14 September 2017
EMA/828231/2017
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment report

QIZENDAY

International non-proprietary name: d-biotin

Procedure No. EMEA/H/C/004153/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Quality

Abbreviation	Definition
ACC	Acetyl-CoA Carboxylase
ADME	Absorption, Distribution, Metabolism, Excretion
AMN	Adrenomyeloneuropathy
APP	Amyloid Precursor Protein
ATP	Adenosine Triphosphate
AUC	Area Under the Curve
BBB	Blood Brain Barrier
BNB	Bisnorbiotin
BSO	Biotin Sulfoxide
CA	Compartmental Analysis
CAS	Chemical Abstracts Service
CEP	Certification of suitability of European Pharmacopoeia
ChREBP	Carbohydrate-responsive element-binding protein
CHMP	Committee for Medicinal Products for Human Use
Cmax	Peak Plasma Concentration
CNS	Central Nervous System
CO2	Carboxyl
CPMP	Committee for Proprietary Medicinal Products
CYP	Cytochrome P450
DKO	Double Knockout
dpi	Days post injection/post infection
EAE	Experimental Autoimmune Encephalomyelitis
EMA	European Medicines Agency
FDA	Food and Drug Administration
GFAP	Glial Fibrillary Acid Protein
GLP	Good Laboratory Practices
hERG	Human Ether-a-go-go Related Gene
ICH	International Conference on Harmonisation
LD50	Lethal Dose 50%
LOAEL	Lowest Observed Adverse Effect Level
LPC	Lysolecithin
LTR	Long Terminal Repeats
MBP	Myelin Basic Protein
MCC	Methylcrotonyl-CoA Carboxylase
MDA	Malondialdehyde
MOG	Myelin Oligodendrocyte Glycoprotein
MS	Multiple Sclerosis
mtDNA	Mitochondrial Desoxyribonucleic Acid
mTOR	Mammalian Target of Rapamycin
NAA	N-acetylaspartate
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
nDNA	Nuclear Desoxyribonucleic Acid
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
p.c.	Post-coitum
PBMC	Peripheral Blood Mononuclear Cells
PC	Pyruvate Carboxylase
PCC	Propionyl-CoA Carboxylase
PCR	Polymerase Chain Reaction
PDCO	Paediatric Committee
PDE	Permitted Daily Exposure
PDP	Paraphenylenediamine

PK	Pharmacokinetics
PLP	Proteolipid Protein
QSAR	Quantitative/qualitative Structure Activity Relationship
RNA	Ribonucleic Acid
ROS	Reactive Oxygen Species
RRT	Relative Retention Time
SD	Standard Deviation
SMI-32	Antibody against neurofilament H non-phosphorylated
SmPC	Summary of Product Characteristics
SMVT	Sodium Multivitamin Transporter
SREBP1c	Sterol Regulatory Element-Binding Protein 1c
TCA	Tricarboxylic Acid
tid	Three times daily
Tmax	Time to reach Maximal Plasma Concentration
TMEV	Theiler's murine encephalomyelitis virus
WT	Wild-Type
X-ALD	X-linked Adrenoleukodystrophy

Clinical

Abbreviation	Definition
9HPT	Nine Hole Peg Test
AE	Adverse Event
BCVA	Best corrected visual acuity
CGI-I	Clinical Global Impression Improvement
CO	Cross-over
CRO	Contract Research Organisation
DB	Double-blind
DMT	Disease Modifying Therapy
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiography
EDSS	Expanded Disability Status Scale
ETDRS	Early Treatment Diabetic Retinopathy Study
MFIS	Modified Fatigue Impact Scale
hERG	Human ether-a-gogo-related-gene
ICF	Informed Consent Form
ITT	Intent-to-treat
LOCF	Last Observation Carried Forward
LogMAR	Logarithm of Minimum Angle of Resolution
MD1003	Biotin
MFIS	Modified Fatigue Impact Scale
MMRM	Mixed-Effect Model Repeated Measure
MO	Major Objection
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MSFC	Multiple Sclerosis Functional Composite
MSQoL-54	Multiple Sclerosis Quality of Life 54 items
MSWS-12	MS Walking Scale
N/A	Not applicable
NEIVFQ-25	The National Eye Institute 25-Item Visual Function Questionnaire
OCT	Optical Computerised Tomography
OL	Open Label
ON	Optic Neuritis
PC	Placebo-controlled
PMS	Progressive multiple Sclerosis
PPMS	Primary Progressive Multiple Sclerosis
PP	Per Protocol
Rando	Randomised

RNFL	Retinal Nerve Fibre Layer
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SF36	Short Form (36) Health Survey
SGI	Subject Global Impression
SOC	System Organ Class
SPI	Spinal
SPMS	Secondary Progressive MS
TID	Ter In Die (three times a day)
TW25	Timed Walk 25 Feet
VEP	Visual Evoked Potential

1. Recommendations

Based on the review of the data on quality, safety and efficacy, the committee considers that the application for QIZENDAY 100mg hard capsules in the treatment of progressive multiple sclerosis (primary or secondary) in adults , is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time.

The major objections precluding a recommendation of marketing authorisation pertain to the following principal deficiencies:

Pharmacokinetic

The clinical PK of biotin has been insufficiently characterised

Efficacy

- The efficacy data are still questionable
- The claimed broad indication is still not acceptable

Safety

Increased relapse rate in RRMS and increased MRI lesions in PMS are matters of concern and require further discussion. The rapporteur considers this issue as resolved.

Questions to be posed to additional experts

N/A

Inspection issues

GMP inspection(s)

N/A

GCP inspection(s)

A triggered inspection regarding study MS-SPI took place in February 2017 at the principal investigator's site and in March 2017 at the applicant's address.

GLP

All definitive safety pharmacology, toxicology, and toxicokinetic studies were conducted in accordance with guidelines issued by the International Conference on Harmonisation (ICH) and with Good Laboratory Practice (GLP).

New active substance status

Not applicable

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

The proposed indication is: QIZENDAY is indicated in adults for the treatment of progressive multiple sclerosis (primary or secondary).

2.1.2. Epidemiology

Multiple Sclerosis (MS) is a disease that damages the myelin of the central nervous system (CNS) and causes neurological impairment and severe disability (Noseworthy et al., 2000). Its clinical manifestations vary according to the localisation of the demyelinating lesions within the CNS (e.g. spinal cord, optic nerve, brainstem, cerebellum or cerebral hemispheres) and signs and symptoms most commonly reflect the areas that are the most demyelinated. It is generally considered that MS is an immune-mediated disease superimposed on a genetic predisposition and environmental triggers; a complex interplay occurs between these factors (Noseworthy et al., 2000; Hauser et al., 2013; Kamm et al., 2014, Chakraborty and Ledeen, 2003).

Traditionally there are two forms of MS based on their clinical presentation: relapsing remitting and progressive forms (EMA, 2015). Relapsing remitting MS is characterised by unpredictable acute episodes of neurological dysfunction or relapses followed by periods of clinical stability and/or recovery. By contrast progressive MS is characterised by a more continuous clinical deterioration and neurodegeneration without recovery that is independent of relapses. Patients who initially directly present with this form of MS are traditionally termed primary progressive, while those who evolve to this progressive state after initially presenting with relapsing remitting MS are termed secondary progressive.

The most common form of MS is relapsing remitting MS which accounts for approximately 85% of the presenting MS patients with more than 50% of them then developing progressive MS within the 10 years following their initial MS diagnosis. Approximately 15% of MS patients present directly with progressive MS (EMA, 2015).

A refinement of the classification of MS patients was issued in 2014 to improve the management of MS which focuses more on the active versus non-active aspects of the disease (Lublin 2014 and also Ontaneda 2015). Progressive disease, which encompasses both primary and secondary progressive MS, is further divided into active or not-active progressive disease. This is based on the existence or not of superimposed inflammatory activity which is defined as clinical relapses assessed at least annually and/or Magnetic Resonance Imaging (MRI) activity i.e. contrast enhancing lesions or new and unequivocally enlarging T2 lesions. If this is present then it is active progressive disease and if it is absent it is not-active progressive disease.

2.1.3. Biologic features

B lymphocytes are believed to contribute to the pathogenesis of all subtypes of MS, including PMS. However the causal neurodegenerative process in progressive MS has been suggested to arise from an increased energy demand in demyelinated axons together with mitochondria dysfunction, creating a virtual hypoxia phenomenon. A medication that acts by attempting re-balance or preventing the energy deficit through either increasing Adenosine Triphosphate (ATP) production or increasing

synthesis of the myelin sheath, could potentially impact the progression of MS, and be of benefit in patients with not-active progressive MS.

2.1.4. Clinical presentation, diagnosis

Diagnosis of MS is based on the application of structured diagnostic criteria that rely on clinical observation, neurological examination, brain and spinal cord magnetic resonance imaging (MRI) scans, and at times evoked potentials, and cerebral spinal fluid (CSF) examination (Polman et al. 2011). Prognosis is highly variable and if left untreated, half of patients with MS require assistance to walk within 15 years of disease onset (Expanded Disability Status Scale [EDSS] 6).

The majority of patients (approximately 85%) present with relapsing-remitting MS which is characterised by alternating exacerbations of neurological dysfunction followed by periods of remission with partial or total recovery and clinical stability which can last for months or years (EMA, 2015). A much lower proportion of patients (approximately 15%) present with a primary progressive form of MS whereby there is sustained neurological deterioration with no periods of remission, although occasional plateaus without progression may occur (EMA, 2015; Confavreux et al., 2000). The third category of MS, secondary progressive MS, relates to those patients that initially presented with the relapsing-remitting form of MS but have now developed sustained deterioration. This latter category occurs in approximately 40 to 70% of patients with relapsing-remitting MS. Patients with secondary progressive MS may also experience superimposed relapses or exacerbations.

The relapses or exacerbations experienced by MS patients are believed to be due to episodes of acute inflammatory demyelination, which may or may not be transient; whereas progressive disease is caused by both inflammation and an axonal neurodegenerative process with a continuum between progressive active forms where inflammation predominates and non-active forms where the axonal degenerative process occurs without any signs of inflammation.

2.1.5. Management

Drugs developed or approved to date target different aspects of multiple sclerosis, although most target the inflammatory activity aspect of the disease. Steroids such as intravenous methylprednisolone have been shown to improve the outcome of acute relapses by reducing inflammation and hence facilitating the recovery from MS relapses, but they do not prevent the occurrence of further relapses. Immunosuppressive or immunomodulatory treatments are aimed at inhibiting the inflammatory reaction and so are effective in decreasing the number or the duration of relapses and active lesions, but they have minimal effectiveness in the not-active progressive form of the disease. Fampridine is a symptomatic drug rather than a disease modifying drug that improves walking in some patients by improving their walking speed.

Overall, there is currently no approved disease modifying therapy that targets the not-active progressive phase of MS (Hauser et al., 2013), and hence a high unmet medical need for progressive MS patients.

In the absence of any approved treatment for PMS, a variety of unapproved agents including mycophenolate mofetil, cyclophosphamide or mitoxantrone, in addition to other therapies approved for the treatment of RMS (such as interferon beta-1a or glatiramer acetate), are used in clinical practice despite the lack of Level 1 evidence. This exposes patients to risk without defined benefits.

Currently, PPMS remains a severely disabling condition with no approved DMTs.

2.2. About the product

MD1003 (biotin) is an immediate release oral formulation with each hydroxypropyl methylcellulose (HPMC) capsule containing 100 mg biotin and the excipients lactose monohydrate, magnesium stearate, croscarmellose sodium and silica colloidal anhydrous. It is provided to patients as cartons containing 6 blister packs, with each blister pack containing 15 capsules and can be stored at room temperature. This provides a convenient formulation for patients for a product required to be taken 3 times a day.

The active moiety in MD1003, biotin, acts as a carboxyl (CO2) transporter in carboxylation reactions involved in the metabolism of carbohydrates, amino acids and fatty acids. Biotin-dependent carboxylases are:

-pyruvate carboxylase (PC),

-3-methylcrotonyl-CoA carboxylase (MCC),

-propionyl-CoA carboxylase (PCC), and

-acetyl-CoA carboxylase (ACC), with the latter enzyme existing in two genetically distinct forms (ACC1 and ACC2), both are cytosolic, ACC2 being anchored at the outer surface of the mitochondria.

Three out of these four carboxylase reactions (PC, MCC, PCC) lead to production of tricarboxylic acid (TCA) cycle intermediates that are central to aerobic energy production (oxaloacetate, succinate and acetyl CoA). The fourth, ACC, is a key regulator of fatty acids synthesis. In the nervous system, ACC1 and ACC2 are expressed mainly in oligodendrocytes, the cells responsible for myelin synthesis, and are found in purified myelin, suggesting that these enzymes are key regulators of myelin synthesis (Chakraborty and Ledeen, 2003).

On this basis, it was hypothesized that MD1003 could increase energy production through feeding the TCA cycle in demyelinated neurons to counter-balance the “virtual hypoxia phenomenon” and potentially also enhance myelin repair through activation of the acetyl-CoA carboxylase in oligodendrocytes, and hence have an impact on the not-active progressive component of MS.

The proposed indication is as follows:

“QIZENDAY is indicated in adults for the treatment of progressive multiple sclerosis (primary or secondary)”.

2.3. The development programme/compliance with CHMP guidance/scientific advice

MedDay was given scientific advices from both the EMA and the French National Health Agency (ANSM) for the development of their product for the treatment of progressive multiple sclerosis (primary or secondary) in adults.

- EMA Scientific advice requested on 25 June 2013 (Procedure EMEA/H/SA/2015/1/203/SME/III). The following recommendations were made:

- Need for additional non-clinical data with MD1003, including non-clinical proof of concept studies, reproductive, developmental toxicity and carcinogenic potential studies
- The composite endpoint chosen in study MS-SPI was not recommended as it was anticipated that it would be mainly driven by the TW25 and the TW25 would need reconsideration as a primary variable

- Addition of Clinical impression of change assessed by the clinician (CGI) and by the patient (SGI) and of the MSWS-12 in study MS-SPI
- The EDSS as primary endpoint in study MS-SPI was discussed and the change from baseline in functional system was recommended
- addition of a proof of concept study and of a withdrawal study
- stratification based on EDSS score and for use of fampridine in study MS-SPI
- introduction of measures to guarantee stable dysfunction at entry by excluding patients with a relapse resulting in increased EDSS or any new medication
- transient improvement/worsening due to natural fluctuation was to be reduced by the addition of a requirement for confirmation of the primary endpoint at month 9 and 12
- Ranking of the secondary and exploratory endpoints in the MS-SPI and MS-ON study

Despite the recommendation by the SAWP, the Applicant went ahead with their choice for primary endpoint. The Applicant did take into consideration other recommendations by the SAWP, like including the following endpoints in the study design: MSWS-12, change from baseline scores in functional systems and time to sustained disability, which were all included as key secondary endpoints or exploratory endpoints.

- ANSM Scientific advice on 06 (initial) and 13 February 2013 for follow up meetings. In February 2013, the Applicant had two follow-up scientific advice meetings with ANSM for the use of MD1003 for progressive MS (initial advice was about the use of MD1003 for a different indication). The meeting that was held on the 06 February 2013 discussed the overall development program and initiation of the clinical program without further non-clinical or healthy volunteer data, and the meeting on the 13 February 2013 discussed the clinical study design.

2.4. General comments on compliance with GMP, GLP, GCP

GMP

Acceptable standards of GMP are in place for this product at all sites responsible for the manufacture and assembly of this product.

Regarding the statement on GMP for the active substance a satisfactory QP declaration is provided from the manufacturer responsible for manufacture of the finished product and batch release situated in the EU.

GLP

Part of the dossier consisted on a bibliographical review, which were identified by the Applicant as non GLP-compliant or unknown status. On the other hand, the Applicant conducted the pivotal nonclinical studies in compliant with GLP standards and international regulations.

GCP

Studies MD1003CT2014-02-PK, MS-SPI and MS-ON presented in this application were undertaken in accordance with national requirements, the principles of the Declaration of Helsinki, and the principles of Good Clinical Practice (GCP).
A triggered inspection was conducted for study MS-SPI. While there are a number of findings that may have impacted the rights of the patients, the quality and integrity of the data and potentially the results of the trial, the source data appeared to be reliable.

2.5. Type of application and other comments on the submitted dossier

- Legal basis

  This MAA is being made on the basis of the "optional scope", article 3 (2) of Regulation (EC) No 726/2004. This application is submitted in accordance with Article 8(3) in Directive 2001/83/EC, known active substance.

- Accelerated procedure

  N/A

- Conditional approval

  The benefit-risk balance is currently negative.

- Exceptional circumstances

  N/A

- Biosimilar application

  N/A

- 1 year data exclusivity

  N/A

- Significance of paediatric studies

  A product-specific waiver for all subsets of the paediatric population has been granted on 29 January 2016 (P/0077/2016).

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The Application is submitted via the Centralised Procedure in accordance to Article 3(2)b- Therapeutic innovation of Regulation (EC) No 726/2004, the eligibility of which was confirmed by the EMA on the 22nd January 2015. Dr. Greg Markey is the Rapporteur of the procedure and Dr Concepcion Prieto Yerro is the Co-Rapporteur.

Biotin is a vitamin (Vitamin B7 or Vitamin H) and has been used in humans for decades, in cosmetic preparations for improving the quality of nails and hair, as a food complement, and as a supplement in multivitamins or individually to treat biotin deficiency.

Biotin is a coenzyme for several carboxylases critical for energy synthesis in the mitochondria and for fatty acid synthesis. Biotin-dependent mitochondrial carboxylases include pyruvate carboxylase (PC), propionyl CoA carboxylase (PCC) and methylcrotonyl CoA carboxylase (MCC). All three enzymes ultimately provide intermediates for the Krebs cycle required for neuronal energy production.

In addition, biotin is a co-factor for the two acetyl CoA carboxylases (ACC), ACC1 and ACC2 that catalyse the first and limiting step of long chain fatty acids synthesis required for membrane lipids synthesis. ACC activity has been detected in purified myelin and ACC immune-reactivity is high in oligodendrocytes suggesting that ACC plays a role in myelin synthesis.

The mechanism of action of biotin in the treatment of progressive multiple sclerosis is considered to be mediated by 1) increasing energy production in demyelinated neurons and 2) stimulating myelin repair through activation of the acetyl CoA carboxylase in oligodendrocytes.

3.1.2. Active Substance

General Information

The drug substance manufacturer holds a valid Certificate of Suitability. The quality of the drug substance is suitably controlled by the current version of the monograph Biotin No 1073 of the European Pharmacopoeia current edition with the addition of specified tests.
The general properties of the active substance have been described. Solubility of D-biotin increases with pH. The active substance presents three stereogenic centres. The biologically active natural isomer is (3aS, 4S, 6aR)-configuration (d (+) biotin).

A discussion has been provided to address the possible polymorphism of D-biotin.

Manufacture, characterisation and process controls

As the proposed drug substance manufacturer holds a CEP, no information has been provided regarding manufacturing process, characterisation, and process controls.

Specification

The drug substance specification proposed by the drug product manufacturer covers the Ph. Eur. tests as per D-biotin monograph no 1073. An additional test is requested by the DP manufacturer in order to suitably control properties of the DS impacting the DP.

Stability

Stability data for the drug substance stored in a specified container have been assessed during the Certification process.

Supportive information of an alternative storage container including a statement of compliance to the EU Regulation and with the relevant Ph. Eur. chapters, has been provided. In addition, stability data results have been provided to support this proposed packing material. The proposed re-test period for biotin packed in this container is considered acceptable.

Comparability exercise for Active Substance

N/A

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

'QIZENDAY 100 mg hard capsules' is an immediate release type 1 hydroxypropyl-methyl cellulose (HPMC) white and green capsule of size 1 containing 100mg of D-biotin.

Qualitative and quantitative composition of the drug product, capsules shell has been provided together with the qualitative composition of the printing ink.

All excipients used are Ph. Eur.:compliant. For all excipients, analytical methods used are Ph. Eur. and therefore validation is not necessary. In view of the manufacturing process, dosage form, development data and intended excipient functions, applicable functionality-related parameters have been added to specified excipient specifications with appropriate limits. All excipients used in the capsule shell are Ph. Eur. All test procedures are Ph. Eur. except for one test which complies with French Pharmacopoeia 10th ed, July 1986.

The excipients used for the drug product are commonly used excipients and their choice is considered suitably justified. In addition, compatibility of the drug substance with the proposed excipients was investigated and results were satisfactory.

The development of the formulation was described.

In order to demonstrate bioequivalence between clinical batches and commercial batches, the Applicant initiated a bio-equivalence single-dose PK study The Applicant will provide study outcomes in Response to D180 Questions.

The dissolution method is not discriminative at the defined conditions. However, according to the Draft reflection paper on the dissolution specification for generic oral immediate release products, for drug products containing active substances with high solubility over the physiological pH range, it may not always be possible to detect any differences in dissolution behaviour after meaningful changes in relevant formulation and/or manufacturing parameters have been made, therefore it is considered acceptable.

Manufacture of the product and process controls

The manufacturing process consists of four steps: blending, lubrication, capsules filling, and capsules packaging in blisters (clinical batches were also packed into bottles).

The proposed commercial batch size is described.

In order to resolve the MO raised at Day 80 of the procedure regarding the active substance content in the capsules observed during the validation process, the Applicant has collected assay data from more and investigated to identify sources and levels of assay variability. Following this exploration, several technical improvement opportunities have been identified and implemented by the drug product manufacturer to reduce assay variability during the capsule filling step. As a result, all assay values are compliant with the specification 95-105%.

Product specification

The proposed tests are acceptable for the proposed pharmaceutical form.

A few points need to be addressed including addition of one test and tightening of the specification of another test.

Analytical methods and their validation reports have been provided. A few points need to be addressed.

The container-closure system has been described and found suitable.

Stability of the product

Formal stability studies were conducted on 'QIZENDAY 100 mg capsules' batches in the proposed commercial packaging A satisfactory stability study protocol has been submitted. The Applicant commits to continue the current stability program for long term studies.

For the proposed packaging, all stability data provided comply with the proposed specification and no out of specification results are obtained. Based on stability data results submitted the proposed shelf-life is considered acceptable.

Comparability exercise for Finished Medicinal Drug Product

N/A

Adventitious agents

N/A

GMO

N/A

3.1.4. Discussion on chemical, pharmaceutical and biological aspects

N/A

3.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

N/A

3.2. Non clinical aspects

3.2.1. Pharmacology

No in vitro pharmacology studies were submitted. Two acute in vivo studies were conducted to investigate the non-immune mediated demyelination and the potential effect of QIZENDAY on neuroprotection and remyelination in animal models of multiple sclerosis in mice. Neither study showed any difference from the control animals.

In a chronic study, wild-type mice and DKO mice (double knockout mice, with both the ABCD1 and ABCD2 transporters inactivated (Abcd1-;Abcd2-/-), were given either control diet or 60 mg/kg/day QIZENDAY mixed in the diet from 12 to 18 months of age. Locomotor tests (Treadmill, Bar-cross and Clasping) were conducted as well as immunochemistry to evaluate the axonal degeneration. Q-PCR was used to measure mitochondria content and biogenesis, inflammation, glucose and lipid metabolism. ATP levels were quantified using a luminescent assay after an acide extraction. In addition, high resolution respirometry was performed to measure respiration ex vivo in spinal cord.

Finally, ROS levels were evaluated using reactive oxygen species (ROS) sensitive probes in human XALD fibroblasts.

After 6 months of treatment, QIZENDAY appeared to normalise locomotor deficits measured in the motor performance tests and improved a third neurological test (clasping test) compared to wild-type mice. Immunohistochemical staining after 6 months of treatment indicated that QIZENDAY prevented activated microglia (Iba1), astrogliosis (GFAP) and axonal degeneration (synaptophysin and APP accumulation in axonal swellings, SMI-32 staining reduction) in Abcd1-;Abcd2-/- (DKO) mice. All the markers studied were completely normalised in the treated DKO mice demonstrating that QIZENDAY halts axonal degeneration and associated glial reactions in the spinal cord of this X-ALD mouse model.

Over-all after at least 3 months of treatment, QIZENDAY was able to prevent locomotor dysfunction, axonal degeneration, as well as energetic failure, mitochondrial content, oxidative lesion markers and inflammation in a model of demyelinating disease and axonal dysfunction. However, mitochondrial respiration was not improved after QIZENDAY administration, while glycolysis and lipogenesis factors and enzymes were generally increased.

