*https://doi.org/10.31925/farmacia.2023.6.24* **ORIGINAL ARTICLE**

# COST-EFFECTIVENESS OF DISEASE-MODIFYING TREATMENTS FOR MULTIPLE SCLEROSIS IN BULGARIA BASED ON EVIDENCE FROM REAL WORLD SETTINGS

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**Abstract**

This study aims to provide insight into the early application of high efficacy 2nd line DMDs (disease-modifying drugs) from a Bulgarian public payer perspective, referring to RWD (real-world data). An Excel-based model was developed to compare the effectiveness of 1st *versus* 2nd line DMDs in terms of ARRs (annualized relapse rate) and the direct medical costs over the 4-year follow-up period. MS (multiple sclerosis) therapies were categorized into two groups (1st and 2nd line) according to public payer guidelines. The results of the cost-effectiveness analysis are presented as an incremental cost-effectiveness ratio (ICER). The annualized relapse rate *per* line of therapy (ARR of 0.385 for 1st line DMDs was significantly higher than the one for 2nd line DMDs, which was 0.153. The direct medical costs were 18,548 BGN (9,485 euros) and 33,857 BGN (17,315 euros) for 1st and 2nd line DMDs respectively. Thus, the ICER was 63 950 BGN (32.700 euros) *per* relapse avoided, which is slightly above the informal threshold of 3 x gross domestic product (GDP) *per capita*. The results of this study showed that escalation to 2nd line DMDs is a cost-effective approach in relapsing-remitting multiple sclerosis (RRMS) patients who do not respond adequately to conventional 1st line DMDs. Although 2nd line DMDs direct medical costs were substantially higher, early escalation might produce long-term savings.

**Rezumat**

Studiul își propune evaluarea farmacoeconomică a medicamentelor care modifică evoluția bolii (*disease-modifying drugs*) din perspectiva pacienților din Bulgaria. Astfel, am comparat eficacitatea terapiei din prima și a doua linie de intervenție în scleroza multiplă cu ratele anuale de recurență și costurile medicale directe pe parcursul a patru ani. Deși costurile terapiei cu medicamente din linia a doua au fost semnificativ mai mari, ameliorarea timpurie a simptomatologiei ar putea genera economii pe termen lung.

**Keywords**: multiple sclerosis, disease-modifying drugs, real-world evidence, cost-effectiveness, RRMS, QALY

## Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease affecting the central nervous system. In Europe, there are over 700,000 people with MS [1], making it one of the most common causes of neurological disability in young adults [2]. The disease typically manifests around the age of 30 and is more prevalent in women than men [3]. The majority of MS patients experience the relapsing-remitting (RRMS) form, characterized by unpredictable relapses and prolonged remission [4, 5].

The clinical manifestation of MS is heterogenic and is characterized by transient and progressive neurological symptoms, *i.e.*, fatigue, pain, depression, seizures, problems with mobility, sexual function, cognition, hearing and vision; difficulties with bowel and bladder function and swallowing [6]. All these symptoms can result in chronic disability, which may affect the quality of life (QOL) and patients' productivity [7].

The disease progression is associated with both a significant increase in costs and substantial changes in costs distribution. The direct medical costs are an immutable part in earlier stages of disease. Unlike in later stages due to relapses and productivity losses the indirect costs are significantly higher [8]. According to Kobelt *et al*. [9], disease-modifying drugs represent 80% of the total direct costs and 61% of the overall costs for patient with mild condition. For patients with severe condition the share of direct cost from all costs were accordingly 4% and 2%. With the rise of Expanded Disability Status Scale (EDSS) scores

from 0 - 1 to 8 - 9, the indirect costs have increased 6 times, and inpatient care costs - 10 times. The largest increase was observed in the cost of informal care.

The pharmaceutical interventions aimed at delaying the progression of disease, measured by EDSS and number of relapses, may help to reduce the economic burden of the disease. There are growing number of evidence that long-term outcomes are more favourable in early application of high efficacy therapies [10-12]. Scalfari *et al*. [11] reported that RRMS patients which have relapses in the first 2 years can influence the course of the disease. A population-based cohort found that in a real-life setting, long-term outcomes were more favourable following early intensive therapy *versus* first-line moderate-efficacy disease-modifying drugs (DMDs) [12]. Early escalation to a high-efficacy therapy was found dominant *versus* switching among immunomodulators, in RRMS patients [13]. Structured real-world data, including patient registries, can add value to existing clinical data and help policy makers and neurologists to provide long and healthy life to the patients with MS.

