National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Biotin for treating primary and secondary progressive multiple sclerosis [ID919]

Response to consultee and commentator comments on the draft remit and draft scope (post-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Association of British Neurology	This is an appropriate topic	Comment noted. No action required.
	MedDay Pharmaceuticals	MedDay believes so; high dose Pharmaceutical-grade Biotin (hdPB) has been developed to treat non-relapsing Progressive Multiple Sclerosis (PMS). Currently there are no licensed treatments for PMS and there is a high unmet medical need for new treatments for this disabling form of MS. Current management consists of rehabilitation; occupational and other supportive therapies, such as physiotherapy, cognitive therapy, fatigue management and eventually palliative care.	Comments noted. No action required.
	MS Society	Biotin may represent a groundbreaking step in MS treatment by potentially becoming one of the first licensed treatment for primary progressive MS (PPMS). However, it is yet to be granted marketing authorisation so a NICE TA must be aligned with the EMA's licensing schedule	Comments noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Biotin has shown some promise in clinical trials as a treatment for people with PPMS and secondary progressive MS (SPMS), with some improvement in disability being witnessed. It has been generally well tolerated with no significant side effects.	
	Multiple Sclerosis Trust	Yes, we understand that the EMA CHMP is currently evaluating a marketing authorisation application for biotin for progressive MS.	Comment noted. No action required.
	NHS England	Yes	Comment noted. No action required.
Wording	Association of British Neurology	The wording is accurate	Comment noted. No action required.
	MedDay Pharmaceuticals	Yes. We have made some suggestions as to wording changes that we believe should be considered below.	Comment noted. Please refer to relevant sections for specific responses. No action required.
	MS Society	Yes	Comment noted. No action required.
	Multiple Sclerosis Trust	Yes	Comment noted. No action required.
	NHS England	Yes	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Timing Issues	Association of British Neurology	There is currently no NIEC-approved disease-modifying treatment of progressive multiple sclerosis, so there is urgency. (Although ocrelizumab is currently undergoing NICE review for this indication)	Comments noted. NICE has scheduled this topic into its work programme. For further details, see the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta10099. No action required.
	MedDay Pharmaceuticals	Given the high degree of unmet need, guidance is urgently required.	Comment noted. NICE has scheduled this topic into its work programme. See the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta10099. No action required.
	MS Society	We welcome NICE's consideration of Biotin on the condition that it receives a positive decision from the EMA and is granted marketing authorisation.	Comment noted. No action required.
	Multiple Sclerosis Trust	Currently there are no licensed treatments that slow down or stop disease progression in secondary or primary progressive MS. If a marketing authorisation is granted, there is likely to be a high demand for biotin. It is vital that NICE appraisal is completed as close as possible to licensing to ensure clarity about eligibility and availability within NHS England. However	Comments noted. NICE has scheduled this topic into its work programme. See the NICE website: https://www.nice.org.uk/

Section	Consultee/ Commentator	Comments [sic]	Action
		the wording of the licensed indication may reference specific subgroups and have a significant impact on the appraisal of clinical and cost effectiveness.	guidance/indevelopment/gid-ta10099. No action required.
	NHS England	There are few current treatment options for primary and progressive MS so an early review of this product would be welcomed.	Comment noted. NICE has scheduled this topic into its work programme. See the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta10099. No action required.
Additional comments on the draft remit	-	-	-

