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ORIGINAL RESEARCH ARTICLE

The Potential Cost-Effectiveness of a Cell-Based Bioelectronic Implantable Device Delivering Interferon-β1a Therapy Versus Injectable Interferon-β1a Treatment in Relapsing–Remitting Multiple Sclerosis

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Abstract

Background Current first-line disease-modifying therapies (DMT) for multiple sclerosis (MS) patients are injectable or oral treatments. The Optogenerapy consortium is developing a novel bioelectronic cell-based implant for controlled release of beta-interferon (IFNβ1a) protein into the body. The current study estimated the potential cost effectiveness of the Optogenerapy implant (hereafter: Optoferon) compared with injectable IFNβ1a (Avonex).

Methods A Markov model simulating the costs and effects of Optoferon compared with injectable 30 mg IFNβ1a over a 9-year time horizon from a Dutch societal perspective. Costs were reported in 2019 Euros and discounted at a 4% annual rate; health effects were discounted at a 1.5% annual rate. The cohort consisted of 35-year-old, relapsing–remitting MS patients with mild disability. The device is implanted in a daycare setting, and is replaced every 3 years. In the base-case analysis, we assumed equal input parameters for Optoferon and Avonex regarding disability progression, health effects, adverse event probabilities, and acquisition costs. We assumed reduced annual relapse rates and withdrawal rates for Optoferon compared with Avonex. Sensitivity, scenario, value of information, and headroom analysis were performed.

Results Optoferon was the dominant strategy with cost reductions (− €26,966) and health gains (0.45 quality-adjusted life-years gained). A main driver of cost differences are the acquisition costs of Optoferon being 2.5 times less than the costs of Avonex. The incremental cost-effectiveness ratio was most sensitive to variations in the annual acquisition costs of Avonex, the annual withdrawal rate of Avonex and Optoferon, and the disability progression of Avonex.

Conclusion Innovative technology such as the Optoferon implant may be a cost-effective therapy for patients with MS. The novel implantable mode of therapeutic protein administration has the potential to become a new mode of treatment administration for MS patients and in other disease areas. However, trials are needed to establish safety and effectiveness.

Key Points for Decision Makers

Innovative technology, such as an implantable device for controlled release of treatment into the body, may potentially lead to cost reductions and health gains in the field of multiple sclerosis.

Cell therapy delivery vehicles have the potential to become a new mode of treatment administration for multiple sclerosis patients and in other disease areas.

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1 Introduction

Multiple sclerosis (MS) is a chronic degenerative disease of the central nervous system. The disease has a prevalence in Europe of 60–120 per 100,000, and 120–150 per 100,000 in North America [1]. Roughly 70% of the persons diagnosed are women, and the age of diagnosis ranges between 20 and 40 years. The most prevalent type of MS is relapsing–remitting MS (RRMS), where patients have periods of neurological dysfunction, known as relapses, alternated with periods of remission [2]. Examples of MS-related problems include vision loss, limb weakness, or erectile dysfunctions. Patients with MS have a high disease burden [3] and lower quality of life (QOL) compared with the general population and patients with other chronic

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diseases [4, 5]. The lower QOL may be due to the unpredictable disease course and the limited curative effects of the disease-modifying therapies (DMTs) available [6].

Currently available DMTs can reduce relapse rate and disease progression, but are also associated with adverse events, thereby resulting in problems with non-adherence. For example, adverse events associated with the first-line DMT interferon-beta (IFN-β) are injection-site reactions, flu-like symptoms, and lipoatrophy [7, 8]. Patients experiencing adverse events can become non-adherent to injectable treatment, discontinue therapy, or switch to other first- or second-line DMTs [9]. Although patients are well aware of the importance of treatment, non-adherence to treatment is a well-known problem acknowledged by both MS patients and health care providers [10], and may have unfavorable clinical and economic consequences. Clinically, non-adherence reduces treatment efficacy thereby increasing risk of relapses [11]. Moreover, from an economic viewpoint, MS patients non-adherent to IFN-β treatment tend to have more hospital admissions, emergency room visits, and outpatient clinic visits than adherent patients [11].

A solution to improve non-adherence and thereby the health outcomes of MS patients can be found in cell therapy delivery vehicles. Cell therapy delivery vehicles are implantable devices that mediate the action of therapeutic cells by integrating confined genetically programmed cells to control the secretion of a therapeutic protein in the body [12]. The Optogenerapy consortium, a European Horizon 2020 project, is developing a cell therapy delivery vehicle for MS patients classified as a combined advanced therapy medicinal product (ATMP). The device integrates optogenetic programmed cells (cells that are genetically modified to release IFN-β 1a in response to near-infrared light) for controlled release of IFN-β 1a protein into the body via a semi-permeable membrane [12, 13]. The optogenetics interface controls the cellular behavior of the cells and is powered wirelessly [12].

The consortium aims to improve QOL of patients, improve treatment efficacy, and tackle non-adherence by developing this new mode of administration. The objective of this study was to estimate the potential cost effectiveness of the Optogenerapy implant (hereafter: Optoferon) compared with injectable IFN-β 1a treatment in early RRMS patients in the Netherlands.

2 Methods

The Markov model estimated the potential cost effectiveness of Optoferon compared with injectable IFN-β 1a treatment Avonex (Biogen, Cambridge, MA, USA) in terms of quality-adjusted life-years (QALYs) and costs included from the societal perspective. The main result was the incremental costs per QALY gained with Optoferon compared with Avonex in the Dutch healthcare setting.

2.1 Patients

Patient characteristics at baseline were a hypothetical cohort of 1000 Dutch RRMS patients. The baseline characteristics (mean starting age of the cohort was set at 35 years old, a 3:1 female to male ratio, and the distribution of disability status based on the patient's current first-line DMT status) reflect the data collected through an online HRQOL survey in the Netherlands [14]. The disability status was measured using the Expanded Disability Status Scale (EDSS, a measure that quantifies disability on a scale from 0 [no disability] to 10 [death] [15]), and the distribution was as follows: EDSS 0 (14%), EDSS 1 (29%), EDSS 2 (29%), EDSS 3 (0%), EDSS 4 (0%), EDSS 5 (14%), EDSS 6 (14%), EDSS 7–9 (0%). We assumed persons to be treatment naïve (i.e., no previous experience with a DMT).

2.2 Intervention and Comparator

The Optoferon therapy consists of a bioelectronic cell-based implant that allows for controlled release of IFN-β 1a into the body [16]. The Optoferon therapy involves IFN-β 1a, secreted by optogenetically programmed mammalian cells. Because it is produced by mammalian cells, the active principle is most similar to the molecular composition of the IFN-β 1a of Avonex. The comparator, therefore, was intramuscular injectable Avonex (dosage 30 µg 1 × per week). Given that no clinical trial has yet taken place to determine the efficacy and side effect profile of Optoferon, results found in the pivotal trials of Avonex were used to populate the model and adapted where deemed necessary.