In general, there is a lack of economic evaluations related to MS treatments in Bulgaria. This increased our interest in the subject and was the main reason to undertake more comprehensive research about clinical characteristics, treatment models and cost-effectiveness of MS therapies in our country. The primary objective of this study is to provide additional insight on the topic of early application of high efficacy 2nd line DMDs by identifying potential pharmacoeconomic evidence, referring to real world data from a local patient-centric database.

## Materials and Methods

*Study design and data sources*

This prospective observational database analysis used Real-World Data from SmartMS, a Bulgarian web-based electronic information system (System for Monitoring, Aid, Registration and Therapy of multiple sclerosis (MS) patients) from January 1, 2016, to December 31, 2019. This anonymous, patient-centric database includes epidemiological, clinical, and therapeutic data for over 2,000 patients (80%) prescribed disease-modifying medicines (DMDs) reimbursed by the National Health Insurance Fund (NHIF). The system provides automated calculation of EDSS, management of documentation, compliance with current regulatory requirements and makes appointment plan for every patient. Data is collected through MS clinical expert committees and patient questionnaires. It is structured in personal electronic health records and MS-specific medical records for all patients, who are enrolled through signed written informed consent. The patient-level enrolment information is a record of demographic variables including gender, age, education, family status, occupational status and clinical and therapeutic variables including family predisposition, age at disease onset and diagnosis, comorbidity, disease severity, line of therapy, therapy course etc.

*Study cohort, inclusion and exclusion criteria*

A nationally representative sample size of 240 randomly selected patients from the SmartMS database was included in the study. Enrolled patients were aged 20 - 62 years, diagnosed with MS (ICD-10) with relapsing-remitting multiple sclerosis (RRMS) disease course. The main inclusion criteria were the initiation of a reimbursed 1st or 2nd line DMD therapy within the 4-year follow up period between the beginning of 2016 and the end of 2019. Patients with primary progressive multiple sclerosis (PPMS) and secondary-progressive multiple sclerosis (SPMS) disease course were not included in the sample, because a reimbursed therapy is either shortly available since beginning of 2019 (PPMS) or not specified in NHIF clinical guidelines for MS treatment (SPMS). Patients not eligible for initiating a reimbursed DMD therapy were those with an Expanded Disability Status Scale (EDSS) score higher than 4, as *per* the NHIF clinical guidelines for MS treatment. We extracted all available information from the SmartMS database in September 2020, so the dataset for analysis contained longitudinal data on demographics, occupational status, year of diagnosis, disease course, EDSS score, relapses, co-morbidities and treatments for enrolled patients. Thus, the study cohort represents a group of patients undergoing routine clinical management in Bulgaria.

*Measurement of outcomes/Clinical inputs*

MS therapies were categorized in two groups according to National Health Insurance Fund clinical guidelines: 1st line (interferon-beta, pegylated interferon-beta, glatiramer acetate, dimethyl fumarate, teriflunomide) and 2nd line (fingolimod, natalizumab, alemtuzumab, cladribine, ocrelizumab) DMDs. Besides, NHIF guidelines imposes mandatory requirements to initiate a 2nd line therapy, including clinical failure of at least two 1st line therapies, at least 2 relapses in the previous year, being treated with a 1st line therapy, combined with increase in the EDSS score, the presence of active lesions, combined with MRI-confirmed disease progression and EDSS score up to 4.

The annualized relapse rate (ARR) was used as a primary outcome measure across the registration trials of all reimbursed DMDs, referring to its Summary of Product Characteristics (SmPCs). Therefore, we used ARR to estimate the clinical effectiveness of 1st and 2nd line DMDs in a real-world setting. The mean ARRs were calculated as the total number of relapses observed divided by the total patient-years of follow-up within a treatment group.

$$ARR_{L_{1-2}} = \frac{R_{total_{L1-2}}}{PY_{L_{1-2}}},$$

where, ARR – annualized relapse rate *per* line of therapy; $L_{1-2}$ – 1st or 2nd line therapy; $R_{total_{L1-2}}$ – total number of relapses for all patients *per* line of therapy within the observed period; $PY_{L_{1-2}}$ – patient years *per* line of therapy within the observed period.

The assumed persistence rate applied to all DMDs was 100%, considering NHIF requirements to discontinue reimbursement of DMDs to all patients, who solely interrupted their therapy for more than 3 months (Table I).