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Association of British Neurology	This is accurate	Comment noted. No action required.
	MedDay Pharmaceuticals	The information provided is both accurate and comprehensive.	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	MS Society	Yes	Comment noted. No action required.
	Multiple Sclerosis Trust	A small number of people will be diagnosed with secondary progressive MS from the outset. Background does not adequately reflect the impact of progressive forms of MS. Complications due to symptoms can arise, for example, falls as a result of mobility and balance problems, pressure sores as a result of immobility etc. Part of the particular challenge in all forms of MS is the interplay between symptoms which occur simultaneously. There are significant challenges to remaining in employment for people with progressive MS and increasing carer burden as the condition progresses.	Comments noted. This section of the scope aims to provide a brief overview of the background for the appraisal; additional details may be considered by the committee, if appropriate, at the time of the appraisal. No action required.
	NHS England	No comment	Comment noted. No action required.
The technology/ intervention	Association of British Neurology	Yes	Comment noted. No action required.
	MedDay Pharmaceuticals	Yes	Comment noted. No action required.
	MS Society	Yes	Comment noted. No action required.
	Multiple Sclerosis Trust	Yes.	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	NHS England	Yes	Comment noted. No action required.
	Novartis Pharmaceuticals UK Limited	Novartis suggests that the intervention should be changed to “high-dose biotin in addition to established clinical management”. The mechanism of action of high doses of biotin involves promoting myelin repair and enhancing energy production in demyelinated neurons. Comparator treatments listed in the draft scope and provisional matrix (interferon beta 1b and ocrelizumab) act by modulating the inflammation process and reducing damage to myelin and neurons. In the pivotal trial MS-SPI, disease modifying therapies (DMTs) were allowed and used concomitantly with biotin (in approximately 40% of participants) and therefore biotin should be appraised as a potential add-on treatment to DMTs rather than as an alternative to DMTs.	Comments noted. The scope has been kept broad to ensure that NICE can appraise the technology within its marketing authorisation. High-dose formulation is specified in the technology description. No action required.
Population	Association of British Neurology	It is defined appropriately. Patients with progressive MS which is relapsing are NOT suitable for this treatment as the one published trial (Tourbah 2016) provides equivocal evidence that biotin may INCREASE inflammatory activity.	Comments noted. The scope has been kept broad to ensure that NICE can appraise the technology within its marketing authorisation. No action required.
	MedDay Pharmaceuticals	Yes. The anticipated license is for adults with progressive multiple sclerosis (primary or secondary). The proposed use might be restricted to patients with non-relapsing disease, i.e. non-active and progressing forms of progressive MS.	Comments noted. The scope has been kept broad to ensure that NICE can appraise the technology within its

Section	Consultee/ Commentator	Comments [sic]	Action
			marketing authorisation. No action required.
	MS Society	Yes	Comment noted. No action required.
	Multiple Sclerosis Trust	Clinical trials of biotin have been conducted in people with not-active progressive MS and an initial EDSS of 4.5 - 7. In the MS-SPI study, approximately 12% of biotin treated patients met the primary outcome measure of a decrease in disability levels (a more ambitious target than previous studies in progressive MS where the main aim of a study is to prevent increases in disability). A larger number of those taking biotin stayed at the same level of disability. The wording of the licensed indication may specify subgroups of patients with progressive MS most likely to benefit from biotin treatment.	Comments noted. The scope has been kept broad to ensure that NICE can appraise the technology within its marketing authorisation. No action required.
	NHS England	Yes the population is defined appropriately – no sub groups identified	Comment noted. No action required.
	Novartis Pharmaceuticals UK Limited	Please can NICE confirm that “people” refers to adults with the age of ≥18 years of age? If this is the case, we would suggest that it would be preferential to use “adults” in the biotin draft scope in order to make it unambiguous as to what population is being considered and remove any doubt about consideration of paediatric patients within this appraisal.	Comments noted. The scope has been amended to specify ‘adults’.
Comparators	Association of British Neurology	Ocrelizumab (underoing NICE appraisal) and standard care are appropriate comparators.	Comment noted. No action required.
	MedDay Pharmaceuticals	The treatment option – established clinical management without hdPB - is currently standard within the NHS. We do not, however, believe that	Comments noted. To ensure the timeliness of

Section	Consultee/ Commentator	Comments [sic]	Action
		ocrelizumab is an appropriate comparator, as the product does not yet have a license for progressive disease and is not in widespread use in the NHS to treat progressive disease. Any attempt to compare the two drugs is likely to be highly challenging: • *Population*: there is some overlap between populations considered in the ocrelizumab clinical trial programme (ORATORIO). However, there are differences in the inclusion/exclusion criteria and concomitant medication rules. • *Endpoints*: the outcome measures of Oratorio are different to MS-SPI to the extent that a sensible comparison could not be made. This is associated with differences in their mechanisms of action. • Given the technical plausibility issues, any attempt to make a robust comparison of effectiveness between hdPB and ocrelizumab will be deeply flawed. The key comparator should remain what patients currently receive.	the scope in the event of possible delay in the appraisal, ocrelizumab has been included as a comparator "*(subject to ongoing NICE appraisal)*". A different mechanism of action does not preclude a comparator being used, as long as it has the same indication and is used in the NHS. No action required.
	MS Society	Beta interferon-1b is mentioned as a treatment for secondary progressive MS with active disease in the background information but is not included as a comparator. What 'established clinical management' without disease modifying agents entails should be elaborated further.	Comments noted. Beta interferons are not currently recommended by NICE (Technology appraisal guidance 32, currently under review). In addition, feedback from consultation suggests that beta interferons are rarely used in clinical practice. Given the variability in clinical practice, specific details on the