The differences in the treatment pathways of Optoferon and Avonex are visualized in Fig. 1. The treatment pathway for Avonex follows the Dutch treatment guidelines for first-line therapy in the Netherlands [17]. The treatment pathway for Optoferon was based on a group discussion with two MS specialists who are members of the Optogenerapy consortium and three independent clinical experts on MS. The device, roughly 6 cm × 2 cm × 0.5 cm, will be placed by a general surgeon underneath the skin in the lower back. A specific insertion toolkit has been developed that allows for a minimally invasive procedure, such that implantation can be performed in a daycare setting without the need for hospital admission. It is assumed that the bioelectronic implanted device would operate in the body for up to 3 years, thereafter the device will have to be replaced in year 4 and year 7. Replacement of the device would follow the same procedure as implantation.

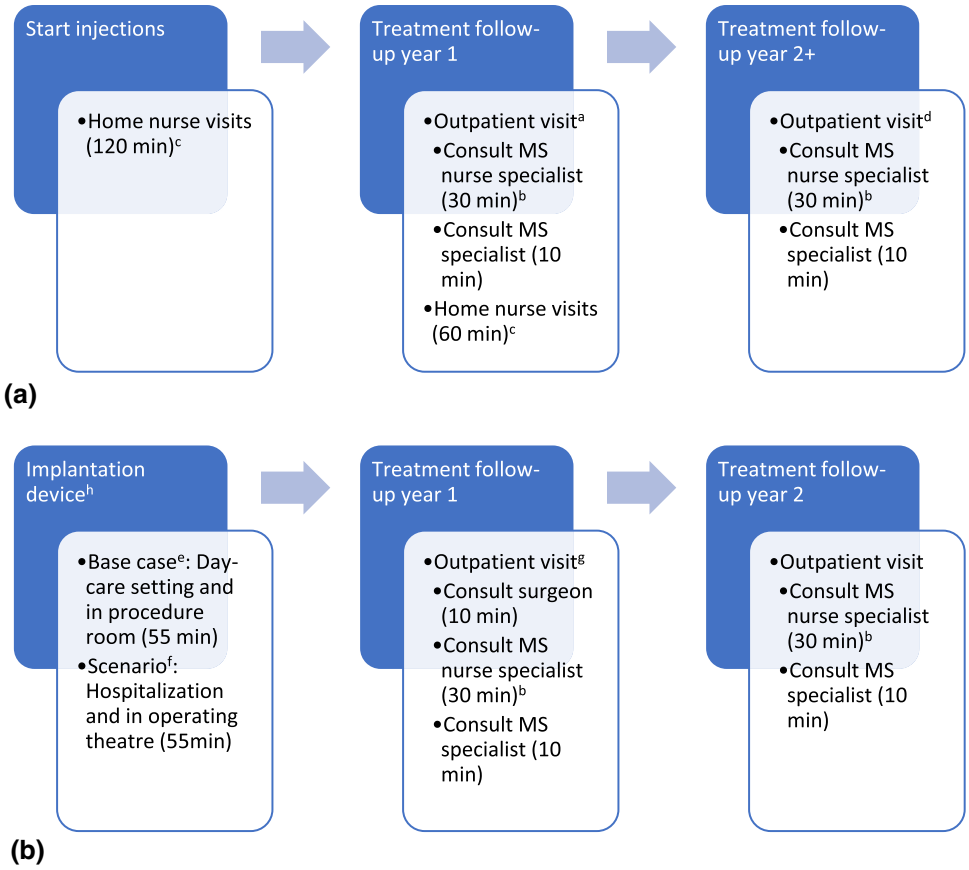

Fig. 1 Treatment pathway for injectable IFN-β 1a (**a**) and Optoferon (**b**). *IFN-β 1a* beta interferon, *min* minutes, *MS* multiple sclerosis. [a]This visit is planned 3 months after the start of injectable IFN-β 1a. [b]Blood pressure measurement and laboratory tests done, including thrombocytes, leukocytes, creatinine, alanine aminotransferase, lactate dehydrogenase, gamma-glutamyl transpeptidase, thyroid stimulating hormone. [c]The home nurse comes to explain how to inject and answer any queries regarding the treatment course. [d]For follow-up beyond, and including year 2, the consult at the outpatient clinic is once per year. [e]In the base-case analysis, the implantation is done in a procedure room in a day-care setting, the costs include procedure-related costs (surgeon, nurse, medication, materials), room-related costs (materials and cleaning) and overhead costs. [f]In the scenario analysis, the implantation is done in an operating theatre and the patient is hospitalized for one night; the costs include procedure-related costs (surgeon, nurse, medication, materials), room-related costs (materials and cleaning) and overhead costs. [g]Post-operative monitoring includes a consult with the surgeon 7 days post-implantation. The consult with the MS nurse specialist and MS specialist occurs 3 months post-implantation. [h]Implantation is performed in years 1, 4 and 7; therefore, if a patient remains on treatment, costs for removal and re-implantation occur in year 4 and 7

2.3 Model Overview and Inputs

A Markov model was developed in Microsoft Excel and adapted from a model previously developed (Fig. 2) [18–20]. The adaptation involved the assumption that persons transition to best supportive care (BSC) rather than to secondary progressive MS (SPMS). The cost effectiveness of Optoferon was modelled with a 1-year cycle and estimated disease progression through 11 health states. RRMS patients progressed within EDSS 0–9; once they withdraw from treatment, patients transition to BSC and continue progression within EDSS 0–9 and death. In each cycle, patients could remain in the same disease state, progress to a higher or lower disease state (disability could worsen or improve), could have a relapse, or withdraw from treatment and continue with BSC. The model did not take into account progression to SPMS or switching to a second-line DMT. Patients that withdraw from treatment could remain in the same disease state, progress to a higher or lower disease state, or have a relapse. Furthermore, it was assumed that patients that reach EDSS 7 or higher stop treatment and switch to BSC.

In accordance with the Dutch economic guidelines, a societal perspective was taken [21]. However, we chose to deviate from a lifetime horizon, as suggested by the Dutch guidelines, and model a time horizon of 9 years. The consortium assumes the device can be implanted in the body for a maximum of 3 years and then needs replacement. Additionally, the consortium did not find it feasible to implant

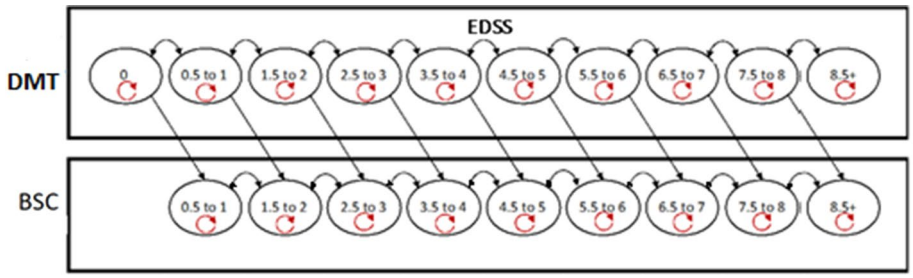

Fig. 2 The Markov model. The model has been adapted from the Institute for Clinical and Economic Review report (ICER report) [18]. BSC best supportive care, DMT disease-modifying therapy (patients receive either Optoferon or Avonex), EDSS expanded disability status scale, Black arrow transition from EDSS state, red arrow relapse

the device more than three times per person because of the potential risk of scar tissue formation with reimplantation, potentially reducing the efficacy of the implant. A half-cycle correction was performed.

