient Access Scheme (WPAS) discount.[2] As the cost-utility analysis of fampridine included a confidential WPAS discount no results were published and so this analysis was not presented to the committee. Similarly, in April 2020, fampridine was accepted for use within NHS Scotland by the Scottish Medicines Consortium (SMC), after incorporating a Patient Access Scheme (PAS) into the model that allowed the drug to be cost-effective.[46] The approval was attained after two previous submissions by the manufacturing company, Biogen, were rejected due to lack of sufficiently robust economic analysis. The results of the models submitted to the SMC with and without the PAS were presented to the committee. Finally, fampridine was also approved in Sweden in 2021[1] following the submission of an economic model to the Swedish dental and pharma benefits agency (TLV). The results of this analysis were also presented to the committee. It is important to note, however, that the cost of fampridine is lower in Sweden compared to the UK list price, as a 28-day supply/56-pack is £109 in Sweden versus £362 according to the BNF.[5]

In this guideline update, the cost-effectiveness of fampridine is one of the areas which will be reconsidered due to the availability of additional clinical evidence since the last guideline (EQ5D evidence from ENHANCE[24] and MOBILE trials[31]) and the limitations of the previous models that did not employ NICE's preferred EQ5D-3L measure and or did not pool the two trials. As the committee were aware that the cost of fampridine remained high and therefore unlikely to be cost-effective, the aim

of the analysis was also to identify the price at which fampridine would be considered a cost-effective treatment.

2 Methods

2.1 Model overview

The cost-utility analysis considered the costs and quality-adjusted life years (QALYs) from a current UK NHS and personal social services perspective. The analysis followed the standard assumptions of the NICE reference case for interventions with health outcomes in an NHS setting including discounting at 3.5% for costs and health effects[34]. An incremental analysis was undertaken. A sensitivity analysis using a discount rate of 1.5% for costs and health effects was conducted.

2.1.1 Comparators

The following comparators were included in the analysis:

1. Best supportive care: all background supportive care that could be used concomitantly to manage MS symptoms (referred to as BSC in the report).
2. Fampridine (10mg twice daily) + best supportive care (referred to as fampridine in the report).

2.1.2 Population

The population of the analysis based on the inclusion criteria for the ENHANCE trial[25] which is the largest RCT of fampridine. This was adults (18 to 70 years) with multiple sclerosis as defined in the revised McDonald criteria for at least three months, investigator-assessed walking impairment and an expanded disability status scale (EDSS) score of 4 to 7.[a]

2.1.3 Deviations from NICE reference case

The analysis deviates from the NICE reference case as it uses a 5-year time horizon to estimate quality-adjusted life years (QALYs) gained, as opposed to considering lifetime QALYs. The reason for this was twofold: firstly, fampridine is not associated with a reduced or increased risk of death, negating the need for a lifetime horizon. Secondly, the model applies EQ-5D utility as the mean change over the 24-week trial period collected from the fampridine and placebo arms, which was then carried forward over the remainder of the 5-year time horizon (assuming a constant mean change score over the whole time horizon). It would be difficult to justify that week 24 utility values would continue to be representative for a period longer than 5 years. The committee considered that extrapolating up to 5 years was appropriate as published evidence suggests that fampridine responders sustained an improved walking speed over 5 years compared with non-responders, with walking speed decreasing over time.[19] Of note, a 4-week withdrawal probability was estimated from two extension studies (up to 5 years)[45] and was incorporated in the model to account for people becoming fampridine non-responders over the model time horizon and therefore will incur none of the costs or benefits of fampridine. Reflecting what would

[a] EDSS is a scale that describes the severity of disability in patients with MS from a score of 0 (no disability) to 10 (death due to MS). EDSS ≥7 is essentially restricted to a wheelchair.

happen in practice (fampridine should be stopped if people no longer respond). Further detail on this available below.

2.2 Approach to modelling

A systematic review of the literature was undertaken to identify existing health economic analyses of fampridine for mobility in adults with MS. This review is summarised in Evidence Review E. All existing models were scrutinised to identify possibly relevant and appropriate model structures. These were presented to the committee and the model structure below was agreed. The structure was an adaptation of the model structure developed in Acosta[1].

The cost-utility analysis was a Markov cohort model which enable the calculation of costs and QALYs over 5 years for each comparator. In a Markov model a set of mutually exclusive health states are defined that describe what can happen to the population of interest over time. The clinical outcomes incorporated in the model were: quality of life (EQ-5D-3L), fampridine treatment response assessed using the 12-item Multiple Sclerosis Walking Scale (MSWS-12), walking ability progression over time using the Timed 25-foot walk (T25FW), non-serious adverse events (AEs) of interventions and death due background mortality (adjusted for an MS population).

The model captured the impact of fampridine in two ways: improvement in quality of life and slower rate of decline in walking speed over time. The latter in turn would reduce healthcare and personal social services (PSS) resource use as it would delay the need for additional interventions associated with reduced mobility. Long-term natural progression of walking speed decline was estimated using T25FW scores due to the absence of long-term clinical data for MSWS-12 (12-item MS walking scale). The data used to inform the T25FW for fampridine and BSC over time are detailed in section 2.3.4.3. Data from an Adelphi study[44] which provided a correlation between T25FW and resource use was used to then estimate total healthcare and PSS resource use for fampridine compared to BSC-treated individuals. It was assumed that once people were classed as fampridine non-responders or withdrew from fampridine treatment, they would have the same natural progression of walking speed decline as BSC-treated individuals.

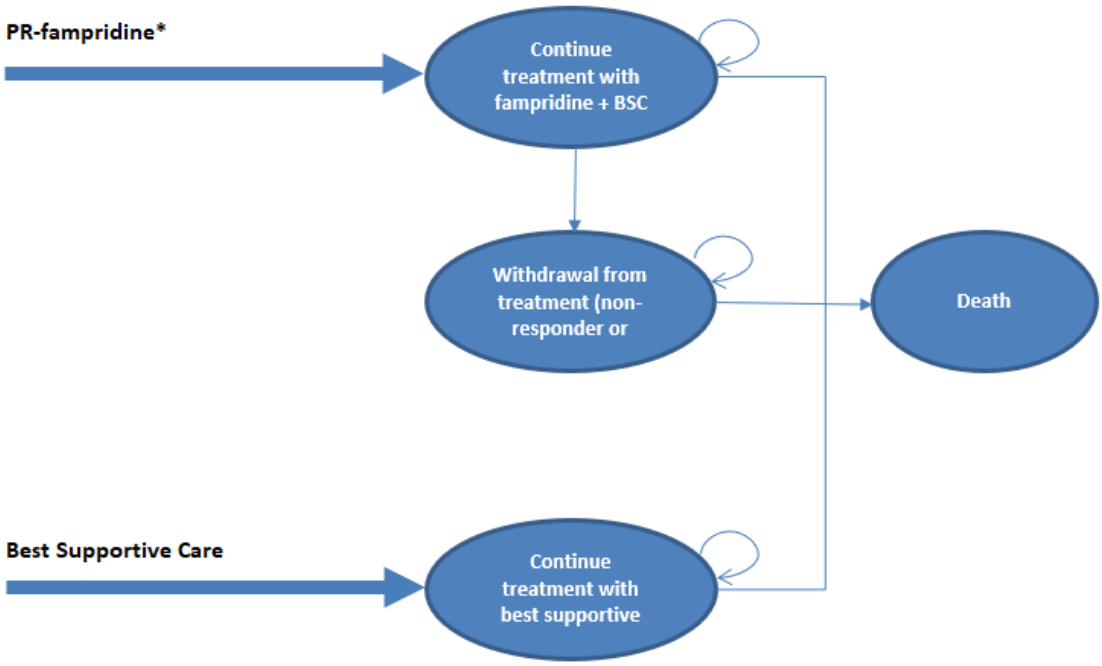
The summary of product characteristics for fampridine[17] clearly state it is indicated for people with an EDSS of 4 to 7 and that if no improvement is observed after two to four weeks, fampridine should be discontinued. Furthermore, it should be discontinued if benefit is not reported by patients or upon re-evaluation initiated by physicians as a result of decline in walking ability. The model therefore included a four-week response assessment and a probability of withdrawal thereafter to account for subsequent lack of benefit. As with other models of fampridine, it was assumed that people whose EDSS was greater than 7 would stop fampridine. In the model, this was proxied using walking speed, as measured by the timed 25-foot walk (T25FW), dropping to zero. Both the SMC and AWMSG submissions assumed that no one progressed to EDSS >7 within a 5-year time horizon. This was discussed with the committee, who agreed that this was a reasonable assumption due to recent evidence suggesting the natural course of disease of MS has become milder in recent years, which may be attributed to improved and earlier diagnosis and availability of disease modifying drugs (DMDs)[8, 12, 27, 47-49].

2.2.1 Model structure

The Markov model was comprised of four health states with four-week cycles (Figure 1). The model includes two treatment strategies: fampridine plus BSC and BSC alone. For those receiving BSC alone, they enter the model in the 'continue treatment with BSC' health state. People receiving fampridine incurred the drug and response assessment costs until the end of the responder-identification period, which is set at four weeks (one cycle) post treatment initiation. Response was defined as any participant who achieved a mean improvement from baseline of at least eight points on the twelve-item multiple sclerosis waking scale (MSWS-12) score over 24-weeks. It was deemed appropriate to use the 24-week mean improvement in MSWS-12 for the 4-week responder-identification as the improvement over placebo reported in ENHANCE was observed from two weeks and maintained over the 24 weeks. This approach was also taken in the previous health economic models. The fampridine summary of product characteristics' therapeutic indication for a responder assessment at two to four weeks was based in part upon this evidence.[25] If they are classified as non-responders, they enter the 'withdrawal from treatment' health state. If they are classified as responders, patients would then enter the 'continue treatment with fampridine and BSC' health state. At each cycle there is a probability that those who are in the 'continue treatment with fampridine and BSC' health state enter the 'withdrawal from treatment' health state due to any reason including lack of response to treatment, AEs or other reasons. Once patients withdraw from fampridine treatment they are assumed to incur costs equal to those in the 'continue treatment with BSC' health state, reflecting clinical practice. Utilities for the BSC were taken from the pooled placebo arm of the MOBILE and ENHANCE trials. Utilities for people in the 'continue treatment with fampridine and BSC' and 'withdraw from treatment' health states were taken from the pooled 'fampridine responders' and 'non-responders' arms of the MOBILE and ENHANCE trials, respectively. See section see section 2.3.5 for further detail on utility inputs. Death was an absorbing state in the model, and patients could transition from any health state to the death state at any cycle in the model.

Despite evidence suggesting an observed walking speed improvement following the re-initiation of fampridine[19] it was conservatively assumed that those who enter the 'withdrawal from treatment' health state cannot transition back to the 'continue treatment with fampridine and BSC' health state and all treatment effects is lost going forward. Details of how different data sources were used in the model are provided in section 2.3.

Figure 1: Model structure



Abbreviations: BSC, best supportive care; PR, prolonged-release
** In the first cycle, participants in the fampridine group incurred treatment costs and assessment costs for both health states to account for response evaluation*

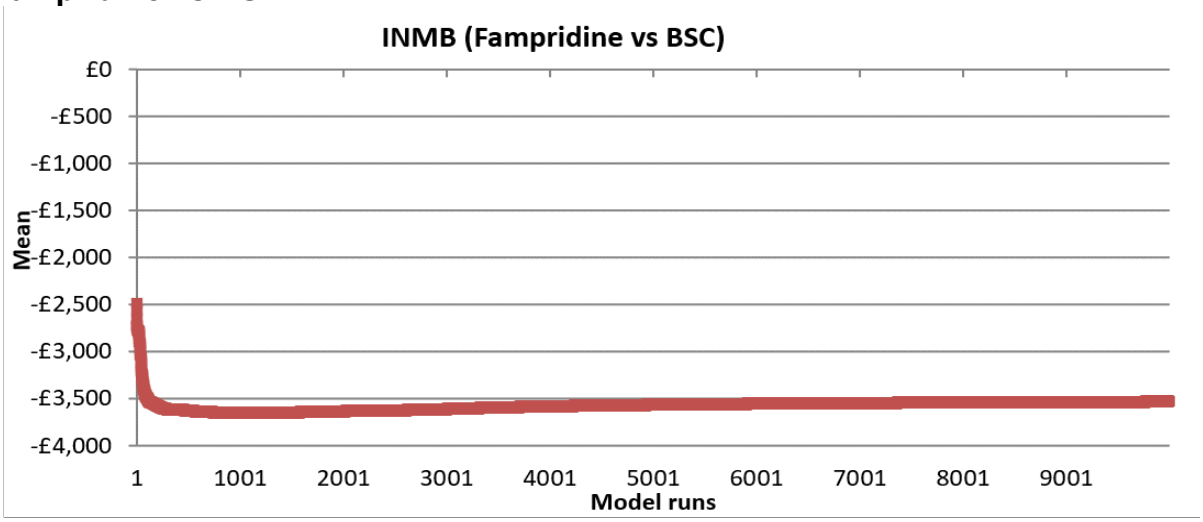
2.2.2 Uncertainty

The model was built probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for each model input parameter. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution; mean costs and mean QALYs were calculated using these values. The model was run repeatedly – 5,000 times for the base case and 5,000 times for each sensitivity analysis – and results were summarised.