Section	Consultee/ Commentator	Comments [sic]	Action
			components of 'established clinical management' was not considered appropriate. No action required.
	Multiple Sclerosis Trust	There is, as yet, no market authorisation for biotin. Our view is that the licensing indication will be helpful in framing the definition of "established clinical management" of a comparator. "Established clinical management" covers a huge range of interventions and should be more specifically defined. The NICE clinical guideline for MS (CG186) and the associated Quality Standard is a basis for this definition but should not be taken as representing the views of MS health professionals as constituting a comprehensive description of care for progressive MS. There is no current evidence-based professional consensus on what constitutes established clinical management for progressive MS or the associated cost. Management of progressive MS focuses on four key areas: symptom management; prevention of complications; maintaining function and promoting general health and wellbeing. Given the wide range of symptoms that individuals with progressive MS may experience, it is important that there is access to a range of therapies delivered by skilled allied health professionals, competent in MS care. These health professionals are generally engaged according to patient need for episodes of treatment focussed on individual problems and goals. In reality, access to NHS and social care interventions to support people living with progressive MS such as physiotherapy or neurorehabilitation are limited, sporadic or even non-existent. The quality of and access to care is highly dependent on where someone lives. Calculation of the cost of	Comments noted. Given the variability in clinical practice, specifying details on the components of 'established clinical management' was not considered appropriate. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		providing "established clinical management" cannot assume an ideal situation where these services are readily available. A key issue for defining established clinical management will be recognising the importance of continuous access to an MS team with a named single point of contact. In practice, this is generally an MS specialist nurse, though there are some examples of this role being fulfilled by an MS specialist allied health professional who is part of the larger multidisciplinary team. We are aware that many people with progressive MS have been effectively 'discharged' from services, either due to a perception that there is no 'treatment' available for progressive MS (by which clinicians generally mean disease modifying treatment) or due to limitations in service capacity. The role of neurorehabilitation services, including rehabilitation physicians is important to management of progressive MS. This includes specialist rehab interventions such as vocational rehabilitation, which can make a significant impact on ability to remain in employment. Neuropsychology services are also in very limited supply. Survey data recently collected by the MS Trust shows that MS neurologists and MS nurses identify many of these therapy services as patchy or insufficient in their area (Improving services for people with advanced MS, November 2016, MS Trust, https://support.mstrust.org.uk/file/MSFV-AMS-report.pdf).	
	NHS England	Yes comparators are appropriate	Comment noted. No action required.
	Novartis Pharmaceuticals UK Limited	Following other recent NICE appraisals in multiple sclerosis, Novartis suggests grouping the relevant comparators by the populations applicable to their respective (anticipated) marketing authorisations. For instance, ocrelizumab has been referred to NICE for appraisal for patients with RMS and PPMS, but not for patients with SPMS without relapses. Therefore,	Comments noted. The subgroups primary and secondary progressive multiple sclerosis have