The consolidated health economic evaluation reporting standard (CHEERS) checklist was used [22] and the Assessment of the Validation Status of Health-Economic (AdViSHE) tool was used to guide model validation [23]. Model validity is warranted because we use a model that is commonly used to assess cost effectiveness of MS treatments [18–20], the input parameters have been assessed at consortium meetings, and cross validation testing will be performed to compare the outcomes to models that address similar problems.

2.3.1 Costs

The costs included in the analysis were based on the expected Dutch treatment pathway of Optoferon and current treatment pathway of Avonex [17] (Fig. 1). Types of costs were based on the Dutch pharmacoeconomic guidelines [21] (Table 1). As such, multiple cost categories were identified: direct health care costs, direct non-health care costs and indirect non-health care costs. Although the Dutch guidelines advise to include indirect medical costs (i.e., all medical costs incurred due to life-years gained) [21], these were excluded in the analysis since Optoferon was not expected to lead to a substantial life expectancy gain versus Avonex. Costs were reported in 2019 Euros (costs were corrected using the consumer price index when necessary) and were discounted at a 4% annual rate [21].

The acquisition costs for Optoferon were set equal to the acquisition costs for Avonex. The Optoferon device was developed using high volume manufacturing techniques that allow for mass fabrication and readily available Optoferon devices to enter the market at a competitive cost (i.e. the production line is already intact, therefore no investments are needed) [13, 24]. Therefore, we do not believe the costs will be higher than the costs for Avonex. The acquisition cost for Avonex was calculated by multiplying the unit costs and treatment regimen. The unit costs for Avonex in the Netherlands were sourced from www.medicijnkosten.nl (accessed on 7 Jan 2020). Administration costs, monitoring costs, adverse events costs, and indirect health care costs (productivity loss due to treatment administration) were based on the Dutch Costing Manual (2015), consultation with clinical experts, www.farmacotherapeutischkompas.nl (accessed on 5 Nov 2019), and www.shl-groep.nl (accessed on 14 Nov 2019). Implantation costs were derived from Kanters et al. [25] since the procedure is somewhat similar, though in a different location. Disease costs per disability state in the model were mainly obtained from the Dutch burden and cost study by Uitdehaag et al. [26]. To approximate the annual cost caused by relapses, the cost was calculated as the difference in costs between patients with and without a relapse over a 3-month period and converted to yearly costs [26].

2.3.2 Utilities

The baseline health utilities for patients with RRMS were obtained from Uitdehaag et al. [26]. A single disutility value due to relapse, and independent from EDSS state, was set at − 0.071 [27]. Equal disutility values were used for common adverse events from Optoferon and Avonex. Two additional adverse events specific to Optoferon were included: superficial post-operative wound infection (defined as a surgical-site infection [SSI] not requiring surgery treated with oral antibiotics) and deep wound infection (SSI requiring removal of the device and oral antibiotics). Two adverse events specific to injectable DMT were included: injection-site reactions and accidental injury caused by injection. The QOL of informal carers for patients with MS was included as disutility [28]. Healthcare effects were discounted at a 1.5% annual rate [21].

Table 1 Model inputs at baseline

Model inputs	Optoferon	Avonex	Standard error	Distribution	Lower bound	Upper bound	References
Costs							
Treatment costs							
Acquisition costs[a]	€12,028	€12,028	€3608	Gamma[g]	6029	20,063	[13, 58]
Administration costs[b]	P: €185 H: €1026	€156	O_P: €56 O_H: €308 A: €47	Gamma	O_P: 93 O_H: 514 A: 78	O_P: 310 O_H: 1711 A: 260	[25, 39][c]
Removal device	P: €277 H: €1210	NA	P: €83 H: €363	Gamma	P: 139 H: 606	P: 463 H: 2018	[25, 39][c]
Monitoring costs[d]							
Year 1	€82	€218	O: €25 A: €65	Gamma	O: 41 A: 110	O: 137 A: 363	[39, 59][c]
Year 2	€62	€140	O: €19 A: €42	Gamma	O: 31 A: 70	O: 103 A: 233	[39, 59][c]
Year 3	€62	€62	O: €19 A: €42	Gamma	O: 31 A: 70	O: 103 A: 233	[39, 59][c]
Indirect costs[e]							
Year 1	€115	€58	O: €35 A: €18	Gamma	O: 58 A: 29	O: 192 A: 96	[39]
Year 2	€12	€23	O: €3 A: €7	Gamma	O: 6 A: 12	O: 19 A: 38	[39]
Year 3	€12	€12	O: €3 A: €3	Gamma	O: 6 A: 6	O: 19 A: 19	[39]
Natural history costs							
Direct medical cost							
EDSS 0–3	€4140	Equal	€1242	Gamma	2075	6907	[26]
EDSS 4–6	€8127	Equal	€2438	Gamma	4074	13,557	[26]
EDSS 7–9	€10,264	Equal	€3079	Gamma	5145	17,121	[26]
Other direct costs							
EDSS 0–3	€705	Equal	€211	Gamma	353	1176	[26]
EDSS 4–6	€2055	Equal	€617	Gamma	1030	3429	[26]
EDSS 7–9	€2080	Equal	€624	Gamma	1043	3470	[26]
Indirect medical costs							
EDSS 0–3	€161	Equal	€48	Gamma	81	269	[26]
EDSS 4–6	€33	Equal	€10	Gamma	16	55	[26]
EDSS 7–9	€21	Equal	€6	Gamma	11	35	[26]
Informal care costs							
EDSS 0–3	€803	Equal	€241	Gamma	403	1340	[26]
EDSS 4–6	€3461	Equal	€1038	Gamma	1735	5773	[26]
EDSS 7–9	€6201	Equal	€1860	Gamma	3108	10,344	[26]
Relapse costs	€12,622	Equal	€3787	Gamma	6327	21,056	[26]
Utilities							
Baseline health utility							
EDSS 0	0.93	Equal	0.28	Beta	0.22	1	[26]
EDSS 1	0.86	Equal	0.26	Beta	0.25	1	[26]
EDSS 2	0.78	Equal	0.24	Beta	0.27	1	[26]
EDSS 3	0.67	Equal	0.21	Beta	0.27	0.96	[26]
EDSS 4	0.70	Equal	0.20	Beta	0.27	0.97	[26]
EDSS 5	0.69	Equal	0.20	Beta	0.27	0.97	[26]
EDSS 6	0.65	Equal	0.20	Beta	0.27	0.94	[26]
EDSS 7	0.53	Equal	0.16	Beta	0.23	0.81	[26]
EDSS 8	0.36	Equal	0.11	Beta	0.17	0.58	[26]
EDSS 9	0.04	Equal	0.01	Beta	0.02	0.07	[26]
Disutility							
Relapse	− 0.07	Equal	0.02	Beta	0.04	0.12	[27]
SSI, superficial	− 0.03	NA	0.01	Beta	0.01	0.05	[60]
SSI deep	− 0.16	NA	0.05	Beta	0.08	0.26	[60]
Flu-like symptoms	− 0.20	Equal	0.06	Beta	0.10	0.33	[61]

Table 1 (continued)