In addition to the X-ALD mouse model, the most frequently used chronic and acute in vivo models of MS were also tested and analysed. Among these studies, only in the case of TMEV model, MD1003 induced a modest beneficial effect in the hanging wire test. However, no correlation with histological analysis was identified. Additional studies in MS animal models (i.e. EAE, cuprizone, lysolecithin) did not result in significant positive results of MD1003 (given only at one dose level). Taking together, the results from the pharmacodynamics studies cannot be considered as convincing. From a nonclinical point of view, the clinical relevance of high-dose biotin could not be established for the intended indication The Applicant goes onto say that biotin has been reported to have stimulatory effects on genes that upon activation favour hypoglycaemia (insulin, insulin receptor, and pancreatic and hepatic glucokinase) and to decrease the expression of hepatic phosphoenolpyruvate carboxykinase, a key gluconeogenic enzyme that stimulates glucose production by the liver (Fernandez-Mejia, 2005). Some non-clinical and clinical results suggest a beneficial effect of biotin administration in the glucose metabolism of diabetic animals and in a small number of patients with diabetes mellitus (Koutsikos et al., 1996). In another publication, biotin was found not to impact glucose metabolism either in diabetic or non-diabetic patients (Baez-Saldana et al., 2004). One case of hypoglycaemia was reported in an insulin-treated diabetic patient during the course of the clinical studies carried out with MD1003. This effect was attributed to MD1003 treatment following withdrawal and re-challenge. Therefore, an influence of biotin on glucose metabolism and the dosage of insulin in diabetic patients cannot be ruled out. The risk of interactions between biotin and insulin in diabetic patients has been identified as a potential risk in the Risk Management Plan and recommendations are made in the Summary of Product Characteristics (SmPC).

The clinical relevance of biotinylation of histones was discussed. According to recent publications biotin does not play a direct role in gene expression, although no conclusive results are reported. See toxicology discussion.

In the hERG assay, a decrease (<12%) of hERG tail current was observed at, 100 µM (~25 times above the estimated steady state human Cmax of MD1003). In a dog study isolated absolute QT interval prolongations were see at 1000 mg/kg/day 4 hours post dosing, however, no clear difference was observed when the QT was corrected with Friderica and Van de Water formulas. Therefore, these findings were not considered toxicologically relevant as occurred at doses in excess of the proposed clinical dose and, in the case of the dog study the Applicant goes onto say that these findings were probably due to lower heart rate recorded in the high dose group since the difference was no longer present when this was corrected for. In this same dogs study Isolated p wave was observed in one male at 100mg/kg/day however this finding was observed before and after dosing, therefore the relationship with treatment is doubtful, according to the Applicant. Atrio-ventricular block was seen in one female at 300 mg/kg/day and junctional premature contraction was seen in one female at 1000 mg/kg/day. These were also considered incidental as they were not observed in the other animals at these doses.

During the clinical development of QIZENDAY, ECG assessments were performed to further evaluate QTc intervals. Absolute changes in QTcB (QT corrected according to Bazett's formula) and QTcF (QT corrected according to Fridericia's formula) and changes in QTcB and QTcF from Baseline were evaluated at Month 6 in Studies MS-SPI and MS-ON as well as at Months 12 and 24 in Study MS-SPI.

Overall, absolute QTcB and QTcF prolongation (>450 ms and >500 ms) and changes from Baseline in QTcB and QTcF (>30 ms and 60 ms) were observed in both the QIZENDAY and placebo treatment groups across the phase 3 studies. No clear difference between the QIZENDAY and placebo groups was observed and no change over the course of the studies with a longer duration of exposure was seen. The Applicant goes onto say that the findings of some occurrences of QTc prolongation, reflect a ventricular repolarization dysfunction, expected in a MS population and has previously been reported (de Seze et al., 2000, de Seze et al., 2001).

Overall, no potential cardiovascular toxicity is expected in humans at biotin plasmatic exposure levels estimated at the human dose of 100 mg tid.

Based on a review of all the relevant non-clinical data, there does not appear to be a risk to the CVS. However, the company is conducting a thorough clinical QT study at present and commits to provide the results for the Day 180 responses. In addition, the clinical PK study MD1003CT2016-01PK has a cardiovascular monitoring component. Cardiac safety profile of the product will be updated following reports from these studies and the informed assessment and conclusions can only be carried out and provided once these data are available**.**

The non-clinical data from rat and dog chronic toxicity studies revealed no evidence of renal toxicity. When compared to biotin human exposure at a MD1003 dose of 100 mg tid, the safety margins for MD1003 were estimated to be at least 5. The few safety data obtained from patients with renal impairment in the early access cohort programme also do not suggest an increased risk of toxicity with MD1003 in this category of patients.

3.2.2. Pharmacokinetics

The data provided are mainly at much lower doses than those to be used clinically.
Following oral administration, biotin is absorbed at the intestinal level via a Na+-dependent system involving the SMVT transporter. In humans it is highly bioavailable with a large fraction of biotin reported to be free (about 81%) in human serum. Following the administration of physiological doses of [14C] biotin at 88 nmol/kg body weight or tracer doses of [3H] biotin at 0.03 to 0.2 nmol/kg body

weight in pigs biotin pharmacokinetics after intravenous injection of 14C was marked by a very short half-life of the initial distribution phase (7 min), followed by a slower plasma elimination phase (T1/2, β of 1.43 hour) and a long apparent terminal half-life T1/2, γ estimated at 22 hours. The rapid initial distribution phase was shown to correspond to the disappearance of biotin from the plasma (central compartment) to the peripheral compartments such as total body water pool or tissue pools (3 compartment model).

Biotin is essentially unbound to plasma proteins of mouse, rat, rabbit, dog and human (% bound in human plasma was 8.51%). No binding of biotin to red blood cells was observed in rats, rabbits and dogs. Furthermore, no binding of BNB and BSO to red blood cells was seen in rats. Following the oral administration of radiolabelled biotin at doses up to 1000 mg/kg/day for 28 days in weaning rats, biotin concentrations were found to increase in all tissues examined (liver, brain, kidney, heart, skeletal muscle, lungs, spleen and testis). At the supplemented dose of 38.4 mg/kg/day (equivalent to ~300 mg/day in humans), mean biotin concentration was measured at around 2.5 nmol/g of brain tissue. In a further study performed in pigs, 4 days after the administration of radiolabelled physiological and tracer doses of biotin, biotin was mainly distributed in the liver, muscle and kidney. The pattern of distribution of biotin noted in these studies were as expected (liver plays an important role in normal biotin physiology and represents the major organ for biotin metabolism and utilisation and is in line with the role of Biotin in the energy mechanism of the muscles acting as a cofactor of carboxylase).

The applicant has submitted data which shows that MD1003 MD1003 (biotin) does not absorb light significantly at any wavelength between 290 and 700 nm. Consequently, MD1003 is not considered to be sufficiently photoreactive to result in direct phototoxicity. The data also shows that MD1003 does not accumulate in tissues exposed to light (eyes and skin). The overall conclusion is that MD1003 does not present a concern for phototoxicity.

Biotin is catabolised mainly in the liver, via two principal pathways leading to two major metabolites, BNB and BSO. There are thought to be two pathways. In the first pathway, biotin is degraded mainly in the mitochondria by β-oxidation of the valeric acid side chain to BNB, tetranorbiotin, and intermediates known to result from β-oxidation of fatty acids (i.e. α,β-dehydro-, β-hydroxy, and β- keto-intermediates). Spontaneous decarboxylation of β-ketobiotin and β-ketobisnorbiotin yields bisnorbiotin methyl ketone and tetranorbiotin methyl ketone. In the second pathway, sulfur oxidation in the tetrahydrothiophene ring leads to the formation of BSO, biotin-d-sulfoxide, and biotin sulfone. Sulfur oxidation in the biotin molecule occurs in the smooth endoplasmic reticulum in a reaction that depends on nicotinamide adenine dinucleotide phosphate.

The results of cytochromes P450 metabolism, induction/inhibition studies suggest that most common CYPs are not responsible for the biotransformation of biotin in human, biotin is not an inducer of CYP1A2 and CYP3A4 in human hepatocytes following 3 days (72 hours) exposure at concentrations of up to 350 µM, or of CYP2B6 at concentrations of at least 200 µM and BNB is not an inducer of CYP1A2, CYP2B6 or CYP3A4 in human hepatocytes following 3 days (72 hours) exposure at concentrations of up to 100 µM. biotin at concentrations up to 350 µM, and BNB at concentrations up to 100 µM were not inhibitory towards any cytochrome P450 enzymes CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5, either with or without a 30-minute pre-incubation.

The metabolite profile of radioisotope-labelled biotin was examined in rats (14C-carbonyl-labelled biotin administered by intraperitoneal injection doses of 6.6 to 1025 pmol/g body weight). Biotin, BNB, and BSO accounted for about 90% of the total urinary radioactivity for the first 24 h and for Days 2 to 5. The radioactivity not attributable to biotin, BNB, or BSO chromatographed as six small peaks. Biotin

accounted for an average of 46 ±9%, bisnorbiotin for 47±11%, and biotin sulfoxide for 8 ±4% of the total of biotin, BNB, and BSO excreted over the 5 days. The variability was thought to do due to animal variation.

In humans, biotin accounts for 52% of total biotin plus metabolites, BNB for 35%, and BSO accounting for 13 %. During the first 24 h, the metabolite profiles for the rats were quite similar to the human profile, but significant differences were observed in the metabolite profile between Day 1 and Days 2 to 5. The proportions attributable to BNB were different between the rat species at Day 5 and humans with a higher proportion of the metabolite BNB in the rat species (47% of total biotin, BNB and BSO) compared to the human (35% of total biotin, BNB and BSO). When considering the BSO metabolite, the opposite trend was observed with a higher proportion in humans (13% of total biotin, BNB and BSO) than in the rat species (8% of total biotin, BNB and BSO.

In pigs given IV doses of radiolabeled biotin at 24, 94 and 195 pmol/kg body weight. The main radioactive form excreted in the urine was biotin. Less than a third was excreted as BSO and about 15% corresponded to the expected products of the β-oxidation of the valeric acid side chain, BNB included.

After IV administration of 14C biotin at the physiological dose of 88 nmol/kg in pigs, rapid excretion occurred with about half of the administered dose recovered in the urine by 72 h, unchanged biotin, BNB and BSO being the major metabolite forms. Of the total biotin, BNB and BSO excreted over the 72 h following an intravenous injection of [14C] biotin, biotin accounted for about 51%, BNB for about 24% and BSO for about 25%. Metabolism in pigs resembles that in humans. Substantial amounts of BNB and BSO, two known biotin metabolites, were also excreted. Bisnorbiotin methyl ketone and biotin sulfone, two other biotin metabolites identified in human urine, were also present in pig urine. In another pig study BNB and BSO were the two major biotin metabolites detected in the plasma. Plasma concentrations of 14C-labelled metabolites were negligible for the first 2 h after biotin infusion. Bisnorbiotin methylketone, an intermediate in biotin β-oxidation, was also detected in very small amounts (<1%). Bisnorbiotin methylketone, an intermediate in biotin β-oxidation, was also detected in very small amounts (<1%).

Across human, rat and pig is almost exclusively renally excreted. The interactions of biotin at concentrations up to 3300 µM and BNB at concentrations up to 66 µM with the ABC transporters P-gp and BCRP were investigated. Additionally, the potential of biotin and BNB to inhibit the uptake transporters OAT1, OAT3, OCT2, OATP1B1 and OATP1B3 were examined at concentrations up to 187.5 µM (for biotin regarding OAT1, OAT3 and OCT2) and 675 µM (for biotin regarding OATP1B1 and OATP1B3), and up to 66 µM for BNB. For all transporters monitored, no inhibition of biotin or BNB was observed with all IC50 values larger than the highest doses tested in all cases.

The potential of MD1003 and BNB to inhibit the MATE1, MATE2K and BSEP transporters at concentrations up to 187.5 µM (MATE1 and MATE2K) and up to 675µM (BSEP) and BNB at concentrations up to 70 µM were investigated. MD1003 and BNB, at relevant concentrations, did not induce any inhibition of these transporters. Similarly, MD1003 and BNB did not inhibit the hepatic transporters OATP1B1 and OATP1B3 at relevant concentrations. In conclusion, these results show that oral administration of MD1003 at 300mg (100mg tid) should not induce any DDI with substrates of the transporters studied.

3.2.3. Toxicology

General toxicology

A suitable series of repeat dose toxicity studies have been conducted with MD1003 following oral administration to rats and dogs, of up to 26 week in the rat and 39 weeks in the dog. No test article related findings were seen in these studies up to the maximum dose of 1000 mg/kg/day, which was determined as the NOAEL. Whitish faeces, was observed in the rat species only. However, this finding was not considered toxicologically relevant as not associated with microscopic or macroscopic observations and probably due to the formulation of MD1003. This is agreed.

the oral administration of MD1003 to female rabbits at 250 mg/kg/day and above exceeded the MTD, with mortality observed at 1000 mg/kg/day and severe effects on body weight and on food consumption at the dose of 250 mg/kg/day. At 100 mg/kg/day, animals showed reduced activity, reduced food intake and body weight loss. gastrointestinal findings (brown liquid intestinal content) were observed at ≥100 mg/kg/day. Dark red foci and lesions were observed in the stomach mucosa at 250 mg/kg/day and 1000 mg/kg/day. The MTD in non-pregnant female New Zealand White rabbits treated daily for 14 days was considered to be 30 mg/kg/day. This was estimated to be equivalent to twice the therapeutic dosage used in humans, when extrapolated on the basis of body surface area as recommended by the FDA guidance on selection of a safe starting dose for an initial clinical trial (FDA, 2005). It is agreed that given that no such effect has been reported in MS patients during the pivotal Phase 3 Studies, these effects were not seen in rat or the dog and the rabbit is known to be susceptible to present disturbance of the alimentary tract, the finding seen in the rabbit are unlikely to be clinically relevant.

Pharmacokinetic Plasma Parameters for Biotin Following MD1003 Administration to Rats, Dogs and Humans

Parameter (unit)	Rat		Dog		Human	
	Repeated oral administration		Repeated oral administration		Single oral administration	Repeated oral administration
	MD1003 1000 mg/kg/day		MD1003 1000 mg/kg/day		MD1003 100 mg	MD1003 100 mg/day tid
	Day 181		Week 39		Day 1	Day 8
	Study MD1003-26W-RAT		Study MD1003-39W-DOG		Study MD1003CT2014-02PK	Simulated model - Study MD1003CT2014-02PK
	Males N=2	Females N=2	Males N=4	Females N=4	N=8	N=7
Mean AUC_{0-t}* ± SD (ng.h/mL)	72633 ± ND	96605 ± ND	165718 ±28872	120773 ±30314	2520.7±560.9	13048.1±ND
Mean C_{max} ± SD (ng/mL)	7188 ± ND	11253 ± ND	38889 ±9947	41262 ±10487	504.8±115.2	961.91±ND
Safety margin**	6	7	13	9	NA	NA

N=number of subjects. ND=Not determined; tid=three times a day

* AUC_{0-t} with t=8 hours in rats and dogs, and t=24 hours in rabbits and humans

** Safety margin calculated as Mean AUC_{0-8} in animal species / Mean AUC_{0-24} in humans at Day 8

Suitable margins of exposure fold cover exist between exposure in dog and rats to those seen clinically.

Genotoxicology

Conventional studies of genotoxicity (Ames test in Salmonella typhimurium and Escherichia coli reverse mutation assay, a chromosomal aberration assay in human peripheral blood lymphocytes and a bone marrow micronucleus assay following oral administration to rats) revealed no genotoxic potential of MD1003.

Carcinogenicity

No carcinogenic studies were conducted with MD1003. Instead, the Applicant provided an extended discussion on the carcinogenic potential of high-dose biotin, although no definitive conclusion could be obtained. Given that the risk for tumorigenesis of high-dose of biotin could not be ruled out, a 26-week study in transgenic rasH2 mice was proposed. The Applicant should provide an estimated date to submit the results.

Reproductive toxicology

The potential toxicity of MD1003 on fertility and early embryonic development was evaluated in one study conducted in rats and the effects on embryo-foetal development were assessed in one pivotal study in rabbits.

The parental NOAEL and the NOEL for pairing, mating and fertility performances were considered to be 1000 mg/kg/day for both sexes. In the pivotal rabbit reproductive toxicology study (Study MD1003-DEV-RAB0) foetal toxicity with skeletal malformations and skeletal variations (cleft palates, misshapen paw, hydrocephalies, marked dilated cerebral ventricles, liquid content in cranial cavity, ventricular septum defect, unossified interparietals and misshapen skullcap) were seen at 30 mg/kg/day. There

were some skeletal malformations that were only seen at 15 mg/kg/day. The Applicant states that these findings were within historical control ranges.

External/soft tissues variations were also observed at 15 and 30 mg/kg/day (liver with coloured nodule and malrotated paw at both doses and domed head, dilated cerebral ventricle in the brain, coloured node in the gall bladder, enlarged ovaries and ureter at 30 mg/kg/day). The Applicant considers the findings at 15 mg/kg/day as 'not toxicologically relevant' however given that malrotated paw and liver with coloured nodule was seen at 30 mg/kg/day these findings cannot be dismissed (or not considered of toxicological significance) at 15 mg/kg/day. This shows a dose related effect. No NOAEL could be established in this study as external variations and soft tissues examination variations were seen at 15 mg/kg/day.

MD1003 has been shown to be teratogenic in the rabbit, but not in the rat. The mechanism of teratogenicity of MD1003 in rabbits remains unknown. The applicant could not explain why no teratogenicity was found in rats at doses up to 1000 mg/kg/day. The applicant claims that no prediction can be made regarding the effect in humans. However, since the teratogenic effects in the rabbit occurred at dose levels at which there was no maternal toxicity, these effects must be considered to be genuine teratogenic effects. Consequently, it would be prudent to consider that a risk of teratogenicity as observed in rabbits could not be excluded in humans treated with MD1003 100 mg tid. Accordingly, MD1003 should be not recommended during pregnancy. The applicant states that the corresponding information is reported in Sections 4.4, 4.6 and 5.3 of the SmPC.

A pre- and post-natal development study in rats was conducted and showed that the NOAEL was 1000 mg/kg/day for the F0 generation and the NOEL was 1000 mg/kg/day for the F0, pups of the F0 and F1 generations. Given the rabbit data MD1003 should be contraindicated in pregnancy and women of childbearing potential advised to use effective contraption while taking MD1003. The current SmPC states that QIZENDAY is not recommended during pregnancy or in women of childbearing potential who are not using a reliable form of contraception. Studies in animals have shown reproductive toxicity. QIZENDAY is not recommended during pregnancy. If a patient becomes pregnant while taking QIZENDAY, therapy should be discontinued. The product literature should also provide advice on how long after contraceptive measures should be in place for after MD1003 is stopped (5x half-lives or otherwise justified).

3.2.4. Ecotoxicity / environmental risk assessment

The active substance is water soluble vitamin a natural substance. Biotin PEC surfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5.

The PECsw was calculated using a refined Fpen value of 0.001 estimated for the proportion of patients with progressive multiple sclerosis (either primary or secondary) in the EU. As the PECsw (0.15 µg/L) based on a daily dose of 300 mg was higher than the action limit of 0.01µg/L, a Phase II Tier A environmental fate and effects analysis of biotin should have been conducted. However the applicant provides a justification for not conducting phase II.

Biotin is a vitamin and is naturally present in the environment and is used in human supplements plus animal feed, the amount of biotin released into the environment from its intended use in progressive multiple sclerosis (primary and secondary) in adults is unlikely to result in a significant risk to the environment. Estimated EU dietary intake 3710 kg, Biotin is commercially available as dietary supplements with daily intakes may vary from tens of micrograms (0.01 mg) to 75 mg and estimated biotin from animal feed in the EU in 2010 was 473 million tons per year (4.73 x 1011 kg). In order to

obtain an estimate of the total amount of biotin which could be available from animal feed additives it has been assumed that 0.1 mg/kg is added: Total = 4.73 x 1011 kg x 0.1 mg/kg = 4.73 x 1010 mg = 47300 kg biotin.

The European Food Standards Agency concluded that the use of biotin in animal nutrition is not expected to pose a risk to the environment (Scientific Opinion on the safety and efficacy of biotin as a feed additive for all animal species based on a dossier submitted by VITAC EEIG. EFSA Journal 2012; 10(11): 2926.

3.2.5. Discussion on non-clinical aspects

The Applicant provides both data from the literature and non-clinical data generated from GLP and non-GLP in-company studies (in vivo pharmacology studies, an in vitro in a hERG ion channel assay, in vitro drug interaction studies, a 6-month rat study and 9-month dogs study (that included safety pharmacology parameters), a standard battery of genetic toxicology studies and fertility and early embryonic development study in rats). A potential mechanism of action of MD1003 was proposed, based on the pharmacological studies conducted in X-ALD (X-linked adrenoleukodystrophy) experimental models. However, the pharmacodynamic effect could not be confirmed in other MS preclinical models, i.e. EAE, cuprizone and lysolecithin. In the secondary pharmacology discussion the Applicant highlights that an influence of biotin on glucose metabolism and the dosage of insulin in diabetic patients cannot be ruled out. The risk of interactions between biotin and insulin in diabetic patients has been identified as a potential risk in the Risk Management Plan and recommendations are made in the Summary of Product Characteristics (SmPC). In addition studies suggest that histones H3 and H4 are post-translationally modified by binding of biotin, catalysed by holocarboxylase synthetase (HCS). A potential mechanism of action of MD1003 was proposed, based on the pharmacological studies conducted in X-ALD (X-linked adrenoleukodystrophy) experimental models. However, the pharmacodynamic effect could not be confirmed in EAE, cuprizone and lysolecithin MS preclinical models. In the hERG assay, a decrease (<12%) of hERG tail current was observed at, 100 µM (~25 times above the estimated steady state human Cmax of MD1003). In a dog study isolated absolute QT interval prolongations were see at 1000 mg/kg/day 4 hours post dosing, however, no clear difference was observed when the QT was corrected with Friderica and Van de Water formulas. Atrio-ventricular block was seen in one female at 300 mg/kg/day and junctional premature contraction was seen in one female at 1000 mg/kg/day. These were also considered incidental as they were not observed in the other animals at these doses (see comments below). CV safety margins of between 6 and 9 for plasma exposure, and at least between 24 and 32 for plasma concentration regarding in vivo cardiovascular function, based on single-dose plasma exposure (AUC) and maximal concentration (Cmax) in dogs versus (1000 mg/kg/day) those estimated in humans, and at least 25 for the in vitro hERG tail current assay (QT prolongation potential), based on the 100 µM concentration tested versus the estimated steady-state mean maximal plasma concentration (Cmax ~4 µM) in humans suggesting that no potential toxicity is expected in humans at biotin plasmatic exposure levels up to at least 6 times and biotin plasma concentrations up to at least 24 times higher than those estimated at the human dose of 100 mg tid.

Based on a review of all the relevant non-clinical data, there does not appear to be a risk to the CVS. However, the company is conducting a thorough clinical QT study at present and commits to provide the results for the Day 180 responses. In addition, the clinical PK study MD1003CT2016-01PK has a cardiovascular monitoring component. Cardiac safety profile of the product will be updated following

reports from these studies and the informed assessment and conclusions can only be carried out and provided once these data are available.

The Applicant provides absorption, distribution, metabolism and excretion (ADME) via data from the literature and from toxicokinetic data from toxicology studies. The data provided are mainly at much lower doses than those to be used clinically.

The non-clinical data from rat and dog chronic toxicity studies revealed no evidence of renal toxicity. When compared to biotin human exposure at a MD1003 dose of 100 mg tid, the safety margins for MD1003 were estimated to be at least 5. The few safety data obtained from patients with renal impairment in the early access cohort programme also do not suggest an increased risk of toxicity with MD1003 in this category of patients.

The potential of MD1003 and BNB to inhibit the MATE1, MATE2K and BSEP transporters at concentrations up to 187.5 µM (MATE1 and MATE2K) and up to 675µM (BSEP) and BNB atconcentrations up to 70 µM were investigated. MD1003 and BNB, at relevant concentrations, did not induce any inhibition of these transporters. Similarly, MD1003 and BNB did not inhibit the hepatic transporters OATP1B1 and OATP1B3 at relevant concentrations. In conclusion, these results clearly show that oral administration of MD1003 at 300mg (100mg tid) should not induce any DDI with substrates of the transporters studied.

MD1003 (biotin) does not absorb light significantly at any wavelength between 290 and 700 nm. Consequently, MD1003 is not considered to be sufficiently photoreactive to result in direct phototoxicity. It does not accumulate in tissues exposed to light (eyes and skin). The overall conclusion is that MD1003 does not present a concern for phototoxicity.

A suitable series of repeat dose toxicity studies have been conducted with MD1003 following oral administration to rats and dogs, of up to 26 week in the rat and 39 weeks in the dog. No test article related findings were seen in these studies up to the maximum dose of 1000 mg/kg/day.