**Table I**

Clinical input parameters

| | 1st line DMDs | 2nd line DMDs |
|---|---|---|
| **Exposure (patient-years)** | 481 | 105 |
| **Total number of relapses during exposure** | 185 | 16 |

*Measurement of service use and costs/Cost inputs*

Total monetary costs incurred by a patient included only direct medical costs, consisting of the following components: 1) the cost of DMD therapy, 2) routine DMDs monitoring costs and 3) the cost of relapses. The cost of DMD therapy was calculated on a yearly basis using the drug's reimbursed value *per* pack, referring to the publicly available Positive Drug List updated at the end of the follow-up period on 02.12.2019. The drug's reimbursed value *per* pack is equal to the amount paid by NHIF for a reimbursed DMD pack, including 20% VAT (Value Added Tax). 10% was deducted from the reimbursed value *per* pack for single sourced products in line with mandatory discount requirements stipulated in the Health Insurance Law. Additional cost deduction (fully growth-related payback) was applied on DMDs in scope of the Ordinance 10 of 2009 for the conditions, procedure, mechanism, and criteria for reimbursement of medicinal products, medical devices and dietetic foods for special medical purposes by National Health Insurance Fund, discount negotiations and compensation of cost over-run due to the application of the mechanism for predictability and sustainability of the budget of the National Health Insurance Fund. The routine monitoring costs were estimated based on the monitoring requirements specified in DMDs SmPCs and corresponding prices, specified in the National Framework Agreement in 2019. Relapse costs were calculated based on the total number of relapses observed in each of the two treatments groups and the price of NHIF clinical path No. 61 "Diagnostics and treatment of MS" in 2019, specified in the National Framework Agreement in 2019. For both treatment groups, the reimbursement with VAT in BGN was 650 (335 euros) for each (Table II, Table III and Table IV).

$$C_{total\ L_{1-2}} = \sum_{p_{t_{1-240}}}^{n_{2016-2019}} \left( \frac{RT_{p_{1-2}} \times (1-X\%) \times (1-Y\%) \times (1-r\%_{p_{1-2}})}{Np_{1-2}} \times AH_{p_{1-2}} \times \frac{PD_{p_{1-2}}}{365} \right) + CR_{p_{1-2}} + CM_{p_{1-2}},$$

where, $C_{total\ L_{1-2}}$ – total direct medical costs *per* line of therapy within the observed period; $RT_{p_{1-2}}$ – reimbursement *per* pack for 1st and 2nd line medicinal product within the observed period; X = 10% – mandatory discount; Y = 20% - payback on growth 2018 - 2017; $r_{p_{1-2}}$ – % payback on growth 2019 - 2018; $r\% = \frac{growth_{2019-2018} \times (1-5{,}8\ \%)}{NHIF_{cost_{p1-2,2019}}}$; $Np_{1-2}$ – number of units *per* pack for 1st and 2nd line medicinal product within the observed period; $AH_{p_{1-2}}$ – annual number of units *per* SmPC for 1st and 2nd line medicinal product within the observed period; $PD_{p_{1-2}}$ – patient – days for 1st and 2nd line medicinal product within the observed period; $CR_{p_{1-2}}$ – relapse costs for 1st and 2nd line medicinal product within the observed period; $CM_{p_{1-2}}$ – monitoring costs for 1st and 2nd line medicinal product within the observed period.

**Table II**

Cost inputs DMDs

| DMD | Unit *per* pack | Reimbursement *per* pack with VAT (BGN/Euros) | Number of units in year 1 | Number of units in year 2+ | Annual reimbursement *per* patient with VAT, including 10% mandatory discount and payments under the mechanism, if applicable in 2018 | Annual reimbursement *per* patient with VAT, including 10% mandatory discount and payments under the mechanism, if applicable in 2019 |
|---|---|---|---|---|---|---|
| **Avonex®** | 4 | 1 457.75/745.37 | 52 | 52 | 18 812 | 18 951 |
| **Aubagio®** | 28 | 1 457.09/745.03 | 365,25 | 365,25 | 14 505 | 16 822 |
| **Betaferon®** | 15 | 1 100.63/562.77 | 183,125 | 183,125 | 13 437 | 13 437 |
| **Extavia®** | 15 | 1 100.63/562.77 | 183,125 | 183,125 | 13 437 | 13 437 |
| **Rebif®** | 3 | 364.44/186.34 | 156 | 156 | 18 812 | 18 951 |
| **Plegridy®** | 1 | 1 399.66/715.66 | 26 | 26 | 26 294 | 31 228 |
| **Copaxone®** | 3 | 318.29/162.75 | 156 | 156 | 16 361 | 16 532 |
| **Remurel®** | 3 | 318.29/162.75 | 156 | 156 | 16 361 | 16 237 |
| **Gilenya®** | 28 | 3 134.30/1602.61 | 365,25 | 365,25 | 36 797 | 36 797 |
| **Tecfidera®** | 56 | 1 729.56/884.35 | 730,5 | 730,5 | 21 215 | 21 518 |
| **Tysabri®** | 1 | 2 741.39/1401.70 | 13 | 13 | 32 074 | 32 074 |