Model inputs	Optoferon	Avonex	Standard error	Distribution	Lower bound	Upper bound	References
Headache	− 0.03	Equal	0.01	Beta	0.01	0.05	[62]
Myalgia/muscle pain	− 0.03	Equal	0.01	Beta	0.01	0.05	
Depression	− 0.45	Equal	0.14	Beta	0.21	0.71	[61]
Fatigue	− 0.06	Equal	0.02	Beta	0.03	0.10	[63]
Fever	− 0.05	Equal	0.01	Beta	0.02	0.08	
Injection-site reaction	NA	− 0.01	0.003	Beta	0.01	0.02	[64]
Accidental injury injecting	NA	− 0.03	0.01	Beta	0.01	0.05	[62]
Carer disutility							
EDSS 0–3	− 0.002	Equal	0.001	Beta	0.001	0.003	[28]
EDSS 4	− 0.05	Equal	0.01	Beta	0.02	0.08	[28]
EDSS 5	− 0.14	Equal	0.04	Beta	0.07	0.23	[28]
EDSS 6	− 0.16	Equal	0.05	Beta	0.08	0.26	[28]
EDSS 7	− 0.17	Equal	0.05	Beta	0.08	0.28	[28]
EDSS 8	− 0.03	Equal	0.01	Beta	0.01	0.05	[28]
EDSS 9	− 0.10	Equal	0.03	Beta	0.05	0.16	[28]
Transition probabilities							
Efficacy							
Disability progression (HR)	0.79	Equal	0.12	Lognormal	0.63	1	[18]
Annual relapse rate	0.66	0.83	O: 0.13 A: 0.06	Lognormal	O: 0.57 A: 0.74	O: 0.74 A: 0.94	[18, 29, 65]
Relapse rate leading to hospitalization	0.79	Equal	0.23	Lognormal			[66]
Withdrawal treatment							
Annual withdrawal rate	2.7%	5.3%	NA	Beta	O: 0.02 A: 0.04	O: 0.04 A: 0.07	[18, 30, 31]
Adverse events (probability)							
SSI, superficial	0.22%	NA	NA	Beta	0.05%	0.54%	[67]
SSI, deep	0.22%	NA	NA	Beta	0.05%	0.54%	[67]
Flu-like symptoms[f]	50%	55%	NA	Beta	O: 48% A: 54%	O: 51% A: 57%	[32, 33, 68]
Headache	24%	Equal	NA	Beta	23%	26%	[68]
Myalgia/muscle pain	14%	Equal	NA	Beta	13%	16%	[68]
Depression	14%	Equal	NA	Beta	13%	15%	[68]
Fatigue	11%	Equal	NA	Beta	10%	12%	[68]
Fever	7%	Equal	NA	Beta	6%	8%	[68]
Injection-site reaction	NA	12%	NA	Beta	11%	13%	[68]
Accidental injury injecting	NA	7%	NA	Beta	7%	8%	[68]

A Avonex, *Equal* equal costs for Optoferon and Avonex, *H* hospital stay, *HR* hazard ratio, *NA* not applicable, *O* Optoferon, *P* procedure room, *SE* standard error, *SSI* surgical-site infections

[a]The acquisition costs for Optoferon are incurred when the device is implanted (i.e., year 1, year 4, year 7, etc.). The acquisition costs for Avonex are annual

[b]The administration costs for Optoferon are incurred when the device is implanted (i.e., year 1, year 4, year 7, etc.). The administration costs for Avonex are incurred only in year 1

[c]Clinical experts

[d]The monitoring costs for Optoferon are cyclical, costs year 1 = year 4, year 2 = year 5, year 3 = year 6, etc. The monitoring costs for Avonex are constant after year 3

[e]The indirect costs for Optoferon are cyclical, costs year 1 = year 4, year 2 = year 5, year 3 = year 6, etc.

[f]Differences in probabilities are due to the assumption that the lower dosage of Optoferon will lead to less flu-like symptoms[32, 33]

[g]This distribution is only applicable to Avonex

2.3.3 Transition Probabilities

Equal disability progression and relapse rate leading to hospitalization values were used for Optoferon and Avonex.

Non-adherence of injectable DMTs reduces the effect they have on the risk of relapse rate [11, 29]. We calculated a 21% reduced risk of relapse for persons with Optoferon because we assume 100% adherence to Optoferon (since

the device will continuously release the drug into the body, thereby avoiding the need for self-administration) and < 80% adherence to Avonex because a systematic review found adherence rates of 63–75% for persons with RRMS taking first-line injectable DMT [9]. Furthermore, the retrospective claims database study by Tan et al. (2011) demonstrated a 21% lower risk of relapse for persons >80% adherent to first-line injectable [29]. As such, the annualized relapse rate (ARR) of Optoferon is derived and dependent on the ARR of Avonex presented in the Institute for Clinical and Economic Review Report (ICER Report), and we assumed an ARR of 0.66 versus 0.83, respectively [18].

Since the withdrawal rate of Optoferon is unknown, we assumed that the discontinuation rates would be comparable to rates found among diabetes patients treated with an insulin pump. This is because the treatment mechanism of the insulin pump is similar to that of Optoferon and because the reasons for discontinuation are mostly driven by adverse events. We assumed that patients receiving Optoferon are 50% less likely to withdraw from treatment compared with those taking Avonex (2.65% vs 5.3%, respectively) based on reported discontinuation rates of Avonex and the discontinuation rates amongst diabetes patients treated with an insulin pump (1% for adults up to 4% among adolescents) [18, 30, 31].

The natural history disease progression transition probabilities for RRMS (with and without treatment) were based on the ICER Report on DMT effectiveness (Appendix 1, see electronic supplementary material [ESM]) [18]. The transition probabilities combined data from the longitudinal London Ontario cohort data and two clinical trials (the DEFINE and CONFIRM trial) [18].

The probability of adverse events was the same for Optoferon and Avonex, with the exception of flu-like symptoms. We assumed that the continued and more frequent release of IFN-β 1a into the body by the Optoferon device compared with weekly injection of Avonex led to a reduced probability of flu-like symptoms [32, 33].

2.4 Base Case, Sensitivity, and Scenario Analyses

2.4.1 Base Case

Patients received the implant at the start of year 1 followed by replacement every 3 years thereafter (i.e., year 4, year 7). The costs of Optoferon were incurred at implantation. The model assumed that the acquisition costs of Avonex remained constant in consecutive years. The Dutch Healthcare Institute considers three willingness-to-pay (WTP) thresholds: €20,000/QALY (for treatments with a low disease severity), €50,000/QALY (medium disease severity), and €80,000/QALY (high disease severity) [34]. Although the disease severity of RRMS can be considered high and the institute for Medical Technology Assessment (iMTA) Disease Burden Calculator (iDBC) calculated a threshold of €80,000/QALY [35], we chose a more conservative approach and €50,000/QALY was considered the WTP threshold [36].

2.4.2 Sensitivity, Scenario, and Value of Information Analysis

To account for uncertainty in the model, we conducted deterministic sensitivity analyses (DSA) and probabilistic sensitivity analyses (PSA). An overview of all parameters used for the DSA and PSA is shown in Table 1. For the DSA, we changed relevant input parameters to values representing upper and lower bounds (at the 95% confidence interval values) of a pre-specified distribution. When no estimates about confidence intervals or standard error (SE) were available, the range of values were set at 30% of the base case value. In the PSA, 1000 Monte Carlo simulations were used to take into account parameter uncertainty by simultaneously varying model inputs given the annual acquisition cost of Optoferon (i.e., this parameter was not varied). The following distributions were used: gamma distribution for costs, beta distribution for probabilities and utilities, and a lognormal distribution for rates. Furthermore, we used the headroom method to assess the maximum additional costs of Optoferon over Avonex for Optoferon to still be deemed cost effective using the WTP threshold of €50,000/QALY [37]. We estimated the headroom per patient and per device unit [38].