In the pivotal rabbit reproductive toxicology study (Study MD1003-DEV-RAB0) foetal toxicity with skeletal malformations and skeletal variations (cleft palates, misshapen paw, hydrocephalies, marked dilated cerebral ventricles, liquid content in cranial cavity, ventricular septum defect, unossified interparietals and misshapen skullcap) were seen at 30 mg/kg/day. There were some skeletal malformations that were only seen at 15 mg/kg/day. The Applicant states that these findings were within historical control ranges (see comments below).

External/soft tissues variations were also observed at 15 and 30 mg/kg/day (liver with coloured nodule and malrotated paw at both doses and domed head, dilated cerebral ventricle in the brain, coloured node in the gall bladder, enlarged ovaries and ureter at 30 mg/kg/day). The Applicant considers the findings at 15 mg/kg/day as ‘not toxicologically relevant’ however given that malrotated paw and liver with coloured nodule was seen at 30 mg/kg/day these findings cannot be dismissed (or not considered of toxicological significance) at 15 mg/kg/day. This shows a dose related effect. No NOAEL could be established in this study as external variations and soft tissues examination variations were seen at 15 mg/kg/day. These findings should be included in section 5.3 of the SmPC (if possible) in relation to expected clinical exposures.

.The current SmPC states that QIZENDAY is not recommended during pregnancy or in women of childbearing potential who are not using a reliable form of contraception. Studies in animals have shown reproductive toxicity. QIZENDAY is not recommended during pregnancy. If a patient becomes pregnant while taking QIZENDAY, therapy should be discontinued. The product literature should also

provide advice on how long after contraceptive measures should be in place for after MD1003 is stopped (5x half-lives or otherwise justified).

No genotoxic potential was seen in the standard battery of genotoxcity tests. The Applicant commits to conduct a 26-week carcinogenicity study in transgenic rasH2 mice (estimated date for submission of the results should be provided by the Applicant).

3.2.6. Conclusion on non-clinical aspects

From a nonclinical point of view, the results from the pharmacodynamic studies could not be considered convincing. The pharmacological effects reported in the X-ALD experimental model were not confirmed in MS models. In the hERG assay, a decrease (<12%) of hERG tail current was observed at, 100 µM (~25 times above the estimated steady state human Cmax of MD1003). In the 39 week dog study atrio-ventricular block was seen in one female at 300 mg/kg/day and junctional premature contraction was seen in one female at 1000 mg/kg/day. Based on a review of all the relevant non-clinical data, there does not appear to be a risk to the CVS. However, the company is conducting a thorough clinical QT study at present and commits to provide the results for the Day 180 responses. In addition, the clinical PK study MD1003CT2016-01PK has a cardiovascular monitoring component. Cardiac safety profile of the product will be updated following reports from these studies and the informed assessment and conclusions can only be carried out and provided once these data are available. No genotoxic effect was observed in the standard battery of genotoxicity tests. Regarding the potential carcinogenic effect of high-dose of biotin, a 6-month study in rasH2 transgenic mice should be conducted and results submitted post-approval (estimated time for submission is requested). In the pivotal rabbit reproductive toxicology study skeletal malformations and skeletal variations were seen at 15 and 30 mg/kg/day. The current SmPC states that QIZENDAY is not recommended during pregnancy or in women of childbearing potential who are not using a reliable form of contraception. Studies in animals have shown reproductive toxicity. QIZENDAY is not recommended during pregnancy. If a patient becomes pregnant while taking QIZENDAY, therapy should be discontinued. The product literature should also provide advice on how long after contraceptive measures should be in place for after MD1003 is stopped (5x half-lives or otherwise justified).

4. Clinical aspects

Table 1: Overview of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK	MD1003CT 2014-02PK	Module 5, Section 5.3.3.1, Study MD1003CT2014-02PK	Evaluate dose proportionality between 100, 200 and 300 mg MD1003 Evaluate food effect at 100 mg MD1003	Randomised, open-label, four-way cross over study, with a wash-out period of at least 7 days between each period	100 mg MD1003 biotin capsules; 100 mg single dose; oral	8	Healthy Subjects	Single dose	Complete; Full
PK	MS-ON	Module 5, Section 5.3.5.1, Study MS-ON	Define steady-state PK	Open-label extension	100 mg MD1003 biotin capsules; 300 mg (100 mg tid); oral	21	Patients successfully completing the DBPC phase of the study	12 months	Complete; Full
Efficacy & Safety	MS-SPI	Module 5, Section 5.3.5.1, Study MS-SPI	Efficacy and Safety	Randomized, double-blind, placebo-controlled	100 mg MD1003 biotin capsules; 300 mg (100 mg tid); oral	154 (103 MD1003; 51 placebo)	Progressive MS patients (primary or secondary) with spinal involvement	12 months	Complete; Full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
			Long-term; Efficacy and Safety	Open-label extension	100 mg MD1003 biotin capsules; 300 mg (100 mg tid); oral	125	Patients successfully completing the DBPC phase of the study	12 months interim (total open label phase will be 24 months)	Complete; Full
Efficacy & Safety	MS-ON	Module 5, Section 5.3.5.1, Study MS-ON	Efficacy and Safety	Randomized, double-blind, placebo-controlled	100 mg MD1003 biotin capsules; 300 mg (100 mg tid); oral	93 (65 MD1003; 28 placebo)	Progressive MS patients (primary or secondary) or relapsing remitting MS patients with optic neuropathy	6 months	Complete; Full
			Long-term; Efficacy and Safety; PK analysis	Open-label extension	100 mg MD1003 biotin capsules; 300 mg (100 mg tid); oral	89	Patients successfully completing the DBPC phase of the study	6 months interim (total open label phase will be at least 24 months)	Complete; Full

A case series in 23 patients with progressive MS is also used as supportive data.

4.1.1. Pharmacokinetics

The absorption, distribution, metabolism and elimination of biotin is well-known and has been subject to extensive scientific publications. In addition the following PK information has been obtained with MD1003:

-Data from a single dose PK study in healthy subjects, Study MD1003CT2014-02PK

-Simulated PK modelling data for steady state at the proposed dosing regimen

-Steady state PK data from a subset of patients in the phase 3 Study MS-ON.

Throughout the dossier the applicant has presented literature data; however the relevance of this data is questionable, primarily due to the many-fold difference in dose. Furthermore, the applicant highlights the limitations of the studies, especially with regard to the accuracy of the analysis methods previously used (an avidin-binding assay known to bind to biotin and its metabolites). Furthermore, as there is non-linear PK of biotin, the significance of these low-dose studies becomes even less relevant.

Three different analytical methods have been used for the determination of biotin in the samples taken during clinical studies. One method was used for the determination of biotin in human blood samples taken during study MD1003CT2014-02PK [validation report no MD1003-VB-HP (method no ATL-14-1234)]; one method was used for the determination of biotin in urine samples taken during study MD1003CT2014-02PK [validation report no MD1003-BIO-ANA-06-HU (method no ATL-14-1238)]; the third method was used for determination of biotin and its two metabolites in human plasma taken during both studies MD1003CT2014-02PK and MS-ON [validation report no MD1003-BIO-ANA-07-HP (method no ATL-15-1311)]. The applicant has provided details of a compartmental analysis of the PK following 100 mg biotin under the fed condition. Compartmental analysis was performed using WinNonlin; based on visual inspection of the goodness-of-fit plots. The PK model was ultimately based on the data of 7 subjects (subject 8 being excluded due to being an outlier). The model, despite being rudimentary appears adequate, but is extremely limited by the data it is based on and as such has limited utilisation for simulation.Regarding bioavailability, the applicant provided two literature references (Bitsch et al and Zempleni et al), however these only investigated significantly lower doses of biotin. Given the potential for saturation of the SMVT transporter these studies cannot be considered relevant. Furthermore, these studies used an avidin-binding assay, which has been critiqued for not distinguishing biotin from its metabolites.

There is a potential for conditions/diseases with an inflammatory component to inhibit the transport of biotin via the sodium dependent multivitamin transporter (SMVT) which the applicant should discuss.

Following single oral administration of 100 mg biotin, there was a delay of 0.5 hour in tmax of biotin in fed condition compared with the fasted condition. There was no significant difference in Cmax or AUClast values between the fed and fasted conditions for biotin, BNB or BSO, however due to the variable nature of the parameter values and low subject number these results should be interpreted with caution. However, there appears minimal impact of food on the absorption of biotin and it can be taken without regard to food. Based on literature and theoretical calculations it is unlikely that dietary sources of avidin i.e. from eggs, which binds to biotin, will interfere with the absorption of biotin.

The fraction unbound in human plasma was >88 The binding of biotin and its metabolites, BNB and BSO to red blood cells was calculated to <10%, <15% and < 23%, respectively. Due to limited duration of sampling Vz/F could not be calculated.

Due to limited duration of sampling, the elimination half-life and derived parameters (AUCinf, CL/F, Vz/F) could not be determined. The applicant should be able to characterise the elimination of the drug, especially in terms of apparent clearance and terminal half-life. The applicant estimates that the percentage of recovered biotin in the urine in the 24 hours following a 100 mg dose is 31% while for a 300 mg dose it is 17%, however given the limited number of subjects included in the analysis (n=4), these results are considered preliminary.

There are 2 main pathways for the metabolism of biotin. The first pathway involves beta-oxidation to BNB. The second pathway the sulphur in the thiophene ring of biotin is oxidised forming BSO.

Biotin contains 3 chiral centres.

For both BNB and BSO, peak plasma concentrations were reached at a median tmax of 2.00 to 2.50 hours post-dose in fasted conditions. A delay in the occurrence of plasma peaks was observed in fed conditions, with a median tmax of 3.00 hours post-dose.

The proposed dose (100 mg fasted or fed), elimination half-life and AUCinf could not be reliably determined over a sufficient time interval for BNB or BSO.

The applicant has not investigated the impact of any genetic polymorphisms that may affect the PK of biotin.

Dose proportionality as assessed by a power model indicated that between 100 mg and 300 mg, biotin was not dose proportional for Cmax or AUClast. The results indicate that the absorption of biotin becomes saturated at doses above 100 mg.

The PK samples collected as part of the study MS-ON were collected at a single time point in the course of the standard laboratory testing, before the next MD1003 intake in the morning or at noon. Thus, presentation of mean concentration data from a sparse sampling scheme without any time-constraints or incorporating it into a PK model renders the data uninterpretable. Futher PK data in the target population is required.

Moderate inter-individual variability for biotin and its metabolites was observed.

No studies investigating the impact of impaired renal or hepatic function has been submitted as patients with hepatic or renal impairment were systematically excluded from clinical trials. Only data from 6 patients with some degree of renal impairment (not reported) included in the ATU program are presented to support the lack of particular safety concerns as none of them reported any AEs. However, this is of limited value to provide recommendations to prescribing physicians, particularly in view of the limited knowledge on the actual role of these organs in the metabolism and excretion of biotin. Therefore, until the PK profile of biotin is not fully characterized, the Applicant´s proposal to not conduct specific PK studies in ReI and HeI patients as well as the proposals for the SmPC cannot be accepted.

No studies or analyses investigating the impact of sex, race or ethnicity, weight/BMI on the PK of biotin or its metabolites have been presented.

No subjects over the age of 35 years were included in the MD1003CT2014-02PK study. Given the sparse sample scheme and the limited number of subjects included over the age of 65 years for the MD1003CT2013-02MS-ON study, investigation of age as a potential covariate on the PK of biotin is not possible. The Applicant has presented additional data from the ATU program. In all 1205 out of 5483 (22%) patients at January 2017 were over 65 years and 216/5483 (3.9%) older than 75 years which is a relevant exposure. However, information available is limited to the SAE cases of spontaneous reports (0.7% of patients), which is substantially lower than the reporting seen in the RCTs (19.4% MS-SPI, 13.8% MS-ON) in the overall population. This speaks in favour of an important underreporting. In addition, safety information beyond the SAEs of these 8 patients is not available, therefore despite the apparent high exposure in the elderly population, data available do not allow making a conclusion of the safety profile in the elderly. Further description of the information from the ATU should be presented.

No pharmacokinetic data are available for paediatric patients. The applicant has been granted a waiver for biotin for the treatment of multiple sclerosis in children (EMA decision P/0077/2016).

The in vitro interaction studies and assessment are summarised in the non-clinical assessment report.

The applicant has provided a review of the literature highlighting potential interactions with pantothenic acid, lipoic acid, smoking, alcohol, and anticonvulsant medications. However, the clinical relevance of these potential interactions studies cannot be determined as the studies investigated significantly lower doses of biotin. Potential interactions with medicinal products expected to be used on the target population have not been investigated and deserve further discussion from the Applicant.

4.1.2. Pharmacodynamics

The active moiety in MD1003, biotin, acts as a carboxyl (CO2) transporter in carboxylation reactions involved in the metabolism of carbohydrates, amino acids and fatty acids. Biotin-dependent carboxylases are:

-pyruvate carboxylase (PC),

-3-methylcrotonyl-CoA carboxylase (MCC),

-propionyl-CoA carboxylase (PCC), and

-acetyl-CoA carboxylase (ACC), with the latter enzyme existing in two genetically distinct forms (ACC1 and ACC2), both are cytosolic, ACC2 being anchored at the outer surface of the mitochondria.

Three out of these four carboxylase reactions (PC, MCC, PCC) lead to production of tricarboxylic acid (TCA) cycle intermediates that are central to aerobic energy production (oxaloacetate, succinate and acetyl CoA). The fourth, ACC, is a key regulator of fatty acids synthesis. In the nervous system, ACC1 and ACC2 are expressed mainly in oligodendrocytes, the cells responsible for myelin synthesis, and are found in purified myelin, suggesting that these enzymes are key regulators of myelin synthesis (Chakraborty and Ledeen, 2003).

On this basis, it was hypothesized that MD1003 could increase energy production through feeding the TCA cycle in demyelinated neurons to counter-balance the “virtual hypoxia phenomenon” and potentially also enhance myelin repair through activation of the acetyl-CoA carboxylase in oligodendrocytes, and hence have an impact on the not-active progressive component of MS.

There is no animal model that recapitulates the entire course of MS. As a consequence, several non-clinical animal models were used to evaluate the pharmacodynamics properties of MD1003: acute models of MS relapses (lysolecithin-induced demyelination and experimental encephalomyelitis (EAE) mouse model) and chronic mouse models (X-linked adrenoleukodystrophy, Theiler’s virus induced demyelination, cuprizone-induced demyelination), with each sharing some aspects of the progressive form of MS. Three main mechanisms may be responsible for progressive MS and can be investigated in these different models: 1) inflammation, 2) axonal degeneration linked to energy metabolism failure, and 3) chronic demyelination.

Regarding axonal degeneration linked to energy failure, results of chronic animal models were mainly based on the X-linked adrenoleukodystrophy(X-ALD) model.

Published non-clinical and clinical data have reported a potential pharmacodynamic interaction effect of biotin on glucose levels resulting in hypoglycaemia via activation of genes that stimulate insulin, insulin receptor upregulation or pancreatic and hepatic glucokinase stimulation. Biotin could also lead to a decrease in the expression of hepatic phosphoenolpyruvate carboxykinase, which is a key gluconeogenic enzyme that stimulates glucose production by the liver (Fernandez-Mejia, 2005). Furthermore, as discussed below, biotin may have an inhibitory effect on fatty acids beta oxidation which may result in hypoglycaemia. These interferences between biotin and glucose metabolism may be particularly relevant in patients who need to manage their glucose levels and one case of

treatement-related hypoglycaemia was reported during the course of the clinical with MD1003 in a insulin-dependent diabetic patient. Overall, an influence of biotin on decreasing glucose levels cannot be ruled out and may result in the need to adapt the dosage of some anti-diabetic drugs. The appropriate information is included in Section 4.4 of the SmPC.

A possible secondary pharmacodynamic effect, with a potential clinical impact relates to fatty acid metabolism as biotin stimulates acetyl coA carboxylase, an enzyme involved in the formation of malonyl CoA. Increasing levels of malonyl coA inhibit carnitine palmitoyltransferase 1 (CPT1) which is responsible for long-chain fatty acid transport into mitochondria leading to fatty acids beta-oxidation. Therefore, the inhibition of CPT1 induced by malonyl CoA could result in reduced fatty acid beta-oxidation. A single case of lipid storage myopathy was reported in the clinical program, and as a result of the plausible pharmacological interaction, is reported as an adverse drug reaction.

Other secondary pharmacodynamic effects of biotin include biotinylation of histones, gene expression regulation especially related to glucose tolerance, as well as a possible role in immune function and cell proliferation.

The proposed mode of action relies mainly on non-clinical data and the data from the clinical development programme are not sufficient to fully elucidate the mode of action of the proposed product in MS. Especially the effect seen on brain volume cannot be fully explained by the hypothesis raised by the applicant of decreased brain water.

4.1.3. Discussion on clinical pharmacology

Overall, the clinical PK of biotin has been insufficiently characterised. There is an incomplete characterisation of the pharmacokinetics of biotin – the apparent volume of distribution, clearance and elimination of biotin has not been described and for the parameters which have provided, these are based on a low number of subjects. The multiple dose data has only been modelled with no clinical confirmation of the results. There is scant PK data available in the target population and the applicant has not provided any PK data for special populations (patients with hepatic impairment or more importantly renal impairment) or investigated any important covariates (sex, race, weight, age), these should be provided or their absence justified. The lack of information on this population should be mentioned in the SmPC. The potential for clinical drug-drug interactions, with biotin as perpetrator and victim, is unclear and depends on the results of the in vitro studies being well described. Also, it is unclear if the differences observed in the dissolution of the two products manufactured at different sites have an impact on the clinical PK of biotin Furthermore, much of the information on PK provided relies heavily on literature data which can be considered irrelevant considering the much higher doses used to support the proposed indication. The applicant needs to address the points above, so that the clinical PK of biotin is characterised sufficiently.

4.1.4. Conclusions on clinical pharmacology

Overall, the clinical PK of biotin has been insufficiently characterised, the applicant needs to address several points regarding this.

4.1.5. Clinical efficacy

Dose-response studies and main clinical studies

No dedicated dose-finding studies or multiple-dose pharmacodynamic studies have been conducted with MD1003, which would have been useful to identify the optimal treatment dose. The dose used in

the phase 3 study was selected empirically, based on observations from a case series that included 23 patients (Sedel et al, 2015; see "supportive study" section, below) who received biotin doses between 100 and 600 mg/day (mostly divided over three daily intakes). The Applicant justified the dose selection based on the observation that several patients treated with 100 mg/day biotin showed some improvement, but that the dose of 300 mg/day (100 mg tid) was associated with the best clinical efficacy without significant adverse events. This evidence seems insufficient to assess the adequacy of the selected dose. Therefore, the adequacy of the therapeutic dose-range will have to be inferred from the results of the pivotal phase 3 study and the supportive study included in this MAA.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 2: Summary of efficacy for trial MS-SPI

Title: Effect of MD1003 in spinal progressive multiple sclerosis: a pivotal randomized double blind placebo controlled			
Study identifier	MS-SPI		
Design	Randomized double-blind placebo controlled for 12 months, followed by an open-label extension phase for 12 months (an additional 12-month extension still ongoing at the time of reporting).		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 months 4 weeks screening period 12 months + 12 months
Hypothesis	Superiority (MD1003 over placebo)		
Treatments groups	MD1003		300 mg/day [100 mg 3 times/day (tid)] for 24 months (12m DB and 12m extension phases).
	Placebo		During the DB Phase: placebo-matched capsules tid during 12 months. During the extension phase: 300 mg/day [100 mg 3 times/day (tid)] for 12 months.
Main Endpoints and definitions	Primary endpoint		Proportions of patients: • with decreased EDSS at M9 confirmed at M12 (where decreased EDSS is defined as a decrease of at least 0.5 point if the initial EDSS was between 6 and 7 and a decrease of at least 1 point if the initial EDSS was between 4.5 and 5.5) compared to the best EDSS score obtained between the screening and baseline visits OR • with improved TW25 of at least 20% at M9 and M12 compared to the best TW25 score obtained between the screening and baseline visits

	Secondary endpoints	Double-blind phase, change from baseline	Proportion of patients with decreased EDSS at M18 confirmed at M24 or with improved TW25 at Month 18 compared to Month 24
			Proportion of patients with improvement (decrease) of EDSS at Month 9 confirmed at Month 12
			Proportion of patients with improved TW25 of at least 20% at M9 confirmed at M12
			MSWS-12 at M12
			CGI-I at M12 and M24
			SGI at M12 and M24
Database lock	24 February 2015 for primary analysis		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat 12 months with extension up to 24 months		
Descriptive statistics and estimate variability	Treatment group	MD1003	Placebo
	Number of subjects	103	51
	Primary: Proportion of patients with decreased EDSS OR improved TW25 at M9 confirmed at M12 (%)	12.6%	0 %
	95% CI	(6.89%, 20.62%)	(0.00%, 6.98%)
	Secondary: Proportion of patients with decreased EDSS or with improved TW25 at M18 confirmed at M24*	13.2	7.1
	95% CI	(7.00%, 21.90%)	(1.50%, 19.48%)

	Proportion of patients with improvement (decrease) of EDSS (M9 confirmed at M12)	9.71%	0.0%
	95% CI	(4.75%, 17.13%)	(0.00%, 6.98%)
	Proportion of patients with improved TW25 of at least 20% at M9 confirmed at M12**	8.74%	0.00%
	95% CI	(4.07%,15.94%)	(0.00%,6.98%)
	MSWS-12 Mean change from baseline to M12	0.79	5.26
	SD	17.12	22.51
	Mean CGI-I at M12	4.05	4.62
	SD	0.81	0.75
	Mean SGI at M12	4.27	4.76
	SD	1.05	0.89
	Mean MFIS at M12	1.38	1.30
	SD	16.04	15.69

Effect estimate per comparison	Primary endpoint	Comparison groups	MD1003 vs. placebo
		Difference in response rates (%)	12.6 %
		Fisher's exact test P-value 95% CI	0.0051 (6.21 %, 19.03 %)
	Secondary endpoints	Comparison groups	MD1003 vs. placebo
		Proportion of patients with improvement (decrease) of EDSS (M9 confirmed at M12)	9.7 %
		p-value 95% CI	0.03 (3.99 %, 15.42 %)
		Proportion of patients with improved TW25 of at least 20% at M9 confirmed at M12**	8.74%
		p-value 95% CI	0.0301 (4.07%,15.94%)

		MSWS-12 mean difference	4.47
		Mann-Whitney P-value 95% CI	0.8118 (-1.98, 10.12)
		CGI mean difference	0.57
		Mann-Whitney P-value 95% CI	<0.0001 (0.30, 0.84)
		SGI mean difference	0.49
		Mann-Whitney P-value 95%CI	0.0094 (0.15, 0.83)
		MFIS mean difference	-0.08
		p-value 95% CI	0.85 (-5.47, 5,31)
Notes	*Number of patients is different in the extension phase **post-hoc analysis to be confirmed Most of these analyses need to be repeated as the handling of missing data may have overestimated the treatment effect. 95% CI for the difference between groups were calculated by the assessors. As for improvement of TW25 at M12, if only 5 patients are considered improved the treatment effect is 4.85% (95% CI: 0.7-0.9, p-value 0.171)		

Table 3: Summary of efficacy for trial MS-ON

Title: Effect of MD1003 in chronic visual loss related to optic neuritis in multiple sclerosis: a pivotal randomized double masked placebo controlled study			
Study identifier	MS-ON		
Design	Randomized double-masked placebo controlled study for 6 months, followed by an open-label extension phase until market authorization application (France) or for 18 months (UK).		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	6 months not applicable 18 months (still ongoing)	
Hypothesis	Superiority of MD1005 over placebo		
Treatments groups	MD1003	100 mg three times a day, 65 patients randomised	
	Placebo	three times a day, 28 patients randomised	
Endpoints and definitions	Primary endpoint	Mean change in best corrected visual acuity (logMAR) at 100% contrast between baseline and month 6 of the diseased eye [where the diseased eye was defined as the eye with the worst visual acuity (<5/10) at baseline and with evidence of worsening during the past three years].	
	Secondary endpoints	Proportion of patients with improvement of VA of the diseased eye of at least logMAR at 100% contrast at M6	
	Exploratory endpoint	Mean change in Retinal Nerve Fiber Layer (RNFL) of all eyes between baseline and M6	
Database lock	2016?		
Results and Analysis			

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat 6 months		
Descriptive statistics and estimate variability of primary endpoint	Treatment group	MD1003	Placebo
	Number of subjects	65	28
	Primary: Mean change at M6 in logMAR in whole population	-0.061	-0.036
	SD	0.206	0.184
	Number of subjects	20	14
	Subgroup: Mean change at M6 in logMAR in progressing subgroup	-0.049	0.043
	SD	0.281	0.179
	Number of subjects	45	14
	Subgroup: Mean change at M6 in logMAR in RR subgroup ----------	-0.066 ----------	-0.116 ----------
	SD	0.165	0.156
	Number of subjects	65	28
	Secondary: Proportion with improvement of at least 0.3logMAR at M6 (diseased eye)	9.23%	7.14%
	95% CI	(3.46%, 19.02%)	(0.88%, 23.50%)
	Number of subjects	65	28
	Exploratory: Mean change at M6 in RNFL thickness (all eyes)	-0.5	-0.3
	SD	2.6	2.7
	Number of subjects	19	14
	Subgroup: Mean change at M6 in RNFL thickness in PMS subgroup	0.2	-0.6

	SD	2	1.3
	Number of subjects	45	14
	Subgroup: Mean change at M6 in RNFL thickness in RRMS subgroup ---------- SD	-0.9 ---------- 2.8	0.1 ---------- 3.7
Effect estimate per comparison	Primary endpoint	Comparison groups	MD1003 vs. placebo
		All subjects: Difference in mean change at M6 in logMAR	-0.01983
		95% confidence interval	[-0.1085; 0.0689]
		ANCOVA p-value	0.6581
		PMS subgroup: Difference in mean change at M6 in logMAR	-0.092
		Mann-Whitney p-value	0.2471
		RRMS subgroup: Difference in mean change at M6 in logMAR	0.050
		Mann-Whitney p-value	0.4371
	Secondary: Proportion with improvement of at least 0.3logMAR at M6 (diseased eye)	Comparison groups	MD1003 vs. placebo
		Proportion with improvement of at least 0.3logMAR at M6 (diseased eye)	2.09%?
		95% confidence interval	Not provided
		Fisher's Exact test p-value	1.0000
	Exploratory endpoint	Comparison groups	MD1003 vs. placebo
		Difference in mean change at M6 in RNFL	-0.3005
		95% confidence interval	[-1.1916; 0.5907]
		GEE model P-value	0.5087
		PMS subgroup: Difference in mean change at M6 in RNFL	0.8
		Mann-Whitney P-value	0.1322
		RRMS subgroup: Difference in mean change at M6 in RNFL	-1
		Mann-Whitney P-value	0.6079
Notes	RRMS: Relapsing Remitting MS; PMS: Progressive MS RNFL: Retinal Nerve Fiber Layer		

Clinical studies in special populations

No clinical trial has been performed in special populations.