| DMD | Unit *per* pack | Reimbursement *per* pack with VAT (BGN/Euros) | Number of units in year 1 | Number of units in year 2+ | Annual reimbursement *per* patient with VAT, including 10% mandatory discount and payments under the mechanism, if applicable in 2018 | Annual reimbursement *per* patient with VAT, including 10% mandatory discount and payments under the mechanism, if applicable in 2019 |
|---|---|---|---|---|---|---|
| **Ocrevus®** | 1 | 454.83/5857.00 | 4 | 4 | 0 | 38 846 |
| **Lemtrada®** | 1 | 15 333.76/7840.35 | 5 | 3 | 57 079 | 68 945 |
| **Mavenclad®** | 1 | 3 967.96/2028.87 | 12,25 | 12,25 | 48 718 | 42 172 |

*Mavenclad® dose calculated for average body weight *per* patient of 70 kg; notes: p.d. – *per* day, p.w. – *per* week, e.o.d – every other day, e.t.w – every two weeks

**Table III**

Cost inputs DMD monitoring

| Cost inputs DMD monitoring | Monitoring requirements referring to SmPCs | Total annual monitoring costs (BGN/Euros) | |
|---|---|---|---|
| | | **Year 1** | **Year 2+** |
| **Aubagio®** | 16 BC, 2 NV / 6.5 BC, 2 NV | 66.88/34.19 | 53.30/27.25 |
| **Avonex®** | 4 BC, 2 FBC, 2 NV / 2 BC, 2 FBC, 2 NV | 57.64/29.47 | 50.82/25.98 |
| **Betaferon®** | 4 BC, 2 FBC, 2 NV / 2 BC, 2 FBC, 2 NV | 57.64/29.47 | 50.82/25.98 |
| **Copaxone®** | 2NV / 2 NV | 44/22.50 | 44/22.50 |
| **Extavia®** | 4 BC, 2 FBC, 2 NV / 2 BC, 2 FBC, 2 NV | 57.64/29.47 | 50.82/25.98 |
| **Gilenya®** | 6 BC, 4 FBC, 1 MRI, 3 NV, 1 OV / 2 BC, 2 FBC, 1 NV | 329.91/168.69 | 28.82/14.74 |
| **Lemtrada®** | 12 BC, 12 FBC, 12 URI, 1 TST, 4 THYT, 0.65 HPV, 2 NV / 12 BC, 12 FBC, 12 URI, 4 THYT, 0.65 HPV, 1 NV | 180.24/92.16 | 180.24/92.16 |
| **Mavenclad®** | 3 FBC, 1 MRI, 2 NV, 1 TST, 1 HCV, 1 HBV / 3 FBC, 1 NV, 1 TST, 1 HCV, 1 HBV | 293.35/149.99 | 45.94/23.49 |
| **Ocrevus®** | 2 FBC, 1 NV, 1 HBV / 2 FBC, 1 NV | 34.46/17.62 | 25.96/13.27 |
| **Plegridy®** | 4 BC, 2 FBC, 2 NV / 2 BC, 2 FBC, 2 NV | 57.64/29.47 | 50.82/25.98 |
| **Rebif®** | 4 BC, 2 FBC, 2 NV / 2 BC, 2 FBC, 2 NV | 57.64/29.47 | 50.82/25.98 |
| **Remurel®** | 2NV / 2 NV | 44/22.50 | 44/22.50 |
| **Tecfidera®** | 3 BC, 3 FBC, 3 URI, 1 MRI, 3 NV / 2 BC, 2 FBC, 2 URI, 1 NV | 304.79 | 30.92 |
| **Tysabri®** | 2 BC, 1 MRI, 2 NV, 1 JCV / 2BC, 1 MRI, 2 NV, 2 JCV | 272.27 | 272.27 |