Due to the correlated uncertainty expected between different resource use coefficient parameters, health care / PSS resource use regression parameters were varied as part of a probabilistic sensitivity analysis (PSA) where the joint uncertainty between parameters can be best captured using the variance/co-variance matrices (see Section 2.3.6.2). The same was approach was taken for the T25FW regression parameters, further detail provided in Section 2.3.4.3.

When running the probabilistic analysis, multiple runs are required to take into account random variation in sampling. To ensure the number of model runs were sufficient in the probabilistic analysis we checked for convergence in the incremental costs, QALYs and net monetary benefit at a threshold of £20,000 per QALY gained for fampridine versus BSC. This was done by plotting the number of runs against the mean outcome at that point (see example in Figure 2) for the base-case analysis. Convergence was assessed visually, and all had stabilised before 5,000 runs.

Figure 2: Convergence plot for incremental net monetary benefit: Fampridine vs BSC



Abbreviations: BSC=best supportive care, INMB = incremental net monetary benefit.

The way in which distributions are defined reflects the nature of the data, so for example event probabilities were given a beta distribution, which is bounded by 0 and 1, reflecting that the probability of an event occurring cannot be less than 0 or greater than 1. All of the variables that were probabilistic in the model and their distributional parameters are detailed in Table 1 and in the relevant input summary tables in section 2.3.1. Probability distributions in the analysis were parameterised using error estimates from data sources.

Table 1: Description of the type and properties of distributions used in the probabilistic sensitivity analysis

Parameter	Type of distribution	Properties of distribution
BSC probability of individual non-serious adverse events	Beta	Bounded between 0 and 1. As the sample size and the number of events were specified alpha and beta values were calculated as follows: • Alpha = (number of patients with non-serious AEs) • Beta = (number of patients) − (number of patients with non-serious AEs)
WinBUGS pooled probability of treatment response	WinBUGS output	A bespoke distribution where you sample from iterations from the WinBUGs analysis rather than using summary statistics. It ensures that you capture in your model the correlation between the different treatment effect estimates.
Baseline T25FW speed, Standardised mortality ratios and fampridine relative risk of each non-serious adverse event.	Lognormal	The natural log of the mean and standard error were calculated as follows: • Mean = ln(mean) − $SE^2/2$ • SE = [ln(upper 95% CI) − ln(lower 95% CI)]/(1.96×2) This formula includes a correction to ensure the mean generated in the probabilistic analysis will be the same as the reported mean[3].
Utilities, 4-weekly probability of withdrawal, and pooled	Beta	Bounded between 0 and 1. Derived from mean and its standard error, using the method of moments. Alpha and Beta values were calculated as follows:

Parameter	Type of distribution	Properties of distribution
probability of non-serious adverse events.		Alpha = mean^2×[(1−mean)/SE^2]−mean Beta = alpha×[(1−mean)/mean]
Utility decrements, Costs	Gamma	Bounded at 0, positively skewed. Derived from mean and its standard error. Alpha and beta values were calculated as follows: • Alpha = (mean/SE)^2 • Beta = SE^2/Mean
T25FW weighted regression, and univariate analysis of healthcare/personal social services resource and T25FW scores.	Cholesky decomposition.	Uses summary statistics and covariance matrix. Assumes a normal distribution.

Abbreviations: 95% CI = 95% confidence interval; SE = standard error; SMR = standardised mortality ratio.

The following variables were left deterministic (that is, they were not varied in the probabilistic analysis):

- the cost-effectiveness threshold (which was deemed to be fixed by NICE)
- age and gender of the model cohort
- the resource, including time and cost of staff, required to implement fampridine treatment and to treat adverse events (assumed to be fixed according to national pay scales and programme content)
- NHS reference costs, drug costs and NHS supply chain catalogue costs as these are list prices and represent national costs
- General population mortality: rates are based on national data and so the level of uncertainty is considered to be very low and so does not warrant incorporation.

In addition, various sensitivity analyses were undertaken to test the robustness of model assumptions. In these, one or more inputs were changed, and the analysis rerun to evaluate the impact on results and whether conclusions on which intervention should be recommended would change. Details of the sensitivity analyses undertaken can be found in methods section 2.4.

2.3 Model inputs

2.3.1 Summary table of model inputs

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources as required. Most of the baseline characteristics used to inform the model were taken from the ENHANCE study, as this was the primary clinical data used in the company's submission to the SMC and AWMSG appraisals[2, 46]. Of note, the health economic model only uses a subset of the RCT evidence reported in the clinical review above. In terms of estimating the probability of fampridine response and quality of life, ENHANCE and MOBILE RCTs were included as they were the only two RCTs that reported the MSWS-12 improvement compared to baseline at 24 weeks and both studies were alone in undertaking post-hoc analyses that collected EQ-5D data. A

summary of the model inputs used in the base-case analysis is provided in Table 2. All model inputs were validated with members of the guideline committee. More details about sources, calculations and rationale for selection can be found in the sections below. Full details of all inputs and their probabilistic parameters is provided in Appendix A:.

Table 2: Overview of parameters and parameter distributions used in the model

Input	Data	Source	Probability distribution
Comparators	Fampridine BSC	ENHANCE Study 2019[25]	n/a
Population	Adults with MS with walking disability (EDSS 4 to 7)	Biogen 2018	n/a
Perspective	UK NHS & PSS	NICE reference case[34]	n/a
Discount rate	Costs: 3.5% Outcomes: 3.5%		n/a
Time horizon	5 years	SMC 2020, AWMSG 2019[2, 46]	n/a
Cohort settings			
Age, years	48.9	ENHANCE 2019[25]	Fixed
Female, n (%)	72%	Public Health England 2020[51]	
Baseline probabilities			
Baseline T25FW (feet per second)	2.10 (SE: 0.2)	Baseline values from MS-F203[22] and MS-F204[21] trials	Lognormal
Age and MS adjusted general population mortality rate	Variable	ONS English life tables 2017-19[41] and MS specific SMRs from Manouchehrinia 2016[32]	SMRs: Lognormal
Treatment effects			
Probability of response to fampridine treatment	0.432	Pooled analysis of ENHANCE (2019)[25] and MOBILE (2016)[26]	WinBUGs output
4-weekly probability of treatment withdrawal	0.007 (95% CI 0.0 to 0.01)	Pooled analysis of long-term extension studies of MSF203 and MS-F204[45]	Beta
Adverse events (AEs)			
Non-serious AE probability – fampridine	0.09 (95% CI 0.06 to 0.12)	ENHANCE[25]	Beta
Non-serious AE probability – BSC	0.06 (95% CI 0.04 to 0.09)		Beta
Utilities			
Placebo	[redacted]	Pooled estimates from ENHANCE and MOBILE mean over 24 weeks)	Beta
Fampridine non-responder	[redacted]		Beta
Fampridine responders	[redacted]		Beta
AE disutility	0.04 (95% CI 0.03 to 0.05)	Acosta 2021[1]	Gamma

Input	Data	Source	Probability distribution
Costs			
28-day supply of Fampyra 10mg modified-release tablets (Biogen Idec Ltd)	£362	BNF, NHS indicative price: 56 tables (Hospital only)[5]	Fixed
Responder assessment at 4 weeks	£38.33	PSSRU 2020[14], 30 min appointment with hospital- based Band 6 physiotherapist and a 5-minute Neurologist visit. Qualification costs included (excluding individual and productivity costs).	Fixed
AE costs			
UTI	£36.99	PSSRU 2020[14], Assumes band 6 nurse, assume 30-minute surgery appointment (Surgery consultation time by a clinical nurse specialist from PSSRU 2015), as well as the average cost of two antibiotics commonly prescribed and urine testing (NHS 2018/2019[38]; Little 2009[30])	Fixed*
Fall	n/a	No cost to NHS as these were described as non-serious adverse events. The committee assumed these events were ones that did not necessitate a healthcare professional visit or any prescription medication but may still have a QoL impact to the person.	
Headache	n/a		
Nasopharyngitis	n/a		
Back pain	£34.89	Calculated assuming 50% visit a GP while the other 50% visit a community physiotherapist, Band 6 (assume 40 min appointment). PSSRU 2020[14], Qualification costs included (excluding individual and productivity costs).	
Upper respiratory tract infection	£3.78	Calculated assuming 10% visit a GP and get amoxicillin prescription (Amoxicillin 500mg three times daily, 5 days). Dose and unit cost from BNF accessed June 2021. PSSRU 2020[14], Qualification costs included (excluding individual and productivity costs). Assumes 9.22 min consultation.	
Cardiovascular disorders	£36.55	PSSRU 2020[14], Qualification costs included (excluding	

Input	Data	Source	Probability distribution
(palpitations, tachycardia, arrhythmia)		individual and productivity costs). Assumes 9.22 min GP consultation.	
Rash	£15.25	PSSRU 2020[14], Qualification costs included (excluding individual and productivity costs). Assumes 9.22 min consultation.	

Abbreviations: AWMSG = All Wales Medicines Strategy Group, BNF = British national formulary, EDSS = Expanded disability status score, PSSRU = Personal social services research unit, SMC = Scottish Medicines Consortium, SMR = Standardised mortality ratio, T25FW = Timed-25 foot walk.

**AE unit costs were fixed but were made probabilistic using estimates of uncertainty for each of the AE rates reported in ENHANCE or clinical review meta-analyses which were used to weight the unit costs of each AE to estimate an average AE cost for BSC and fampridine (see section 2.3.6.3 for details).*

2.3.2 Initial cohort settings

The model cohort population characteristics were taken from the ENHANCE phase III study population, comprised of adults with MS with walking disability (EDSS scores 4-7), in accordance with the approved European Medicines Agency (EMA) indication of fampridine[10, 18]. The mean starting age 48.9 years with an average time since diagnosis was 137 months. Because the model also includes T25FW, which was not measured in the ENHANCE (or MOBILE) trials, this was assumed to be on average 2.1 feet per second, to match the baseline values observed in the MS-F203[22] and MS-F204 trials[21]. Of note, MS-F203 and MS-F204 trials have a higher percentage of people with secondary progressive MS compared to ENHANCE (52.8%/50% compared to 31%). Median time since diagnosis was longer for MS-F203/MS-F204 trials (14.1 years) compared to ENHANCE (10 years).

In the model base case it was assumed 72% were women, based on figures from Public Health England (2020)[51] where the incidence and prevalence of multiple sclerosis (MS) within the UK was estimated between 1990 and 2010. This was selected rather than the proportion of women in ENHANCE (58% female) as the committee wanted to the model cohort to be representative of the MS population in England. A sensitivity analysis was conducted where the female cohort proportion from ENHANCE is applied instead.

In the ENHANCE trial, concomitant use of approved disease-modifying therapies and medications for fatigue or spasticity were allowed if the drug and dose remained stable throughout the study; physiotherapy and rehabilitation therapy were also allowed. In the MOBILE trial most stable concomitant therapies for treatment of MS were permitted. In both studies, number of people receiving disease-modifying therapies was not reported.

2.3.3 Baseline probabilities

2.3.3.1 Mortality

No impact on mortality is associated with receiving fampridine, therefore, gender-specific standardised morality ratios (SMR) for patients with MS compared to the general population from Manouchehrinia, 2016[32] were applied to English general population age-related mortality rates[41] Manouchehrinia included 12 studies covering 27,423 patients over the period 1949–2012. This study was chosen as it meta-analysed the all-cause, cause-specific and gender-specific SMRs for adults with MS to estimate the rate of change of SMRs over the past 50 years, with most of the cohorts in the analysis living in Northern Europe and Canada. The resulting probability of death was used for both treatment arms.