Analysis performed across trials (pooled analyses AND meta-analysis)

Patient Disposition

The majority of patients completed the studies as planned with a low proportion of patients prematurely withdrawing from the studies. The higher proportion of patients prematurely discontinuing from Study MS-SPI may be due to the duration of the double-masked phase being 12 months in this study, rather than only 6 months in Study MS-ON.

Table 23 Patient Disposition in the Double-Masked Phase of Studies MS-SPI and MS-ON – ITT Populations

	Study MS-SPI	Study MS-ON
Randomised (N)	154	93
Completed (N, %)	133 (86.4)	92 (98.9)
Premature withdrawal (N, %)	21 (13.6)	1 (1.1)
Adverse event (n)	7	1
Protocol violation (n)	2	0
Consent withdrawn (n)	12	0

N=number of patients in group; n=number of patients with data
Source: Study MS-SPI, Table 14.1.1; Study MS-ON, Table 14.1.1

Demographic and Disease Characteristics

Across the two double-masked studies patients were well matched for age, height, weight and BMI. A slightly higher proportion of female patients than males were included in both studies (Table 24).

Table 24 Baseline Demographic Characteristics in the Double-Masked Phase of Studies MS-SPI and MS-ON – ITT Populations

Parameter Statistic	Study MS-SPI (N=154)	Study MS-ON (N=93)
Sex		
Male, n (%)	71 (46.1)	43 (46.2)
Female, n (%)	83 (53.9)	50 (53.8)
Age (years)		
N	154	93
Mean (SD)	51.4 (8.9)	41.5 (10.5)
Range	21 to 68	20 to 66
Height (cm)		
N	152	92
Mean (SD)	169.0 (9.4)	170.0 (9.1)
Range	148 to 194	153 to 190
Weight (kg)		
N	150	93
Mean (SD)	69.25 (14.87)	70.62 (14.41)
Range	42.0 to 115.0	47.0 to 131.0
BMI (kg/m^2)		
N	150	92
Mean (SD)	24.24 (4.64)	24.267 (4.008)
Range	16.6 to 44.3	17.47 to 44.28
MS type		
N	154	93
Progressive MS, n (%)	154 (100.0)	34 (36.6)
Primary progressive, n	55	14
Secondary progressive, n	99	20
Relapsing-remitting MS, n (%)	0 (0.0)	59 (63.4)
Duration of MS (years)*	***Primary progressive*** ***Secondary progressive***	
N	55 99	93
Mean (SD)	7.52 (5.83) 15.19 (8.47)	8.14 (7.62)
Range	0.6 to 33.0 0.6 to 40.1	0.2 to 35.4

N=number of patients in group; n=number of patients with data available; SD=standard deviation
*calculated as time from diagnosis to first treatment
Source: Study MS-SPI, Tables 14.1.4.1.1 and 14.1.4.2.1, and Study MS-ON, Tables 14.1.4.1.1 and 14.1.4.2.1 and Listing 16.2.4.8

Supportive study (Sedel et al. 2015)

The clinical development program for the use of MedDay's biotin formulation, MD1003, for the treatment of progressive MS, started with a case series of 23 successive patients with primary or secondary progressive MS who were treated with daily doses from 100 to 600 mg (Sedel et al, 2015).

In a case series of 23 patients suffering from primary or secondary progressive forms of multiple sclerosis with an involvement of either spinal cord, optic nerves or brain white matter, also resulted in significant clinical improvements within a mean of 3 months treatment without experiencing any safety concern. These patients from three different French MS reference centres received biotin doses between 100 and 600 mg/day (mostly divided over three daily intakes) for a treatment duration of between 2 to 36 months (mean = 9.2 months).

In four patients with prominent visual impairment related to optic nerve injury, visual acuity improved significantly. Visual evoked potentials in two patients exhibited progressive, reappearance of P100 waves, with normalization of latencies in one case. Proton magnetic resonance spectroscopy (H-MRS) in one case showed a progressive normalization of the Choline/ Creatine ratio. One patient with left homonymous hemianopia kept on improving from 2 to16 months following treatment's onset. Sixteen patients out of 18 (89%) with prominent spinal cord involvement were considered as improved as confirmed by blinded review of videotaped clinical examination in 9 cases. In all cases improvement was delayed from 2 to 8 months following treatment's onset.

The dose of 300 mg/day (100 mg tid) was shown to be associated with the best clinical efficacy without significant adverse events. Indeed, seven patients started to improve with biotin 100 mg/day and five of these seven patients improved even more after having their biotin dose increased to 300 mg/day. Nine other patients showed first signs of clinical improvement at doses of 200 or 300 mg/day. Several attempts to decrease or increase the dosage were performed. Increasing the dose to 600 mg/day in one patient was not associated with additional benefit whereas decreasing the dose to 100 mg/day in one patient was associated with worsening. Moreover, when biotin treatment was stopped a marked worsening was reported within the next days, as notably reported for patient 11 who presented with progressive MS associated with spinal lesion and tetraparesis. Therefore the clinical observations with the dose titration suggested that a total daily dose of 300 mg/day would be optimal.

4.1.6. Discussion on clinical efficacy

Discussion on clinical efficacy

Design and conduct of clinical studies

Two superiority placebo-controlled studies were submitted:

- Study MS-SPI (pivotal), a randomised, multi-centre, double-blind (12 months + 12 months), randomised, parallel group study to evaluate the efficacy and safety of MD1003 100mg tid in progressive MS patients with spastic paraparesis due to spinal cord involvement (with 12 month open-label extension). Since the second 12-month extension phase is still on-going, the Applicant was requested to provide the expected timeframe for study completion and an update on the efficacy (and safety), if available. In their responses, the Applicant clarifies that the last patient´s visit of their OLEs was in December 2016 and provides updated efficacy and safety data.
- Study MS-ON, a randomised, multicentre, double-blind (6 months), randomised, parallel group study to evaluate the efficacy and safety of MD1003 100mg tid in MS patients with chronic visual loss due to optic neuritis (with 6 month open-label extension data available but ongoing). This

study is not pivotal as it included patients with visual loss due to any form of MS (RRMS, SPMS without relapse and PPMS)). As for study MS-SPI the last patient's visit was in December 2016. The Applicant has provided updated safety data.

The duration of these studies is short considering that the EU guideline now recommends up to 5 years to demonstrate a clear effect on disability. Furthermore no withdrawal study was performed and maintenance of treatment beyond 12 months can only be assessed from study MS-SPI, from open label data. These studies are evaluating the effect of MD1003 in two models of function that are deemed adequate, with both including patients with Progressive MS.

Patient population

The two studies enrolled MS patients aged 18 to 75 years diagnosed according to the revised McDonald criteria 2010 (and Lublin criteria 1996 for MS-SPI). A more recent revision of the Lublin criteria (published July 2014) became available a few months after the randomization of the first patient in study MS-SPI (29 October 2013). A higher age limit than that originally foreseen was requested by the DSMB that was set up in 2013. MS-SPI was performed exclusively in France and MS-ON included one centre in the UK. This is a limitation regarding the external validity of the studies.

MS-SPI: patients with progressive MS (primary or secondary) and clinical evidence of spastic paraparesis were included. Progression was defined as increase of EDSS (at least 1 point if EDSS between 4.5 and 5.5 and at least 0.5 point if EDSS between 6 and 7), in the past 2 years. In addition inflammatory active forms of the disease were to be excluded on the basis of relapses or Gd+ lesions in the year before inclusion but inclusion/exclusion criteria could not ensure that purely non-active progressive MS patients were included. However the applicant confirms in their response that the exclusion of active disease was not possible in this study and refers to the population being “relapse-free” progressive MS.

103 patients were randomized to MD1003 and 51 to placebo. Stratification for PPMS and SPMS was not included and difference in baseline characteristics were noted with more patients with PPMS in the placebo group. The Applicant argues that, in their view, the target population (i.e., “not-active progressive MS”) is a single entity and therefore there is no need to stratify according to MS type. Although the question can be formally considered solved, important concerns remain related to the external validity of the study.

Following triggered inspection a number of majorfindings were noted with regards to the conduct of the study,including a new point about the actual definition of progressive MS that was used by the various investigators. Two groups of patients were actually recruited, one labelled “totally progressors”, and another labelled “fluctuating” as their EDSS score would have varied in the last two years. The latter group concerned 48 out of the total population of 154 in this study.

Also in their response the applicant mentions that in the updated study report for MS-SPI that includes data up to M36 (Section 10.2.1), there were 3 patients identified during the blind review that did not fully comply with the entry criteria per amendment 7 of the protocol. The impact of these deviations on the study results should be discussed.

MS-ON: both RRMS and progressive MS were included and MS patients had to have worsening uni-or bilateral optic neuropathy with worst eye VA ≤ 5/10 confirmed at 6 months and worsening of visual acuity during the last three years. 65 patients were randomised to MD1003 and 28 to placebo.

Treatment regimen

Placebo was chosen as control in study MS-SPI, which is in compliance with the CHMP's MS guideline (EMA/CHMP/771815/2011 Rev. 2) and is considered acceptable, as no medicinal product is currently available for the treatment of Progressive MS. Treatment was added to stable MS therapy in both MS-SPI and MS-ON.

No formal dose finding study was performed. The proposed dosing regimen of 100 mg biotin three times a day rests on a case series. In this case series 23 patients on biotin 100mg a day did better when receiving 300mg a day but not when increased to 600mg a day.

The proposed treatment regimen is for one capsule containing 100mg of biotin to be taken three times a day. This treatment regimen was used in the two main studies. Although the three times a day administration is supported by PK data in healthy volunteers, no data have been submitted from patients with Multiple Sclerosis (MS) and the long-term administration is not supported by multiple dose data in patients either.

Randomisation was 2:1 ratio. The population in MS-SPI was not stratified for baseline EDSS or use of fampridine as had been suggested.

Endpoints

MS-SPI: the primary endpoint was a composite for the proportion of patients with decreased EDSS at M9 confirmed at M12 (where decreased EDSS is defined as a decrease of at least 0.5 point if the initial EDSS was between 6 and 7 and a decrease of at least 1 point if the initial EDSS was between 4.5 and 5.5) compared to the best EDSS score obtained between the screening and baseline visits or with improved TW25 of at least 20% at M9 and M12 compared to the best TW25 score obtained between the screening and baseline visits. This composite endpoint has not been previously validated and its limitations were discussed at length during a SA held with the CHMP (EMEA/H/SA/2615/1/2013/SME/III). Both components are very focused on walking and neither of them fully captures improvement in other symptoms. The applicant has also not explained why success in one of the components but not the other is considered clinically meaningful for individual patients. A composite endpoint where success is expected in both the components would make it more difficult to demonstrate a treatment effect but if it was achieved, the results would be more convincing. The separate analysis of the individual components is important to interpret the results.

In this case clinical meaningfulness of the change in EDSS is adequate with change confirmed at 3 months, although confirmation at 6 months is recommended in the EU MS guideline; also, the same physician performed both treatment and evaluation. These two elements are a departure from the normal methodology in MS studies.

The secondary endpoints included individual change of EDSS, whether increased (worsened) or decreased (improved), change from baseline in TW25, MSWS-12, CGI-/SGI-I (as it was effectively improvement in CGI/SGI), SF-36 (and MSQoL-54, although results are not clearly given in the clinical study report), 9HPT (for upper limb function) and sub-scores of the Kurtzke functional score. There was no specific evaluation of cognition or spasticity measurements, and conventional MRI was performed in a subgroup of patients for safety assessment while non-conventional MRI were performed for investigating the mechanism of action in the same subgroup of patients.

MS-ON: the primary endpoint was mean change in best corrected visual acuity (logMAR) at 100% contrast between baseline and month 6 of the diseased eye [where the diseased eye was defined as the eye with the worst visual acuity (<5/10) at baseline and with evidence of worsening during the past three years]. A very high number of secondary endpoints and exploratory endpoints were

included, either prior to database lock or post-hoc. Visual acuity was the main variable with assessment of change from baseline of at least 0.3logMAR, Visual field, Visual Evoked Potential, CGI-SGI, NEIVFQ-25, SF-36, MSQoL-54 and Retinal Nerve Fiber Layer (RFNL).

Sample size

MS-SPI: sample size was calculated assuming a 90% power to detect a difference of 30% between treatment groups. Originally 35 patients were expected in the placebo group and 70 patients in the MD1003 group. However due to high screening number and amendment of the protocol allowed recruitment of 154 patients in total. The total number of patients included in this study is not large and may be in part due to the fact that the study was restricted to one country, although the recruitment was quite easy as demonstrated by the fact that. The study population had to be increased after more patients than expected had been screened prior to randomisation.

MS-ON: sample size assumed a 99% power to detect an improvement of 0.3logMAR in the MD1003 over placebo, with a total of 70 patients in the active group and 35 in the placebo group.

Statistical plan

There was no plan to control the type I error across the multiple endpoints. Therefore, statistical significance can only be declared for the primary endpoint in both studies.

MS-SPI: the primary efficacy analysis was performed on the ITT population. *Primary endpoint analysis compared the proportion of responders at M9* between the MD1003 group and the placebo group using a Fisher's exact test. Subjects with missing outcome were counted as non-responders. For the secondary endpoints of EDSS and TW25 the missing data were not imputed. For some of the other secondary endpoints LOCF has been used to handle missing data. Sensitivity analyses have been submitted to assess the impact of withdrawals on the treatment effect. By comparing the p-values, it can be seen that they are generally higher when the missing data are imputed rather than ignored.

MS-ON: The primary efficacy analysis was performed on the ITT population. To evaluate the primary endpoint, an ANCOVA on the mean absolute change at M6 in VA (logMAR), with adjustment at baseline was performed.

Drop-outs

MS-SPI: 12/103 (11.6%) of patients in the MD1003 group and 9/51 (17.6%) in the placebo group discontinued in the double blind phase mainly due to consent withdrawal. Also 17/91 (18.7%) of patients in the MD1003/MD1003 and 4/42 (9.5%) in the placebo/MD1003 group discontinued in the extension phase, mainly due to consent withdrawal and lack of efficacy.

MS-ON: There was only 1/65 drop-out due to adverse event in the double-blind phase. The first 6 months of the extension phase were unremarkable.

Efficacy data and additional analyses

MS-SPI

The study spanned less than 2.5 years and included patients from one country only. This departs from other clinical trials in MS, although this is not considered a major objection by the Rapporteurs. Information has been provided with regards to inspections at the CRO and a triggered inspection took place in May 2017.

Approximately 40% (49/154) of patients were taking “MS medications” (including corticoids and other DMTs) at baseline. The term "MS medications" covers all medications that were associated with the MS

condition, including the many co-morbidities and symptoms such as spasticity, bladder disorders, depression, pain, walking difficulties etc. a larger proportion of patients in the placebo group (in both, PPMS and SPMS subgroups) received symptomatic treatments, than those treated with MD1003. These differences are more obvious in the PPMS subgroup (38.1% and 61.5%). The meaning of these differences is unclear, since it is unknown whether these treatments were present at baseline or initiated during the study, as allowed by the study protocol. It cannot be ruled out whether these differences could be related to the observed imbalance between groups in terms of certain disease characteristics (e.g., at baseline, patients in the placebo group had higher EDSS, than those treated with MD-1003).

Regarding the use of DMTs, a total of 10 patients with PPMS were treated with any of these agents, possibly in an off-label manner. In patients with SPMS, a population in which these agents are indicated, a larger proportion of patients in the MD1003 group were treated with DMTs, in comparison with placebo. Overall, the number are very small to reach a sound conclusion, but they add more questions to the uncertain internal/external validity of the study. Additionally, 4 patients in active group received fampridine during the double-blind period which renders that exact interpretation of the efficacy data more difficult, as patients taking fampridine are more difficult to treat. In that respect the use of fampridine should be discouraged in the SmPC.

Primary endpoint

The *primary endpoint* corresponds to the analysis at M9 confirmed at M12. The study was positive with regards to the primary endpoint with a treatment effect of 12.6 % (13/103 patients) in the active group and 0% (0 patient) in the placebo group (Fisher's exact test p=0.0051). The per-protocol analysis was consistent with the ITT analysis.

The effect of MD1003 on the primary endpoint was more pronounced in patients with lower baseline EDSS in the range 4.5 to 5.5, where the proportion of responders reaches 21.4% and only 9.45 % for a baseline EDSS of 6 to 7.. It cannot be assumed that any difference will be seen in patients with a higher EDSS, also considering the postulated mode of action of MD1003 which requires neurons to be able to increase energy production. This might also be correlated to the lower treatment effect seen in patients with PPMS compared to SPMS (9.5% vs. 14.8%, respectively)

Although there is also an improvement in the more severe group (EDSS 6-7) the difference is only 9.3% and relates to 7 patients only. It isn't clear that an improvement would be seen in patients with EDSS above 7 therefore this treatment cannot be recommended in patients with EDSS above 7 considering the absence of sufficient data in this population. A reanalysis was provided of the primary endpoint adjusting for *covariates* of e.g. EDSS score class, MS type and fampridine. Though the regression model cannot really give the same estimates that would have been obtained with a balanced randomisation, the new analysis provides reassurance that the baseline imbalances may not have clearly affected the conclusions obtained from the primary analysis. It is however difficult to quantify the treatment effect given that the confidence intervals for the multivariate analysis are so wide.

The fact that treatment with fampridine (or myorelaxant) was not controlled is an issue and it is shown above that the effect on EDSS is smaller in patients taking fampridine. Considering that the overall treatment effect is rather limited the concomitant use with fampridine should be discouraged; this should be reflected in the SmPC.

Additional information was provided on the 13 responders which confirms that they were mainly male and with lower disability although the influence of gender is not clear.

After 12 months, the percentage of responders for the primary endpoint remains at around 12-13% when patients in the placebo group returned to baseline following an improvement after 3 months. Patients in the placebo group during the double-blind phase were switched to active treatment in the extension phase. A number of patients were not included in the analysis for the open-label phase and this is not considered appropriate since this phase aimed to demonstrate the effects of long term treatment, and the numbers are small. Of the 13 patients who responded at M9 confirmed at M12 only 6 were still responding at M30 confirmed at M36. This is a major concern for the demonstration of maintenance of treatment. The number of responders went from 13 at month 9 to 10 at month 12 and then 14 at month 24, so it does not seem to be the same subjects maintaining the effect, but rather some subjects loose the response they had achieved and others become responders later on.

Secondary endpoints

Two analyses were conducted for the *mean change in EDSS*, one pre-planned (MMRM) and one post-hoc (Mann-Whitney). Both demonstrated a small treatment effect and though the applicant claims statistical significance for the post-hoc analysis, this cannot be accepted as there was no type I error control over the multiple testing of the secondary endpoints. It should also be noted that for this analysis subjects with missing data have been excluded and this has been shown to overestimate the treatment effect, as subjects that withdraw from treatment are likely to be non-responders. Change from baseline in EDSS is not recommended in the guideline for the development of medicinal products for the treatment of multiple sclerosis therefore these results have low impact on the overall benefit risk for this product.

For the *MSWS-12* the baseline score was rather high in both groups at approximately 77; the mean difference after 12 months was 4.47 (p-value=0.8118), on a scale of 0 to 100.

At Month 12 the *mean CGI-I* was 4.05 in the MD1003 and 4.62 in the placebo group, with a treatment difference of 0.57 ($p<0.0001$). The corresponding values for the SGI are 4.27 and 4.76, with a treatment difference of 0.49 ($p=0.0094$). Although an improvement is seen in the MD1003 group over the placebo group for CGI-I and SGI-I, statistical significance cannot be assumed from a statistical point as the type I error was not controlled. Also, the difference is mainly linked to the items of no change or minimally worse, which is confirmed by the fact that the difference from baseline between groups is around 0.5 point, i.e. half way between no change and minimally worse. Of note the CGI-I/SGI-I was based on a scoring of improvement since the beginning of treatment, I.e. 12 months in the double blind or the extension phase.

There was a clear difference between groups at baseline, with a mean *TW25* value of 21.94 in the MD1003 group and 30.59 in the placebo group. Treatment difference for mean change in TW25 at Month12 was -18.56 (95%CI [-58.57; 21.46], $p=0.36$) using the MMRM analysis. Considering the number of patients is different at each visit it is not possible to appreciate the percent change. This should be discussed together with the fact that the value at 24 months seems to have doubled in both study groups. Also, baseline differences and their impact should be discussed. The 20% improvement for TW25 confirmed at the next visit was performed post-hoc. However, considering that this analysis is deemed necessary for the evaluation of the primary endpoint this post-hoc analysis is considered necessary to confirm the use of the second variable in the composite primary endpoint.

With regards to an *improvement in EDSS* the results are in favour of treatment with MD1003 as compared to placebo, although the magnitude of improvement is less than for the composite primary endpoint at 9.71% (with $p=0.0311$) compared to 12.64% ($p=0.0051$). *Worsening of EDSS* was seen in 4.21% of patients in the MD1003 group and 13.64% of the placebo group in the double-blind phase,

with a difference of 9.43%, with a p value of 0.0727. The applicant explains the overall treatment effect results in improvement and less progression

Improvement in both EDSS and TW25 scores: this endpoint was pre-defined and differs from the primary endpoint in that it includes an improvement in both the EDSS and the TW25F when the primary endpoint was for an improvement in one or the other. When looking at the proportion of patients with a stable EDSS at M9 confirmed at Month 12, no significant difference is seen between groups with little change across visits in the double-blind phase and decrease in the open label phase.

From the post-hoc survival analysis improvement of EDSS (not confirmed) was first seen after 3 months on active, whilst worsening was seen after 6 months in the placebo group, this reflects the change seen in the MD1003 and stresses that fact that progression was slow in the placebo group.

The MSWS-12 is a test filled in by the patient with 12 questions giving a maximum score of 64 (worse) that is transformed on a scale from 0 to 100%. Very little difference is seen between groups at Month 12.

In the double-blind phase, the *modified FIS (M-FIS)* results remained stable (mean change of 1.38 and 1.30 respectively in the active and the placebo groups for a total score between 0 and 84) and no difference was observed between the MD1003 and placebo groups. Similarly, in the M12-M24 extension phase, the results were stable and no difference was observed between the biotin and placebo groups.

No substantial change was seen for the 9HPT or the SF-36.

None of the *sub-scores of the EDSS* saw clinically significant improvement following 12 months of treatment with MD1003, especially with regards to pyramidal or cerebral.

The Applicant acknowledges that MSQoL-54 was not referenced in the protocol or clinical study report, rather the SF36 was the pre-planned assessment. It is not clear whether the SF59SEP is validated to be used in additional languages and whether retroactive calculation of SF36 is valid .