*BC – biochemistry test 1.43 BGN, FBC – full blood count 1.98 BGN, HPV – human papilloma virus test Not reimbursed, MRI – magnetic resonance imaging 225.41 BGN, NV – neurology visit 22.00 BGN, OV – ophthalmology visit 22.00 BGN, THYT – thyroid function test 20.68 BGN, TST – tuberculin skin test Not reimbursed, URI – urinalysis with urine cell counts 1.05 BGN, JCV – JC virus test Not reimbursed, HCV – hepatitis C virus test 9.50 BGN, HBV – hepatitis B virus test 9.50 BGN. Prices referring to National Framework Agreement 2019

**Table IV**

Cost inputs for relapses

| | 1st line DMDs | 2nd line DMDs |
|---|---|---|
| **Reimbursement with VAT in BGN/Euros*** | 650/332.35 | 650/332.35 |

*Prices referring to National Framework Agreement 2019, Clinical pathway 61

*Model design, study analysis and assumptions*

An Excel-based model was developed to compare the effectiveness of the 1st *versus* the 2nd line DMDs in terms of the number of relapses (ARRs) and the direct medical cost components throughout a 4-year follow-up. The cost-effectiveness evaluation was conducted from the perspective of a public payer, the National Health Insurance Fund in Bulgaria (only direct medical costs considered). The primary economic endpoint was cost *per* relapse avoided. During the observational period, patients switched within the first line and between the first and second-line therapies. Therefore, for each patient, the follow-up time was segmented according to the start and end dates of treatment periods and treatment effectiveness and cost-effectiveness were measured in patient-years.

The results of the cost-effectiveness analysis are presented *via* incremental cost-effectiveness ratio (ICER). The value of ICER indicates the extra costs to be paid to avoid one relapse. The following formula was applied:

$$\text{ICER} = \frac{\Delta c}{\Delta E} = \frac{\text{2nd line DMDs direct medical costs} - \text{1st line DMDs direct medical costs}}{\text{number of relapses (ARR) for 2nd line DMDs} - \text{number of relapses (ARR) for 1st line DMDs}}.$$

A multiway probabilistic (Monte Carlo) sensitivity analyses was conducted on key input variables, *i.e.*, ARRs and total direct medical costs *per* treatment group, to assess their impact on the cost *per* relapse avoided. Gamma distribution was used to simulate 1000 random values for ARRs and direct medical costs for 1st and 2nd line DMDs and to estimate the corresponding ICERs and the probability for cost-effeteness *versus* predefined ICER threshold of 3 x GDP *per* capita equal to 50 918 BGN (26 035.04 euros). Due to minor effects costs related to adverse effects during DMDs application, administration costs, and

salvage therapy costs were not taken into account in the research. Cost related to comorbidities were not included due to limited information in the SmartMS database. Mortality rates were not accounted for, as it is assumed these have similar consequences across the treatment groups. The annualized relapse rate and the average annual direct medical costs were calculated for the total patient-years within the 4-year time horizon; therefore, both the effect and the costs were not discounted.

## Results and Discussion

*Demographic and clinical characteristics*

For the purpose of this study, we recruited 240 RRMS patients. The mean age at inclusion in the SmartMS database was 39.8 years (SD = 9.4) and over two thirds (70%) were female. The mean age at diagnoses was 31 years (SD = 8.8), whilst the mean disease duration at inclusion in SmartMS database was 7.0 years (SD = 6.4). The demographic and clinical characteristics are presented in Table V.

The follow up time for all 240 patients was average 2.6 years and the mean EDSS score at inclusion in the database was 2.5. We observed that the mean EDSS score for this cohort of patients advanced slightly over the 4 years of observation (from 2.5 to 2.8). However, the disease progression is illustrated by transitions to more severe states levels: 91% of patients were with an EDSS score below 4 at inclusion compared to 79% at the end of the follow up.

**Table V**

Characteristics of the Bulgarian RRMS study cohort

| Characteristic | All patients (n = 240) | 1st line DMDs (n = 206) | 2nd line DMDs (n = 34) |
|---|---|---|---|
| **Age, years, mean (SD)** | 39.8 (9.4) | 39.1 (9.4) | 44.2 (7.9) |
| **Female, n (%)** | 168 (70.0%) | | |
| **Male, n (%)** | 72 (30.0%) | | |
| **Age at diagnosis, years, mean (SD)** | 31.0 (8.8) | 31.3 (8.5) | 29.0 (8.5) |
| **Disease duration, years, mean (SD)** | 7.0 (6.4) | 5.9 (5.8) | 13.3 (6.2) |
| **Follow up time, years, mean (SD)** | 2.6 (0.9) | 2.6 (0.9) | 2.8 (0.6) |
| **EDSS at inclusion, Kurtzke score, mean** | 2.5 | 2.4 | 3.4 |
| **EDSS last assessment, Kurtzke score, mean** | 2.8 | | |

There were in total 512 treatment-years in 207 patients treated with 1st line DMDs and 110 treatment-years in 48 patients treated with 2nd line DMDs. Figure 1 shows the total number of patients and total treatment exposure by single drugs. The use of 2nd line DMDs appears still limited, as a consequence of the stringent NHIF switch criteria for at least two relapses, whilst treated with a 1st line DMD until 2017, further restricted by the requirement to fail to at least two 1st line DMDs to have reimbursement access to 2nd line DMDs since beginning of 2018.