Scenario analyses were performed to explore the effects of (1) a higher acquisition cost of Optoferon (€20,000 and €50,000); (2) implanting Optoferon in an operation theater (thus requiring a one-night hospitalization) rather than in a procedure room; (3) yearly replacement of Optoferon, (4) no difference in withdrawal rate between Optoferon and Avonex, and (5) no difference in ARR between Optoferon and Avonex.

Value of information analysis was performed to examine whether it is worthwhile to invest more money to reduce decision uncertainty. We did so by estimating the expected value of perfect information (EVPI), which is the maximum amount a decision maker should be willing to pay to eliminate decision uncertainty [39]. Given the results of the PSA, the EVPI can be calculated as the average of the maximum net benefits across all PSA outcomes minus the maximum average net benefit for the different health technologies. Depending on the result of the EVPI (if the costs of the EVPI are higher than future costs of research), we may consider further analyses such as the expected value of partial perfect information (EVPPI) to examine the contribution of individual parameters to the overall decision uncertainty [39].

3 Results

3.1 Base Case

An overview of the base case results is given in Table 2. Optoferon dominated because it led to cost reductions (− €26,966) and health gain (0.45 QALYs gained). The main driver behind the cost reduction was the acquisition cost, with acquisition cost for Optoferon being 2.5 times less compared with the cost for Avonex (an incremental cost difference of − €47,333). Furthermore, Optoferon led to fewer adverse events costs and monitoring costs. However, its administration costs, indirect treatment costs, and total disease costs were higher compared with Avonex (incremental cost differences of €752, €217, and €15,355, respectively). The higher total disease costs for Optoferon are due to the slight increase in life years. The cumulative total cost per patient over time is presented in Fig. 3a.

The lower withdrawal rate from Optoferon to BSC, compared with Avonex, led to more patients remaining in a higher EDSS state resulting in an incremental QALY gain of 0.45 for patients receiving Optoferon. Patients receiving Optoferon experienced slightly more adverse event disutility, and there were no differences in carer disutility and relapse disutility. The cumulative QALYs gained per patient is visualized in Fig. 3b. Over the 9-year period, there was an incremental life-year gain of 0.63 for patients receiving Optoferon.

Table 2 Results from the base-case analysis

	Optoferon	Avonex	Incremental optoferon vs avonex
Total cost per patient	€153,621	€180,587	− €26,966
Treatment costs			
Total AE costs per year	€310	€330	− €19
Removal device costs	€483	€0	€483
Acquisition	€30,395	€77,729	− €47333
Administration	€901	€149	€752
Monitoring	€498	€616	− €118
Indirect	€345	€128	€217
Total	€32,932	€78,951	− €46,019
Discounted costs	€29,639	€69,157	− €39,517
Disease cost			
Direct medical	€36,828	€32,919	€3909
Indirect medical	€947	€845	€102
Other direct	€7427	€6643	€784
Informal care	€10,391	€9300	€1091
No hospital relapse	€39,566	€35,269	€4297
Hospital relapse	€47,614	€42,443	€5171
Total	€142,773	€127,418	€15,355
Discounted	€123,982	€111,431	€12,551
QALYs per patient			
EDSS utility	5.58	4.99	0.59
AE disutility	− 1.22	− 1.14	− 0.09
Carer disutility	− 0.03	− 0.03	0.00
Relapse disutility	− 0.02	− 0.02	0.00
Total QALYs	4.30	3.80	0.50
Total QALYs discounted	3.82	3.37	0.45
Life years per patients			
Total LY	7.24	6.46	0.77
Total LY discounted	6.29	5.66	0.63
Incremental cost per QALY gained			− €60,255
Incremental cost per LY gained			− €42,612

AE adverse events, *EDSS* expanded disability status scale, *LY* life years, *QALYs* quality-adjusted life-years

3.2 Sensitivity Analysis

The ten parameters that had the greatest impact on the ICER per QALY and life-year (LY) are shown in Fig. 4a and b. We found a range of possible ICERs based on the three main parameters identified with the deterministic sensitivity analysis. The ICER/QALY was most sensitive to variations in the annual acquisition costs of Avonex (range − €161,824 to €15,550), annual withdrawal rate of Avonex (range − €161,064 to − €24,651), and annual withdrawal rate of Optoferon (range − €129,561 to − €34,434). The ICER/LY was most sensitive to variations in the disability progression of Avonex (range − €389,345 to €378,399), annual acquisition cost of Avonex (range − €114,443 to €11,011), and annual withdrawal rate of Avonex (range − €118,854 to − €17,156). Furthermore, EDSS 1–4 utility affects the ICER/QALY, whereas the ICER/LY was affected by hospital relapse costs and direct medical costs.

Optoferon remains dominant in all but one scenario—the lower bound of the 95% confidence interval (CI) of the hazard ratio on disability progression of Avonex (improved effect of Avonex compared with Optoferon). This leads to higher negative incremental costs (total costs per patient for Avonex increases) and negative incremental QALYs (more QALY gain compared with Optoferon), which leads to a positive ICER of €39,470. Both annual acquisition costs and withdrawal rates for Avonex and Optoferon affect the ICER per QALY and per LY. Furthermore, the lower bound of the 95% CI of the hazard ratio on disability progression of Optoferon (improved effect of Optoferon compared with Avonex) leads to less negative incremental costs (total costs for Optoferon increase compared with Avonex), which leads to an increase in LY gain, resulting in a less negative ICER/LY (− €7766).

Figure 5 shows the cost-effectiveness plane visualizing the uncertainty around the cost-effectiveness outcomes. Most of the estimates lie within the southeast quadrant (health gains and lower costs) or northeast quadrant (health gains and higher costs). Figure 6 shows the cost-effectiveness acceptability curve for Optoferon and Avonex. If a WTP threshold of €50,000/QALY is used, there is a probability of cost effectiveness for Optoferon of 99.6%.