The effect on brain volume has been linked by the applicant to a decrease in water content contemporary to the treatment effect. MRI assessment was only done in a subset of patients in selected centres. The Applicant should justify that comparison to placebo is reliable and further describe the clinical relevance of the results considering that decrease in brain volume over 12 months is a concern and longer term data assessment is hampered by placebo patients being switched to active treatment.

The Applicant clarified that no patients with renal/hepatic impairment were included in the pivotal study MS-SPI. This information should be provided in the SmPC.

Overall, the treatment effect over the primary and secondary endpoints is small and little effect is seen on variables not related to walking such as upper limb function, fatigue or cognition. The exact treatment effect seems to have been overestimated for most secondary endpoints; in that respect the exact data including 95% CI are being requested

<u>MS-ON</u>

No attempt was made to control the type I error for the multiple secondary endpoints so statistical significance can only be tested for the primary endpoint and all other p-values should be interpreted with caution. Finally, No definition was given for a priori regarding he MS type RRMS, Progressive MS (both post-hoc analyses with source data unknown), progressive chronic optic neuropathy or non-progressive sequelae of an acute optic neuritis subtypes that were used for the subgroup analyses.

Patients presented with baseline differences with regards to MS type with 30.8% of PMS in the MD1003 group compared to 50% in the placebo group. There was also a longer duration of MS in the placebo group; 92.3% of patients in the MD1003 group taking Disease Modifying Therapy (DMT) as compared to 75% in the placebo group; finally 36.9% of patients presenting with progressive optic neuropathy in the MD1003 as compared to 25% in the placebo group, with differences in visual acuity.

Of note EDSS scores have not been recorded in the CRF.

The mean treatment difference from baseline at Month 6 in logMAR at 100% contract of the selected eye was -0.01983 (95% CI [-0.11, 0.07], p-value: 0.0803). The treatment difference between the two groups is far from clinically relevant. Study MS-ON failed on the primary endpoint and is therefore only supportive; all additional analyses are considered exploratory. Study MS-SPI is therefore the only pivotal study for the claimed indication and the efficacy results should be compelling from a clinical and statistical point of view as per points to consider on applications with one pivotal study (CPMP/EWP/2330/99).

The difference for the primary endpoint in patients with progressive neuropathy for the primary endpoint is 0.09 logMAR which is not clinically significant, although the trend is positive. There is no clear evidence of maintained effect in the open label phase. Also, the visual acuity seems to improve spontaneously in the non-progressive group which should be explained. It should be noted that patients receiving placebo in the non-progressive group seem to be improving spontaneously hence it would be difficult to demonstrate a treatment difference. Also, very few patients were taking fampridine at baseline and it is unlikely that concomitant medication with this product would have influenced the results. There was little difference after 6 months in the proportions of patients with an improvement of at least 0.3 logMAR which is considered to be a threshold in terms of clinical improvement. This supports the failure of the primary endpoint.

When looking at an improvement of at least 0.3logMAR at 100% contrast in the selected eye, although there seems to be a positive effect in the progressive MS subtype, patients with RRMS tend to do better in the placebo group than in the MD1003 group.

There was no substantial difference between treatment groups at 6 months for P100 waves, CGI/SGI, NEIFVQ-25 or the SF36 subscores, although a trend was seen for an improvement in the health change score for the latter. With regards to visual acuity at 5% contrast, when looking at the non-selected (better eye) for subclinical dysfunction, the exploratory efficacy analyses showed no significant difference in logMAR at 100% contrast of the non-selected eye and logMAR at 100% contrast in binocular visual acuity.

There is an improvement of 0.92 logMAR with MD1003 over placebo in the selected eye (100% contrast) in the progressive MS group, although of minimal clinical significance, although the effect seems to be maintained in the following 6 month extension period. However the difference in the RRMS group is more intriguing. The main absolute change from baseline to Month 6 for the logMAR at 100% contrast (selected eye) is -0.116 in the placebo group, and -0.066 in the MD1003 group. A similar trend is seen when looking at 5% contrast in the non-selected eye or at RNFL thickness (all eyes), although the changes are minimal.

Altogether the pre-planned subgroup analyses there was clearly no effect in the group with non-progressive sequelae of an acute optic neuritis for all measures related to optic nerve involvement. In the progressive chronic optic neuropathy subgroup there was a slight trend favouring active treatment over placebo but the differences were neither clinically nor statistically significant.

Considerations for a single pivotal trial application

Several issues have been identified regarding the requirements for this type of applications. According to the EMA guideline, "…submission with a single pivotal trial, this has to be particularly compelling with respect to internal/external validity, clinical relevance, statistical significance, data quality and internal consistency". In this case, internal and external validity are questioned, since there are concerns regarding an important imbalance in baseline prognostic factors between both treatment groups and the representativeness of the included population is at question in terms of the adequate characterisation of the progressive MS patients. Additionally, there are serious doubts on the clinical relevance of the effects, as well as the internal consistency, since several of the relevant sub-group analyses were performed post-hoc. Finally the proposed mode of action remains mainly hypothetical, also taking into account that a decrease in overall brain volume was noted in study MS-SPI.

4.1.7. Conclusions on clinical efficacy

Biotin (QIZENDAY, MD1003, vitamin B7 or vitamin H) is a coenzyme for several carboxylases involved in energy synthesis in the mitochondria and is also a coenzyme for the acetyl CoA carboxylase (ACC) which is key in fatty acid synthesis and hence for myelin synthesis. It is proposed that biotin may activate energy production in neurons to counter balance the "virtual hypoxia phenomenon" as well as potentially stimulate myelin production so reversing or stabilising PMS. The exact mode of action is not clearly elucidated and decrease in brain volume was observed.

Patients with progressive MS, that is non-relapsing SPMS and PPMS, were included in study MS-SPI whereas no restriction on the subtype of MS was in place for MS-ON. Study MS-ON failed on the primary endpoint. Study MS-SPI is therefore the only pivotal study and the efficacy results should be compelling from a clinical and statistical point of view as per points to consider on applications with one pivotal study (CPMP/EWP/2330/99).

A number of methodological questions were raised on the statistical analyses, including missing data imputation and analysis of the change from baseline in TW25, or the 12-month improvement in EDSS which prompted a triggered inspection. Several major findings were noted and an additional question was raised regarding the inclusion criterion or progression in the last 2 years. The applicant in the response acknowledge that the definition of progression in the last 2 years was not adhered to by the recruiting centres resulting in two subgroups of what is called "total progressors" and "fluctuating" populations. There are clear differences between the two populations in terms of responses in the different variables that were evaluated by the Applicant. In particular, the treatment effect for the primary is halved in the fluctuating population, although it is only very moderately improved in the totally progressing population as compared to the whole study population. Additionally, the applicant chose to provide data for proportion of patients with worsening EDSS, and not improvement as per one of the components of the primary endpoint, where the difference in treatment effect is very limited between the whole population of the totally progressors. No patient worsened on placebo in the fluctuating population as compared to a few in the active group, while in the progressors population 20.7 % of patients worsened on placebo compared to 4.85% in the active group. This clearly raises questions about the population that was effectively recruited in study MS-SPI.The applicant also identified further 3 patients who did not fulfil the inclusion criteria, without consequence of this finding on the study results since they were non-responders on nor EDSS neither TW25.

The treatment effect on the primary endpoint was 12.6% (95% CI: 6.21%-15.42%, p=0.0051) and seems to be driven by the EDSS score.

Improvement in EDSS favours treatment with MD1003 over placebo, although the magnitude of improvement is less than for the composite primary endpoint at 9.71% (with p=0.0311). The proportion of patients with 20% improvement in TW25, as used in the primary endpoint, was analysed post-hoc with only 5 patients showing such improvement, i.e. 4.85% of patients.

The primary endpoint chosen for study MS-SPI (Proportion of patients with confirmed improvement in either EDSS or TW25) was not recommended during scientific advice; both components are very focused on walking and neither of them fully captures improvement in other symptoms. The applicant has also not explained why success in one of the components but not the other is considered clinically meaningful for individual patients. A composite endpoint where success is expected in both the components would make it more difficult to demonstrate a treatment effect but if it was achieved, the results would be more convincing.

Only the function systems of pyramidal and sensory seem to benefit from treatment with MD1003. and extrapolation to all patients with progressive MS who present with e.g. visual impairment, is not possible.

The effect relates mainly to the improvement on walking and is not supported by a statistical improvement in other endpoints specifically relating to walking such as the MSWS12, even if the applicant points to a positive trend. Of note the endpoint of improvement in EDSS AND in TW25 did not show clear difference between the groups.

In MS-SPI the treatment effect with MD1003 is mainly seen on ambulation with little support from an improvement in quality of life, which doesn't fully comply with the EU guideline on MS that requires that effects on EDSS to be supported by positive effects on daily activities. Changes were seen on CGI-I (and SGI-I), it is only of 0.5 point, between minimally improved and no change. The adequacy of the calculation of the SF36 is further questioned. Also, because type I error was no controlled in the analysis, the p value for endpoints apart from the primary endpoint should be regarded with caution.

The concomitant treatment was not controlled and the applicant highlights that fact that differences were seen in treatment effect depending on whether fampridine was taken or not, which is a concern when assessing the overall results. The use of fampridine with the proposed product should be discouraged.

Improvement in EDSS appeared after 3 months of treatment and there are little data on maintenance of effect. In effect, only 6 of the 13 responders at Month 12 remained responders at Month 30 which questions maintenance of effect. Median TW25 values over time up to M36 have been also provided for each treatment group showing slight fluctuation at intermediate time points, but no clear improvement. Concerns on the relevance of the effect still remain.

Finally the relevance of the MRI data needs to be further justified together with the finding of decreased brain volume in the double-blind period.

Considering all the above deficiencies, the need for a confirmation in a second study in the chosen population is needed also taking into account the issues with the choice of primary endpoint or the absence of a clear effect on secondary variables, including on MRI data. This should include sufficient data to clearly conclude on the maintenance effect as it is seen from this study that only 6/13 patients who responded in the double-blind phase maintained that response at Month 36. The absence of data following withdrawal of the active treatments points to insufficient data provided with this application.

The proposed indication is not supported by data outside of ambulation, or in patient with more severe disability (EDSS>7). The data presented are not sufficient to conclude of the overall benefit of MD1003 in the claimed population.

4.1.8. Clinical safety

Patient exposure

The clinical program for the safety evaluation of MedDay's MD1003 capsules (containing 100 mg biotin) included three clinical studies: a phase 1 pharmacokinetic (PK) study and two phase 3 studies:

• Study MD1003CT2014-02-PK (EudraCT Number 2014-000766-22): a randomised 4-way cross-over PK and food effect study in healthy volunteers with a single administration of 100 mg, 200 mg and 300 mg of MD1003

• Study MS-SPI (EudraCT Number 2013-002113-35): a randomised, double-masked placebo-controlled efficacy and safety study in progressive MS patients with clinical evidence of spastic paraparesis, followed by an open label extension phase. The total daily dose of MD1003 evaluated was 300 mg taken as 3 divided doses of 100 mg.

• Study MS-ON (EudraCT Number 2013-002112-27): a randomised double-masked placebo-controlled efficacy and safety study in MS patients with chronic visual loss due to optic neuritis, followed by an open label extension phase. The total daily dose of MD1003 evaluated was 300 mg taken as 3 divided doses of 100 mg.

A case series of 23 patients with progressive MS who received biotin at doses of 100 to 600 mg/day (hospital preparation) were also used in the safety evaluation.

In addition, an evaluation of any spontaneous reports from an ongoing early access program (ATU) were assessed where the MD1003 total daily dose is per the proposed posology of 300 mg. As of the cut-off date of 12 January 2017 a total of 5,483 patients had received treatment with MD1003 in this program.

The two phase 3 Studies conducted in MS patients (Study MS-SPI and Study MS-ON) were presented by the applicant as the key data for the assessment of safety.

Overall across the double-masked and open label phases of Studies MS-SPI (up to Month 24) and MS-ON (up to Month 12), a total of 238 patients have been exposed to MD1003 at a dose of 300 mg/day. Overall 174 patients received MD1003 over at least a 12 Month period and 74 patients over at least a 24-Month period.

Table: Number of Patients Exposed in Study MS-SPI up to Month 24 and Study MS-ON up to Month 12 (Safety Population)

	Double-masked exposure			Open label MD1003 exposure (300 mg/day)	Overall MD1003 exposure (300 mg/day) double-masked or open label
	MD1003 (300 mg/day)	Placebo	Total		
Study MS-SPI					
Any exposure	103	51	154	133	145
≥ 12 months	91	42	133	74	129
≥ 24 months	NA	NA	NA	0	74
Study MS-ON					
Any exposure	65	28	93	92	93
≥ 12 months	NA	NA	NA	0	45
≥ 24 months	NA	NA	NA	0	0
Both studies					
Any exposure	168	79	247	225	238
≥ 12 months	91	42	133	74	174
≥ 24 months	NA	NA	NA	0	74

mg=milligram; NA=not applicable
Source: Study MS-SPI, Table 14.1.1, Study MS-ON, Table 14.1.1

The mean duration of treatment was evaluated by calculating the date of first intake to the date of last intake. For Study MS-SPI the mean duration of treatment during the double-masked phase was similar between the treatment groups at 10.19 months and 9.95 months in the MD1003 and placebo groups, respectively. In Study MS-ON, the mean duration of treatment during the double-masked phase was lower than Study MS-SPI (in line with the difference in the study design), again with similar durations between the treatment groups i.e. 5.61 and 5.56 months in the MD1003 and placebo groups, respectively. In the open label phases, the mean duration of treatment was 10.10 months in Study MS-SPI up to Month 24 and 5.30 months in Study MS-ON up to Month 12.

Table: Summary of Duration of Treatment and Duration of Exposure in Study MS-SPI up to Month 24 and Study MS-ON up to Month 12 (Safety Population)

Parameter Statistics	Study MS-SPI			Study MS-ON		
Double-Masked Phase						
Duration of treatment[a] (months)						
	MD1003	Placebo	Overall	MD1003	Placebo	Overall
N	103	51	154	65	28	93
Mean (SD)	10.187 (2.962)	9.995 (3.048)	10.123 (2.982)	5.605 (0.472)	5.562 (0.308)	5.592 (0.428)
Range	0.03-12.45	0.03-12.29	0.03-12.45	2.73-6.44	5.03-6.41	2.73-6.44
Duration of exposure[b] (months)						
N	103	51	154	65	28	93
Mean (SD)	10.148 (2.968)	9.986 (3.062)	10.094 (2.991)	5.539 (0.624)	5.437 (0.503)	5.508 (0.590)
Range	0.03-12.45	0.03-12.29	0.03-12.45	2.23-6.44	3.29-6.05	2.23-6.44
Open Label Phase						
Duration of treatment[a] (months)						
	MD1003/ MD1003	Placebo/ MD1003	Overall	MD1003/ MD1003	Placebo/ MD1003	Overall
N	91	42	133	64	28	92
Mean (SD)	9.824 (3.233)	10.684 (1.587)	10.095 (2.841)	5.427 (1.000)	4.997 (1.661)	5.296 (1.245)
Range	0.03-12.45	5.72-11.83	0.03-12.45	2.33 – 6.74	0.03 -6.47	0.03-6.74
Duration of exposure[b] (months)						
N	91	42	133	64	28	92
Mean (SD)	9.747 (3.286)	10.676 (1.586)	10.041 (2.886)	5.419 (0.995)	4.969 (1.657)	5.282 (1.242)
Range	0.03-12.45	5.72-11.83	0.03-12.45	2.33-6.54	0.03-6.47	0.03-6.54

N=number of patients, SD=standard deviation

[a] (Date of last administration of study drug in double-masked phase – date of first administration of study drug in corresponding phase +1 Day)*12/365.25

[b] (Date of last administration of study drug in double-masked – date of first administration of study drug in corresponding phase +1 Day-Number of drug-free days)*12/365.25

Source: Study MS-SPI Tables 14.1.4.5.1 and 14.1.4.5.3 and Study MS-ON Tables 14.1.4.5.1 and 14.1.4.5.3

In Studies MS-SPI and MS-ON, slightly more female patients (53.9% (83/154) in Study MS-SPI and 53.8% (50/93) in Study MS-ON) than male patients (46.1% (71/154) and 46.2% (43/92) in Studies MS-SPI and MS-ON, respectively) were enrolled. This was also the case in each individual treatment group across both studies. The overall mean age was 51.4 years in Study MS-SPI and 41.5 years in Study MS-ON and was similar across the treatment groups in both studies. Other demographic and physical characteristics i.e. weight, height and body mass index (BMI) were within similar ranges in both Studies and were also similar across the two treatment groups.

With respect to MS characteristics, in Study MS-SPI all patients had progressive MS with clinical or radiological evidence of spinal cord involvement, whereas in Study MS-ON all patients had chronic optic neuropathy due to MS but could have had either progressive MS or relapsing remitting MS. Overall in Study MS-SPI, more of the patients presented with secondary progressive MS compared to primary progressive MS and in Study MS-ON more patients presented with relapsing remitting MS compared to progressive MS.

In Study MS-SPI almost all patients (99.4%, 153/154) took at least one concomitant medication. In Study MS-ON, all patients took at least one concomitant medication.

The core safety data for the product comes from the two phase III studies (MS-SPI and MS-ON). Both studies had a double-masked and an open-label phase. Overall 238 patients in these studies were exposed to the product in the doses within the proposed posology. This number is relatively low,

especially considering the prevalence of the condition. The overall exposure is also supported by the small number of patients enrolled in the PK studies. The early access programme with 5,483 patients enrolled is also supportive of the claim that the overall exposure was sufficient to describe the safety. The safety from this population is, however, reported spontaneously and it does not have the same weight as the data from the closely monitored phase III studies.

The number of patients exposed to the product for over a year is 174, which can, generally, be accepted as sufficient to meet the requirement for the long term safety characterisation. A considerable number of patients (74) were exposed for over two years.

The calculations of the mean duration of treatment, which would be more conservative, also confirm the extent of exposure as similar to what was seen in nominal reports.

Demographically and in the sense of pathology the safety population can be accepted as representative of the population in general.

In conclusion, while the numbers exposed to over a year are sufficient, the overall numbers are on the lower limit of the acceptable. The data from the early access programme due to the high numbers of patients involved do provide additional assurance. While the exposure covering the short term safety is lower than desirable, there are no grounds for requesting further short term studies focused on safety.

The applicant is expected to provide further data as some aspects of the development programme are reported as still ongoing.

Adverse events

The presented analysis of adverse events focusses on the treatment emergent adverse events (TEAEs) that were reported in the phase III studies MS-SPI and MS-ON. An overview of TEAEs reported in the double-masked phases of Study MS-SPI and Study MS-ON is provided in the table below.

Table: Overview of TEAEs in Double-Masked Phases of Studies MS-SPI and MS-ON (Safety Population)

	Number (%) of Patients			
	Study MS-SPI		Study MS-ON	
	MD1003 N=103	Placebo N=51	MD1003 N=65	Placebo N=28
Any TEAE	84 (81.6)	43 (84.3)	49 (75.4)	22 (78.6)
Any treatment-related TEAE	20 (19.4)	12 (23.5)	9 (13.8)	5 (17.9)
Any severe TEAE	5 (4.9)	4 (7.8)	3 (4.6)	2 (7.1)
Any treatment-related severe TEAE	2 (1.9)	0 (0.0)	1 (1.5)	0 (0.0)
Any treatment emergent SAE	20 (19.4)	12 (23.5)	9 (13.8)	3 (10.7)
Any treatment-related treatment emergent SAE	1 (1.0)	0 (0.0)	1 (1.5)	0 (0.0)
Any TEAE leading to withdrawal*	7 (6.8)	7 (13.7)	1 (1.5)	1 (3.6)
Any treatment emergent SAE leading to withdrawal	1 (1.0)	1 (2.0)	1 (1.5)	0 (0.0)
Any fatal TEAE	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)

N=Number of patients; SAE=Serious adverse event; TEAE=Treatment-emergent adverse event
* includes patients in whom the TEAE resulted in drug discontinuation/interruption followed by withdrawal

During the 12-month double-masked phase in Study MS-SPI, a slightly lower proportion of patients experienced at least one TEAE in the MD1003 treatment group (81.6%) compared to the placebo group (84.3%). The reported TEAEs were assessed by the investigator to be related to the study treatment in 19.4% of patients in the MD1003 treatment group and 23.5% of patients in the placebo group. During the 6-month double-masked phase in Study MS-ON, the proportion of patients who experienced at least one TEAE was also slightly lower in the MD1003 treatment group (75.4%)

compared to the placebo group (78.6%); these TEAEs were considered by the investigator to be related to the study treatment for 13.8% of patients treated with MD1003 and 17.9% of those receiving placebo.

In each of these studies, < 5% of the patients treated with MD1003 reported severe TEAEs during the double-masked phases, which was a lower proportion than in the placebo group (approximately 7-8%).The proportion of patients reporting SAEs was lower in the MD1003 group compared to the placebo group in Study MS-SPI (19.4% versus 23.5%), and this was the converse for Study MS-ON (13.8% versus 10.7%).

In both studies, the proportion of patients experiencing TEAEs leading to withdrawal was lower in the active treatment group (6.8% and 1.5% of the patients in Studies MS-SPI and MS-ON, respectively) than in the placebo group (13.7% and 3.6% of the patients in Studies MS-SPI and MS-ON, respectively).

One death was reported in the double-masked phases (suicide). The TEAE occurred in Study MS-SPI, in a patient treated with MD1003 and was not considered to be related to the study treatment.

An overview of TEAEs reported in the open label phases of Studies MS-SPI and MS-ON, where all patients received MD1003, is provided in the table below.

Table: Overview of TEAEs in Open Label Phases of Studies MS-SPI up to Month 24 and MS-ON up to Month 12 (Safety Population)

	Number (%) of Patients					
	Study MS-SPI			Study MS-ON		
	MD1003/ MD1003 N=91	Placebo/ MD1003 N=42	Overall N=133	MD1003/ MD1003 N=64	Placebo/ MD1003 N=28	Overall N=92
Any TEAE	49 (53.8)	25 (59.5)	74 (55.6)	32 (50.0)	12 (42.9)	44 (47.8)
Any treatment-related TEAE	7 (7.7)	5 (11.9)	12 (9.0)	0 (0.0)	2 (7.1)	2 (2.2)
Any severe TEAE	6 (6.6)	2 (4.8)	8 (6.0)	1 (1.6)	2 (7.1)	3 (3.3)
Any treatment-related severe TEAE	2 (2.2)	2 (4.8)	4 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any treatment emergent SAE	14 (15.4)	6 (14.3)	20 (15.0)	6 (9.4)	4 (14.3)	10 (10.9)
Any treatment-related treatment emergent SAE	2 (2.2)	2 (4.8)	4 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any TEAE leading to withdrawal	2 (2.2)	0 (0.0)	2 (1.5)	1 (1.6)	0 (0.0)	1 (1.1)
Any treatment emergent SAE leading to withdrawal	2 (2.2)	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Any fatal TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

N= Number of patients; TEAE=Treatment-emergent adverse event

In the open label phase of Study MS-SPI, overall 55.6% (74/133) of the patients experienced at least one TEAE: 59.5% (25/42) of patients in the placebo/MD1003 arm and 53.8% (49/91) in the MD1003/MD1003 arm. In the open label phase of Study MS-ON, 47.8% (44/92) of the patients experienced at least one TEAE which corresponded to 42.9% (12/28) in the placebo/MD1003 arm and 50.0% (32/64) of patients in the MD1003/MD1003 arm.

Overall, four patients experienced treatment-related SAEs in the open label phase, all of the cases were reported in Study MS-SPI (thyroiditis and myopathy in the placebo/MD1003 arm; multiple sclerosis relapse and hypoglycaemia in the MD1003/MD1003 arm).

Three patients experienced TEAE leading to study drug withdrawal (one case reported in Study MS-ON and 2 cases in Study MS-SPI). Two of these cases were also SAEs (breast cancer and loss of weight) and were reported in patients in the MD1003/MD1003 arm of Study MS-SPI.

No deaths occurred in the open phases of either Study MS-SPI or MS-ON.

A summary of the most commonly reported TEAEs (≥2% of patients in either treatment group in combined data) in the double-masked phases of the studies is presented in Table below.