Table 3: Mortality model inputs

Input	Data	Source	Probability distribution
Age adjusted general population mortality rate	Variable	ONS English life tables 2017-19[41]	n/a
Multiple Sclerosis SMR – applied to general population mortality rate above			
Females	3.06 (95% CI 2.97 to 3.17)	Manouchehrinia 2016[32]	Lognormal
Males	2.56 (95% CI 2.47 to 2.66)		

2.3.4 Relative treatment effects

2.3.4.1 Fampridine treatment response

Fampridine treatment response was estimated by pooling efficacy data from the ENHANCE and MOBILE RCTs (Table 4). In both trials, participants were defined as responders when they had an improvement in their MSWS-12 of eight points or more from baseline to 24-weeks, with responders measured at the end of the 24-week trial period. It was deemed appropriate to use the 24-week mean improvement in MSWS-12 for the 4-week responder-identification as the improvement over placebo reported in ENHANCE was observed from two weeks and maintained over the 24 weeks. This approach was also taken in the previous health economic models. The fampridine summary of product characteristics' therapeutic indication for a responder assessment at two to four weeks was based in part upon this evidence.[25]

WinBUGs was used to generate pooled probability of fampridine response. A fixed effects model was selected as it had a lower deviance information criterion (DIC) than a random effects model. Pooling the MOBILE and ENHANCE estimates was regarded as an ideal approach as this would incorporate the broadest evidence base into the model.

Table 4: Fampridine treatment response inputs

Study	Probabilities	r	n
ENHANCE	0.432	136	315
MOBILE	0.485	33	68
Pooled	0.4318	n/a	n/a

2.3.4.2 Fampridine treatment withdrawal

As was done in previous models, a 5-year retention probability was estimated from pooled MS-F203 EXT and MS-F204 EXT studies[45] for patients responding to fampridine, which was then used to determine the probability of 4-weekly withdrawal probability (assumed to be constant) for any reason, including patients' perceived lack of treatment effect, the decline in T25FW, and AEs. The 4-week withdrawal probability was 0.007 (95% CI 0.0 to 0.01); this was only applied from week 24 as the number of responders was measured at 24 weeks, meaning that this would have captured any treatment withdrawal up to that point. Withdrawal due to mortality is considered separately (see section 2.3.3.1).

2.3.4.3 Natural history and treatment effect

There is no existing clinical trial or resource use data from MSWS-12. Therefore, disease evolution and fampridine treatment effect were defined according to T25FW. Replicating the approach from Acosta 2021[1], the rate of long-term natural progression of MS was taken from the placebo arm of the IMPACT trial[28]. This trial reported T25FW scores over 24 months to compare walking speeds of interferon beta-1a intramuscular versus placebo for people with MS. The IMPACT trial was chosen because it captured T25FW in a population with advanced MS, which closely matches the fampridine population. This trial could be considered a conservative choice, as the placebo arm reports the slowest published rate of T25FW decline, and therefore its use in the model may underestimate the true impact of fampridine. T25FW progression was extrapolated beyond the 24-month trial period using weighted linear regression parameters (Table 5) reported in Acosta to find T25FW scores for BSC-treated across a 5-year period (Figure 3). Once those who were randomised to fampridine were classified as non-responders or withdrew from treatment, it was assumed they had the same T25FW scores as those receiving BSC.

For the fampridine responder intervention group, results from MS-F203EXT and MS-F204EXT[19] were used to model the corresponding progression of T25FW over time. These were open-label extension studies evaluating the long-term effect of fampridine on walking speed in patients who had been participants in MS-F203 and MS-F204, respectively. Patients were followed up over a period of up to 3.8 years (MS-F204EXT) or up to 5.3 years (MS-F203EXT). Of note this study was not included in the clinical review as it was open-label and therefore participants and researchers are not blinded, thus not meeting the clinical review protocol. Results for both studies showed that walking speed of responders remained greater than that of non-responders; however, both groups experienced continuously decreasing walking speeds over time, which were similar to baseline levels by the end of the study. Manufacturers have reported that the decline in walking speed over time in the extension studies could be due to progression of disease or lack of maintenance of effect[11]. Similar to what was done with IMPACT and the BSC group, the T25FW weighted linear regression parameters (Table 5) based on the extension studies that were reported in Acosta were applied to this model to calculate the change in walking speed over time for fampridine responders (Figure 3). The variance-covariance matrices for the BSC and fampridine weighted regression were provided by Biogen following a data request and are confidential (Table 23 Appendix A:).

These were required to ensure correlations were maintained when undertaking the probabilistic sensitivity analysis (see further explanation below).

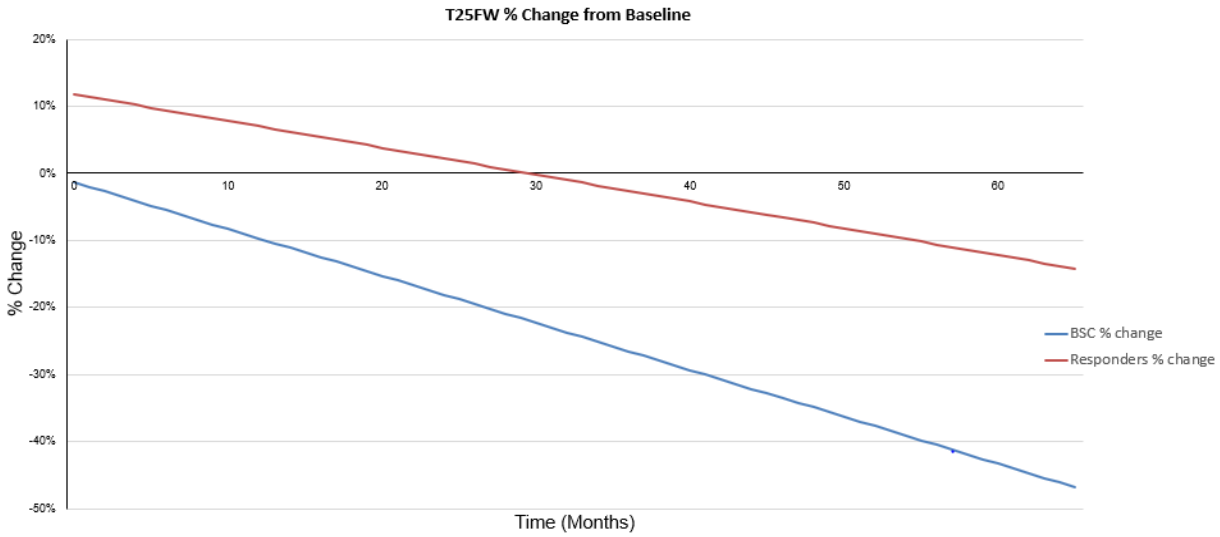
Table 5: T25FW regression parameters

Parameter	Mean value	Standard error
BSC, weighted regression T25FW, Intercept	-0.013	Variance-covariance
BSC, weighted regression T25FW, slope	-0.007	Variance-covariance
Fampridine responders, weighted regression T25FW, Intercept	0.118	Variance-covariance
Fampridine responders, weighted regression T25FW, Slope	-0.004	Variance-covariance

Note: Variance/covariance matrices were provided by Biogen and are confidential.

The T25FW regression parameters in Table 5 were varied as part of the probabilistic sensitivity analysis using variance/co-variance matrices and the Cholesky decomposition method[6], as this is how the joint uncertainty between parameters are best captured (see Table 23). Figure 3 shows the change in T25FW scores over a 5-year period. The trend line shows that the decline in walking speed was slower over time in fampridine responders compared to the BSC group. This reflects the regression parameters in Table 5 as the slope for the BSC group has a greater negative value than that for fampridine responders.

Figure 3: Long-term T25FW using a linear regression



2.3.4.4 Adverse events

AE rates of non-serious AEs associated with fampridine and BSC were taken from the ENHANCE study and the clinical review, which reported pooled data for adverse events including risk ratios for UTI, seizures (this shows no difference), falls, headaches. Incorporating AE rates from ENHANCE was deemed appropriate by the committee as the European Medicines Agency (EMA)[18] based its safety conclusions on ENHANCE trial data. Fampridine is not a disease-modifying drug, therefore,

incorporating relapses that occur in both groups would over-complicate the model. As such, MS relapses were assumed to be unrelated to fampridine treatment and associated with inflammatory disease activity and were therefore excluded from the model. Only adverse events occurring in ≥ 5% of patients were included in the analysis. As only non-serious adverse events occurred in ≥ 5% of patients these were the only AEs incorporated in the model. This was deemed appropriate by the committee and followed the approach used in the previous economic models. No serious adverse events are included in the analysis these did not occur in ≥ 5% of patients. For example, serious urinary tract infection and serious falls each occurred in <1% of fampridine or placebo patients. In addition, no medicine-related serious adverse events were recorded in the fampridine arm[25].

The treatment-related non-serious AE rates (26 week follow up) from ENHANCE where 18% and 13% for fampridine and placebo respectively. The probability of non-serious AEs was incorporated into the model as a per-cycle probability of any non-serious AE by first calculating the 26-week risk, then converting into a 4-week probability by assuming a constant rate. Which resulted in a per cycle probability of non-serious AEs of 0.09 (95%CI 0.06 to 0.12) and 0.06 (95%CI 0.04 to 0.09) for fampridine and BSC respectively. This method of estimating non-serious AE probabilities aligns with the previous fampridine models. Further detail is available in section 2.3.6.3 on how the average AE costs was estimated by intervention.

2.3.5 Utilities

Estimates were taken from two fampridine RCTs (ENHANCE and MOBILE). Of note, the utility values were taken from post hoc responder analyses of ENHANCE and MOBILE. As these were post hoc responder analyses, they did not meet the clinical review protocol and so were not included in clinical review above but are presented in the full here. The committee agreed it was appropriate to pool both studies as it would allow for the broadest inclusion of available data for fampridine's effect on quality of life. In addition to incorporating the largest evidence base, pooling the RCTs helped address issues raised in the previous economic model submissions to the SMC and AWMSG for using the smaller and more favourable to fampridine MOBILE clinical trial.

In the base-case analysis, health state utilities were derived from EuroQoL-5 Dimensions-3 Level (EQ-5D-3L) taken from post-hoc analyses of ENHANCE[26] and MOBILE RCTs[31] which reported utility data at baseline and weeks 2, 4, 8, 12, 16, 20 and 24 for each treatment by responders and non-responders (original data as reported in published studies presented in Table 6 and Table 7 below). MOBILE EQ-5D-5L was mapped to EQ-5D-3L using an algorithm by van Hout[53]. The SMC, AWMSG and Swedish appraisals did not report the mapped inputs and so they were incorporated into the model following a request for the data to be provided confidentially by the manufacturer, Biogen (Table 25 Appendix A:).

Table 6: MOBILE 5L utility data

MOBILE EQ5D 5L data [31]			
	Placebo	Fampridine non-responder	Fampridine responder
n	64	35	33

MOBILE EQ5D 5L data [31]			
baseline mean	0.51	0.52	0.56
baseline SD	0.23	0.2	0.21
LSM change over 24 weeks	-0.03	-0.073	0.064
LSM change over 24 weeks LCI	-0.07	-0.12	0.01
LSM change over 24 weeks UCI	0.01	-0.02	0.12

Table 7: ENHANCE utility data informing base case analysis

ENHANCE EQ5D 3L [24]			
	Placebo	Fampridine non-responder	Fampridine responder
n	316	179	133
baseline mean	0.61	0.60	0.635
baseline SD	0.199	0.209	0.207
LSM mean over 24 weeks	0.64	0.63	0.68
LSM change over 24 weeks	0.027	0.022	0.070
LSM change over 24 weeks LCI	0.008	0.001	0.046
LSM change over 24 weeks UCI	0.046	0.043	0.095
LSM mean 95% LCI	0.62	0.61	0.66
LSM mean 95% UCI	0.66	0.65	0.70

Although meta-analysis could be undertaken simply using the final values at each timepoint, it was decided that meta-analysing EQ-5D change scores (i.e., change from baseline in the fampridine and usual care groups from each study) would be the most precise way of using the data from the trials, removing treatment-specific baseline utility differences from the model as well. This would also address previous critiques from the AWMSG model submission towards applying 24-week utilities across the remainder of the time horizon.