Section	Consultee/ Commentator	Comments [sic]	Action
		Novartis suggests grouping the relevant comparators by the following populations, as applicable: • For patients with PPMS • For patients with SPMS with relapses • For patients with SPMS without relapses	been added to the scope.
Outcomes	Association of British Neurology	These are all appropriate, except for mortality. It is very doubtful that there would be a treatment effect on mortality over such a short time.	Comments noted. Outcomes listed in the scope are considered relevant to the decision problem and does not consider availability of evidence because of duration of studies. No action required.
	MedDay Pharmaceuticals	These are the correct outcome measures, though given the duration of clinical trials, mortality data are not available.	Comments noted. No action required.
	MS Society	Yes	Comment noted. No action required.
	Multiple Sclerosis Trust	Composite measures of MS progression, combining data from timed 25 ft walk, 9 hole peg test, EDSS and others are emerging as more sensitive measures of disability progression compared to EDSS alone.	Comment noted. Composite measures will be captured in the outcome 'disability' where appropriate. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	NHS England	Yes	Comment noted. No action required.
Economic analysis	Association of British Neurology	Appropriate	Comment noted. No action required.
	MedDay Pharmaceuticals	We agree with the points made in the draft scope.	Comment noted. No action required.
	MS Society	The statement, "costs will be considered from an NHS and Personal Social Services perspective" does not adequately address the costs to patients and carers or to society and the economy in general. MS can have a devastating effect on a person's ability to remain in employment and on the levels of informal care they require. A report by the Work Foundation found that up to 80 per cent of people with MS stop working within 15 years of the onset of diagnosis and 44 per cent retire early because of the condition (Bevan, S., Zheltoukhova, K., McGee, R. and Blazey L. (2011) Ready to Work? Meeting the Employment and Career Aspirations of People with Multiple Sclerosis. London: Work Foundation). The MS Society found that employment rates for people with MS amongst survey respondents were 20 per cent below the national average. It must be taken into account that MS is frequently a chronic progressive condition that has a significant impact on the quality of life of individuals with the condition and also the lives of family members. MS Society research suggests 15% of people with MS regard their family or carer as their key contact for health and support. Consequently the appraisal committee should take into account:	Comments noted. In line with NICE reference case, costs are considered from the NHS and Personal Social Services perspective. The committee, at its discretion, may request non-reference case analyses if appropriate. In previous multiple sclerosis appraisals, carer's quality of life has been considered. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		- ability to remain in the workforce - stay in work or reduce absenteeism - independence for carers (The Work Foundation report found that the "professional careers of 57 per cent of relatives are adversely affected by MS of a family member 2011: 4) - the value of informal care (unpaid care in the UK has been estimated at £132bn, almost exactly the value of health spending in the UK, £134bn. Carers UK State of Caring 2016) - the impact of informal care on carers - 87 per cent said caring for a family member or friend has had a negative impact on their mental health and 64 per cent carers blamed their poor health on a lack of practical support and 50 per cent on not enough financial support (In Sickness and in Health, 2012, Carers Week). - increased tax revenue (Kennedy, 2009: 27)	
	Multiple Sclerosis Trust	We recognise it will be challenging to calculate benefits over the longer term against the backdrop of a progressively deteriorating condition.	Comment noted. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Given the

Section	Consultee/ Commentator	Comments [sic]	Action
			progressive nature of multiple sclerosis, a lifetime horizon will be considered appropriate. No action required.
	NHS England	No comment	Comment noted. No action required.
Equality and Diversity	Association of British Neurology	There are no equality concerns	Comment noted. No action required.
	MedDay Pharmaceuticals	There are no specific equality issues of which we are aware.	Comment noted. No action required.
	NHS England	No comment	Comment noted. No action required.
Innovation	Association of British Neurology	Biotin is highly innovative in its mechanism of action and target population.	Comment noted. The Appraisal Committee will discuss the potentially innovative nature of this technology. No action required.
	MedDay Pharmaceuticals	hdPB should be regarded as an innovative technology and should also be distinguished from OTC biotin.	Comments noted. The scope has been kept broad to ensure that NICE can appraise the