Table: Summary of the Number (%) of Patients for TEAEs Occurring in ≥ 2% of Patients in Either Treatment Group from the Overall Population Across the Double-Masked Phases of Studies MS-SPI (up to Month 12) and MS-ON (up to Month 6) (Safety Population)

	Study MS-SPI		Study MS-ON		Overall	
System Organ Class Preferred Term – n (%)	MD1003 N=103	Placebo N=51	MD1003 N=65	Placebo N=28	MD1003 N=168	Placebo N=79
Any TEAE	84 (81.6)	43 (84.3)	49 (75.4)	22 (78.6)	133 (79.2)	65 (82.3)
Endocrine disorders	5 (4.9)	0 (0.0)	1 (1.5)	0 (0.0)	6 (3.6)	0 (0.0)
Hyperthyroidism	4 (3.9)	0 (0.0)	1 (1.5)	0 (0.0)	5 (3.0)	0 (0.0)
Gastrointestinal disorders	13 (12.6)	12 (23.5)	8 (12.3)	4 (14.3)	21 (12.5)	16 (20.3)
Abdominal pain	2 (1.9)	2 (3.9)	0 (0.0)	0 (0.0)	2 (1.2)	2 (2.5)
Abdominal pain upper	2 (1.9)	1 (2.0)	2 (3.1)	1 (3.6)	4 (2.4)	2 (2.5)
Constipation	4 (3.9)	2 (3.9)	1 (1.5)	1 (3.6)	5 (3.0)	3 (3.8)
Diarrhoea	2 (1.9)	1 (2.0)	0 (0.0)	1 (3.6)	2 (1.2)	2 (2.5)
Nausea	3 (2.9)	2 (3.9)	1 (1.5)	0 (0.0)	4 (2.4)	2 (2.5)
General disorders and administration site conditions	9 (8.7)	7 (13.7)	7 (10.8)	5 (17.9)	16 (9.5)	12 (15.2)
Asthenia	2 (1.9)	0 (0.0)	2 (3.1)	2 (7.1)	4 (2.4)	2 (2.5)
Fatigue	1 (1.0)	4 (7.8)	2 (3.1)	1 (3.6)	3 (1.8)	5 (6.3)
Infections and infestations	35 (34.0)	17 (33.3)	18 (27.7)	9 (32.1)	53 (31.5)	26 (32.9)
Bronchitis	5 (4.9)	6 (11.8)	2 (3.1)	1 (3.6)	7 (4.2)	7 (8.9)
Cystitis	3 (2.9)	1 (2.0)	0 (0.0)	1 (3.6)	3 (1.8)	2 (2.5)
Gastroenteritis	4 (3.9)	2 (3.9)	1 (1.5)	3 (10.7)	5 (3.0)	5 (6.3)
Influenza	0 (0.0)	2 (3.9)	2 (3.1)	0 (0.0)	2 (1.2)	2 (2.5)
Laryngitis	0 (0.0)	2 (3.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.5)
Nasopharyngitis	5 (4.9)	3 (5.9)	8 (12.3)	1 (3.6)	13 (7.7)	4 (5.1)
Urinary tract infection	10 (9.7)	6 (11.8)	4 (6.2)	1 (3.6)	14 (8.3)	7 (8.9)
Injury, poisoning and procedural complications	7 (6.8)	6 (11.8)	2 (3.1)	2 (7.1)	9 (5.4)	8 (10.1)
Fall	3 (2.9)	2 (3.9)	0 (0.0)	1 (3.6)	3 (1.8)	3 (3.8)
Investigations	7 (6.8)	3 (5.9)	0 (0.0)	1 (3.6)	7 (4.2)	4 (5.1)
Gamma-glutamyltransferase increased	1 (1.0)	2 (3.9)	0 (0.0)	0 (0.0)	1 (0.6)	2 (2.5)
Metabolism and nutrition disorders	7 (6.8)	5 (9.8)	1 (1.5)	1 (3.6)	8 (4.8)	6 (7.6)
Hypercholesterolaemia	2 (1.9)	2 (3.9)	0 (0.0)	1 (3.6)	2 (1.2)	3 (3.8)

	Study MS-SPI		Study MS-ON		Overall	
System Organ Class Preferred Term – n (%)	**MD1003 N=103**	**Placebo N=51**	**MD1003 N=65**	**Placebo N=28**	**MD1003 N=168**	**Placebo N=79**
Any TEAE	**84 (81.6)**	**43 (84.3)**	**49 (75.4)**	**22 (78.6)**	**133 (79.2)**	**65 (82.3)**
Musculoskeletal and connective tissue disorders	**13 (12.6)**	**10 (19.6)**	**15 (23.1)**	**2 (7.1)**	**28 (16.7)**	**12 (15.2)**
Arthralgia	0 (0.0)	2 (3.9)	2 (3.1)	0 (0.0)	**2 (1.2)**	**2 (2.5)**
Back pain	4 (3.9)	3 (5.9)	3 (4.6)	1 (3.6)	**7 (4.2)**	**4 (5.1)**
Pain in extremity	2 (1.9)	1 (2.0)	2 (3.1)	0 (0.0)	**4 (2.4)**	**1 (1.3)**
Tendonitis	2 (1.9)	2 (3.9)	2 (3.1)	0 (0.0)	**4 (2.4)**	**2 (2.5)**
Nervous system disorders	**28 (27.2)**	**20 (39.2)**	**17 (26.2)**	**6 (21.4)**	**45 (26.8)**	**26 (32.9)**
Dizziness	3 (2.9)	2 (3.9)	0 (0.0)	2 (7.1)	**3 (1.8)**	**4 (5.1)**
Headache	4 (3.9)	3 (5.9)	3 (4.6)	3 (10.7)	**7 (4.2)**	**6 (7.6)**
Multiple sclerosis	12 (11.7)	7 (13.7)	2 (3.1)	1 (3.6)	**14 (8.3)**	**8 (10.1)**
Multiple sclerosis relapse	5 (4.9)	4 (7.8)	9 (13.8)	1 (3.6)	**14 (8.3)**	**5 (6.3)**
Muscle spasticity	4 (3.9)	6 (11.8)	0 (0.0)	0 (0.0)	**4 (2.4)**	**6 (7.6)**
Neuralgia	2 (1.9)	2 (3.9)	0 (0.0)	0 (0.0)	**2 (1.2)**	**2 (2.5)**
Psychiatric disorders	**10 (9.7)**	**5 (9.8)**	**4 (6.2)**	**5 (17.9)**	**14 (8.3)**	**10 (12.7)**
Anxiety	2 (1.9)	2 (3.9)	0 (0.0)	2 (7.1)	**2 (1.2)**	**4 (5.1)**
Depression	2 (1.9)	0 (0.0)	0 (0.0)	2 (7.1)	**2 (1.2)**	**2 (2.5)**
Insomnia	2 (1.9)	2 (3.9)	2 (3.1)	1 (3.6)	**4 (2.4)**	**3 (3.8)**
Skin and subcutaneous tissue disorders	**5 (4.9)**	**2 (3.9)**	**3 (4.6)**	**2 (7.1)**	**8 (4.8)**	**4 (5.1)**
Pruritus	1 (1.0)	2 (3.9)	1 (1.5)	1 (3.6)	**2 (1.2)**	**3 (3.8)**

N=number of patients in group; n=number of patients with data

In the MD1003 group, the most commonly reported TEAEs (≥5% of the patients in a treatment group in the pooled population) were multiple sclerosis, multiple sclerosis relapse, urinary tract infection and nasopharyngitis.

These commonly reported TEAEs related mainly to signs or symptoms commonly associated with MS (e.g. multiple sclerosis relapse, multiple sclerosis, back pain, fatigue, urinary tract infection) or other events that may be expected over the duration of follow up period (e.g. nasopharyngitis).

Only three treatment-related TEAEs occurred in more than 2% of the patients (in any treatment group in pooled data), all of which were reported in patients who received placebo. Muscle spasticity was reported as treatment-related in 3.8% (3/79) of the patients who received placebo and 0.6% (1/168) of the patients treated with MD1003. Nausea and anxiety were both reported as treatment-related in 2.5% (2/79) of the patients who received placebo and 0.6% (1/168) of the patients treated with MD1003.

Overall, the most common TEAEs reported in patients treated with MD1003 in the open label extension phases were consistent with the TEAEs reported in the double-masked phases.

Table: Summary of Number (%) of Patients for TEAEs Occurring in ≥2% of Patients in the Overall Population in the Open Label phases of Studies MS-SPI up to Month 24 or MS-ON up to Month 12 (Safety Population)

	Number (%) of Patients						
	Study MS-SPI		Study MS-ON		Overall		
System Organ Class Preferred Term	MD1003/ MD1003 N=91	Placebo/ MD1003 N=42	MD1003/ MD1003 N=64	Placebo/ MD1003 N=28	MD1003/ MD1003 N=155	Placebo/ MD1003 N=70	Both arms N=225
Any TEAE	**49 (53.8)**	**25 (59.5)**	**32 (50.0)**	**12 (42.9)**	**81 (52.3)**	**37 (52.9)**	**118 (52.4)**
Endocrine disorders	**3 (3.3)**	**2 (4.8)**	**0 (0.0)**	**1 (3.6)**	**3 (3.7)**	**3 (8.1)**	**6 (5.1)**
Hyperthyroidism	3 (3.3)	1 (2.4)	0 (0.0)	1 (3.6)	3 (3.7)	2 (5.4)	5 (4.2)
General disorders and administration site conditions	**4 (4.4)**	**4 (9.5)**	**4 (6.3)**	**2 (7.1)**	**8 (9.9)**	**6 (16.2)**	**14 (11.9)**
Influenza like illness	1 (1.1)	3 (7.1)	1 (1.6)	0 (0.0)	2 (2.5)	3 (8.1)	5 (4.2)
Infections and infestations	**14 (15.4)**	**10 (23.8)**	**11 (17.2)**	**1 (3.6)**	**25 (16.1)**	**11 (15.7)**	**36 (16.0)**
Bronchitis	3 (3.3)	2 (4.8)	1 (1.6)	0 (0.0)	4 (2.6)	2 (2.9)	6 (2.7)
Nasopharyngitis	2 (2.2)	0 (0.0)	3 (4.7)	0 (0.0)	5 (3.2)	0 (0.0)	5 (2.2)
Urinary tract infection	8 (8.8)	6 (14.3)	1 (1.6)	1 (1.6)	9 (5.8)	7 (10.0)	16 (7.1)
Nervous system disorders	**13 (14.3)**	**4 (9.5)**	**8 (12.5)**	**7 (25.0)**	**21 (13.5)**	**11 (15.7)**	**32 (14.2)**
Headache	2 (2.2)	0 (0.0)	1 (1.6)	3 (10.7)	3 (1.9)	3 (4.3)	6 (2.7)
Multiple sclerosis	1 (1.1)	2 (4.8)	3 (4.7)	0 (0.0)	4 (2.6)	2 (2.9)	6 (2.7)
Multiple sclerosis relapse	7 (7.7)	2 (4.8)	3 (4.7)	3 (10.7)	10 (6.4)	5 (7.1)	15 (6.7)

N=number of patients

Overall, 6.2% (14/225) of the patients experienced treatment-related TEAEs during the open phase of the studies. No treatment-related TEAE occurred in more than one patient.

The rates of adverse events when compared between placebo and active were slightly higher in the placebo groups. Similar small difference in rate was observed with serious adverse events and with adverse events leading to discontinuation, in both cases the active treatment appeared better. However, the difference was small as were the numbers of patients. No reliable clinical conclusions can be drawn from this and the rates should be regarded as essentially similar in the placebo and the active treatment arms in the double-masked phases of the controlled phase III studies.

The AE rates including the rates of the serious adverse events and those resulting in discontinuation were lower in the open label extensions of the two phase III studies to those seen in the double-masked phases. Interestingly, the rates of AEs in those who moved to open label treatment form the placebo arm were also lower than those who received active treatment at the beginning of the study. This is most likely the function of selection of patients for the study and during the study due to discontinuations.

In both phases, the double-masked and the open label, the most frequent events were related to infections and to nervous system. There was also relatively high frequency of AEs related to gastrointestinal system, but smaller than the other two. There is no indication that renal function is affected with these high doses of biotin. Some of these events are expected considering the underlying pathology. Higher rate of infections are relatively unexpected, but they occur in similar rate in both arms (placebo and active). All other rates were also relatively balanced between the active and the placebo group. The applicant has also analysed events of particular interest and came up with the proposed list of specific side-effects of the treatment (see below).

Safety data collected from the 5,483 patients enrolled in the early access programme as of 12 January 2017, have been reviewed by the Applicant. The most common non-serious and serious AEs were

disease progression. Most TEAEs are mild-moderate in intensity. Nevertheless, information on the actual rate of treatment discontinuations due to AEs is missing, and should be presented in order to characterize the overall tolerability.

Serious adverse events and deaths

Deaths

One death was reported across the double-masked and extension phases of the phase 3 studies. The death was due to a suicide and occurred in a patient treated with MD1003 who had a prior and ongoing medical history of anxiety. This case was not considered to be related to study treatment. An overview of this case and any other reported events potentially associated with suicidal behaviour is discussed in this report in the section dealing with events of special interest.

The applicant is claiming that the event is not related to the administration of study medication. The actual report of the case has been provided with the responses to the initial list of questions.

In addition there were two deaths in the case series. One of them was due to cardiac causes and the applicant will need to confirm if the condition existed prior to commencement of the therapy with biotin.

Other Serious Adverse events

Double-Masked Phases

Across the double-masked phases of Study MS-SPI and Study MS-ON, a lower proportion of patients in the MD1003 group (17.3% (29/168)) than in the placebo group (19.0% (15/79)) experienced at least one SAE.

The most commonly reported SAE across the studies and in both treatment groups was multiple sclerosis relapse which was reported in 8.3% (14/168) and 6.3% (5/79) of patients in the MD1003 and placebo groups, respectively. The only other SAE preferred term (PT) reported in more than one patient was multiple sclerosis which was reported in 0.6% (1/168) and 2.5% (2/79) of patients in the MD1003 and placebo groups, respectively.

Two SAEs were considered related to the study drug by the investigator:

-Mucocutaneous rash further discussed in the section on events of special interest.

-Retinal artery occlusion: this event was reported in a patient with progressive chronic optic neuropathy. Prior to this event, the patient reported MS relapse involving visual deterioration, therefore no relationship between the intake of MD1003 and the onset of retinal artery occlusion was established.

Extension Phases

During the open label extension phases of Study MS-SPI and Study MS-ON, a total of 13.3% (30/225) of patients experienced at least one SAE. Overall, the proportion of patients who experienced SAE during the extension phases was lower than during the double-masked phase (17.8% (44/247) of patients).

SAEs reported in more than one patient were multiple sclerosis relapse (6.2%, 14/225) and multiple sclerosis (0.9%, 2/225). No other SAE PT was reported by more than one patient. However, there were 2 patients who reported cancer during the 12-month open label phase, although these were

reported to different PT's (breast cancer and rectal cancer). A further patient was reported with cancer (testicular) after the 12 month analysis and is also included for completeness. All cases of cancer have been discussed below.

A total of 4 SAEs were reported as treatment-related by the investigator in the open label phases (thyroiditis, MS relapse, hypoglycaemia and myopathy).

Multiple sclerosis has been reported as the most common serious adverse event. This and other relevant cases of serious adverse events have been discussed in the following section of this report.

TEAEs of Special Interest or Significance

Following the Analysis of Adverse Events by Organ System or Syndrome the events of special interest or significance presented here:

•Multiple sclerosis relapse

•Allergic dermal skin reactions

•Hypoglycaemia

•Myopathy

•Cancer

•Suicide and related events

Multiple Sclerosis Relapse

Overall, 8.3% (14/168) of the patients in the MD1003 treatment group reported the TEAE of MS relapse across the 2 studies during the double-masked phases, compared to 6.3% (5/79) of the patients in the placebo group.

When the treatment groups were taken into account, a difference between the MS populations was also highlighted in the double masked phase. In the progressive MS subgroup, the incidence of MS relapse was similar between the active and placebo treatment groups (6.5% (8/123) and 6.2% (4/65) of the patients in the MD1003 and placebo groups, respectively). In the relapsing remitting subgroup population, there was a higher incidence of MS relapse in the MD1003 group (13.3% (6/45) of the patients) than the placebo group (7.1% (1/14) of the patients.

In the extension phases of the studies, the frequency of the MS relapses was similar between the progressive and relapsing remitting forms of MS (6.6% (11/166) and 6.8% (4/59) of patients, respectively). However, the duration of follow-up was only 6 months in the relapsing remitting MS population compared to 12 months in the progressive population, so over the same time period the incidence is likely to be higher in the relapsing remitting MS population than in the progressive population.

Table: Summary of Number (%) of Patients with TEAE of MS Relapse by Type of MS in Studies MS-SPI up to Month 24 and MS-ON up to Month 12 (Safety Population)

	Progressive MS		Relapsing remitting MS	
Masked Phases	**MD1003**	**Placebo**	**MD1003**	**Placebo**
MS-SPI				
N	103	51	NA	NA
Number (%)	5 (4.9)	4 (7.8)	NA	NA
MS-ON				
N	20	14	45	14
Number (%)	3 (15.0)	0 (0.0)	6 (13.3)	1 (7.1)
Overall				
N	**123**	**65**	**45**	**14**
Number (%)	**8 (6.5)**	**4 (6.2)**	**6 (13.3)**	**1 (7.1)**
Open Label Phases	**MD1003/MD1003**	**Placebo/MD1003**	**MD1003/MD1003**	**Placebo/MD1003**
MS-SPI				
N	91	42	NA	NA
Number (%)	7 (7.7)	2 (4.8)	NA	NA
MS-ON				
N	19	14	45	14
Number (%)	0 (0.0)	2 (14.3)	3 (6.7)	1 (7.1)
Overall				
N	**110**	**56**	**45**	**14**
Number (%)	**7 (6.3)**	**4 (7.1)**	**3 (6.7)**	**1 (7.1)**

N= Number of patients

While the numbers seen in the safety section are certainly not sufficient to draw reliable conclusions, it appears that using the product doubles the rate of relapses in the relapsing-remitting type of MS. Since appearance of new lesions has been seen as a safety rather than efficacy measure initially this has not been sufficiently investigated. This was further queried as a major public health concern. From the applicant's responses it appears that patients on placebo when given the active treatment in the open label phase did not follow the pattern of relapses and new lesions seen in those enrolled on the active treatment from the beginning indicating that there may be clinical difference between the two populations. The Co-rapporteur regards the safety related major objection unresolved, while the rapporteur sees the presented data sufficient to regard this issue as no longer a major safety related public health concern.

Allergic Dermal Skin Reactions

A serious case of mucocutaneous rash was reported as treatment related and other potential allergic dermal reactions were also noted to have occurred. Therefore a systematic review of TEAEs reported in the High Level Group Term (HLGT) 'Epidermal and Dermal Conditions' was performed.

Overall, in the double-masked phases of the studies, a lower proportion of patients treated with MD1003 (3.0% (5/168)) reported TEAEs of this HLGT than in the placebo group (3.8%; 3/79). The event pruritus was reported in a lower proportion of patients treated with MD1003 (1.2%; 2/68) than patients treated with placebo (3.8%; 3/79). However, the TEAEs mucocutaneous rash, eczema and blister were reported only in subjects treated with MD1003 (0.6%; 1/168).

In the extension phases of the studies, 2.2% (5/225) of the patients reported TEAEs in the 'Epidermal and Dermal Conditions' HLGT. The TEAEs were eczema (1.3%, 3/22) and pruritus (0.9%; 2/225).

Mucocutaneous rash

The case of mucocutaneous rash was serious and was reported as treatment related five days after the start of treatment with MD1003. Allergy testing by chamber patch was negative to D biotin and to any excipient of MD1003, and re-challenge with MD1003 that subsequently occurred when the patient

entered the early access program did not induce new allergic dermal skin reaction. Therefore this case is not considered definitive with respect to its relationship to treatment with MD1003. However, an additional case of mucocutaneous rash was spontaneously reported in the early access program with a patient presenting with a dermal reaction, including a macular rash 2 weeks after initiating treatment with MD1003, so mucocutaneous rash is conservatively considered as an adverse drug reaction.

Eczema

Overall, four cases of eczema were reported in three patients across the phase 3 studies with MD1003. None of the patients had history of eczema or other allergic conditions. Among other TEAEs reported for these patients, only one TEAE (erythema migrans) was considered of possible relevance, however this event was not considered linked to the patient's subsequent onset eczema. Eczema is therefore considered as an adverse drug reaction.

Blister

Across the phase 3 studies with MD1003, one case of blister was reported. The event was considered possibly related to the study drug by the investigator. No action was taken regarding the study drug and the event resolved. In view of the potential relationship of the event with the intake of MD1003 and of the other skin sensitivity reactions reported with MD1003, blister is therefore considered as an adverse drug reaction.

The applicant has conducted additional analyses covering the safety signal. The conservative approach of including the selected dermatological conditions as adverse drug reactions is supported. It is of relevance that these events were not frequent.

Hypoglycaemia

One serious case of hypoglycaemia was reported across the phase 3 studies following treatment with MD1003. The episode of hypoglycaemia was reported in the open label extension phase of the study after the patient had already been treated with MD1003 for a year. After the event occurred, treatment with MD1003 was interrupted, and no hypoglycaemic events were reported in the subsequent month. After re-challenge with MD1003, new hypoglycaemic events were reported and the investigator referred the patient for an evaluation of their insulin dosage.

Other events in the HLGT of 'Glucose Metabolism Disorders' were reviewed. Only one other event of a glucose metabolism disorder, hyperglycaemia, was reported in a patient treated with placebo.

Overall, one case of hypoglycaemia was reported across the phase 3 studies with MD1003 and the pharmacological plausibility means that a potential impact of MD1003 cannot be ruled out. Therefore, hypoglycaemia is considered as an adverse drug reaction (ADR) and the potential interaction of biotin on glucose metabolism in susceptible patients is also addressed in the warning and precautions section of the SmPC.

While the applicant's conservative approach of including this event as adverse drug reaction is acceptable in this case, the event was rare and the connection was primarily made based on the known mechanism of action.

Cancer

MD1003 is a medicinal product that is not considered to present a carcinogenic potential.

During the clinical development of MD1003 to date, 1.8% (4/225) of the patients reported cancer. One case (thyroid adenocarcinoma – originally reported as preferred term of goitre) was reported in a

patient treated with MD1003 in the double masked phases and the three other cases of cancer were reported (breast cancer, testicle cancer and rectal cancer) in patients exposed to MD1003 in the open label extension phases of the clinical studies, all of whom also received MD1003 in the double-masked phase of the studies. One of these cases occurred beyond the 12 month cut-off for the extension analysis, but is included for completeness (patient MS-ON-00040002). None of these cancers presented particular characteristics that would suggest an iatrogenic origin. The four cases are summarised below:

-Thyroid adenocarcinoma: papillary thyroidadenocarcinoma with no staging was reported in a 47-year-old woman. This patient had history of thyroid nodules for more than 20 years. The patient's medical history and the short exposure to MD1003 (about a year between the start of treatment and thyroidectomy) are in favour of a sporadic form of thyroid cancer.

-Breast cancer: a Grade 1 breast adenocarcinoma positive to the E-Cadherin, the oestrogen receptor (ER +) and negative to the progesterone receptor(PR+) was reported in a 57-year old woman. No risk factor (familial, exposition to other drugs) was identified. Biotin is not known to interact with the female hormonal system, therefore, this case of cancer was considered as a sporadic postmenopausal cancer.

-Rectal cancer: a Grade T3 N+ carcinoma was reported in a57-year old patient. The patient had dyslipidaemia for 10 years and diabetes for 6 years and was considered predisposed to gastrointestinal cancer. This case is therefore considered a sporadic form of rectal cancer in a patient with metabolic and nutritional risk factors.

-Testicle cancer: a malignant non-seminomatous testicle cancer was reported in a 23 year old man. No known risk factor of cancer or testicle cancer was identified in this patient. The absence of atypical characteristics of the tumour, the short exposure to MD1003 (1.5 years) and the absence of known carcinogenic potential of MD1003 are in favour of a sporadic form of non-seminomatous testicle cancer.

The incidence of all cancers reported in MD1003 clinical development (1.8%) and of the specific cancer cases reported (0.4% of the patients with thyroid, testicular, breast and rectal cancer) is consistent with the expected occurrence of cancers in MS patients in this age range. Based on the reported cases and reported incidence of cancer in MS patients, it is considered that there is no relationship between the onset of the cases of cancer reported in the clinical development of MD1003 and the intake of MD1003.

The applicant claims that the frequency of the occurrence of cancers is expected for the MS population in general. This was further queried. To address this concern the Applicant has reviewed the cancer cases reported during the RCT and their safety follow up and during the early access program where a total of 6775 patients were treated with biotin. One additional case was reported (placebo-biotin) in the RCT. In the ATU program, 9 cases had been reported. Based on the review of the type of cancer, latency from the start of treatment, and presence of risk factors, no accumulation of a particular type of cancer was noted.

The incidence rate of cancer in Study MS-SPI was 1.3% (4 cases / 304.9 patient years) and in the early access programme with MD1003 was 0.2%, which is below the reported incidence of cancer in MS patients (4.39%). Thus, based on the available data, a particular carcinogenicity risk following treatment with biotin cannot be concluded. Nevertheless, data are limited to firmly concluded. Until a full evaluation of the risk is completed, malignancies should be included as a potential risk in the RMP.