For both studies, the Least Square Mean (LSM) change over 24 weeks was estimated using the Mixed Model Repeated Measures (MMRM) model on individual change in utility index score from baseline adjusted for screening EDSS and baseline utility index score as covariates. For ENHANCE the authors report adjusting for prior aminopyridine (fampridine) use also, this was not done for MOBILE trial. For MOBILE, the manufacturer did report the data was based on the MSWS-12 multiple imputation to apply responder/non-responder definition. Of note, the manufacturers stated that the Week 24 LSM mean change from baseline does not commonly agree with the difference between LSM at Week 24 and baseline from MMRM model on the utility index score post baseline, adjusted for EDSS and baseline utility index score as covariates. Of note, MMRM can give biased results if important covariates are excluded (for example prior fampridine use) or if the data are missing not at random (such as reasons for missingness are still related to the outcome after adjusting for covariates). For example, if change in EDSS is associated with

missingness this is also expected to be associated with the outcome and just adjusting for baseline EDSS wouldn't remove the relationship between missingness and outcome. The potential concerns with the MMRM analysis and lack of adjustment for prior fampridine use for the MOBILE trial were identified as potential limitations of this data.

For the ENHANCE RCT, the LSM change over 24 weeks, referred to here as the change from baseline (CFB) over 24 weeks for each comparator as well as the mean difference in CFB between comparators were reported in the poster by Hobart (2017)[24]. As stated above, a data request was made to Biogen that the MOBILE data be provided in the same format (see Table 25, Appendix A:) to allow for pooling of the two studies. This was provided to us in academic confidence and incorporated into the model. The mean difference in CFB were pooled for ENHANCE and MOBILE thus accounting for any baseline differences between treatment arms and studies. In the base case, the pooled BSC baseline utility was used. The base-case utilities used in the model are summarised in Table 8. A number of sensitivity analyses were conducted around the utilities, see section 2.5 for more detail. As previously noted, those who withdraw from fampridine treatment are assumed to have the same utility as non-responders as no data is available for withdrawal only.

Table 8: Base-case utilities informing treatment effect

Base case: Pooled estimates using pooled BSC as baseline		
	Mean	SE
BSC	[redacted]	[redacted]
Fampridine non-responder	[redacted]	[redacted]
Fampridine responder	[redacted]	[redacted]

2.3.5.1 Adverse events

In the base-case analysis, those who experienced an adverse event were assigned a disutility of 0.04 per adverse event for one-cycle and a one-time cost. This approach reflects that taken in Acosta 2021[1]. Of note, the source of this utility decrement was not reported. In the AWMSG model[2] utility decrements for adverse events were selected from the closest available matches in the Sullivan 2011 utility catalogue[50]. When looking for the closest available matches for the non-serious adverse events reported in ENHANCE in this catalogue the following disutilities were identified: ICD-9 429 (Ill-Defined Heart Disease) for cardiovascular disorders: 0.0868, ICD-9 599 (Other Urinary Tract Disorders) for UTIs: 0.0054 and ICD-9 724 (Back Disorder) for back pain: 0.0866. Overall, therefore the committee considered that an average disutility of 0.04 per adverse event assumed in the Acosta model seemed reasonable. The committee assumed that this disutility would be short lived given the adverse events are non-serious and was applied for 7 days per adverse event in the model. There were concerns that by using the trial reported QoL, the impact of adverse events on QoL may have already been captured and therefore applying a disutility may be considered double counting. To explore this uncertainty a sensitivity analysis was conducted were the disutility associated with an adverse event was removed.

2.3.6 Resource use and costs

2.3.6.1 Intervention costs

The model includes the unit cost of fampridine for all patients in the fampridine arm up until 4 weeks and beyond 4 weeks for those who respond to treatment until treatment withdrawal or death. The cost of responder assessment occurring at week 4 was also applied to those who initially entered the model as fampridine treated participants. Administration costs associated with fampridine were not included on the basis that it was an oral treatment. BSC was not costed as this assumed to be equal in both treatment arms. The treatment cost of fampridine 10mg twice daily was £362 per 28-day supply, and was taken from the UK BNF[5]. The committee raised concerns that the cost of fampridine to the NHS would be higher unless a home delivery scheme was incorporated as this would be exempt from VAT. However, cost-effectiveness analyses are usually done excluding VAT and the BNF tariff does not include VAT. Therefore, current practice involving home delivery services does not impact this analysis. Based on committee expert opinion, it was assumed that the week 4 hospital-based response assessment would include a 30-minute assessment from a Band 6 hospital-based physiotherapist and 5-minute consultant neurologist appointment. The unit costs were taken from PSSRU 2020[14] and included qualification costs but excluded individual and productivity costs. The total cost of responder assessment at 4 weeks was £38.33. Due to the uncertainty around the practicality of a neurologist only providing a 5-minute consultation, a sensitivity analysis was conducted where a non-face-to-face consultant led follow-up appointment was costed instead (see section 2.5 for further detail).

2.3.6.2 Healthcare and PSS resource use estimates

Health care resource use
Resource use in the base-case analysis was informed using univariate analyses on the relationship between healthcare resource use (HCRU) and walking speed, based on data from the Adelphi MS disease-specific program (Pike 2012[44]). The Adelphi study evaluated the prevalence, severity and burden of walking and mobility problems (WMPs) using survey data from five European countries (France, Germany, Italy, Spain, UK). Records were available for 3572 patients of whom 2171 also completed a questionnaire that allowed researchers to analyse the link T25FW and direct HCRU, walking aid use and modifications to daily living. The survey data was limited, however, as T25FW data was only available for 5.1% of respondents. HCRU included the following visits: general practitioner, neurologist, MS specialist, MS nurse, ER doctor, ER visits, internist, physiotherapist, ophthalmologist, urologist, gastroenterologist, psychiatrist, other physician and hospitalisation. This was incorporated into the model using the approach from Acosta 2021[1]; walking speed, measured using the T25FW, was set as the independent variable in the univariate analyses to produce univariate equations that were used in the base-case analysis for all resource use items. The resulting constants and coefficients reported in Acosta 2021 are presented in Table 21 in Appendix A:. The variance-covariance matrices for these constants and coefficients were provided in confidence by Biogen (Acosta) following a data request (Table 24, Appendix A:). For example, the equation below estimates the impact of a participant's T25FW score on the number of visits to a neurologist they require annually:

$$Number\ of\ Neurologist\ visits = e^{T25FW \times -0.0013631 + 1.41821}$$

These resulting annual HCRU were then multiplied by the unit cost of each HCRU item respectively. Each HCRU was then adjusted to the cycle duration of 4 weeks and added together to calculate the total HCRU cost per cycle. As noted in section 2.3.4.3, T25FW changed over time and at different rates for BSC and fampridine responders, therefore the estimated HCRU cost per cycle was different for each cycle and comparator. Please note that resource use estimates for the annual number of visits to an ER department, an ER doctor, an ophthalmologist, and MS-related hospitalisations were excluded from the model following concerns raised by the committee regarding the high level of resource use reported for these relative to current UK NHS clinical practice. Furthermore, the effect from the T25FW changes on these resource items was so small that the difference between the fampridine responders and BSC arms over a 5-year time horizon was likely to be negligeable. Therefore the effect of excluding them from the analysis was not expected to impact the cost-effectiveness results. Unit costs for HCRU items were taken from published sources such as PSSRU 2020 and NHS reference costs. These are presented alongside the baseline annual costs based on a walking speed of 2.1 ft/s in Table 9.

PSS costs

Acosta 2021 also conducted univariate analyses on the relationship between personal social services (PSS) resource use and walking speed based on the Adelphi study and this allowed for the calculation of PSS resource use cost per cycle per comparator. The PSS resource use items included were professional care, walking aids and home modifications. Table 10 describes the mean annual costs and assumptions used for these PSS resource use items included in the model. As well as the baseline annual costs based on a walking speed of 2.1ft/s. As was done is Acosta, the model incorporated the proportion of adults with MS using these resources as well as the quantity used from a Swedish study by Berg 2006[4] which were used to weight the cost of each PSS unit cost. This study analysed the costs and quality of life of multiple sclerosis related to disease severity in Sweden. Questionnaire responses were collected from 1,339 patients registered with the Swedish organisation of patients with neurological diseases (Neurologiskt Handikappades Riksförbund; NHR). Berg was deemed appropriate for use as it contained a similar patient population to the model cohort: 73% of patients were female, with a mean age of 53 and a mean age at diagnosis of 39. The mean EDSS score was 5.1, with over 70% of respondents having an EDSS over 4.). Table 22 in Appendix A: reports the details of the proportion using each resource reported in Berg, as well as the mean equipment and staff time unit costs, which were estimated using guidance from the HE subgroup committee discussion and PSSRU unit cost data. All PSS costs estimated for this model were found to be similar to those reported in Acosta with the exception of walking aids.

The cost of providing a bed lift was excluded from the costing for home modifications as this was only used by for 0.1% of people with MS in Berg (2006) and the unit cost was unavailable from PSSRU. Transportation costs, which were included as part of professional care in the Acosta 2021 model, were also excluded as it was unclear how these were calculated in Berg and Acosta studies[1, 4]. Excluding these may lead

to an underestimate in total PSS costs in the model both for fampridine and BSC. The impact was considered to be minimal however and not expected to impact the overall cost effectiveness results. Major home modifications with high one-off costs (building extensions, bathroom conversions) were annuitized over a 10-year period and discounted at 3.5%, based on HM Treasury guidance on how to appraise and evaluate policies, projects and programmes[23].

Car and work modifications, which were both reported in the Adelphi study and incorporated in Acosta 2021, were not included in the model as such provisions are not funded by the NHS or social care and so are outside of the NICE reference case. Non-professional care was not included in the base case, only in a sensitivity analysis (see 2.5.1.13).

Table 9: Base case model inputs: HCRU consumption costs based on baseline walking speed of 2.1 ft/s (measured by T25FW)

Cost per visit	Unit cost	Annual cost for baseline T25FW speed	Source
Physiotherapy	£26	£113	PSSRU 2020[14]. Qualification costs included (excluding individual and productivity costs). Assumes band 6 hospital-based physiotherapist, assume 30-minute appointment
Neurologist	£187	£771	NHS reference costs 2019-2020[39], face to face consultant led follow up appointment
GP	£37	£79	PSSRU 2020[14] Qualification costs included (excluding individual and productivity costs). Assumes 9.22 min consultation
MS Specialist	£187	£97	Assumed to be same cost as neurology visit above
MS Nurse	£15	£6	PSSRU 2020[14] Qualification costs included (excluding individual and productivity costs). Assumes band 7 nurse, assume 15-minute surgery appointment (Surgery consultation time by a clinical nurse specialist from PSSRU 2015)
Psychiatrist	£243	£73	NHS reference costs 2019-2020[39], face to face consultant led first appointment, assume Liaison psychiatry
Urology (nurse)	£26	£7	PSSRU 2020[14] Qualification costs included (excluding individual and productivity costs). Assumes band 6 hospital-based nurse, assume 30-minute appointment
Internist	£159	£26	NHS reference costs 2019-2020[39], face to face non-consultant led first appointment, assume general medicine
Other Physician	£37	£2	Assume cost of GP visit. PSSRU 2020[14] Qualification costs included (excluding individual and productivity costs). Assumes 9.22 min consultation
Gastroenterologist	£133	£5	NHS reference costs 2019-2020[39], face to face non-consultant led first appointment
Hospitalised for MS	£2,700	£2,460	NHS reference costs 2019/2020[39], weighted average of non-elective short and long stays, weighted by CC score

Cost per visit	Unit cost	Annual cost for baseline T25FW speed	Source
ER	£182	£47	NHS reference costs 2019-2020[39], weighted average of all A&E attendances
Ophthalmologist	£120	£22	NHS reference costs 2019-2020[39], face to face non-consultant led first appointment
ER Doctor	£144	£1	NHS reference costs 2019-2020[39], face to face non-consultant led first appointment

Table 10: PSS resource consumption costs for baseline walking speed of 2.1 ft/s (measured by T25FW)