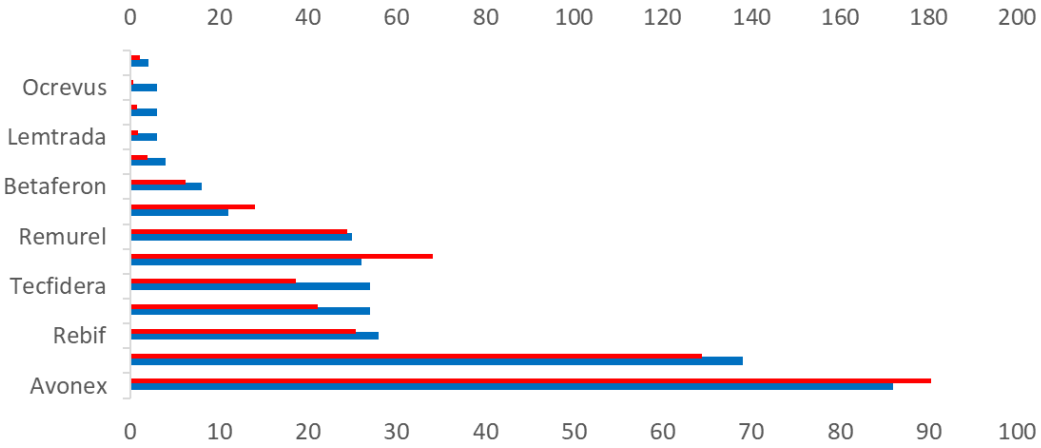


**Figure 1.**

Total number of patients and total treatment duration in years by single drugs

Blue bars indicate the total number of patients ever exposed to each drug during the follow-up; red bars indicate the cumulative treatment time for each drug

*Clinical outcomes and costs*

The costs results are presented in Table VI and Table VII. The mean annualized relapse rate of 0.385 (95% CI: 0.381 - 0.388) for 1st line DMDs was significantly higher than the one for 2nd line DMDs, which was 0.153 (95% CI: 0.142 - 0.163) (Table VI).

The direct medical costs *per* patient-year, including DMD costs, costs of relapses and monitoring costs were 18548 BGN (95% CI: 18.548 - 19.607), 9483.84

euros (95% CI: 9483.84 - 10025.32) and 33 857 BGN (95% CI: 21.009 – 42.297), 17315.53 euros (95% CI: 10742.18 - 21607.01) for 1st and 2nd line DMDs respectively. The significant difference is mainly driven by much higher cost of 2nd line DMDs, whilst the costs of relapsed and the monitoring costs had marginal impact on the total direct medical costs. Besides, the mandatory payback cost deduction had a marginal impact on the overall cost, being recently implemented only in 2019 (Table VII).

Based on these results, the incremental cost-effectiveness ratio (ICER) was 63 950 BGN (32698.47 euros) *per* relapse avoided (Table VIII), which is slightly above the informal threshold of 3 x GDP *per* capita of almost 51.000 BGN (26076.97 euros) (higher threshold).

The probabilistic sensitivity analysis (N = 1000 simulations) showed that 2nd line DMDs were cost-effective *vs.* 1st line DMDs in 12% of cases, using a willingness to pay threshold of 51,000 BGN (26076.97 euros) *per* relapse avoided, in 52% of cases, using a willingness to pay threshold of 63,950 BGN (32698.47 euros) *per* relapse avoided and in 90% of cases, using a willingness to pay threshold of 85,000 BGN (44461.61 euros) *per* relapse avoided. The results are presented in a scatter plot the cost-effectiveness acceptability curve (Figure 2 and Figure 3).

To our knowledge, this is the first attempt to explore the clinical and economic outcomes and to evaluate the cost-effectiveness of 1st *versus* 2nd line DMDs in Bulgaria. With this study we were able to capture two relevant inputs of the health technology assessment: number of relapses and costs. The clinical data used to conduct the present analysis is derived from the Bulgarian real-world patient database SmartMS, spanning over 4 years (from 2016 to 2019).