Myopathy

One case of myopathy was reported during the clinical development of MD1003. The case was serious and considered probably related to the study drug by the investigator. The patient fully recovered from the event when treatment with MD1003 was stopped.

A causal relationship with MD1003 to the case of myopathy cannot be ruled out as biotin exposure could result in lipid storage myopathy by induction of beta-oxidation pathway deficiency.

Based on the nature of the reported SAE 'lipid storage myopathy' and the pharmacological plausibility, the myopathy is considered an adverse drug reaction.

A review of other events in the HLGT 'Muscle Disorders' did not suggest additional muscle disorders related to MD1003 as, unlike the above myopathy case, the events reported could be confounded with clinical manifestations of MS. In the double-masked phase of the phase 3 studies, a higher proportion of patients treated with MD1003 (3.0% (5/168)) reported TEAEs on Muscle Disorders than in the placebo group (1.3% (1/79)). The TEAEs reported in the MD1003 group were muscle spasms, amyotrophy and torticollis. The TEAE reported by the patient treated with placebo was myalgia. In the extension phase, two cases were reported: muscle spasms and myopathy (case described above).

It is agreed that there is a possibility in this case that myopathy was connected with the exposure to the product. The difficulty in assessing this event in respect to the symptoms of the underlying condition is also acknowledged. Adding it to the list of adverse drug reactions is supported.

Suicide and Related Events

One case of completed suicide was reported across the studies. This case was reported in the double-masked period of Study MS-SPI. The patient committed suicide 6 months after the start of treatment with MD1003 and had suffered from anxiety prior to and during the study.

A review of all other events in the HLGT's 'Suicidal and self-injurious behaviours', 'Anxiety disorders and symptoms' and 'Depressed mood disorders and disturbances' did not suggest suicidal or related behaviours with the intake of MD1003. Overall during the double-masked phases there was a lower proportion of patients reporting at least one TEAE in these HLGT's in the MD1003 treatment group compared to the placebo group (4.2% of patients (7/168) and 7.6% of patients (6/79), respectively). In the extension phase there was a decrease in the proportion of patients reporting these terms relative to the double-masked phase in both the MD1003/MD1003 treatment arm (1.9%, 3/155) and placebo/MD1003 treatment arm (1.4%, 1/70).

Based on the additional analysis, at this stage it is agreed in principle, that the case of suicide was not related to the use of the product. The additional details about this event were requested and provided by the applicant. Further clarification regarding monitoring of safety events occurring after prolonged period of time (delayed reactions) has been requested.

Conclusion - Adverse Drug Reactions

The methodology and detailed discussion relating to the assessment of adverse drug reactions for MD1003 in patients with MS is presented above. The summary of the findings is presented in the following table.

Table: Adverse Reactions for MD1003 by System Organ Class and Frequency

MedDRA SOC	Adverse Reaction (preferred term)	Frequency	Frequency category*
Metabolism and nutrition disorders	Hypoglycaemia	0.4%	Uncommon
Skin and subcutaneous tissue disorders	Blister	0.6%	Uncommon
	Eczema	0.6%	Uncommon
	Mucocutaneous rash	0.6%	Uncommon
Musculoskeletal and connective tissue disorders	Myopathy	0.4%	Uncommon

* Very common (≥ 1/10), common (≥ 1/100, <1/10), uncommon (≥ 1/1000, <1/100), rare (≥ 1/10000, <1/1000), very rare (<1/10000 and not known (cannot be estimated from the available data)

The proposed events are accepted. However, suicide and cases of cancer have been queried further and the issues remain open until more information has been provided.

Laboratory findings and investigations

QT Interval

During the nonclinical development of MD1003, isolated cardiovascular findings were observed in the safety pharmacology evaluation. In an in vitro study, a small decrease (<12%) of hERG tail current was observed at the highest dose of MD1003 tested, 100 µM. In a dog study isolated absolute QT interval prolongations were recorded at the high dose of 1000 mg/kg/day 4 hours post dosing, however, no clear difference was observed when the QT was corrected with Friderica and Van de Water formulas. Therefore, these findings were not considered toxicologically relevant as occurred at doses far in excess of the proposed clinical dose and, in the case of the dog study, they were probably due to lower heart rate recorded in the high dose group since the difference was no longer present when this was corrected for.

For the Phase 3 studies, ECG's were performed at Baseline, Month 6, Month 12 and Month 24 in Study MS-SPI, and at Baseline and Month 6 in Study MS-ON. In the Phase 1 PK study, ECG's were performed at screening and at the end of study visit; no clinically relevant changes were observed.

Some discrepancies were identified in the reading of the ECG in the Phase 3 Studies at Baseline corresponding to very low PR interval values (<<120 ms). All of these abnormal values were recorded in patients who participated in one study centre in Study MS-SPI and abnormalities were found to be due to an erroneous instrument.

Therefore, the data in this Section on ECG exclude the patients from this centre (centre #15) for the analyses where Baseline values were utilised (i.e. Proportion of patients with absolute QTcB and QTcF prolongation at baseline and proportion of patients with significant changes in QTcB and QTcF from Baseline), although they are still included in the original statistical analysis tables. This corresponded to 6 patients in MD1003 group and 2 patients in the placebo group for these analyses.

Overall, absolute QTcB and QTcF prolongation (>450 ms and >500 ms) and changes from Baseline in QTcB and QTcF (>30 ms and 60 ms) were observed in both the MD1003 and placebo treatment groups across the phase 3 studies. No clear difference between the MD1003 and placebo groups was observed and no change over the course of the studies with a longer duration of exposure was seen. The findings of some occurrences of QTc prolongation, reflecting a ventricular repolarisation dysfunction,

were expected in a MS population and has previously been reported (de Seze et al., 2000, de Seze et al., 2001).

Table: Summary of Proportion of Patients (%) with Absolute QtcB and QTcF Prolongation in the Double-Masked Phase of Study MS-SPI and Study MS-ON (Safety Population)

	Study MS-SPI N=154				Study MS-ON N=93				Overall (across both studies) N=247			
	MD1003		Placebo		MD1003		Placebo		MD1003		Placebo	
Parameter description Visit	QTc > 450 ms	QTc > 500 ms	QTc > 450 ms	QTc > 500 ms	QTc > 450 ms	QTc > 500 ms	QTc > 450 ms	QTc > 500 ms	QTc > 450 ms	QTc > 500 ms	QTc > 450 ms	QTc > 500 ms
Absolute change QTcB – Bazett's Correction Formula												
Month 0	n=97*		n=47*		n=64		n=26		n=161		n=73	
N (%)	11 (11.3)*	0 (0.0)*	4 (8.5)*	0 (0.0)*	2 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	13 (8.1)	0 (0.0)	4 (5.5)	0 (0.0)
Month 6	n=94		n=47		n=63		n=28		n=157		n=75	
N (%)	9 (9.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	11 (7.0)	0 (0.0)	0 (0.0)	0 (0.0)
Month 12	n=93		n=42		NA		NA		n=93		n=42	
N (%)	3 (3.2)	0 (0.0)	2 (4.8)	0 (0.0)	NA	NA	NA	NA	3 (3.2)	0 (0.0)	2 (4.8)	0 (0.0)
Absolute change from baseline QTcF– Fridericia's Correction Formula												
Month 0	n=97*		n=47*		n=64		n=26		n=161		n=73	
N (%)	4 (4.1)*	0 (0.0)*	0 (0.0)*	0 (0.0)*	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)
Month 6	n=94		n=47		n=63		n=28		n=157		n=75	
N (%)	3 (3.2)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)
Month 12	n=93		n=42		NA		NA		n=93		n=42	
N (%)	3 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA	NA	NA	3 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)

ms=millisecond; N=number of subjects in safety population, n=number of subjects in treatment arm, NA=Not applicable; QTc=Corrected QT Interval
* Patients from Study MS-SPI Centre # 15 excluded

The company has done some investigation of the cardiovascular effects of the drug as part of the phase III studies. The analysis only provides categorical data, but no central tendency analysis has been presented. The justification for not conducting a thorough QT study has not been provided. In addition all patients from one centre (centre #15 from the study MS-SPI) have been excluded from ECG analyses. All these issues have been queried. In response, the applicant has decided to conduct a thorough QT study the results of which will be submitted with the responses to the Day 180 list of questions.

Brain White Matter Lesions

Brain MRI safety evaluations were performed on a subset of patients in the double-masked phase of Study MS-SPI at baseline, Month 12 (N=70 with MRI evaluations) and in the open label extension phase at Month 24 (N=58 with MRI evaluations).

Brain MRI results at Month 12 showed that 20.0% (14/70) of the patients assessed had at least one new T2 lesion at the end of the double-masked phase. A higher proportion of patients in the MD1003 treatment group (23.4% (11/47)) presented at least one new T2 lesion than patients in the placebo group (13.0% (3/23)). T2 lesions with increased volume and new T1 Gd+ lesions at Month 12 compared to baseline were observed only in the MD1003 treatment group (8.5% (4/47) and 4.3% (2/47) of the patients, respectively).

The MRI results at Month 24 compared to Month 12 showed that a lower overall proportion of patients had at least one new T2 lesion in the extension phase (8.6% (5/58)) than in the double masked phase (20.0% (14/70)) (Table 11, Figure 17). In the group of patients who switched from placebo to MD1003, the proportion with new T2 lesions at Month 24 was 5.6% compared to 13.0% when receiving placebo in the double-masked phase and the corresponding proportion in the patients continuing to take MD1003 was 10.0% versus 23.4%. There were no T2 enlargements identified in either treatment arm and one patient presented with a new T1 Gd+ lesion.

This pattern of T2 lesions does not suggest an effect of MD1003, however a detailed per patient evaluation for the 14 patients with new T2 lesions at Month 12 was performed that encompassed other safety parameters as well as baseline characteristics and efficacy outcomes. No clinical pattern

emerged with respect to the occurrence of new T2 lesions, other safety findings or the patient experiencing efficacy with MD1003.

A comparison of the occurrence of MS relapses in patients with new T2 lesions at Month 12 compared to Baseline versus those who did not exhibit new lesions illustrates that although the overall occurrence of MS relapse across the double masked and open label phases is higher in patients with new T2 lesions (respectively, 21.4% and 10.7% of patients with and without new lesions), the proportion of patients with new T2 lesions and presenting MS relapse was higher in the placebo group (66.7%) than in the MD1003 group (9.1%). However, it must be recognised that the numbers are small so need to be interpreted with caution.

The evaluation of the pattern of new T2 lesions across the double-masked and extension phases of the study as well as the pattern with respect to MS relapses, does not suggest that MD1003 was clearly associated with new T2 lesions or that the occurrence of brain white matter lesions in patients treated with MD1003 was associated with clinical manifestations.

Table: Summary of Brain MRI Results in Study MS-SPI (Safety Population – MRI Subset)

Double-masked phase Month 12	MD1003 (N=50)	Placebo (N=25)	p-value
At least one new T2 lesion N n (%)	 47 11 (23.4)	 23 3 (13.0)	 0.3612*
Enlargement of T2 lesion N n (%)	 47 4 (8.5)	 23 0 (0.0)	 0.2950*
At least one new T1 Gd+ lesion N n (%)	 47 2 (4.3)	 22 0 (0.0)	 1.0000*
Open label phase Month 24	**MD1003/MD1003 (N=47)**	**Placebo/MD1003 (N=20)**	**p-value**
At least one new T2 lesion N n (%)	 40 4 (10.0)	 18 1 (5.6)	 1.0000*
Enlargement of T2 lesion N n (%)	 NA 0 (0.08)	 NA 0 (0.0)	 NA
At least one new T1 Gd+ lesion N n (%)	 38 1 (2.6)	 17 0 (0.0)	 1.0000*

N= Number of patients; n= Number of patients with event; NA=Not Applicable; Gd+= Gadolinium contrast
*Fisher's Exact test

While the patient numbers are low and it is consequently difficult to interpret the results, what is seen in the MRI imaging appears to be in line with the results about higher relapse rate in those treated with the product. The MRI imaging supports the concern that the product may be accelerating progression of the underlying illness. This was identified as a serious concern which was further queried. The MRI reanalysis presented, conducted in a subset of patients with MRI testing at baseline from Study MS-SPI showed no differences in the proportion of patients with T1 Ga+ or T2 lesions between biotin and placebo at M12. Differences were seen in the proportion of patients with T1 unenhancing lesions at M12 between biotin (26%) and placebo (11.1%), which may reflect a likely imbalance in the baseline proportion of patients with inflammatory lesions. However, a small increase in the proportion of patients with T2 and T1 Ga+ lesions from M12-24 was seen in the biotin treatment arm. No such effect is seen in placebo. These findings are in line with the higher TEAE reporting from 12-24 months in biotin vs placebo: 7.7% vs 4.8%, respectively. A trend for a higher reporting with longer term follow up is observed, unfortunately MRI data are not available beyond 24-month.

Following the company's responses the rapporteur no longer regards this as an issue of observed reaction to the treatment but rather issue of selection into the two arms of the trial, while co-rapporteur requires further clarification .

Safety in special populations

Renal impairment

No clinical studies were performed with MD1003 in patients with renal impairment. As biotin is excreted by the renal route, there is a potential risk of accumulation of the product in patients with renal impairment. Therefore, it is recommended in the SmPC that caution should be taken when MD1003 is administered to patients with renal impairment.

The proposed approach is acceptable.

Hepatic impairment

No clinical studies were performed in patients with hepatic impairment. MD1003 does not need to be metabolised in the liver to be active, therefore no impact on the efficacy of MD1003 is expected in patients with hepatic impairment.

Any anticipated lower metabolism of biotin in patients with impaired hepatic function would be expected to increase the proportion of plasma biotin due to less elimination. However, biotin is readily excreted in the urine and has been demonstrated not to accumulate in healthy volunteers. In addition no in vitro interaction has been observed with CYPs or main liver transporters (P-gP and BCRP) so no risk is anticipated in patients with hepatic impairment.

The proposed rationale is acceptable in principle.

Elderly

In the clinical development of MD1003, adult patients up to 75 years of age were eligible for inclusion into the studies. Overall, 3 patients above 65 years of age were included in the clinical studies and received MD1003. No increased risk in these patients was evidenced after a review of these.

The number of patients above 65 is too low to generalise the safety conclusions. The applicant was asked to provide justification about the safety in elderly or limit the use to the population included in the studies. The provided responses were not seen as sufficient and this issue is further queried.

Use in Pregnancy and Lactation

Although no teratogenic effects were seen in studies on rats at doses far exceeding the recommended clinical dose, a nonclinical reproduction study with MD1003 in rabbits identified a teratogenicity risk at doses relevant to the proposed clinical indication. At a dose that was approximately twice the recommended total daily dose for the treatment of progressive MS patients, an increase in malformations and variations were reported.

Therefore MD1003 should not be used in patients who are pregnant and women of childbearing potential should be using a reliable form of contraception. In addition, there is no information on whether MD1003 can be transmitted though breast milk. However, it has been reported in the literature that biotin and its metabolites can be found into human milk. Therefore, MD1003 should also not be used while breast feeding as a risk of transmission through breast milk cannot be ruled out. The relevant information is included in Section 4.6 of the SmPC.

Two pregnancies in patients treated with MD1003 have been reported during the clinical program of MD1003 for the treatment of progressive MS. In one case the patient became pregnant while she had been treated with MD1003 for 9 months, she gave birth to a healthy baby after 40 weeks of amenorrhea. In the other case, the patient decided to have an abortion during the first month of pregnancy.

The proposed restriction is acceptable. There were no additional safety signals identified in the two pregnant individuals enrolled in the studies.

Safety related to drug-drug interactions and other interactions

Interference with Laboratory Testing

MD1003 is a medicinal product containing the active substance biotin. There is therefore a potential for interactions of biotin with immunoassays that use a biotinylated reagent i.e. based on a biotin/streptavidin interaction (Kwok et al., 2012 and Wijeratne et al., 2012). In these immunoassays, high plasma levels of biotin could result in falsely low values with sandwich-type immunoassays and falsely high values with competitive-type immunoassays. Laboratory tests using such methods include assays for anaemia, cardiology, fertility, pregnancy, endocrinology (especially thyroid panel), oncology, bone metabolism, inflammation biomarkers, infectious disease antigens and antibody titration. Some immunohistochemistry methods used in diagnostic pathology may be also affected.

During the clinical development of MD1003, interactions between biotin and immunoassays were evidenced by the reporting of false cases of hyperthyroidism and/or thyroid dysfunction. This resulted in a detailed review of all potential cases that included all TEAEs reported in the high level group term (HLGT) of 'Thyroid Gland Disorders' as well as 2 other potentially associated events.

The detailed review included an evaluation of the available information on the assay used and associated thyroid function test results, medical history and whether other tests to confirm thyroid abnormality was performed. Additional follow up information was available for 10 patients. Six reports of false biological hyperthyroidism, likely due to interference of biotin with the assay, were identified. In all cases, normal values on thyroid function were obtained after re-testing using a non-biotin dependent assay. Four cases were assessed as hyperthyroidism, however in two of these cases the patients were predisposed to hyperthyroidism by either already having a history of thyroid dysfunction or having long history of diabetes; the two remaining patients did not appear to have any identified risk factors from the available information.

The risk of interference between MD1003 and laboratory immunoassays using a biotinylated agent is confirmed in clinical practice. Measures to minimise this risk are included in Sections 4.4 and 4.5 of the SmPC, including a card to be carried by the patient.

Lipid storage myopathy

A possible secondary pharmacodynamic effect, with a potential clinical impact relates to fatty acid metabolism as biotin stimulates acetyl coA carboxylase, an enzyme involved in the formation of malonyl CoA. Increasing levels of malonyl coA inhibit carnitine palmitoyltransferase 1 (CPT1) which is responsible for long-chain fatty acid transport into mitochondria leading to fatty acids beta-oxidation. Therefore, the inhibition of CPT1 induced by malonyl CoA could result in reduced fatty acid beta-oxidation. A single case of lipid storage myopathy was reported in the clinical program, and as a result of the plausible pharmacological interaction, is reported as an adverse drug reaction (see above).

The proposed warnings in the SmPC are acceptable. The cases of thyroid dysfunction are dealt with in the appropriate section of the report (see above).

Post marketing experience

MD1003 is not marketed in any country. Therefore, no post-marketing data are available.

An early access program (ATU) with MD1003 is currently ongoing in France in patients with progressive MS. At the cut-off date of 31 March 2016, 1361 patients have received MD1003 under this program. Four spontaneous reports have been made to MedDay as of this cut-off date, none of them were SAEs:

•Patient reported events associated with a skin rash: skin dry (skin dry), patches on the skin, some of which are red (blotchy), itchy skin in particular on arms (itchy skin), flush sensation on the face (flushed face).

•Thyroid nodule (thyroid nodule).

•Patient reported feeling less well (reduced general condition)

•Patient reported inability to fall asleep (insomnia)

The early access scheme data is subject to spontaneous reporting of AEs. The reported AEs are in line with what was observed in the controlled studies. This data does not change the overall safety conclusions.

Other Safety Related Information

Safety Study Narrative for Study MD1003CT2014-02PK

Study MD1003CT2014-02PK was A phase 1 PK study conducted in healthy adult volunteers. The objective of the study was to evaluate the PK, dose-proportionality and food effect of MD1003 following a single oral administration of MD1003 at the doses of 100 mg, 200 mg and 300 mg. Eight subjects participated in the study (4 male, 4 female). The study consisted of 4 treatment periods (100 mg fed /300 mg fasted / 200 mg fasted /100 mg fasted) each administration was separated by a wash-out period of at least 7 days. Safety parameters including physical examination, vital signs, ECG, biochemistry, haematology and urinalysis laboratory tests were assessed and analysed.

No TEAE was reported during the study. Though there were transient fluctuations in individual parameters, no laboratory test, vital sign, ECG, or physical examination result was considered clinically significant by the investigator.

There were no safety signals identified during this study.

Safety Study Narrative for Case Series MS

Overall, 23 patients with progressive multiple sclerosis were treated with hospital preparations of biotin at doses between 100 and 600 mg/day for 2 to 35 months with a mean time of treatment of 9.3 months.

Out of the 23 patients, 20 patients did not report any adverse event. Only two patients reported minor adverse events, which were transient diarrhoea. One patient reported a SAE: death following a cardiac failure.

Laboratory testing was performed in 6 patients. Mild hyperleucocytosis was noted in one patient and mild leucopenia in another patient. No signs of anaemia and thrombopenia were found. Ionogram, creatinine and bilirubin values were found normal in all cases. One patient had increased levels of gamma-GT.

ECG was performed in 6 patients and was found to be normal in 5 patients who also had no symptoms of cardiac dysfunction. Abnormal ECG with bradycardia was observed in one patient who subsequently

died from cardiac failure. One further patient died during the evaluation period and both cases are summarised below:

•Patient #1 aged 73 years died from cardiac failure 36 months after the treatment start with biotin. Mild aortic valvulopathy with dilatation of the ascending aorta together with a first-degree atrio-ventricular block were observed 18 months after the treatment start. It is not known if these abnormalities were present before the treatment with biotin. No relation could be established between the treatment start, mild cardiac abnormalities and death (Sedel et al., 2015).

•Patient #15 died one year after the start of treatment with biotin from a pneumopathy. Sigmoid volvulus surgery had been performed on this patient a few days before. No relationship could be established between the death of this patient and the intake of biotin (Sedel et al., 2015).

The frequency of deaths does appear high for such a small number of patients. This population was not analysed together with the main safety data. The death of cardiac failure in particular is of potential relevance considering the paucity of the data on cardiac toxicity.

4.1.9. Discussion on clinical safety

The core safety data come from the two controlled phase III studies. This covers 238 patients which is considered limited. The additional patient data from PK studies is also analysed, but the contribution is very modest. The product is also subject of an early access scheme in France were additional 5483 patients were enrolled. The safety from this population is only reported spontaneously. A total of 174 patients have been exposed for longer than a year in cinical studies. In summary the numbers of patients exposed is low. The early access scheme does provide additional reassurance that the most common adverse events are captured and recorded. A total of 74 patients in the pivotal trial had an exposure of at least 24 months. The applicant has submitted an update on the numbers exposed to the treatment but further questions remain.

Overall treatment emergent adverse events rates are slightly higher in the placebo arm. Both the recorded difference and the patient numbers are low and it can be accepted that overall there is no difference in the rates of adverse events between the active and the placebo arm.

The AE rates including the rates of the serious adverse events and those resulting in discontinuation were lower in the open label extensions of the two phase III studies to those seen in the double-masked phases.

In both phases, the double-masked and the open label, the most frequent events were related to infections and to nervous system. There was also relatively high frequency of AEs related to gastrointestinal system, but smaller than the other two.

The applicant has also analysed events of particular interest and came up with the proposed list of specific side-effects of the treatment. The following were analysed as events of special interest: Multiple sclerosis relapse, Allergic dermal skin reactions, Hypoglycaemia, Myopathy, Cancer, Suicide and related events.

Of these, Hypoglycaemia, Blister, Eczema, Mucocutanous rash and Myopathy are found to be uncommon related adverse reactions. The occurrences of suicide and cancer has been queried and following the responses the questions remain.

Only four AEs have been reported in the early access scheme at the time of initial marketing authorisation application submission. They are in line with what was seen in the controlled studies. Safety data collected from the 5,483 patients enrolled in this programme as of 12 January 2017, have

been reviewed by the Applicant. The most common non-serious and serious AEs were disease progression. The overall incidence of AEs and SAEs increase substantially with continued treatment making the safety profile of biotin less benign than initially claimed (in fact, the incidence of SAEs is now double than initially reported (28.6% vs 15%)). Most TEAEs are mild-moderate in intensity. Nevertheless, information on the actual rate of treatment discontinuations due to AEs is missing, and should be presented in order to characterize the overall tolerability.

There has been one case of death due to suicide in the clinical studies with MD1003. The applicant has provided information on this event and concluded that it cannot be linked to the biotin treatment with certainty but there should be monitoring for possible issues.

Multiple sclerosis relapse has been described as serious treatment emergent adverse event. The rates of this event appear higher in the active arm then in the placebo treated patients but only for patients of relapsing-remitting type of illness.

Table: Summary of Number (%) of Patients with TEAE of MS Relapse by Type of MS in Studies MS-SPI and MS-ON (Safety Population)

	Progressive MS		Relapsing remitting MS	
Masked Phase:	MD1003	Placebo	MD1003	Placebo
MS-SPI				
N	103	51	NA	NA
Number (%)	5 (4.9)	4 (7.8)	NA	NA
MS-ON				
N	20	14	45	14
Number (%)	3 (15.0)	0 (0.0)	6 (13.3)	1 (7.1)
Overall				
N	**123**	**65**	**45**	**14**
Number (%)	**8 (6.5)**	**4 (6.2)**	**6 (13.3)**	**1 (7.1)**

Considering that the indication does restrict the use to those with progressive type of illness where this effect was not observed. However, the indication does include those who have secondary progressive form. This would imply that the product is not safe for the patients with relapsing-remitting type until the illness advances to the progressive stage when it becomes safe.