Cost	Mean annual cost	Annual cost for baseline T25FW speed	Source
Non-professional care	£4,436	£2,527.69	PSSRU 2012[13] for methodology, using minimum wage opportunity cost approach, with minimum wage. Using national minimum wage unit cost per hour[52].
Professional care	£16,365	£6,642.39	Sum of costs below
Nurse home visits	£426		PSSRU 2020[14], qualification costs included (excluding individual and productivity costs). Assumes band 6 nurse.
Home help	£1,656		PSSRU 2020[14], qualification costs not included home care worker cost per hour
Personal assistant	£14,283		PSSRU 2020[14], qualification costs not included home care worker cost per hour. Assume cost of personal assistant same as cost of home care worker.
Walking aids	£29	£13.82	Sum of costs below
Walking aids	£2		NHS supply chain catalogue[40] walking stick wooden OT assessment for provision (appointment duration assumed 1 hour, community OT, band 6 including qualifications, PSSRU 2020[14])
Wheelchair	£4		PSSRU 2020[14], cost per year of self or attendant propelled chair. OT assessment band 7 hospital OT, 1 hour.
Electric wheelchair/scooter	£23		PSSRU 2020[14], cost per year of powered chair, OT assessment band 7 hospital OT, 1 hour
Home modifications	£290	£141.46	Sum of stairlift, ramps/rails/other modifications below
Stairlift (straight)	£8		PSSRU 2020[14], major home adaptations p90 Table 1 and 4.
Ramps/rails	£1		Average of rails and ramp costs below
Internal handrail	£12		PSSRU 2020[14], minor home adaptations p90 Table 2 and 3.
External handrail	£15		
Bath handrail	£8		
Ramp to front/back door	£77		

Cost	Mean annual cost	Annual cost for baseline T25FW speed	Source
Other modifications	£281		Sum of costs below
Level access shower	£806		PSSRU 2020[14], major home adaptations p90 Table 1 and 4
Convert room for downstairs WC/washroom	£1,647		
Build downstairs extension for WC/washroom	£3,633		
Build downstairs extension for bedroom	£4,260		
Build downstairs extension for bedroom and ensuite facilities	£5,261		

Abbreviations: OT = Occupational therapist

2.3.6.3 AE costs

To calculate the cost of having an adverse event (AE) into the model, we first used the probability of experiencing each AE (Table 12) from the ENHANCE trial (Table 11) for the BSC arm to accurately weight the unit cost of AEs for the BSC arm (Table 13). For the fampridine group, to estimate these probabilities the fampridine relative risk of having each AE was applied to the baseline BSC risk. The relative risks for UTIs, falls and headaches were based on meta-analyses of studies reporting these AE rates, respectively (Table 12). For the other AEs, the relative risks were estimated from ENHANCE. This calculated the probability of each AE for those treated with fampridine which were then used as weights to find the average unit cost of an AE for fampridine. These costs were made probabilistic.

Unit costs in Table 13 were estimated through committee discussion on staff time and equipment required for each AE, which were then costed using 2020 PSSRU unit costs. Falls, headache and nasopharyngitis, all described as non-serious in the trials, were not incorporated into the model in terms of costs as these were not considered to necessitate medical intervention from a health care professional or prescribed medication, thus not incurring any costs for the NHS. Falls for example in this context may result in minor cuts or bruising that could be managed by the patient at home.

Table 11: Number of non-serious AEs (ENHANCE trial)

AE, n (%)	Fampridine (n=316)	Placebo (n=319)
Most common treatment-emergent AEs by MedDRA* preferred term (≥ 5% in any treatment group)		
UTI	41 (13)	30 (9)

AE, n (%)	Fampridine (n=316)	Placebo (n=319)
Fall	24 (8)	19 (6)
Back pain	16 (5)	11 (3)
Headache	15 (5)	15 (5)
Nasopharyngitis	15 (5)	18 (6)
Upper respiratory tract infection	15 (5)	10 (3)
Treatment-emergent AEs of special interest by MedDRA* preferred term (≥ 1% in any treatment group)		
Cardiovascular disorder (palpitations, tachycardia, arrhythmia)	6 (2)	2 (<1)
Rash	8 (3)	4 (1)

**Medical Dictionary for Regulatory Activities (MedDRA®)*

Table 12: AE rates

AE	BSC probability (see Table 11)	Fampridine RR (95% CI)	Fampridine probability
UTI	0.09	1.18 (0.89-1.56) (a)	0.11
Fall	0.06	0.98 (0.73-1.32) (b)	0.06
Headache	0.05	1.3 (0.92-1.82) (c)	0.06
Nasopharyngitis	0.06	0.84 (0.43-1.64)(d)	0.05
Back pain	0.03	1.47 (0.69-3.11) (d)	0.05
Upper respiratory tract infection	0.03	1.51 (0.69-3.32) (d)	0.05
Cardiovascular disorders (palpitations, tachycardia, arrhythmia)	0.006	3.03 (0.62-14.89) (d)	0.018
Rash	0.013	2.02 (0.61-6.64) (d)	0.025

CI = Confidence Interval
(a) Meta-analysis of studies from the clinical review [15, 20-22, 25, 26, 33, 54, 55]
(b) Meta-analysis of studies from the clinical review [7, 15, 20-22, 25, 26]
(c) Meta-analysis of studies from the clinical review [7, 15, 20-22, 25, 26, 43, 54, 55]
(d) ENHANCE[25]

Table 13: AE costs incorporated into the base case analysis

Adverse event (adjusted to weight)	Unit costs	Placebo	Fampridine	Source
UTI	£36.99	£3.48	£4.10	PSSRU 2020[14], Assumes band 6 nurse, assume 30-minute surgery appointment (Surgery consultation time by a clinical nurse specialist from PSSRU 2015), as well as the average cost of two antibiotics commonly prescribed and urine testing (NHS 2018/2019[38]; Little 2009[30]).
Fall	n/a	n/a	n/a	
Headache	n/a	n/a	n/a	

Adverse event (adjusted to weight)	Unit costs	Placebo	Fampridine	Source
Nasopharyngitis	n/a	n/a	n/a	No cost to NHS as these were described as non-serious adverse events.
Back pain	£34.89	£1.20	£1.77	Calculated assuming 50% visit a GP while the other 50% visit a community physiotherapist, Band 6 (assume 40 min appointment). PSSRU 2020[14], Qualification costs included (excluding individual and productivity costs).
URTI	£3.78	£0.12	£0.18	Calculated assuming 10% visit a GP and get amoxicillin prescription (Amoxicillin 500mg three times daily, 5 days). Dose and unit cost from BNF accessed June 2021. PSSRU 2020[14], Qualification costs included (excluding individual and productivity costs). Assumes 9.22 min consultation
Cardiovascular disorders (d)	£36.55	£0.23	£0.69	PSSRU 2020[14], Qualification costs included (excluding individual and productivity costs). Assumes 9.22 min GP consultation.
Rash	£15.25	£0.19	£0.39	PSSRU 2020[14], Qualification costs included (excluding individual and productivity costs). Assumes 9.22 min consultation
Total AE cost	£5.22	£7.20		Sum of costs above

2.4 Computations

The model was constructed in Microsoft Excel 2010 and was evaluated by cohort simulation. Time dependency was built in by cross referencing the cohorts age as a respective risk factor for mortality.

Patients start in cycle 0 in an alive health state. Patients moved to the dead health state at the end of each cycle as defined by the mortality transition probabilities. Transition probabilities for fampridine responders were derived from pooling the treatment response rate from two RCTs. The transition probability of dying for each of the health states was determined by applying a standardised mortality ratio (SMR)

to age-dependant general population mortality rates from England life tables (ONS life tables for England 2017-19).

The manufacturer provided the variance-co-variance matrix for the T25FW regressions, which were then used to calculate the Cholesky decomposition (see Table 24). This technique was also undertaken following the provision of variance-covariance matrices for each of the constants and coefficients for each healthcare/PSS resource use items, which were also made available by the manufacturer. This meant that the coefficient for each resource use variable was made probabilistic and thus allowed the model to account for uncertainty towards the effect of T25FW score on healthcare and PSS utilisation. Mortality rates were converted into transition probabilities for the respective cycle length (4 weeks) before inputting into the Markov model. The annual probability of death was converted into a rate, before being converted into a probability appropriate for the cycle length. The above conversions were done using the following formulae:

$Selected\ rate\ (r) = \frac{-\ln(1-P)}{t}$	Where *P*=probability of event over time *t* *t*=time over which probability occurs (1 year)
$Transition\ Probability\ (P) = 1 - e^{-rt}$	Where *r*=selected rate *t*=cycle length (4 weeks)

Life years for the cohort were computed each cycle. To calculate QALYs for each cycle, Q(t), the time spent in the alive state of the model (4 weeks or 0.08 years) was weighted by a utility value that is dependent on the time spent in the model and the treatment effect. A half-cycle correction was applied. QALYs were then discounted to reflect time preference (discount rate 3.5%). QALYs during the first cycle were not discounted. The total discounted QALYs were the sum of the discounted QALYs per cycle. The total discounted QALYs were the sum of the discounted QALYs per cycle. Costs per cycle, C(t), were calculated in the same way as QALYs. Costs were discounted to reflect time preference (discount rate 3.5%) in the same way as QALYs using the following formula:

Discounting formula:

$\text{Discounted total} = \frac{\text{Total}}{(1+r)^n}$	Where: *r*=discount rate per annum *n*=time (years)

2.5 Sensitivity analyses

All the sensitivity analyses were undertaken probabilistically and deterministically. Threshold prices produced from the deterministic sensitivity analyses were then set as the cost of fampridine for each scenario in the PSA so that they would inform the probabilistic ICERs (except for the base case where the price for the probabilistic analysis was manually identified).

Cohort settings

2.5.1.1 SA1 Gender split ENHANCE

A sensitivity analysis was conducted where the cohort proportion of females was set to 58% based on the ENHANCE trial, as this proportion was used in the previous model submissions. In the base case analysis, the proportion of females in the model cohort was based on data from Public Health England[51] was which said that 72% of MS diagnoses were women.

NHS reference case edits:

2.5.1.2 SA2 Discounting rate 1.5%

As recommended in the reference case, a sensitivity analysis using a discount rate of 1.5% for costs and health effects was conducted.

Data validation (see Table 14 below):

2.5.1.3 SA3 Pooled utility estimates based on ENHANCE and MOBILE, adjusted to placebo baseline from ENHANCE

This scenario analysis used the same pooled estimates as the base case but rather than adjusting to the pooled placebo baseline utility value from ENHANCE and MOBILE, it was adjusted to the ENHANCE baseline placebo utility value, thus accounting for baseline differences in EQ5D between arms.

2.5.1.4 SA4 MOBILE EQ5D 3L (adjusted to placebo baseline) and MOBILE response rate

This scenario analysis was conducted to isolate the treatment effect of MOBILE trial data on the conclusion of the results, considering that the MOBILE trial reported a higher treatment response rate that ENHANCE but a smaller sample size. In this sensitivity analyses the MOBILE treatment response rate was applied along with the MOBILE EQ5D-3L utility values, adjusted to the placebo baseline, thus accounting for baseline differences in EQ5D between arms.

2.5.1.5 SA5 MOBILE EQ5D 3L (unadjusted to placebo baseline) and MOBILE response rate

A scenario analysis was conducted using the MOBILE treatment response rate and the unadjusted MOBILE EQ5D-3L utility values (thus keeping the observed baseline difference in EQ5D between arms). This scenario analysis replicates the approach taken for the base-case analysis of the model submitted to the SMC which resulted in the approval of fampridine for use in Scotland, minus the inclusion of a patient access scheme.

2.5.1.6 SA6 MOBILE EQ5D 5L (unadjusted to placebo baseline) and MOBILE response rate

A scenario analysis was conducted using the MOBILE treatment response rate and the unadjusted MOBILE EQ5D-5L utility values (thus keeping the observed baseline difference in EQ5D between arms). This scenario analysis replicates the approach

taken for one of the analysis of the model submitted to the SMC, minus the inclusion of a patient access scheme.

2.5.1.7 SA7 ENHANCE EQ5D 3L (adjusted to placebo baseline) and ENHANCE response rate

Similar to SA5, this scenario analysis was conducted to isolate the treatment effect of ENHANCE trial data on the conclusion of the results. In this sensitivity analysis the ENHANCE treatment response rate was applied along with the ENHANCE EQ5D-3L utility values, adjusted to the placebo baseline, thus accounting for baseline differences in EQ5D between arms.

2.5.1.8 SA8 Pooled utility from Acosta 2021

This scenario analysis applied the pooled utility estimates that were reported as part of a scenario analysis in Acosta in order to compare the difference in pooling methodology. Specifically, they combined the utility values reported for non-responders and placebo groups, which were then adjusted to the baseline utility reported for fampridine responders. Acosta pooled ENHANCE and MOBILE using the mapped EQ-5D-3L from MOBILE. As no measures of uncertainty were reported in Acosta, an assumption that the standard deviation would equal the mean was made in order to include these inputs in the probabilistic sensitivity analysis. As the base case of this model is based on calculations which include unpublished EQ5D-3L from MOBILE that must remain confidential as requested by Biogen, this scenario analysis has the benefit of providing an alternative base case to allow pooled data to be published.