**Table VI**

Clinical outcomes *per* RRMS treatment group

| | **1st line DMDs** | **2nd line DMDs** |
|---|---|---|
| **Annualized relapse rate (95% CI)** | 0.385 (0.381 - 0.388) | 0.153 (0.142 - 0.163) |
| **Relapses avoided** | N/A | 0.232 |

**Table VII**

Direct medical costs *per* RRMS patient-year in BGN/Euros

| | **1st line DMDs** | **2nd line DMDs** |
|---|---|---|
| **DMD costs (95% CI)** | 18 548 (15 132 - 19 607) 9483.84 euros (95% CI: 9483.84 - 10025.32) | 33 857 (21 009 - 42 297) 17315.53 euros (95% CI: 10742.18 - 21607.01) |
| **Costs of relapses** | 250/127.83 | 99/50.62 |
| **Monitoring costs** | 56/28.53 | 91/46.53 |
| **Direct medical costs** | 18 854/9640.30 | 34 046/17408.17 |

**Table VIII**

Incremental cost-effectiveness ratio

| | **Effect (ARR)** | **Incremental effect** | **Cost** | **Incremental cost** | **ICER** |
|---|---|---|---|---|---|
| **1st line DMDs** | 0.38 | | 17 728/9064.56 | | |
| **2nd line DMDs** | 0.15 | 0.23 | 32 546/16641.20 | 14 819/7577.15 | 63 950/32698.47 |

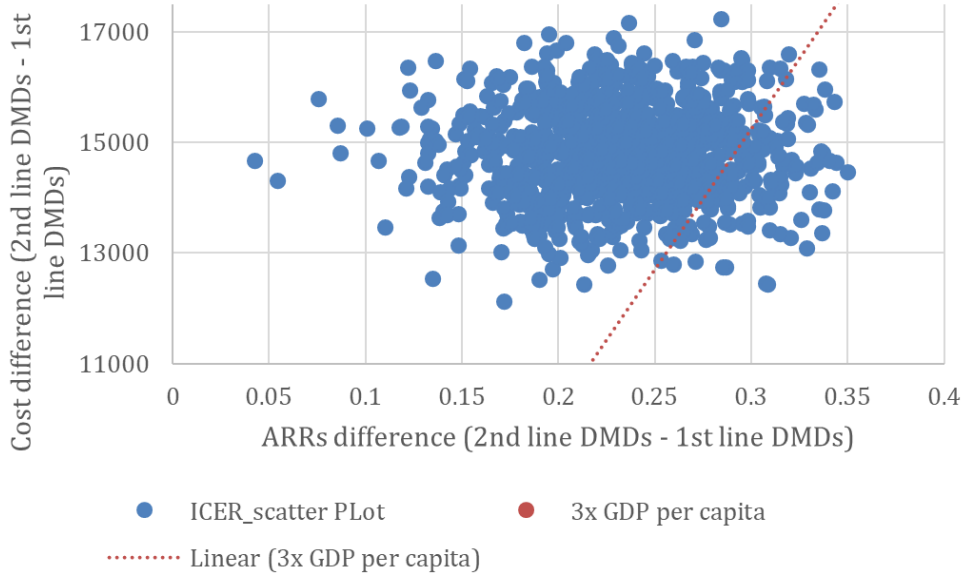


**Figure 2.**

Cost-effectiveness plane: probabilistic sensitivity analysis

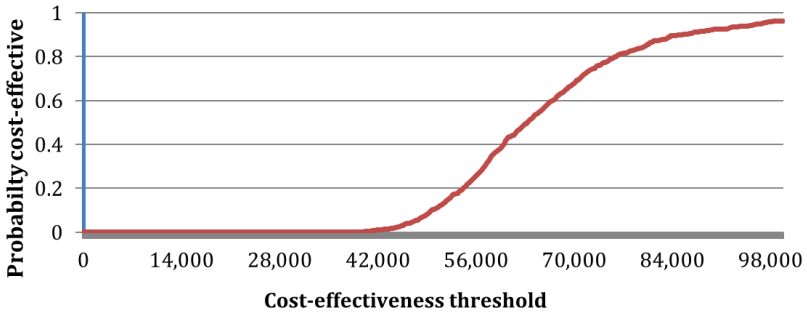


**Figure 3.**
Cost-effectiveness acceptability curve: probabilistic sensitivity analysis

Randomized controlled trials (RCTs) are the most reliable to evaluate efficacy. However, they are insufficient to evaluate real-world effectiveness and the corresponding cost-effectiveness of interventions. Long-term evidence derived from comparative prospective observational studies support optimal decision making by stakeholders in the healthcare system [14, 15]. Real-world patient databases, like SmartMS, are an important tool for generating such evidence and brings major benefits in the healthcare decision-making.