Of concern are the findings of MRI imaging from the study MS-SPI that demonstrate increased rate of new lesions in those treated with the product.

Table: Summary of Brain MRI Results in Study MS-SPI (Safety Population – MRI Subset)

Double-masked phase Month 12	MD1003 (N=50)	Placebo (N=25)	p-value
At least one new T2 lesion			
N	47	23	
n (%)	11 (23.4)	3 (13.0)	0.3612*
Enlargement of T2 lesion			
N	47	23	
n (%)	4 (8.5)	0 (0.0)	0.2950*
At least one new T1 Gd+ lesion			
N	47	22	
n (%)	2 (4.3)	0 (0.0)	1.0000*

While the numbers are too low to make any definite conclusions, both these findings indicate that there potentially exists a significant safety problem with the product and an important gap in knowledge about the effect on the progression of the underlying illness.

This has been further queried and following presented data, the rapporteur sees it as possible that the observed differences between placebo and active arms of the studies are due to the differences in the baseline population characteristics of the different arms of the trial. In the co-rapporteur's opinion this

issue is still a matter of concern. MRI findings, TEAEs and the ARR results, particularly in the SPMS, show a trend for a numerical increase in inflammatory T1 Ga+ and T2 lesions and for the TEAE reporting of MS relapse with long-term exposure to biotin. No such effect is observed in placebo when switching to biotin in the short-term. However, the limited number of patients and the lack of an exhaustive imaging evaluation across the studied population, together with baseline differences in the presence of inflammatory lesions between treatment arms, preclude drawing firm conclusions on the potential pro-inflammatory effect of biotin. Further, discrepancies are observed in the total incidence of TEAEs during the follow-up of both MS-SPI and MS-ON trials based on the data presented in the responses. This requires further clarification.

A total of 4 malignancies were reported in the 2 studies, all of them in biotin-treated patients. Considering the small sample size and the absence of non-clinical carcinogenicity data, this imbalance was seen a concern and it has been queried. Following the applicant's response the issue is seen as partially resolved and until further data becomes available this should be regarded as a potential risk.

From the animal studies there was an indication that high doses of biotin may affect cardiac conduction. The applicant did not carry out a thorough QT study and a justification for its absence has not been given. ECG recordings have been done in the study MS-SPI but the applicant did not provide the central tendency analysis. The gap in knowledge about the compound in regards to the cardiovascular safety has been queried. In response, the applicant has decided to conduct a thorough QT study and provide results with the responses to Day 180 list of questions.

The applicant reports limited data on the elimination in patients with renal and hepatic impairment. Since all biotin which cannot be metabolised in the liver is excreted in urine, the warning in the SmPC has only been added for the cases of renal impairment. This was found acceptable.

The number of patients over 65 included in the development programme is 3. This is seen as too low for any conclusions to be made. The applicant has expected to include in the SmPC the notice of lack of information on elderly. They are also expected to provide plans for gathering this information prior to authorisation.

The lack of information on the clinical safety in pregnancy and lactation is addressed by appropriate warnings in the product literature.

Biotin has a potential to interfere with certain immunoassays. In these immunoassays, high plasma levels of biotin could result in falsely low values with sandwich-type immunoassays and falsely high values with competitive-type immunoassays.

4.1.10. Conclusions on clinical safety

The patient exposure is low and possibly responsible for the identified gaps in knowledge about the safety of the compound. Substantial number of patients have been included in the early access scheme, and although this information is only of the level similar to post-marketing safety information, it provide some reassurance.

The most frequently reported treatment emerging events were CNS related. Amongst them the MS relapse rates appear to be higher in those exposed to the product than in the placebo arms of the studies. While this seems to affect only relapsing remitting patients, the MRI imaging suggests that the rate of occurrence of new lesions is increased in those who are treated with the product regardless of the MS type they suffer. This was seen as major public health concern and further queried. Co-

rapporteur continues to regard it as major concern following the company responses while the rapporteur considers this issue as solved.

Cardiovascular safety of the product has not been investigated prior to submission, but a QT study is ongoing and the results will be available later in the procedure.

In the analyses of the events of special interest, Hypoglycaemia, Blister, Eczema, Mucocutaneous rash and Myopathy were found to be uncommon but related adverse drug reactions. However, the occurrences of suicide and cancer have been queried and the issues remain open.

The number of patients over 65 included in the development programme is too low to characterise the safety in elderly. The applicant will have to provide a plan of further investigation of safety in this population.

Studies MS-SPI and MS-ON are ongoing and further FU data will be provided. Additional data will be generated from the French ATU and from the short term and long-term use of MD1003 in progressive MS patients from the phase3 Study SPI2, that is currently ongoing in the USA and in some EU countries. Details on the expectations in terms of timelines for data submission, overall exposure data, etc, should be provided.

Following the applicant's response to the initial list of questions co-Rapporteur maintains that the major public health concerns remain regarding this product while the rapporteur regards the remaining safety related issues not of major public health concern.

4.2. Risk management plan

Safety Specification

The applicant identified the following safety concerns in the RMP:

Table: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	- Interference with laboratory tests based on a biotin/streptavidin interaction - Allergic skin reactions - Hypoglycaemia - Myopathy
Important potential risks	- Use in pregnant women - Off-label use in patients with relapsing remitting MS
Missing information	- Use in patients with renal impairment - Use in breastfeeding women

The following changes should be made to the Summary of Safety Concerns:

- "Embryo-foetal toxicity" instead of "Use in pregnant women"
- "*Multiple sclerosis relapse*" instead of "Off-label use in patients with relapsing remitting MS"
- "Use in lactation" instead of "Use in breast-feeding women"

Pharmacovigilance Plan

Table: Ongoing and planned studies in the PhV development plan

Activity / Study title (type of activity, study title [if known] category 1-3)*	**Objectives**	**Safety concerns addressed**	**Status Planned, started,**	**Date for submission of interim or final reports (planned or actual)**
Category 3: Study MS-SPI: Effect of MD1003 in progressive multiple sclerosis: randomized double blind placebo controlled study 12 months & open label extension of at least 36 months	Completion of the additional extension phase: long term treatment with MD1003	Long term data for evaluation of frequency of adverse events identified as important risks (allergic skin reactions, hypoglycaemia, myopathy); the completion of the additional open label phase of this study will provide additional long term safety data	Ongoing	CSR completed in June 2016 (includes 12 months double blind phase and up to 12 months extension phase data) CSR completed in June 2017 (includes data up to 24 months of extension phase) Final CSR: Q3 2018
Category 3: Study MS-ON: Effect of MD1003 in chronic visual loss related to optic neuritis in multiple sclerosis: Randomized double blind placebo controlled study 6 months & open label extension for at least 36 months	Completion of the additional extension phase: long term treatment with MD1003	Long term data for evaluation of frequency of adverse events identified as important risks (allergic skin reactions, hypoglycaemia, myopathy); the completion of the additional open label phase of this study will provide additional long term safety data	Ongoing	CSR completed in June 2016 (includes 6 months double blind and 6 months extension phase data) CSR planned in Q3 2017 (includes data up to 18 months extension phase) Final CSR: Q4 2018

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
Category 3: Study SPI2 (ongoing): Effect of MD1003 in progressive multiple sclerosis: a randomized double blind placebo controlled study 15 months & open label extension up to 12 monthsSPI2	Short term and long term treatment with MD1003 in progressive MS patients	Increase the size of the safety population to evaluate the frequency of adverse events identified as important risks (allergic skin reactions, hypoglycaemia, myopathy); the completion of the double blind and open label phases of this study will provide additional placebo-controlled and long term safety data	Ongoing	Final CSR: Q3 2020

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

CHMP comments:

The studies proposed are not PASS. PAS studies are specifically designed to assess safety issues, being powered to provide relevant responses. These studies should be removed from the PhV plan or improved. A true PASS study should be planned with focused safety objectives linked to specific safety concerns, including interference with biotin-based laboratory assays and its relevance on the patient safety. Additionally, and also considering the potential risk of off-label, it would be important to also assess any new events (relapses) and their impact on QoL Therefore, the applicant should make an improved proposal with focused safety objectives linked to specific safety concerns, and demonstrate that the study/ies will be adequately powered to enable relevant analysis and conclusions.

Also, it is requested a protocol in which it is specified how effectiveness of aRMM will be determined.

Risk minimisation measures for QIZENDAY

Table: Summary table of additional Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Interference with laboratory tests based on a biotin/streptavidin interaction (Important identified risk)	Listed in the SmPC, Section 4.4.	Patient alert card Educational website
Allergic skin reactions (important identified risk)	Listed in the SmPC, Sections 4.3; 4.8.	None
Hypoglycaemia (important identified risk)	Listed in the SmPC, Sections 4.4; 4.5; 4.8	None
Myopathy (important identified risk)	Listed in the SmPC, Sections 4.5; 4.8.	None
Use in pregnant women (important potential risk)	Listed in the SmPC, Sections 4.4; 4.6; 5.3. Prescription only medicine	None
Off-label use in patients with relapsing remitting MS (important potential risk)	Listed in the SmPC, Section 4.4. Prescription only medicines Medical prescription restricted to physicians experienced in the management of multiple sclerosis	None
Use in patients with renal impairment (missing information)	Listed in the SmPC, Sections 4.2; 4.4; 5.2. Prescription only medicine	None
Use in breastfeeding women (missing information)	Listed in the SmPC, Section 4.6, 5.3. Prescription only medicine	None

CHMP comments:

The addition of QR codes or links to Company's website in the Patient Alert Card cannot be endorsed as they are not patient based risk minimisation measures. Moreover, if patients can have access to this information written for HCP and not lay persons, they may be prone to misinterpretation, feel stressed by the risks and ultimately suffer from iatrogenic.

The educational material (website) for healthcare professionals to address the risk(s) of biotin – streptavidin interference with laboratory tests needs to be improved so that it can be considered a relevant RMM. It is not sufficient to identify immunoassays which use the biotin-streptavidin coupling and recommend that these should be substituted by other type of tests on patients being treated with biotin. Specific available alternatives should be recommended to the practicing clinician, or, when there are no available alternatives, information on the length of time required for the patient to stop biotin treatment until the test is no longer influenced by the treatment should be provided.

Also, the applicant should clarify how the HCP will have access to this material since it is considered

that it should not be available through the Patient Alert Card.

Public summary of the RMP

The public summary of the RMP may require revision.

There is a mismatch between text in *Unknowns relating to treatment benefits: "Efficacy of QIZENDAY in patients with the relapsing remitting MS has not been demonstrated."* and the one in *Important potential risks*: "QIZENDAY is not efficacious in the treatment of patients with relapsing remitting multiple sclerosis."

Also, the Additional risk minimisation measures and Planned post authorisation development plan need to be updated following response to RfSI.

PRAC Outcome

During the plenary meeting held on 29 August – 01 September, the PRAC, having considered the above, agreed by consensus decision that:

Pharmacovigilance (PhV) Plan

- Routine PhV activities are sufficient to identify and characterise the risks of the product in the proposed indication;

The PRAC also noted the revised PRAC rapporteur's position on the initially proposed PASS study (linked to specific safety concerns, such as biotin – streptavidin interference with laboratory tests and the potential for off label use), no further required.

- The Applicant should remove from the RMP Part III (PV plan) the proposed category 3 studies MS-SPI, MS-ON and SPI2, as these are efficacy studies;
- Additional PhV activities are deemed necessary to measure the effectiveness of the proposed RMMs (Educational website and Patient alert Card). Therefore, the Applicant should develop a study focused on such evaluation, and submit the protocol for PRAC review and endorsement within the response to the D180 List of Outstanding Issues (LoI).

Risk Minimisation Measures (RMMs)

- The proposed RMMs are not sufficient to minimize the risks of the product in the proposed indication. Therefore the Applicant should:
    - Remove the QR codes or links to Company's website in the Patient Alert Card, because they cannot be endorsed as patient based RMMs; furthermore, if patients access information written for HCPs and not lay persons, they may be prone to misinterpretation, and feel stressed by the risks.
    - Improve the educational material (EM) for the Health Care Professional (HCPs) to address the risk of biotin – streptavidin interference with laboratory tests. The PRAC considered not

sufficient to identify immunoassays which use the biotin-streptavidin coupling and recommended substitution with other type of tests on patients being treated with biotin. Specific available alternatives should be recommended to the practicing clinicians, or, in the absence of any alternatives, information on the length of time required for the patient to stop biotin treatment, until the test is no longer influenced by the treatment, should be provided accordingly.

- Clarify how the HCPs will access this EM, which should not be available through the Patient Alert Card, as proposed by the Applicant.

The PRAC has also been informed about approx. 5483 (at the data lock point of 12 January 2017) patients receiving QIZENDAY in a Compassionate Use Cohort Programme in France. The Applicant should provide up to date information about this compassionate use programme within the response to the D180 List of Outstanding Issues (LoI).

4.3. Pharmacovigilance system

The statement should be signed by an individual who can act on behalf of the legal entity of the applicant/MAH and by the qualified person responsible for pharmacovigilance (QPPV). The title, role and responsibility of each individual signing the statement should be clearly specified in the document.

5. Orphan medicinal products

Orphan designation

N/A

Similarity

N/A

Derogation from market exclusivity

N/A

6. Benefit risk assessment

6.1. Therapeutic Context

6.1.1. Disease or condition

Claimed indication: QIZENDAY is indicated in adults for the treatment of progressive multiple sclerosis (primary or secondary).

The proposed indication is for first line treatment in the broad MS population with progressive MS, that with non-relapsing Secondary progressive and primary progressive MS, without restriction of disease severity or functional system.

Progressive MS is characterised by a continuous clinical deterioration and neurodegeneration without recovery that is independent of relapses. Approximately 50%% of MS patients present progressive MS (primary or secondary). The aim of the treatment is delay disease progression.Available therapies and unmet medical need

No treatment is currently licensed for the treatment of non-relapsing SPMS or PPMS. Treatment currently relies on physiotherapy, treatment for spasticity and other symptoms. There is therefore a clear unmet medical need.

6.1.2. Main clinical studies

The clinical development of MD1003 was initiated following encouraging results in a series of treatment in patients with progressive MS. A dosing regimen of 100 mg three times a day was chosen for the PK study in healthy volunteers and the two pivotal studies, one in a model of MS with spinal involvement (MS-SPI), the other in MS patients with Optic Neuritis (MS-ON).

Two superiority placebo-controlled studies were submitted:

- Study MS-SPI, a randomised, multi-centre, double-blind (12 months), randomised, parallel group study to evaluate the efficacy and safety of MD1003 100mg tid in progressive MS patients with spastic paraparesis due to spinal cord involvement (with 12 month open-label extension at time of primary analysis)
- Study MS-ON, a randomised, multicentre, double-blind (6 months), randomised, parallel group study to evaluate the efficacy and safety of MD1003 100mg tid in MS patients with chronic visual loss due to optic neuritis (with 6 month open-label extension data available at time of primary analysis) where only a few patients with PMS were included.

6.2. Favourable effects

Study MS-SPI was positive with regards to the primary endpoint (improvement of EDSS or TW25) with a treatment effect of 12.6 % (13/103 patients) in the active group and 0% (0 patient) in the placebo group (Fisher's exact test p=0.0051).

Improvement in EDSS the results favour of treatment with MD1003 as compared to placebo, although the magnitude of improvement is less than for the composite primary endpoint at 9.71% (with p=0.0311).

At Month 12 the *mean CGI-I* was 4.05 in the MD1003 and 4.62 in the placebo group, with a treatment difference of 0.57 (p<0.0001). The corresponding values for the SGI are 4.27 and 4.76, with a treatment difference of 0.49 (p=0.0094). However, change from baseline for this variable and proportion of patients "much-very much improved" should be given in the SmPC.

In study MS-ON, a positive trend was seen in patients with progressive chronic optic neuropathy but the study failed on the primary endpoint.

6.3. Uncertainties and limitations about favourable effects

Study MS-ON failed on the primary endpoint and it included patients with all types of MS. Study MS-SPI is therefore the only pivotal study and the efficacy results should be compelling from a clinical and statistical point of view as per points to consider on applications with one pivotal study (CPMP/EWP/2330/99).

The double-blind period of study MS-SPI only spanned 12 months which makes it difficult to draw absolute conclusions on the disease modifying claim, also taking into account that a decrease in whole brain volume. This study was only conducted in France and the same physician was in charge of treatment and assessment.

Following triggered inspection, the application was asked to confirm the definition of “progression” used for recruitment. It was confirmed that various investigators used progression in the past 2 years with no return to baseline or progression at any point in the 2 years which may have an impact on internal validity. In addition, 3 new deviations to the inclusion criteria were identified in the response which require further discussion and it was confirmed that the criteria used to exclude active disease were not really effective. Also a number of other points were raised regarding integrity of the MRI data and the fact that post-hoc analyses were unblinded.

The proportion of patients with 20% improvement in TW25, as used in the primary endpoint, was analysed post-hoc and only 5 patients showed such improvement, that is 4.85% of patients with 20% improvement. This questions the robustness of the primary endpoint and the clinical relevance of the results.

The treatment effect observed on the primary and secondary endpoints is small and its clinical relevance is debatable. The effect becomes even smaller when missing data are considered.

The effect relates mainly to the improvement on walking through the EDSS score and is not supported by a statistical improvement in other endpoints specifically relating to walking such as the MSWS12, even if the applicant points to a positive trend. This again does not comply with the MS guideline that clearly notes that an effect on EDSS alone is not sufficient.

Analyses of most secondary endpoints had to be repeated to account for missing data. Treatment effect was shown to be less than previously seen. Estimates of treatment effect after imputation, with 95% CI, are still needed before the results of secondary endpoints can be presented in the SmPC. The exact value for 20% improvement in TW25 with 95% CI should be provided and used in the SmPC.

The lack of consistency of results across the relevant endpoints and subgroups, along with the absence of control over confounding factors (e.g., imbalances at baseline and during the conduct of the study) remains an issue that seriously questions the internal validity of the study.

Concomitant treatment was not controlled and the applicant highlights that differences were seen in treatment effect depending on whether fampridine was taken or not, which is a concern when assessing the overall results. The use of fampridine with the proposed product should be discouragedIt is not clear whether the SF59SEP is validated to be used in additional languages and whether retroactive calculation of SF36 from that scale is valid. Also, the Applicant clarified that no patients with renal/hepatic impairment were included in the pivotal study MS-SPI.

The clinical relevance of treatment with QIZENDAY on MRI imaging still requires further discussion in the light of e.g., decrease in total brain volume.

The co-Rapporteur requested a copy of the final SAP.

Notwithstanding the Major Objection on efficacy which contains a number of issues with the submitted data it should be noted that the wording of the indication as proposed is not acceptable per se.

6.4. Unfavourable effects

The most frequently reported treatment emerging events were CNS related. The Applicant has provided an updated safety analysis showing rather consistent safety profile in qualitative terms, although, not unexpectedly, incidences of TEAEs and SAEs clearly increase with increased exposure. In the extension of Study MS-SPI up to Month 36, the overall TEAES was 70.7%, the most common SOC were infections and infestations (30.1%) and nervous system disorders (25.6%). The most common TEAEs was UTI 15.0%, followed by MS relapse 10.5% and MS 6.8%. The incidence of treatment

related AEs was 11.3%, the most common being MS relapse. Severe TEAEs were reported by 11.3% of patients, SAEs by 28.6% of patients, being MS relapse 9.9% and MS 4.4% the most common. A similar profile was observed in the MS-ON trial.

In the analyses of the events of special interest, Hypoglycaemia, Blister, Eczema, Mucocutaneous rash and Myopathy were found to be uncommon but related adverse drug reactions. The occurrences of suicide and cancer have been queried and remain insufficiently addressed.

The MS relapse rates appear to be higher in those exposed to the product than in the placebo arms of the studies. While this seems to affect only relapsing remitting patients, the MRI imaging suggests that the rate of occurrence of new lesions is increased in those who are treated with the product regardless of the MS type they suffer. This was seen as a major public health concern and further queried. The additional data provided indicate that the observed findings can be artefact of the defence between the active treatment and placebo populations The CHMP remains of opinion that the major public health concern remains given the limited number of patients and the lack of an exhaustive imaging evaluation across the studied population, together with baseline differences in the presence of inflammatory lesions between treatment arms, preclude drawing firm conclusions on the potential pro-inflammatory effect of biotin.

Cardiovascular safety of the product has not been investigated separately prior to submission but a thorough QT study is currently ongoing. In addition, there was a death of cardiac failure in the “case series” proof of concept study.

6.5. Uncertainties and limitations about unfavourable effects

The overall number of exposed patients was low, only 238 patients. Consequently, the reliable safety conclusions may be difficult to make. The concerns about the MS relapse rates and cardiac toxicity can also be regarded as major gaps in the knowledge about safety of the product until the further data has been provided.

The data from the early access programme while based on the use of the product by 5483 patients,are product of spontaneous reporting only. The adverse events reported in this population are much lower than the rate of AEs observed in the controlled studies. Due to this limitation, it is possible that a number of adverse events, including those of special interest may have been missed.

The number of patients over 65 included in the development programme is too low to characterise the safety in elderly.

6.6. Effects Table

Effects Table for QIZENDAY for the treatment in adults of progressive multiple sclerosis (secondary or primary)

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Improvement of EDSS or TW25	Primary endpoint: Proportion of patients with an improvement of EDSS or TW25 at M9 confirmed at M12	Proportion of patients (%)	12.6	0	P=0.0051 Composite endpoint	Study MS-SPI
CGI-I	Mean difference between groups over 12 months	Mean difference	4.05	4.62	P<0.0001 Type I error not controlled	Study MS-SPI
SGI-I	Mean difference between groups over 12 months	Mean difference	4.27	4.76	P=0.0094 Type I error not controlled	Study MS-SPI
Unfavourable Effects						
Relapse in MS	There is indication that those exposed to the product experience higher rates of MS relapse than those on placebo	Number of patients	Therapeutic doses of the proposed product	Placebo	The overall numbers of patients are low for reliable safety analysis.	
MRI confirmed new CNS lesions	There is indication that those exposed to the product experience higher rates of appearance of new CNS lesions than those on placebo	Number of patients	Therapeutic doses of the proposed product	Placebo	The overall numbers of patients are low for reliable safety analysis.	
QT Prolongation	There is indication that those exposed to the product experience QT prolongation more frequently than those on placebo	Number of patients with QT prolongation	Therapeutic doses of the proposed product	Placebo	The overall numbers of patients are low for reliable safety analysis.	

Abbreviations: CGI-I: Clinical Global Impression - Improvement; SGI: Subject Global Impression; M: Month; MS: Multiple Sclerosis

6.7. Benefit-risk assessment and discussion

6.7.1. Importance of favourable and unfavourable effects

There is a clear important medical need for a treatment with a positive benefit risk ratio for patients presenting with Progressive Multiple Sclerosis. However, a number of questions are still outstanding with regards to the pharmacokinetic profile of the proposed product.

Additionally the clinical relevance of the treatment effect with MD1003 is not confirmed considering the uncertainties about the exact population that was recruited and the absence of consistency between the two components of the primary endpoint which was not recommended following scientific advice provided to the applicant. Additionally, there is a lack of robust effect on additional endpoints not related to walking or on global health.

The single pivotal study doesn't provide compelling evidence of efficacy and a confirmation in a second study in the chosen population is needed. This should include sufficient data to clearly conclude on the maintenance effect as only 6 of the initial 13 responders maintained that response at Month 30.

The safety major objection relating to the effect of the proposed product on relapses is still raised as a major objection by the co-Rapporteur.

Also, safety questions have been raised in regards to the absence of appropriate evaluation of Qt impact.

6.7.2. Balance of benefits and risks

A major objection is maintained with regards to the qualification of the pharmacokinetic profile for the proposed product, especially with regards to multiple dose administration in patients.

The treatment effect seen in the only positive pivotal study is not considered robust enough and a number of issues relating to e.g., the characteristics of the population recruited, the consistency between endpoints or maintenance of effect are a major concern.

Also, the impact of treatment with MD1003 on MRI variables in PMS and on the occurrence of relapses in patients with RRMS should be thoroughly discussed in order to better evaluate the benefit risk for the treatment of patients with PMS.

Finally, it is considered the broad indication sought is not supported by the data submitted.

In conclusion the benefit-risk is currently negative and this application is not approvable.

6.7.3. Additional considerations on the benefit-risk balance

Conditional approval is not an option as current benefit risk is negative.

6.8. Conclusions

The overall benefit risk for QIZENDAY in the treatment of adults with progressive MS is negative.