Table 14: Utility and treatment response rate inputs for data validation scenario analyses

Scenario analysis	Mean	Standard error (SE)
Probability of treatment response		
ENHANCE (n=315)	0.432	
MOBILE (n=68)	0.485	
Pooled	0.4318	
SA3 Pooled utility estimates based on ENHANCE and MOBILE, adjusted to placebo baseline from ENHANCE		
	Mean	**SE**
BSC	[redacted]	[redacted]
	Mean difference	**SE**
Fampridine responder	[redacted]	[redacted]
Fampridine non-responder	[redacted]	[redacted]
SA4 MOBILE EQ5D 3L (adjusted for placebo baseline) and MOBILE response rate		
	Mean	**SE**
BSC	[redacted]	[redacted]
	Mean difference	**SE**
Fampridine responder	[redacted]	[redacted]
Fampridine non-responder	[redacted]	[redacted]
SA5 MOBILE EQ5D-3L (unadjusted for baseline) and MOBILE response rate		
	Mean	**SE**

Scenario analysis	Mean	Standard error (SE)
BSC	[redacted]	[redacted]
	Mean difference	**SE**
Fampridine responder	[redacted]	[redacted]
Fampridine non-responder	[redacted]	[redacted]
SA6 MOBILE EQ5D-5L (unadjusted for placebo baseline) and MOBILE response rate		
	Mean	**SE**
BSC	0.480	0.03
	Mean difference	**SE**
Fampridine responder	0.140	0.033
Fampridine non-responder	-0.033	0.033
SA7 ENHANCE EQ5D 3L (adjusted for placebo baseline) and ENHANCE response rate		
	Mean	**SE**
BSC	0.665	0.01
	Mean difference	**SE**
Fampridine responder	0.020	0.013
Fampridine non-responder	0.000	0.015
SA8 Pooled utility from Acosta 2021 (adjusted for placebo baseline)		
	Mean	**SE**
BSC	0.665	0.01
	Mean difference	**SE**
Fampridine responder	0.020	0.013

Note: Beta distribution was applied for both treatment response rates and utility inputs when modelled probabilistically.

2.5.1.9 SA9 Excluded AE disutility

The base case assigned a utility decrement of 0.04 per adverse event for 7 days, based on the disutility reported in Acosta 2021. There were concerns that this would be considered as double counting, given that the overall quality of life was captured within the same trials that informed the adverse event model inputs. Therefore, this utility decrement was removed in this scenario analysis.

2.5.1.10 SA10 Assessment costs including full neurology appointment

To account for uncertainty surrounding the length of time a neurologist is typically involved in the responder assessment at four weeks, the unit cost of a face-to-face consultant led follow up appointment from NHS reference costs 2019-2020 (£90) was included rather than the 5 minutes of consultant neurologist time (£12) included in the base case. This would increase the total assessment cost from £38 to £116 per person.

2.5.1.11 SA11 Include only healthcare costs associated with T25FW walking speed

Due to uncertainty with regards to the costing and resource use data for PSS, a sensitivity analysis was conducted where the PSS costs were excluded. Thus, only the impact of walking speed on HCRU visits was captured.

2.5.1.12 SA12 Exclude healthcare and PSS costs associated with T25FW walking speed

To estimate the cost-effectiveness of fampridine when there is no cost-savings to the NHS for long-term (5-year) walking improvement for fampridine responders. This was done to address uncertainty expressed by committee members towards the suggestion from the Adelphi study that fampridine has the potential to be cost saving in terms of healthcare and PSS resource use over time.

2.5.1.13 SA13 Societal perspective, include non-professional care in PSS costs

This scenario analysis would highlight the impact of including non-professional care on the results. Non-professional care costs were estimated similarly to HCRU and PSS costs, in that they were taken from the univariate analyses from Adelphi study linking T25FW walking speed to non-professional care utilisation (see Table 21 in Appendix B for figures). The proportion needing non-professional care and the quantity used was also taken from Berg 2006[4] which is shown in Table 22. As there is no single recommended approach for assigning the cost of non-professional care, for simplicity an opportunity cost method was adopted here PSSRU 2012[13], whereby minimum wage was used (£8.91/hour)[52]. This is outside of the NICE reference case and therefore for information only, not decision making. This perspective was also the base case analysis for Acosta (2021)[1] and was also a reported as a scenario analysis in the AWMSG Model[2].

2.5.1.14 SAs 14-27 Threshold analyses on cost of fampridine in combination with base-case and the SAs

In these analyses one input parameter is varied until the conclusions of the model results change. Threshold analyses will be conducted on the base-case and all other scenarios to identify the per-cycle cost of fampridine required in order for fampridine to be cost effective at a threshold of £20,000 per QALY.

2.6 Summary of Model assumptions:

Clinical inputs

- Long-term natural progression of decline in walking was estimated using T25FW scores due to lack of long-term clinical data for MSWS-12 (12-item MS walking scale).
- No participants were modelled to progress to EDSS score >7 over the 5-year time horizon.
- Fampridine responders who withdrew from treatment become non-responders and lose all associated utility gains and treatment costs.
- Non-responders could not reinitiate treatment.

Quality of life

- Post-hoc analyses from ENHANCE and MOBILE were used to apply utility estimates, provided by responder status.

- Utility of fampridine non-responders were applied to those who withdrew from fampridine for any reason.
- Utility values that were carried forward to the 5-year time horizon account for changes over 24-week trial period and therefore differences in baseline utility.

Costs and resource use

- Administration costs associated with fampridine were assumed as zero due to it being an oral treatment.
- Resource use for adults with MS was based on an Adelphi study that collected from 5 European countries including the UK.
- Model assumed no intervention costs were incurred for the BSC group.
- Adverse event resource use was estimated using weighted average from the AE frequencies reported in ENHANCE and meta-analysis of clinical review RCTs for UTIs.
- No costs to NHS associated with headaches, falls and nasopharyngitis as these were classified as non-serious in clinical trials.

2.7 Model validation

The model was developed in consultation with the committee; model structure, inputs and results were presented to and discussed with the committee for clinical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs. The model was peer reviewed by a second experienced health economist from the NGC; this included systematic checking of many of the model calculations.

2.8 Estimation of cost effectiveness

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with 2 alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$

Where: Costs(A) = total costs for option A; QALYs(A) = total QALYs for option A

Cost effective if:
- ICER < Threshold

When there are more than 2 comparators, as in this analysis, options must be ranked in order of increasing cost then options ruled out by dominance or extended dominance before calculating ICERs excluding these options. An option is said to be dominated, and ruled out, if another intervention is less costly and more effective. An option is said to be extendedly dominated if a combination of 2 other options would prove to be less costly and more effective.

It is also possible, for a particular cost-effectiveness threshold, to re-express cost-effectiveness results in term of net monetary benefit (NMB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the total costs (formula below). The decision rule then applied is that the comparator with the highest NMB is the cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost.

$Net\ Monetary\ Benefit(X) = (QALYs(X) \times \lambda) - Costs(X)$ *Where: λ = threshold (£20,000 per QALY gained)*	Cost effective if: • Highest net benefit
$Net\ Health\ Benefit\ (X) = (QALYs(X)) - Costs(X) / \lambda$ *Where: λ = threshold (£20,000 per QALY gained)*	Cost effective if: • Highest net benefit

Both methods of determining cost effectiveness will identify exactly the same optimal strategy. For ease of computation NMB is used in this analysis to identify the optimal strategy.

Results are also presented graphically where total costs and total QALYs for each treatment are shown. Comparisons not ruled out by dominance or extended dominance are joined by a line on the graph where the slope represents the incremental cost-effectiveness ratio.

2.9 Interpreting results

NICE sets out the principles that committees should consider when judging whether an intervention offers good value for money.[34, 36, 37] In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

3 Results

3.1 Base case

The deterministic and probabilistic base case results are presented in Table 15 and Table 16. Fampridine was associated with higher costs and higher QALYs. The incremental cost effectiveness ratio (ICER) for the probabilistic analysis was £82,099 per QALY gained and £82,847 in the deterministic analysis. Both base cases show that the ICER is significantly higher than the NICE threshold of £20,000, and therefore fampridine would be not considered cost effective. The probability of fampridine being cost effective was very low, 7%. The main driver of the results was high cost of fampridine for a marginal benefit over the 5-year time horizon. The current list price used for a 28-day supply of fampridine is £362. The deterministic threshold analysis found that fampridine would be considered cost-effective by NICE if the drug cost was £195 for a 28-day supply. The probabilistic threshold analysis found the cost to be slightly higher at £202 if fampridine were to be considered cost-effective.

Table 17 presents a breakdown of the probabilistic results, which shows that 27% of the model cohort were still on treatment after 5 years. AE costs were similar between for fampridine (£28) and BSC (£20). There was also only £54 difference in healthcare costs (£5,988 for fampridine versus £6,042 for BSC), however, PSS costs were £3,480 higher for BSC compared to fampridine over the time horizon.

The results are also presented graphically where total costs and total QALYs for each treatment are shown (Figure 4). Comparisons not ruled out by dominance or extended dominance are joined by a line on the graph where the slope represents the incremental cost-effectiveness ratio.

Table 15: Deterministic Base case results

Intervention	Total costs undiscounted	Total costs discounted	Total LY undiscounted	Total LY discounted	Total QALYs undiscounted	Total QALYs discounted	Incr. Costs	Incr. QALYs	ICER fampridine vs BSC	NMB @£20K	Rank @£20K	NMB @£30K	Rank @£30K
Base-case results: Fampridine vs best supportive care (a)													
Fampridine	£54,938	£50,250	4.91	4.51	3.06	2.81	£4,760	0.06	£82,847	£5,935	2	£34,027	2
BSC	£49,867	£45,490	4.91	4.51	3.00	2.75	n/a	n/a	n/a	£9,546	1	£37,063	1
Threshold analysis on cost of fampridine in combination with base case (28-day supply of fampridine cost of £194.57 creates £20,000 ICER)													
Fampridine	£51,038	£46,639	4.91	4.51	3.06	2.81	£1,149	0.06	£20,000	£9,546	1	£37,638	1
BSC	£49,867	£45,490	4.91	4.51	3.00	2.75	n/a	n/a	n/a	£9,546	2	£37,063	2

Abbreviations: BSC: best supportive care, CE: cost effective, ICER: incremental cost effectiveness ratio, LYs: life years, NMB: net monetary benefit, QALYs: quality adjusted life years, £20k: £20,000 per QALY gained, £30K: £30,000 per QALY gained.

(a) Fampridine list price cost for 28-day supply (4 weeks): £362

Table 16: Probabilistic Base case results

Intervention	Total costs undiscounted	Total costs discounted	Total LY undiscounted	Total LY discounted	Total QALYs undiscounted	Total QALYs discounted	Incr. Costs	Incr. QALYs	ICER fampridine vs BSC	NMB @£20K	Rank @£20K	Probability CE @£20K	NMB @£30K	Rank @£30K
Base-case results: Fampridine vs best supportive care (a)														
Fampridine	£56,646	£51,807	4.91	4.51	3.06	2.81	£4,662	0.06	£82,099	£4,357	2	0.07	£32,438	2
BSC	£51,685	£47,145	4.91	4.51	3.00	2.75	n/a	n/a	n/a	£7,883	1	0.93	£35,397	1
Threshold analysis on cost of fampridine in combination with base case (28-day supply of fampridine cost of £202 creates £20,000 ICER)														
Fampridine	£53,227	£48,633	4.91	4.51	3.06	2.81	£1,141	0.06	£19,746	£7,551	2	0.48	£35,644	1
BSC	£52,071	£47,493	4.91	4.51	3.00	2.75	n/a	n/a	n/a	£7,537	1	0.52	£35,051	2

Abbreviations: BSC: best supportive care, CE: cost effective, ICER: incremental cost effectiveness ratio, LYs: life years, NMB: net monetary benefit, QALYs: quality adjusted life years, £20k: £20,000 per QALY gained, £30K: £30,000 per QALY gained.