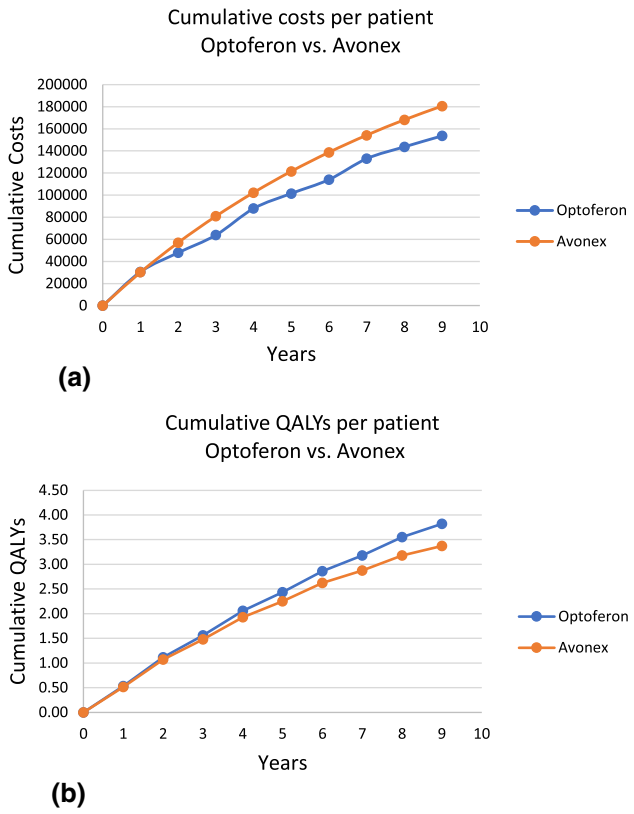

Fig. 3 The cumulative costs (**a**) and quality-adjusted life-years (QALY) (**b**) per patient of Optoferon vs Avonex. *QALYs* quality adjusted life years

3.3 Headroom

Table 3 shows the maximum additional costs of Optoferon over Avonex for Optoferon that are possible to ensure that Optoferon can be still deemed cost effective based on a WTP threshold of €50,000/QALY. Taking into account cost savings and assuming the potential cost savings will be fully recouped by the manufacturer in the sales product price, the headroom per patient was (€50,000 * 0.45) + €26,966 = €49,343. As expected, the headroom decreases as acquisition costs increase; if the acquisition costs were €50,000, Optoferon is no longer cost saving versus Avonex.

3.4 Scenario and Value of Information Analysis

The scenario analyses showed that Optoferon remains the dominant strategy in four scenarios (Optoferon acquisition costs of €20,000; hospitalizing the patient for the implantation and removal the device; setting withdrawal rates of treatment equal; and setting ARR of treatment equal) (Table 4). Optoferon was no longer a cost-effective strategy when increasing the acquisition costs to €50,000 (with higher costs and QALYs gained). Optoferon remained a cost-effective strategy if the implant would be implanted and replaced yearly. The estimated EVPI per person is equal to €13.60. Given that the EVPI is less than costs of future research, we refrained from estimating the EVPPI.

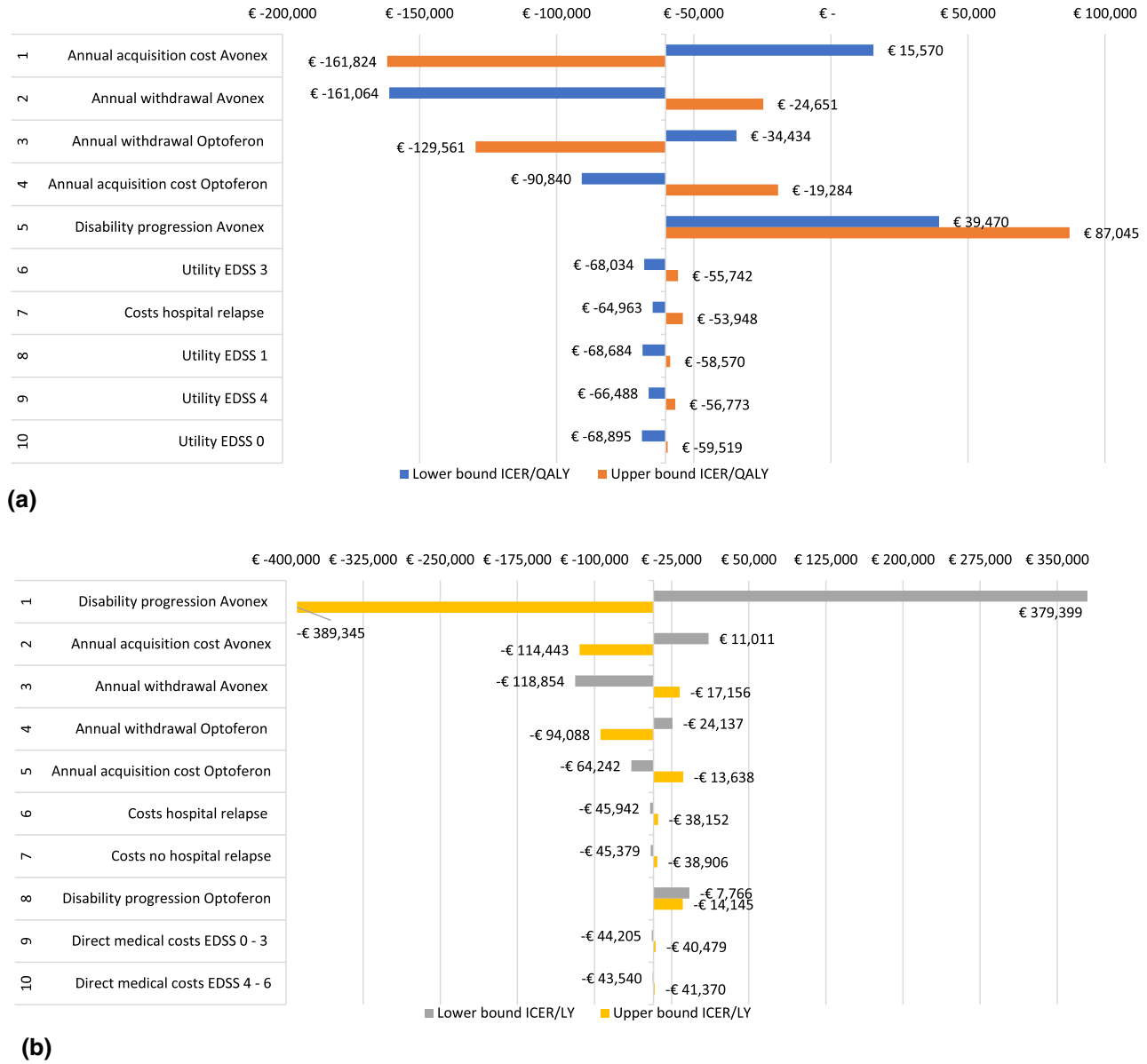

Fig. 4 Tornado diagram to show the impact of uncertainty of model parameters on the model outcomes. Incremental cost-effectiveness ratio (ICER) per quality-adjusted life-year (QALY) (**a**) and per life-year (LY) (**b**). *EDSS* expanded disability status scale

4 Discussion

We performed an early cost-effectiveness analysis (CEA) of a potentially disruptive innovation in the field of drug delivery for MS patients. This early CEA finds that the novel mode of implantable combined ATMP DMT administration, Optoferon, for patients with RRMS is a dominant strategy when compared with the injectable administration of Avonex. Use of the Optoferon therapeutic strategy has the potential to reduce costs and improve health outcomes as long as it fulfills expectations regarding safety, effectiveness, and acquisition costs.