Section	Consultee/ Commentator	Comments [sic]	Action
		- OTC formulations of biotin in pharmacies used as dietary supplements contain low doses, requiring patients to ingest tens to hundreds of pills per day in order to achieve therapeutic levels. - Uncontrolled high dose formulations of biotin available on the internet do not meet regulatory agency (FDA and EMA) requirements to be used as a drug with demonstrated safety & efficacy. - Level of impurities in such available formulations (OTC or those available on internet) are unknown, and may impact safety (including genotoxic potential) when taken at high dose. Health professionals and patients should be aware of this and not confused by any generic use of the term to describe the active ingredient (hdPB), which is the subject of this Single Technology Appraisal. This hdPB formulation has not been used in the investigation or treatment of any other indication(s). Furthermore, as noted above, this product addresses an area of high unmet medical need.	technology within its marketing authorisation. High-dose formulation is specified in the technology description. Innovation will be considered by the appraisal committee when formulating its recommendations. The company will have an opportunity to provide evidence on the innovative nature of its product in its submission. No action required.
	MS Society	Biotin could represent a highly innovative step in MS treatments. If given a marketing license, Biotin could be one of the first licensed treatments for primary and secondary progressive MS.	Comment noted. The Appraisal Committee will discuss the potentially innovative nature of this technology. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Multiple Sclerosis Trust	Yes, there are no treatments currently available to treat progressive MS. An effective treatment for people with progressive MS would be truly life changing. The availability of a treatment for progressive MS will provide hope for people diagnosed with this type of MS and will lead to a more optimistic and constructive interaction with neurologists. Drug treatment will be one element in the holistic management of progressive MS.	Comment noted. The Appraisal Committee will discuss the potentially innovative nature of this technology. No action required.
	NHS England	Whilst biotin has been available for some years this might be considered innovative with respect to its use in MS	Comment noted. The Appraisal Committee will discuss the potentially innovative nature of this technology. No action required.
Other considerations	MedDay Pharmaceuticals	There are no further considerations beyond the points made in the draft scope.	Comment noted. No action required.
	NHS England	None	Comment noted. No action required.
	Novartis Pharmaceuticals UK Limited	There are three different subgroups which could be considered in the scope of this appraisal: • Patients with PPMS • Patients with SPMS with relapses • Patients with SPMS without relapses	Comments noted. The subgroups primary and secondary progressive multiple sclerosis have been added to the scope.

Section	Consultee/ Commentator	Comments [sic]	Action
		Novartis requests consideration of the evidence in each of these subgroups separately to determine if biotin is more clinically effective and cost effective in some of these than in others.	
Questions for consultation	Association of British Neurology	1. Biotin should not be used in people with relapsing progressive multiple sclerosis (rational given above). 2. Comparators are accurate as above (ocrelizumab and standard care). 3. Under current NHS England criteria, interferon beta is approved for the treatment of progressive multiple sclerosis ONLY when associated with disabling relapses. These patients are NOT suitable for biotin. So, interferon beta is NOT a suitable comparator. 4. The outcomes are appropriate except for mortality. Outcomes in progressive multiple sclerosis are focused on disability; in relapsing-remitting disease outcomes also include relapse rate but this is not appropriate for progressive disease. 5. The current NICE pathway for progressive multiple sclerosis has no disease-modifying therapy. Biotin will potentially fit here.	1. Comment noted. The scope has been kept broad to ensure that NICE can appraise the technology within its marketing authorisation. No action required. 2. 4. and 5. Comments noted. No action required. 3. Comments noted. Beta interferons are not currently recommended by NICE (Technology appraisal guidance 32, currently under review). In addition, feedback from consultation suggests that beta interferons are rarely used in clinical practice and therefore have not been included in the list of comparators. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	MedDay Pharmaceuticals	Q. Will hdPB be considered for use in people with active disease? A. No	Comment noted. The scope has been kept broad to ensure that NICE can appraise the technology within its marketing authorisation. No action required.
		Q. Have all relevant comparators for hdPB been included in the scope? A. MedDay considers established clinical management to be an appropriate comparator. The Company has reservations about the use of ocrelizumab and other immunosuppressive drugs as comparator for the following reasons: - The therapies' MoAs are substantially different - Where there is population overlap (PMS), the inclusion criteria and outcomes for the clinical trials for ocrelizumab are different from hdPB. hdPB clinical trial used a unique and stringent endpoint (reversal of disability) compared to ocrelizumab (time to onset of confirmed disability progression). "Reversal of disability" is both: • More challenging to achieve • More relevant to patients than "confirmed disability progression".	Comments noted. To ensure the timeliness of the scope in the event of possible delay in the appraisal, ocrelizumab has been included as a comparator "*(subject to ongoing NICE appraisal)*". A different mechanism of action does not preclude a comparator being used, as long as it has the same indication and is used in the NHS. No action required.
		Should NICE require ocrelizumab to be a comparator, we request that issues of non-comparability are clearly stated.	Comments noted. Given the variability in clinical practice,