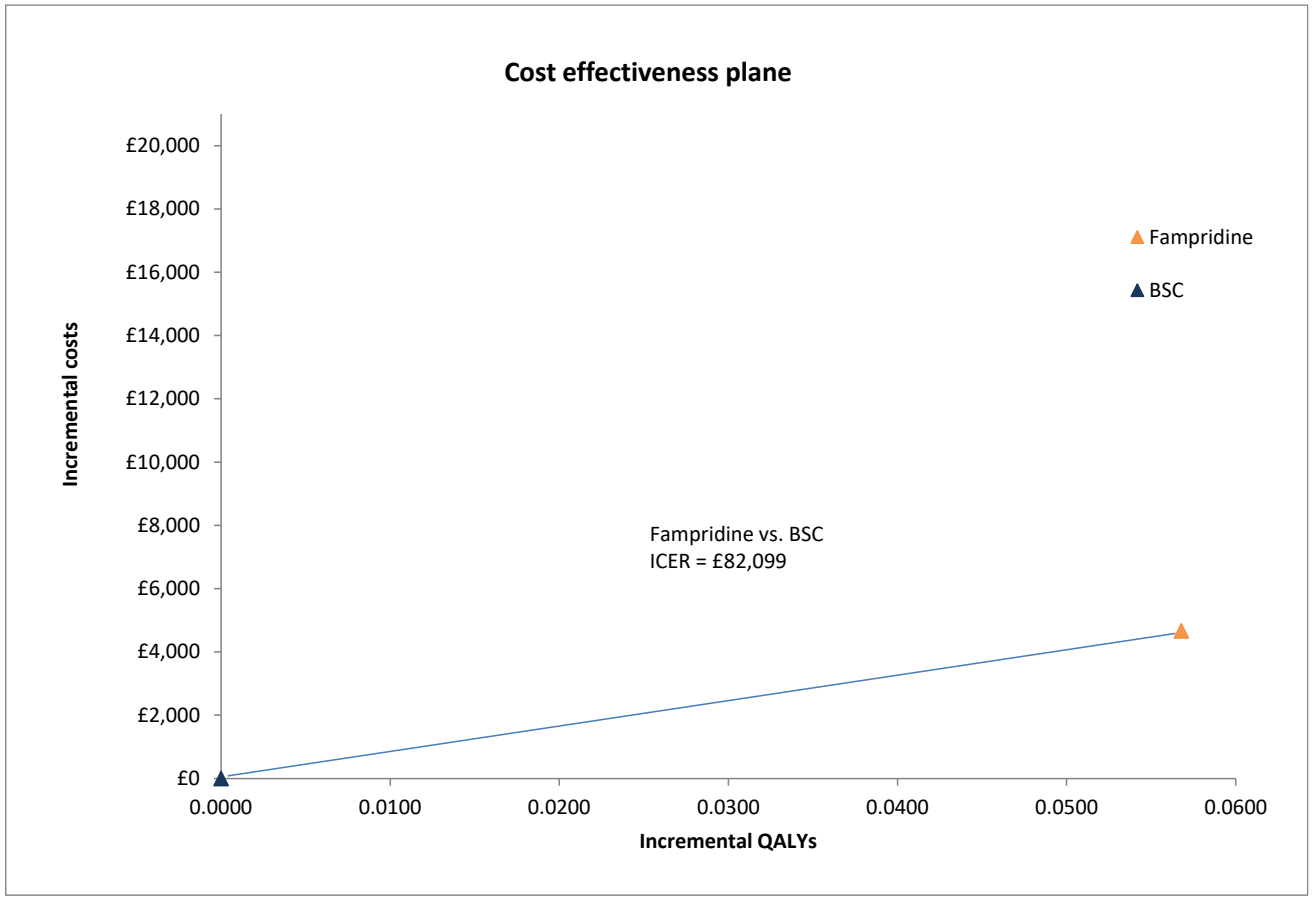
(a) Fampridine list price cost for 28-day supply (4 weeks): £362

Table 17: Costs and events breakdown for probabilistic results

Proportion in each state at 5 years					Event breakdown per 1000 people	Cost breakdown			
	On treatment	Withdrawn	Continue BSC	Dead	AEs	Treatment	AEs	HC costs	PSS costs
Fampridine	0.27	0.69		0.04	4523	£8,488	£28	£5,988	£42,143
BSC			0.96	0.04	8751	£0	£20	£6,042	£45,622

Abbreviations: AEs: non-adverse events, BSC: best supportive care, HC costs: healthcare costs, PSS costs: personal and social services costs.

Figure 4: Cost effectiveness plane



3.2 Sensitivity analyses

A number of sensitivity analyses were conducted and are described in detail in section 2.5. The probabilistic results of the sensitivity analyses SA1 to SA27 are presented in Table 18 and Table 19 below. These are presented separately for the scenario and threshold analyses.

Best supportive care remained cost effective in all sensitivity analyses. Changes that did not significantly impact the results were including the proportion of females from the ENHANCE trial (SA1), applying a 1.5% discount rate for cost and outcomes (SA2), applying pooled utility estimates to the baseline placebo value from ENHANCE (SA3), excluding AE disutility (SA9) and increasing the cost of the responder assessment to include a full appointment time with a neurologist (SA10).

SA5, which replicated the base case approach from the SMC[46] submission (minus the PAS), had the lowest ICER (£[redacted]). This is unsurprising considering that this scenario used MOBILE EQ-5D-3L utility data and treatment response rates alone, rather than the pooled estimates with ENHANCE. MOBILE reported a higher proportion of fampridine responders and greater benefits in terms of quality of life than the ENHANCE RCT, but when these two studies are pooled in the base case, the larger ENHANCE trial carries more weight.. Treatment-specific utilities were also not adjusted in this scenario; considering that fampridine responders had the highest baseline utility in the MOBILE trial, this would have further benefited fampridine in the results. A similar outcome was seen in SA6 which produced an ICER of £30,603 from applying the same approach as SA5 but using EQ-5D-5L values from MOBILE instead of EQ-5D-3L.

Removing the benefit of fampridine in terms of reduced healthcare and PSS resource use linked to better walking ability had the most significant impact on the results and created the largest ICERs (SA11 and SA12).

Applying a societal perspective to the analysis, including non-professional care costs associated with changes in T25FW speed (in addition to healthcare and PSS costs included in the base case), was not sufficient to produce a cost-effective result for fampridine, as the ICER was only reduced to £66,052 per QALY.

Table 19 presents the probabilistic results of the threshold analyses. The threshold price that would allow fampridine to be cost-effective (£20,000/QALY) for each of the SAs was first found deterministically, except for the base-case which was estimated manually. This price was then applied as the drug cost and the model was ran probabilistically. Due to the uncertainty surrounding the HCRU and PSS costs were incorporated in model, the probabilistic and deterministic costs aren't quite the same. The prices from these threshold analyses using the sensitivity analyses inputs align with the results from Table 18 (base case). In particular, SA15-17 produced similar prices to the base case. However, SA25 and SA26 were significantly lower (£51.19 and £53.26), reflecting the lower of value of fampridine when the reduction in resource use from a slower decline in walking speed is removed from the model. The price in SA19 and SA20, when the MOBILE EQ5D-3L and 5L utilities (unadjusted for

baseline differences) were used, was higher at £323 and £285 respectively. These higher costs reflect the more favourable MOBILE trial EQ5D data being used.

Table 18: Scenario analyses results

Intervention	Total costs discounted	Total QALYs discounted	Incr. Costs	Incr. QALYs	ICER fampridine vs BSC	Probability CE @£20K
Base case						
Fampridine	£51,807	2.81	£4,662	0.06	£82,099	0.07
BSC	£47,145	2.75	n/a	n/a	n/a	0.93
SA1 Gender split ENHANCE						
Fampridine	£51,612	2.81	£4,649	0.06	£80,266	0.07
BSC	£46,963	2.75	n/a	n/a	n/a	0.93
SA2 1.5% discount rate						
Fampridine	£54,503	2.95	£4,807	0.06	£82,538	0.06
BSC	£49,696	2.89	n/a	n/a	n/a	0.94
SA3 Pooled utility, adjusted to placebo baseline from ENHANCE						
Fampridine	£51,854	2.93	£4,649	0.06	£84,333	0.07
BSC	£47,205	2.87	n/a	n/a	n/a	0.93
SA4 MOBILE EQ5D 3L (adjusted to placebo baseline) and MOBILE response rate						
Fampridine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA5 MOBILE EQ5D-3L (unadjusted for baseline) and MOBILE response rate						
Fampridine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA6 MOBILE EQ5D-5L (unadjusted for baseline) and MOBILE response rate						
Fampridine	£52,594	2.33	£5,153	0.17	£30,603	0.34
BSC	£47,441	2.17	n/a	n/a	n/a	0.66
SA7 ENHANCE EQ5D 3L and ENHANCE response rate						
Fampridine	£51,997	2.92	£4,642	0.05	£88,952	0.06
BSC	£47,355	2.87	n/a	n/a	n/a	0.94
SA8 Pooled utility from Acosta 2021						
Fampridine	£51,997	2.92	£4,642	0.05	£88,952	0.06
BSC	£47,355	2.87	n/a	n/a	n/a	0.94
SA9 Excluded AE disutility						
Fampridine	£52,071	2.81	£4,641	0.06	£75,693	0.07
BSC	£47,430	2.75	n/a	n/a	n/a	0.93
SA10 Assessment costs including full neurology appointment						
Fampridine	£52,048	2.81	£4,687	0.06	£81,426	0.06
BSC	£47,361	2.75	n/a	n/a	n/a	0.94
SA11 Include only healthcare costs associated with T25FW walking speed						

Intervention	Total costs discounted	Total QALYs discounted	Incr. Costs	Incr. QALYs	ICER fampridine vs BSC	Probability CE @£20K
Fampridine	£13,379	2.81	£7,812	0.06	£133,422	0.00
BSC	£5,566	2.75	n/a	n/a	n/a	1.00
SA12 Exclude healthcare and PSS costs associated with T25FW walking speed						
Fampridine	£7,894	2.81	£7,876	0.06	£132,813	0.00
BSC	£18	2.75	n/a	n/a	n/a	1.00
SA13 Societal perspective, include non-professional care in PSS costs						
Fampridine	£65,459	2.81	£3,850	0.06	£66,052	0.12
BSC	£61,609	2.75	n/a	n/a	n/a	0.88

Table 19: Results from threshold analyses on the cost of fampridine

Threshold analyses	Fampridine cost
SA14 Threshold analysis on cost of fampridine in combination with base case	£202
SA15 Threshold analysis on cost of fampridine in combination with gender split	£194.55
SA16 Threshold analysis on cost of fampridine combined with 1.5% discount rate	£196.18
SA17 Threshold analysis on cost of fampridine in combination with pooled utility, separate utility applied to non-responders	£194.57
SA18 Threshold analysis on cost of fampridine in combination with MOBILE 3L/response	£218.34
SA19 Threshold analysis on cost of fampridine combined with MOBILE 3L unadjusted/response	£323.40
SA20 Threshold analysis on cost of fampridine in combination with MOBILE 5L unadjusted/response	£284.81
SA21 Threshold analysis on cost of fampridine in combination with ENHANCE 3L/response	£191.83
SA22 Threshold analysis on cost of fampridine in combination with Pooled utility Acosta	£183.24
SA23 Threshold analysis on cost of fampridine in combination with AE disutility excluded	£195.02
SA24 Threshold analysis on cost of fampridine in combination with Assessment costs	£191.00
SA25 Threshold analysis on cost of fampridine in combination with HC costs only	£53.26
SA26 Threshold analysis on cost of fampridine in combination with Exclude HC PSS costs	£51.19
SA27 Threshold analysis on cost of fampridine in combination with Societal costs included	£228.22

4 Discussion

4.1 Summary of results

The base case and all sensitivity analyses found that fampridine was not the cost effective option at a threshold of £20,000 per QALY (probability of being most cost effective 7% in base case). Fampridine would be considered cost effective if the drug price was reduced to £202 per 28-day supply from the current list price of £362.

A data validation exercise was undertaken to compare the utility data in our model to the EQ5D data used in the SMC, AWMSG and Acosta. While there were differences in the ICERs, no scenario analysis performed produced a result that determined fampridine to be cost-effective. The two scenarios that produced results closest to the £20,000 threshold would not be sufficient to base a recommendation on as they are not an appropriate use of data (i.e. they only used a single trial (MOBILE) and did not include an adjustment for baseline differences).

The model was sensitive to changes in utility data sources and whether the model incorporated a reduction in healthcare resource utilisation stemming from improved walking speed (SA11 and SA12). Committee discussion had previously highlighted concerns towards the accuracy of the T25FW univariate analyses that were used to calculate annual healthcare resource use which creates uncertainty towards the robustness of the results.