This study shows that there is a potential market for a bio-electronic implantable cell-based device within the field of MS. Though we only examined the possibility of an implantable device with IFN-β 1a delivery, the device described here can be used to administer other DMTs. More efficacious first- and second-line DMTs reduce relapse rate, slow down disease progression [40], improve work productivity [41], and can be cost effective compared with IFN-β 1a in both Europe and the USA [42]. As therapeutic antibodies are difficult to manufacture and always require injections (with drawbacks such as injection-related side effects), there is a growing need for an alternative delivery route like an

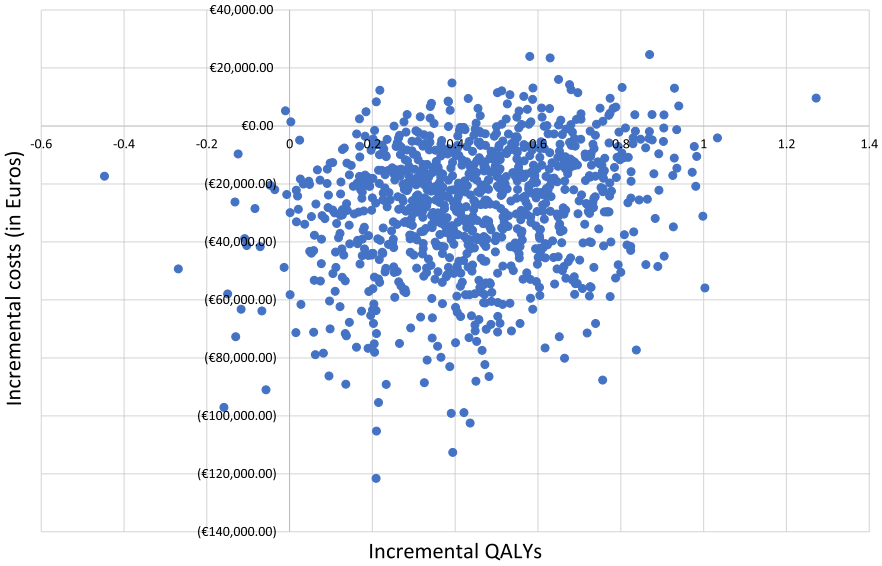

Fig. 5 The cost-effectiveness plane of Optoferon vs Avonex. *QALYs* Quality-adjusted life-years

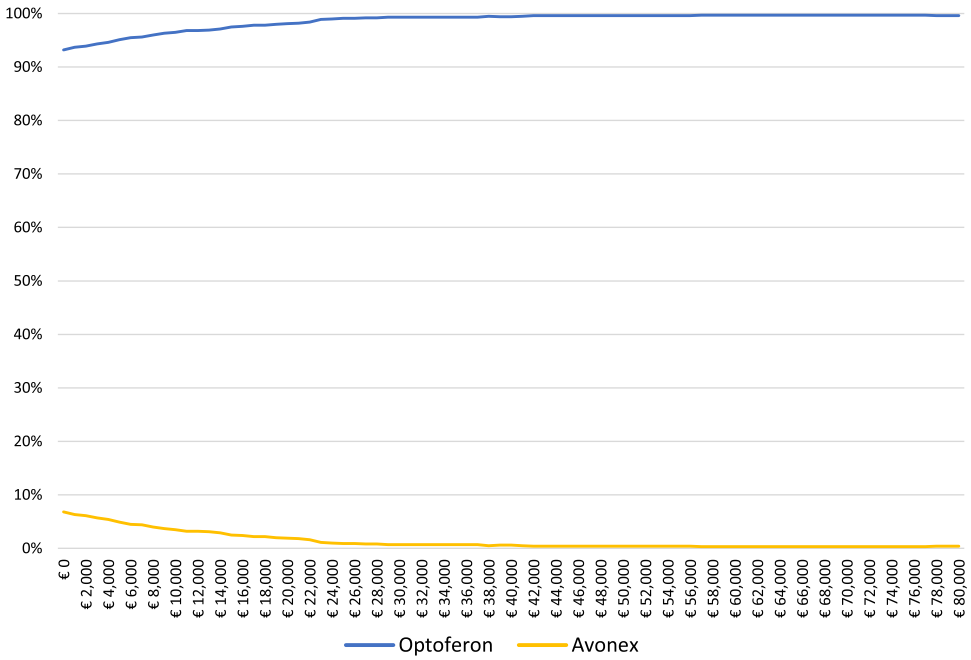

Fig. 6 Cost-effectiveness acceptability curve of Optoferon vs Avonex

Table 3 Results from the headroom analysis

Optoferon acquisition cost	Δ QALYs	Δ Cost	Headroom per patient	Headroom per device unit[a]
€12,028	0.45	− €26,966	€49,343	€49,343
€20,000	0.45	− €8775	€31,153	€31,153
€50,000	0.45	€59,678	− €37,301	− €37,301

QALYs quality-adjusted life-years, Δ difference in

[a]$N = 1$ patient per device unit

Table 4 Results from the scenario analyses

	Total cost per patient	Incremental costs (Optoferon vs Avonex)	Incremental QALYs	Incremental LY	ICER/QALY	ICER/LY
Base case	€153,621	– €26,966	0.45	0.63	– €60,255	– €42,612
Optoferon acquisition cost: €20,000	€171,812	– €8775	0.45	0.63	– €19,607	– €13,866
Optoferon acquisition cost: €50,000	€240,265	€59.678	0.45	0.63	€133,348	€94,305
Hospitalization patient for the implantation and removal device	€156,764	– €23,823	0.45	0.63	– €53,232	– €37,646
Optoferon implanted and replaced yearly	€203.948	€23,361	0.45	0.63	€52,200	€36,916
Optoferon withdrawal rate set equal to Avonex	€138,968	– €41,619	0.02	0	– €2,552,470	NA
Optoferon ARR set equal to Avonex	€153.621	– €26.966	0.44	0.63	– €60,741	– €42,612

ARR annual relapse rate, *ICER* incremental cost-effectiveness ratio, *LY* life-year, *NA* not applicable, *QALY* quality-adjusted life-year

in-situ controlled drug delivery using an implantable cell-based device [12].

The bioelectronic device can be used in a wide variety of diseases to potentially improve health outcomes and healthcare efficiency. The constantly growing portfolio of therapeutic antibodies offers many new therapeutic avenues to treat chronic diseases, including several forms of cancer. Implantable cell-based biologic delivery devices are currently being tested for the treatment of diabetes [43], ophthalmic disease [44], and neurodegenerative conditions [45]. In principle, the cell-therapy vehicle can be genetically programmed to secrete other therapeutic proteins, cytokines, or even efficacious DMT antibodies like natalizumab and alemtuzumab.

Headroom analysis may help the industry to position the product on the market [46]. However, it may be questionable whether the whole headroom should be utilized. There might be reasons to position the product at a lower price and focus on value generated rather than revenue. The value of new technology for innovation policy is driven by the potential business opportunities it may create, whereas in health policy, the emphasis should be on health gains to society [47]. There are widespread inequalities regarding the access to MS care across Europe [48]. This is caused by different regional pricing and health technology assessment (HTA) processes in which cost effectiveness, the burden of the disease, quality of evidence and the healthcare budget of countries determine the access to care [48], along with differing market access strategies from the industry. However, all stakeholders involved in MS care should have a say in how scarce resources are allocated. While the use of stakeholder preferences in HTA decisions may cause problems due to the heterogenous results of preferences, the use of generic QOL measures, such as the EQ-5D, enables conformity across HTA decisions [49]. However, it remains important to examine closely the added value a product has to the patient and consequentially the market.

We had to make assumptions regarding adherence, withdrawal, and relapse rates. However, we found comparable results to a similar cost-effectiveness analysis of first-line DMTs (peginterferon beta vs IFN-β 1a) performed by Hernandez et al. [20]. The same conceptual model is used, along with a short time horizon (10-year horizon), and the results are most sensitive to variations of the treatment effect on disability progression and acquisition costs [20].