Section	Consultee/ Commentator	Comments [sic]	Action
		Q. How should current clinical management of PMS (without hdPB) be defined? A. Current clinical management consists of rehabilitation and is tailored to the needs of individual patients. These are occupational, and other supportive, therapies such as (but not limited to) physiotherapy, cognitive therapy, fatigue management and eventually palliative care. Disease modifying treatments are rarely used, and pharmacological interventions are used to complement symptomatic management of these patients whose disability invariably increases with time, though time-lines vary for different individuals. It is therefore very difficult to define precisely the current clinical management of PMS.	specifying details on the components of 'established clinical management' was not considered appropriate. No action required.
	Multiple Sclerosis Trust	**Would biotin be considered for use in people with active disease?** As noted above, the MS-SPI study was undertaken in people with not-active progressive MS. Those with clinical or radiological evidence of inflammatory activity within the previous year were excluded. We would anticipate that the marketing authorisation will reflect the study population.	Comment noted. The scope has been kept broad to ensure that NICE can appraise the technology within its marketing authorisation. No action required.
		Have all relevant comparators for biotin been included? See our comments above. We anticipate that "established clinical management" will be a problematic comparator to quantify and will be very unlikely to reflect the true availability of services to people with progressive MS. **How should established clinical management be defined?**	Comments noted. Given the variability in clinical practice, specific details on the components of 'established clinical management' was not

Section	Consultee/ Commentator	Comments [sic]	Action
		See our comments above. Management of progressive MS focuses on four key areas: symptom management; prevention of complications; maintaining function and promoting general health and wellbeing.	considered appropriate. No action required.
		Is interferon beta 1b an option for treating active secondary progressive MS? We do not believe that interferon beta 1b should be considered as a comparator. Beta interferons can be prescribed for secondary progressive MS with relapses (active MS), while biotin is being proposed for SPMS without relapses (not-active MS). NHS England Clinical Commissioning Policy for Disease Modifying Therapies covers beta interferon for SPMS and makes no distinction between beta interferon 1a or 1b, if the appraisal intends to include one of the beta interferons as comparator, it should include all of them.	Comments noted. Beta interferons are not currently recommended by NICE (Technology appraisal guidance 32, currently under review). In addition, feedback from consultation suggests that beta interferons are rarely used in clinical practice and therefore have not been included in the list of comparators. No action required.
		Are the outcomes listed appropriate? See our comments above.	Comment noted. See relevant section for specific response. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Are the subgroups suggested in other considerations appropriate? As noted in our comments on population, the wording of the licensed indication may specify subgroups of patients with progressive MS most likely to benefit from biotin treatment. The MS-SPI study was undertaken in people with not-active progressive MS and EDSS 4.5 - 7. Those with clinical or radiological evidence of inflammatory activity within the previous year were excluded. We would anticipate that the marketing authorisation will reflect the study population.	Comments noted. The scope includes consideration of subgroups of people with primary or secondary progressive multiple sclerosis, with or without active disease. No action required.
		Where do you consider biotin will fit into the existing NICE pathway for MS? We would expect biotin to be offered as soon as possible after diagnosis of primary or secondary progressive MS.	Comment noted. No action required.
		Have all relevant outcomes for primary and secondary progressive MS been included? Do outcome assessments in primary and secondary progressive MS differ from assessments in relapsing remitting disease? See our comments above. Outcome assessments for relapsing remitting MS include relapse rate, severity of relapse and freedom from disease activity but are not relevant for progressive MS and should not be listed.	Comments noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	NHS England	No further comment	Comment noted. No action required.
Additional comments on the draft scope	Association of British Neurology	If the treatment effect seen in Tourbah 2016 is replicated, biotin will be a game-changer in the management of progressive multiple sclerosis. However, I am sceptical that it will.	Comment noted. No action required.
	MedDay Pharmaceuticals	Q. Is inteferon-beta 1b an option for treating active secondary progressive MS? A. Yes, but active secondary progressive PMS, as evidenced by relapses, is not a target indication for this appraisal, hence is not a comparator for this appraisal. Q. Are the outcomes listed appropriate A. Yes, with modification. Mortality has not been studied *per se* due to the length of the studies, and symptoms of MS are appropriate where they have been measured within the randomised clinical trials. End points such as EDSS, TW25, CGI, SGI, 12 item scale MS Walking Scale, SF-36, modified Fatigue Impact, Kurtze EDDS functional sub-scores have been evaluated. Q. Are the subgroups suggested in 'other considerations' appropriate? Are there any other subgroups of people in whom biotin (hdPB) is expected to be more clinically effective and cost effective or other groups that should be examined separately? A. People with non-relapsing progressive (primary or secondary) MS would form a sub-population. Additionally, clinical studies focused on those with ongoing progression within two years prior to treatment. Overall the	Comment noted. No action required. Comments noted. No action required. Comments noted. The scope includes consideration of subgroups of people with primary or secondary progressive