4.2 Limitations and interpretation

The model was limited in terms of the data source that could be included as a treatment effect, as utility values were taken from post-hoc analyses that were only available up to week 24. The mean utility over 24 weeks reported in the trial was applied in the model for this time as well as up to 5 years. Alongside this, due to the lack of long-term clinical trial or resource use data for 12-item MS walking scale (MSWS-12) that was used to measure treatment response, disease progression was defined using a different measure (T25FW). The MSWS-12 is patient reported and thus considered to be a relatively subjective measure of walking ability, whereas the T25FW is assessed by a healthcare professional and considered to be more objective. Using MSWS-12 for responder identification and T25FW for disease progression may therefore have generated different results then if it had been possible to use MSWS-12 for both outcomes. There was also uncertainty around the relationship between the resource use (and therefore costs) and the treatment effect; the values used for resource use data were obtained from data from 5 European countries (albeit including the UK), with data regarding T25FW scores only reported in <10% of respondents. Furthermore, several assumptions had to be made in order to estimate unit costs and resource use.

4.3 Generalisability to other populations or settings

This cost effectiveness analysis is taken from a UK NHS setting. The model used NHS reference costs and the cost effectiveness of fampridine was assessed using NICE's £20,000 threshold. Therefore, the results of this cost effectiveness may not be transferable to other countries or settings.

4.4 Comparisons with published studies

Four health economic studies with relevant comparisons were included in the pharmacological management of mobility review (Evidence Review E), three of which had a UK NHS perspective. Table 20 presents the results of the previously published studies, including various scenario analyses. Note, the incremental QALYs are different between the three studies above (NICE 2014, SMC 2020 and Acosta 2021) due to the economic analyses adopting different time horizons (1 year, 5 years and 20 years) and the use of different clinical evidence to estimate QALYs (Goodman 2009:[22] MSWS-12 scores mapped to EQ5D-3L, MOBILE RCT:[26] EQ5D-5L mapped to 3L and ENHANCE RCT:[24] EQ5D-3L). In addition, both Acosta and the SMC analyses applied baseline utilities that differed between comparators, accounting for the higher QALY gain. The SMC has the highest QALY gain due to applying MOBILE utility data and treatment response rates, which were more favourable to fampridine compared to estimates from ENHANCE, which Acosta used for the base case.

The AWMSG analysis[2] was not included as it did not report any results due to commercial confidentiality around the PAS. In all instances except Acosta (where the cost of fampridine in Sweden is less than a third of NHS indicative price (£109 versus £362), fampridine was not cost-effective compared to best supportive care when there was no patient access scheme in place.

Table 20: Base case results compared to published studies evaluating fampridine versus best supportive care

Analysis	Used PAS	Incremental QALYs	ICER (£ per QALY gained)
NCGC analysis (2021) Probabilistic base-case results using pooled ENHANCE and MOBILE (EQ5D-3L, adjusted to placebo baseline) and list price	No	0.06	£82,099
SMC (2018) using ENHANCE utility data (EQ5D-3L) and list price	No	NR	£149,659
SMC (2018) MOBILE EQ5D-5L mapped to EQ5D-3L and list price	No	NR	£92,961
SMC (2018) using MOBILE utility data (EQ5D-5L, not mapped to EQ5D-3L) and list price	No	NR	£44,739
SMC (2020) using MOBILE EQ5D-5L mapped to EQ5D-3L	Yes	0.16	£13,156

Analysis	Used PAS	Incremental QALYs	ICER (£ per QALY gained)
NCGC Analysis (2014)	No	0.029	£160,884
Acosta (2021) [1]	No	0.12	£10,411

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; PAS, patient access scheme; NR: not reported; QALY, quality adjusted life year

4.5 Conclusions

Fampridine in combination with best supportive care is not cost-effective compared to best supportive care alone at its current list price. Conclusions about fampridine not being the most cost-effective intervention were unchanged in all sensitivity analyses.

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Appendices

Appendix A: Additional information

The tables below summarise all probabilistic inputs in the model and the distribution parameters used.

Table 21: Univariate analyses on relationship between HCRU/PSS consumption and T25FW (independent variable) from Adelphi MS disease-specific program.

Item	Constant	SE	T25FW coefficient	SE	Resource use over 12 months	Unit cost	Baseline cost [a]
HCRU							
Physiotherapy	2.22	0.31	-0.36	0.1	4.32	£25.98	£112.75
Neurologist	1.42	0.09	-0.0014	0.03	4.13	£187.17	£770.76
GP	1.22	0.2	-0.21	0.05	2.18	£36.55	£79.39
MS Specialist	-0.89	0.26	0.11	0.06	0.52	£187.17	£96.57
MS Nurse	-0.82	0.54	-0.06	0.12	0.39	£15.25	£5.99
Psychiatrist	-1.14	0.59	-0.03	0.15	0.30	£243.48	£72.83
Urology (nurse)	-0.62	0.42	-0.37	0.19	0.25	£26.29	£6.52
Internist	-1.92	0.65	0.05	0.14	0.16	£158.60	£25.79
Other Physician	-2.35	0.65	-0.24	0.24	0.06	£36.55	£2.12
Gastroenterologist	-2.52	0.58	-0.33	0.21	0.04	£132.90	£5.35
PSS							
Non-professional care	0.17	0.43	-0.35	0.18	0.57	See Table 22	£2,527.69
Professional care	0.20	0.43	-0.52	0.17	0.41		£6,642.39
Walking aids	-0.13	0.41	-0.28	0.12	0.48		£13.82
Home modifications	-0.28	0.43	-0.21	0.13	0.49		£141.46
Excluded HCRU from model							

Item	Constant	SE	T25FW coefficient	SE	Resource use over 12 months	Unit cost	Baseline cost [a]
Hospitalised for MS	-0.09	0.16	-0.001	0.03	0.91	£2,699.89	£2,459.95
ER	-1.38	0.31	0.02	0.08	0.26	£181.90	£47.37
Ophthalmologist	-1.78	0.45	0.03	0.1	0.18	£120.05	£21.67
ER Doctor	-4.87	0.99	0.12	0.22	0.01	£143.93	£1.40

(a) Based on baseline T25FW speed (2.1 ft/s)

Table 22: PSS unit costs

	Proportion using resources (a)	Quantity used in 1-month recall period (hours) (a)	Unit cost	Mean cost per person for recall period	Mean annual cost per patient	Source
Non-professional care	56.60%	73	£8.61	£653	**£4,436**	PSSRU 2012, minimum wage applied to cost of unit cost per hour
Professional care						
Nurse home visits	5.90%	12	£52	£602	£426	PSSRU 2020, qualification costs included (excluding individual and productivity costs). Assumes band 6 nurse.
Home help	11.80%	49	£24	£1,169	£1,656	PSSRU 2020, qualification costs not included home care worker cost per hour
Personal assistant	16.80%	299	£24	£7,085	£14,283	PSSRU 2020, qualification costs not included home care worker cost per hour. Assume cost of personal assistant same as cost of home care worker.
Total cost professional care					**£16,365**	**Sum of costs above**
Walking aids	**Proportion using resources (a)**	**Unit cost**	**OT unit cost**	**OT assessment duration, hr**	**Mean annual cost per patient**	

	Proportion using resources (a)	Quantity used in 1-month recall period (hours) (a)	Unit cost	Mean cost per person for recall period	Mean annual cost per patient	Source
Walking aids	4%	£3.59	£50	1	£2	NHS supply chain catalogue walking stick wooden OT assessment for provision (appointment duration assumed 1 hour, community OT, band 6 incl. qualifications, PSSRU 2020)
Wheelchair	2.20%	£103	£62	1	£4	PSSRU 2020, cost per year of self or attendant propelled chair. OT assessment band 7 hospital OT (1 hour)
Electric wheelchair/scooter	4.20%	£481	£62	1	£23	PSSRU 2020, cost per year of powered chair, OT assessment band 7 hospital OT, 1hr
Total cost walking aids					**£29**	**Sum of costs above**
Home modifications	**Proportion using resources (a)**	**Mean annual equipment cost**	**Mean staff time for provision**	**Annuity factor, 10 years, 3.5%**	**Mean annual cost per patient**	
				8. 61		
Stairlift (straight)	2.20%	£272	£654	£76	£8	PSSRU 2020, major home adaptations p90 Table 1 and 4.
Ramps/rails	3.30%				£1	Average of rails and ramp costs below
Internal handrail		£4	£71	£8	£12	PSSRU 2020, minor home adaptations p90 Table 2 and 3.
External handrail		£6	£76	£9	£15	
Bath handrail		£3	£47	£5	£8	
Ramp to front/back door		£46	£268	£31	£77	
Other modifications	9%				£281	Sum of costs below
Level access shower		£673	£1,146	£133	£806	PSSRU 2020, major home adaptations p90 Table 1 and 4
Convert room for downstairs WC/washroom		£1,426	£1,901	£221	£1,647	
Build downstairs extension for WC/washroom		£3,264	£3,180	£369	£3,633	

	Proportion using resources (a)	Quantity used in 1-month recall period (hours) (a)	Unit cost	Mean cost per person for recall period	Mean annual cost per patient	Source
Build downstairs extension for bedroom	£3,866		£3,395	£394	£4,260	
Build downstairs extension for bedroom and ensuite facilities	£4,867		£3,395	£394	£5,261	
Total cost home modifications					**£290**	**Sum of stairlift, ramps/rails/other modifications above**

(a) Taken from Berg (2006)

Table 23: PSA inputs for T25FW weighted regressions (CONFIDENTIAL)

Direct Resource Item	**Weighted covariance matrix**		**Cholesky Decomposition**	
	Intercept	Slope	Intercept	Slope
Fampridine responders				
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Slope	[redacted]	[redacted]	[redacted]	[redacted]
BSC/fampridine non-responders				
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Slope	[redacted]	[redacted]	[redacted]	[redacted]

Table 24: PSA inputs for HCRU and PSS items (CONFIDENTIAL)

Direct Resource Item	Univariate analysis		Cholesky Decomposition (T)	
	T25FW coefficient	Constant	T25FW coefficient	Constant
MS Hospitalisation				
T25FW coefficient	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]
ER visits				
T25FW coefficient	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]
Neurologist				
T25FW coefficient	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]
GP				
T25FW coefficient	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]
MS Specialist				
T25FW coefficient	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]
MS Nurse				
T25FW coefficient	[redacted]	[redacted]	[redacted]	[redacted]

Direct Resource Item	Univariate analysis		Cholesky Decomposition (T)	
	T25FW coefficient	Constant	T25FW coefficient	Constant
Constant	[redacted]	[redacted]	[redacted]	[redacted]
Internist				
T25FW coefficient	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]
ER doctor				
T25FW coefficient	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]
Physiotherapy				
T25FW coefficient	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]
Ophthalmologist				
T25FW coefficient	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]
Urologist				
T25FW coefficient	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]
Gastroenterologist				
T25FW coefficient	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatrist				

Direct Resource Item	Univariate analysis		Cholesky Decomposition (T)	
	T25FW coefficient	Constant	T25FW coefficient	Constant
T25FW coefficient	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]
Other Doctor				
T25FW coefficient	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]
Non-professional care				
T25FW coefficient	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]
Professional care				
T25FW coefficient	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]
Walking Aids				
T25FW coefficient	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]
Home modifications				
T25FW coefficient	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]

(a) <Insert Note here>

Table 25: MOBILE EQ-5D-5L mapped to 3L using van Hout 2012 (CONFIDENTIAL)

	Placebo	Fampridine non-responder	Fampridine responder
n	[redacted]	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]	[redacted]
Baseline SD	[redacted]	[redacted]	[redacted]
Calculated change over 24 weeks using LSM mean over 24 weeks and minus baseline	[redacted]	[redacted]	[redacted]
LSM mean over 24 weeks	[redacted]	[redacted]	[redacted]
LSM mean 95% LCI	[redacted]	[redacted]	[redacted]
LSM mean 95% UCI	[redacted]	[redacted]	[redacted]
LSM change over 24 weeks	[redacted]	[redacted]	[redacted]
LSM change over 24 weeks LCI	[redacted]	[redacted]	[redacted]
LSM change over 24 weeks UCI	[redacted]	[redacted]	[redacted]

Abbreviations: LSM = least square mean, UCI = Upper confidence interval, LCI = lower confidence interval