We estimated the EVPI to be €13.60 per person, however this is based on an economic evaluation performed in the Netherlands, and more information is needed to reduce decision uncertainty. Therefore, more research is needed to obtain a better estimate of the cost effectiveness of Optoferon. A multi-country RCT with a follow-up of at least 3 years is needed to establish the efficacy and safety of the device, along with the gathering of all relevant data needed for CEAs such as (in)direct (non-)health care costs. Such cost categories can be collected at certain follow-up moments and we recommend the use of the iMTA Productivity Cost Questionnaire and the iMTA Medical Consumption Questionnaire [50, 51]. RCT results can replace the important assumptions that we used in this model and a head-to-head trial is strongly recommended over combining efficacy data from individual trials (different study designs, populations, and outcome measures) [52]. Furthermore, the RCT data can be used to refine the model, for example by using shorter model cycles.

Early economic evaluations inform manufacturers whether it is advisable to continue developing a medical technology (a go/no-go recommendation). Even though medical innovation development is mostly paid for by public and private investors and not directly by patients and physicians, a more holistic view should be adopted when deciding on the continuation of technological advancements. Techniques such as multiple criteria decision analysis (MCDA) and discrete choice experiments (DCEs) can elicit patient and stakeholder preferences to help establish the societal value of the product

[46]. Furthermore, the preferences can be incorporated during technology development [53] and there is consensus from the industry, regulatory authorities, and HTA bodies to do so [54]. Thus, we encourage future go/no-go recommendations to also include patient elicitation methods and not just clinical and economic factors, such as cost effectiveness.

This study has some limitations. Firstly, the main assumption of this model is based on the premise that Optoferon can improve adherence and thereby ARR. However, ARR does not really affect QALYs, which means that it is not one of the top 10 parameters affecting the ICER. What does have a profound effect on the ICER/QALY and ICER/LY is the disability progression of Avonex and Optoferon, respectively. Slower disability progression (i.e., less progression) means that persons will be less disabled for a longer period of time, resulting in increased QALYs and LYs. Such results have also been found in a comparable economic evaluation by Hernandez et al. [20]. Secondly, we did not examine other first-line DMTs, for example oral dimethyl fumarate, resulting in a limited comparison of the current first-line treatment landscape. Oral DMTs have been found to be cost effective compared with IFN-β 1a [19, 55–57]. Oral DMTs need to be considered as comparators to Optoferon in future clinical trials and economic evaluations because national HTA agencies will probably consider this in their decision-making process. Thirdly, we used a 9-year time horizon instead of the lifetime time horizon recommended in the Dutch economic guideline [21]. However, based on our findings, a longer time horizon would have only increased the expected cost savings and health gain from using Optoferon (see Fig. 3). Fourthly, indirect future medical costs were not incorporated in our analysis. Since we estimated a gain in life expectancy of 0.69 years from Optoferon, inclusion of indirect costs would have reduced the cost effectiveness of Optoferon. Finally, the model did not include SPMS patients or the ability to switch to another DMT, thus not reflecting clinical practice and limiting the generalizability of the results. We agree with and repeat the advice given by Hernandez et al. (2018), that future economic models should model sequential treatment courses [52]. Ideally, the development of the device could incorporate such needs, thus Optoferon initially releases first-line DMT into the body, and when deemed necessary, switch the cells to release a second-line DMT and model that accordingly.

5 Conclusion

This early CEA suggests that innovative cell-based bioelectronic implant technology within the field of MS can reduce costs and have positive health effects. In light of all the uncertainties presented in this economic evaluation, Optoferon may be a cost-effective solution and has the potential to become a new mode of treatment administration for patients with MS. The cell therapy vehicle may also become a mode of administration for second-line therapy for MS patients, or for treatments in other disease areas, because genetically programming the cells to secrete other therapeutic proteins is, in principle, possible. It is important to determine the added value of the product to the patient and the market, therefore trial data and stakeholder preferences are needed.

Appendix

Appendix 1A The natural history disease progression transition probabilities based on the London Ontario set [19]

EDSS state at the beginning of the year	EDSS state end of the year									
	0	1	2	3	4	5	6	7	8	9
0	0.312	0.289	0.312	0.07	0.016	0.001	0	0	0	0
1	0.179	0.231	0.419	0.127	0.039	0.004	0.001	0	0	0
2	0.061	0.13	0.493	0.215	0.088	0.011	0.002	0	0	0
3	0.019	0.055	0.299	0.322	0.241	0.044	0.013	0.003	0.004	0
4	0.004	0.017	0.127	0.251	0.411	0.121	0.048	0.014	0.007	0
5	0.001	0.004	0.033	0.096	0.252	0.295	0.211	0.085	0.023	0
6	0	0.001	0.009	0.034	0.123	0.257	0.329	0.19	0.056	0.001
7	0	0	0.002	0.013	0.057	0.169	0.309	0.257	0.189	0.004
8	0	0	0	0	0	0	0	0	0.995	0.005
9	0	0	0	0	0	0	0	0	0	1

Appendix 1B The natural history disease progression transition probabilities adapted from the Institute for Clinical and Economic Review report (ICER report) on DMT effectiveness [19] with the Optoferon and Avonex disease progression hazard ratio (0.79 for both treatment options). *EDSS* expanded disability status scale

EDSS state at the beginning of the year	EDSS state end of the year									
	0	1	2	3	4	5	6	7	8	9
0	0.456	0.228	0.246	0.055	0.013	0.001	0.000	0.000	0.000	0.000
1	0.233	0.301	0.331	0.100	0.031	0.003	0.001	0.000	0.000	0.000
2	0.067	0.143	0.541	0.170	0.070	0.009	0.002	0.000	0.000	0.000
3	0.021	0.060	0.327	0.352	0.190	0.035	0.010	0.002	0.003	0.000
4	0.004	0.018	0.133	0.263	0.431	0.096	0.038	0.011	0.006	0.000
5	0.001	0.004	0.036	0.105	0.277	0.324	0.167	0.067	0.018	0.000
6	0.000	0.001	0.010	0.036	0.131	0.275	0.352	0.150	0.044	0.001
7	0.000	0.000	0.002	0.014	0.060	0.177	0.325	0.270	0.149	0.003
8	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.996	0.004
9	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.000

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Declarations

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Conflict of interest L.A. Visser has no conflicts of interests to declare. M. Folcher has no conflicts of interests to declare. C. Delgado Simao has no conflicts of interests to declare. B. Gutierrez Arechederra has no conflicts of interests to declare. E. Encarna has no conflicts of interests to declare. C.A. Uyl-de Groot has no conflicts of interests to declare. W.K. Redekop has no conflicts of interests to declare.

Availability of data and material (data transparency) The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability (software application or custom code) The code that supports the findings of this study is available from the corresponding author on reasonable request.

Authors' contributions Conceptualization: LAV, WKR. Methodology: LAV, WKR. Formal analysis and investigation: LAV. Writing original draft preparation: LAV. Writing review and editing: MF, CDS, BGA, EE, CAUdG, WKR. Funding acquisition: MF, BGA, WKR. Supervision: CAUdG, WKR.

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