Section	Consultee/ Commentator	Comments [sic]	Action
		treatment should be restricted to patients with progressive MS, non-relapsing and with evidence of recent disease's progression. This constitutes a focused population with the highest unmet medical need and the most severe prognosis.	multiple sclerosis, with or without active disease. No action required.
		Q. Where do you consider biotin (hdPB) to fit into the treatment pathway for MS? A. The majority (85%) of people upon diagnosis with MS fall into the category of relapsed-remitting MS and are currently treated with immunomodulatory DMTs. About 50% of these patients, following a period (usually many years) of relapsing and remission, begin a gradual decline in their MS (progression) and a decline of inflammatory activity of the disease (with fewer and fewer relapses). These patients fit into the clinical description of secondary progressive MS, and currently only rehabilitation (as previously prescribed) is available for management. During the transition period of RRMS to SPMS with superimposed relapses due to inflammatory activity, patients are still treated with immunomodulatory or immunosuppressive drugs (beta interferons, mitoxantrone, in case of high activity). It is envisaged that hdPB would fit into the treatment pathway at this point in SPMS, when the activity is absent but the patient is still worsening. HdPB has no anti-inflammatory effect. A small sub population of people with MS, however, do not follow the relapse-remitting pathway and move directly towards a progressive decline (primary progressive MS). This population is believed to have an inflammatory activity and some patients may present with relapses, whilst others do not. The latter patient group is where hdPB is intended for use.	Comments noted. The scope includes consideration of subgroups of people with primary or secondary progressive multiple sclerosis, with or without active disease. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		In summary, hdPB is likely to be used in progressive MS patients, either primary or secondary, with disability progression, despite absence of inflammatory activity assessed by the absence of relapses within the past 12 months. This subpopulation corresponds to the Lublin classification of progressing not-active patients. Q. Have all relevant outcomes for primary and secondary progressive multiple sclerosis been included in the scope? Do outcome assessments in primary and secondary progressive multiple sclerosis differ from assessments in relapsing-remitting disease? A. Outcomes for primary and secondary progressive MS in clinical trials are different from those of relapsing-remitting disease, such that they are not comparable. Succinctly, the primary endpoints for relapsing-remitting studies look at reduction in frequency or reduced number of patients relapsing within a given time-frame, whilst primary end points for progressive MS studies look at changes in the extent of a patient's chronic disability. In development of immunomodulatory or immunosuppressive drugs in progressive MS, EMA guideline recommends the time to confirmed progression (EDSS worsening). For hdPB the Applicant has investigated a new clinical endpoint which was the reversion of disability progression. This clinical endpoint is clinically meaningful and reachable only for products that have a strong neuroprotective effect. Q. In particular, please tell us if the proposed remit and scope:	Comments noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		□ could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which biotin will be licensed; □ could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; □ could have any adverse impact on people with a particular disability or disabilities. A. The company is not aware of any negative impact that this appraisal might have regarding the above. Q. Do you consider biotin (hdPB) to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? A. Yes; hdPB is the first treatment to demonstrate a degree of reversal of the disability that people with progressive MS experience. as measured by EDSS.	Comment noted. No action required. Comments noted. Innovation will be considered by the appraisal committee when formulating its recommendations. The company will have an opportunity to provide evidence on the innovative nature of its product in its

Section	Consultee/ Commentator	Comments [sic]	Action
			submission. No action required.
		Q. Do you consider that the use of biotin (hdPB) can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? A. Yes; full details to be described as part of the clinical- and economic-effectiveness analyses that will support this STA submission.	Comment noted. No action required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Roche Products Ltd