Despite the limited sample of 240 patients, the results of the present analysis confirm that 2nd line DMDs achieve a better clinical outcome, in terms of relapse activity, based on a 4-year follow-up. Referring to the informal willingness to pay (WTP) threshold of 3 x GDP *per* capita, recommended by WHO, but not officially introduced in Bulgarian legislation, this superior clinical outcome represents good value for money, considering the estimated ICER of around 63,950 BGN (32698.47 euros) *per* relapse avoided. The pay-back cost reduction was equally distributed between the growing DMDs in 1st and 2nd line, so it had limited impact on the ICER result. However, the rising payments under the mechanism in 2020 and very likely onwards, will decrease even further costs of new DMDs, so its importance on cost-effectiveness in the future should be evaluated carefully.

We should consider the implications of the analysis findings on clinical practice, taking into consideration the NHIF clinical guidelines in Bulgaria. Due to the slow progression of the disease, outcomes in MS need to be analysed over a longer period of time. The short-term clinical trial data will not provide significant results, due to the introducing of new products in the last few years, switching between DMDs or disease management and external conditions change [16]. During the time period concerned, five DMDs got marketing authorizations in EU were introduced in the NHIF MS clinical guide-line. Three of the five DMDs were 2nd line therapies with two of them showing superiority *versus* a 1st line DMD, based on short-term 2-year head-to-head randomized clinical trials, having ARRs as a primary outcome.

Relapses have long been an obvious risk factor for disease progression [17)] The main goal of MS treatment is to reduce relapses thus slowing the progression. At the same time, the disease progression is associated with significantly costs increase, especially those for informal care [8, 9].

The rules for reimbursement of DMDs in Bulgaria are very strict when initiating treatment with 1st line DMDs and especially when switching to the newer and more expensive 2nd line DMDs. Despite the National clinical consensus of Bulgarian Society of Neurology and the Ordinance on Pharmacotherapeutic Guideline in Neurology does not stipulate such rule, the currently effective NHIF clinical guideline, issued in February 2020 allows switching to 2nd line DMDs only after treatment failure on at least two 1st line DMD therapies. The results of this study showed that patients' exposure to reimbursed 1st line DMDs is much broader, which suggest that NHIF guidelines are strictly followed by Bulgarian MS specialists and early switch to 2nd line DMDs is rather an exception. A review of studies of all DMDs approved in Europe until May 2015 recommends that, in the case of breakthrough on first-line therapy, second-line therapy should be instituted. Switch to 2nd line DMDs, upon failure on 1st line DMDs is recommended by many countries and European treatment guidelines [18]. The findings of this study provide economic evidence that such approach is also cost-effective and support more flexible NHIF clinical guidelines, allowing earlier introduction of 2nd line DMDs in long-term treatment continuum, if appropriated from clinical perspective.

A number of methodological limitations in this study require discussion when interpreting the results. The analysis of treatment effectiveness is complicated by the fact that administrative rules drive therapy with no random allocation to treatment. There are differences in the disease between the patients on 1st and 2nd line DMDs, with only patients with the most active disease being on 2nd line therapy, whilst predominantly patients with inactive and benign disease being on 1st line treatment. Considering all these factors, we acknowledge that the present health economic analysis does not

represent a conclusive guidance for early switch to 2nd line DMDs, which depends on several clinical factors. The findings of this analysis should be rather considered as a long-term proof of the fact that the current economic evidence supports this escalation in the Bulgarian setting when this approach is considered appropriate from a clinical perspective. Therefore, caution should be taken around the validity of such conclusions in other countries.

The second limitation is related to the fact that the cost calculations are based on the Summary of Product Characteristics dosage regime and not on the real dosage utilization. The adherence to therapy is out of the scope of this study, but we do recognize that it could influence the cost and outcomes of the therapy.

## Conclusions

The results of this study showed that switching to 2nd line DMDs due to inadequate response to 1st line DMDs is a cost-effective approach in RRMS patients. The escalation approach decreased the number of relapses *per* patient, but increased the costs of the NHIF. Despite the substantially higher direct medical costs of 2nd line DMDs compared to 1st line DMDs, early escalation might produce long-term savings.

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## Conflict of interest

The authors declare no conflict of interest.

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