

# Budget Impact Analysis of Biosimilar Natalizumab in the US

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**M**ultiple sclerosis (MS) is a chronic disease characterized by neural inflammation, demyelination, and neurodegeneration, mainly affecting young adults around the world. Most individuals with MS experience a variety of debilitating symptoms with periodic neurological relapses that impact their quality of life, employment, social relationships, and productivity.<sup>1,2</sup> The global incidence and prevalence of MS is rising; in 2020, 2.8 million individuals were living with MS compared with 2.3 million in 2013.<sup>3</sup> The US is among the countries with the highest prevalence of MS, with 288 MS cases per 100,000 individuals,<sup>4,5</sup> and a recent study reported that approximately 1 million adults are living with MS nationwide.<sup>2</sup> MS disproportionately impacts women; it is nearly 2 to 3 times more prevalent in women than men.<sup>6</sup> MS can occur at any age, and the mean age of diagnosis is 32 years.<sup>5</sup> The peak MS prevalence was observed among both male and female patients aged 45 to 49 years,<sup>7</sup> and the peak incidence was observed in patients aged 25 to 29 years.<sup>8</sup> MS also has a strong racial and ethnic component and disproportionately affects more individuals with northern European ancestry and Black individuals.<sup>9</sup>

Relapsing-remitting MS (RRMS) is the most common phenotype, accounting for approximately 85% of cases.<sup>10</sup> Patients with RRMS experience episodic flare-ups of symptoms followed by periods of remission.<sup>10</sup> Disease-modifying therapies (DMTs) are used to treat MS and significantly reduce clinical relapses, slow disease disability and progression, minimize MRI lesion activity, and improve patient quality of life.<sup>11-14</sup> High-efficacy DMTs such as natalizumab (NTZ), ocrelizumab, and alemtuzumab are biologic therapies commonly given in infusion centers and are known for average relapse reduction of more than 50%.<sup>15</sup> MS is one of the costliest chronic diseases for payers in the US. Its estimated total economic burden was \$85.4 billion in 2019 in both direct and indirect costs to patients.<sup>16</sup> Based on one large payer's analysis, the MS drug category ranks fourth in spend, behind the autoimmune, cancer, and HIV drug categories.<sup>17</sup> A study by Bebo et al estimated the economic burden of MS in the US and found that the direct medical cost for a patient with MS was \$65,612 per year, with the majority of that being the cost of DMTs (53.6%).<sup>16</sup> Among individuals

## ABSTRACT

**OBJECTIVES:** Biosimilars provide an opportunity for a more sustainable and cost-effective treatment for multiple sclerosis (MS). This study evaluated the potential financial impact of implementing a formulary change from reference to biosimilar natalizumab (NTZ) from the US commercial payer perspective.

**STUDY DESIGN:** The budget impact of transitioning to biosimilar NTZ for the treatment of relapsing-remitting MS (RRMS) was estimated over a 3-year time horizon based on real-world dosing. Additional scenario analyses were conducted by varying the price differential of biosimilar NTZ.

**METHODS:** The target population was estimated from a 1-million-member hypothetical commercial health plan. Model inputs were drug acquisition costs and treatment-related and patient coinsurance costs. Budget impact and cost savings per member per year were calculated by assuming a biosimilar uptake of 10% in year 1 to 20% in year 3.

**RESULTS:** Over 3 years, 255 patients were estimated to be treated with high-efficacy disease-modifying therapies for RRMS. The inclusion of biosimilar NTZ onto a formulary would result in cumulative cost savings to payers of \$452,611 over 3 years, with mean savings per treated member per year of \$1179, \$1769, and \$2359 in years 1, 2, and 3, respectively. One-way sensitivity analyses indicated that budget impact results were most sensitive to drug acquisition costs of both reference and biosimilar NTZ.

**CONCLUSION:** Adoption of biosimilar NTZ can yield considerable cost savings to US health plans that could result in increased treatment access for patients with RRMS.

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TAKEAWAY POINTS

Disease-modifying therapies (DMTs) for relapsing-remitting multiple sclerosis have been available for more than 25 years, yet DMT-related costs continue to be a concern, especially with the advent of biologic DMTs. We estimated the financial impact of implementing a formulary inclusion of biosimilar natalizumab from a US payer perspective:

- ▶ The inclusion of biosimilar natalizumab onto a formulary would result in mean savings per treated member per year of \$1179, \$1769, and \$2359 in years 1, 2, and 3, respectively.
- ▶ Annualized costs for a biosimilar natalizumab can be lower than those for reference high-efficacy DMTs when considering real-world dosing patterns.

TABLE 1. Budget Impact Model Overview

Perspective	US payer
Health plan	Hypothetical 1-million-member commercial health plan
Time horizon	3 years
Population	Existing or new patients with RRMS currently treated with or starting high-efficacy DMT
Treatments	Infused high-efficacy DMTs: reference natalizumab, ocrelizumab, alemtuzumab, biosimilar natalizumab
Costs	Drug acquisition, pretreatment, administration and monitoring, relapse treatment, adverse event management
Outcomes	Annual budget impact, cumulative budget impact, cost per treated member per year, cost per member per year, cost per member per month, annual cost per new patient, annual cost per existing patient
Currency	2021 US\$
Sensitivity analyses	1-way sensitivity analysis, price sensitivity analysis

DMT, disease-modifying therapy; RRMS, relapsing-remitting multiple sclerosis.

using DMTs, annual DMT costs ranged from \$57,202 to \$92,719.<sup>16</sup> In a survey among patients with RRMS, high out-of-pocket (OOP) costs were frequently reported as a DMT access barrier.<sup>18</sup>

There is evidence in the US of health care cost savings following the entry of generic MS drugs. For example, the launch of generic glatiramer acetate coincided with a decline in gross sales of glatiramer acetate injection from approximately \$4.5 million (2015) to approximately \$2.5 million (2019); glatiramer acetate injection accounted for 33% and 32% of total DMT prescriptions in 2015 and 2019, respectively.<sup>19</sup> In a similar manner, the introduction of a biosimilar for the treatment of RRMS could help address issues of high spending and access barriers to high-efficacy MS therapies.<sup>20</sup> Sandoz Inc’s biosimilar NTZ is the first biosimilar NTZ approved in the US.<sup>21</sup> A confirmatory phase 3 study demonstrated the matching efficacy and safety of biosimilar NTZ to that of the reference medicine.<sup>22</sup> The purpose of this economic analysis was to estimate the potential financial impact from the payer perspective of the inclusion of biosimilar NTZ onto a drug formulary.

METHODS

A budget impact model was developed in Excel (Microsoft) to estimate the financial impact of introducing biosimilar NTZ to the high-efficacy DMT space for treatment of adult patients with

RRMS in a hypothetical 1-million-member US commercial health plan over a 3-year time horizon. The model was developed according to Modeling Good Research Practices guidance from ISPOR—The Professional Society for Health Economics and Outcomes Research.<sup>23</sup> A schematic of the model structure is shown in eAppendix Figure 1 (eAppendix available at [ajmc.com](http://ajmc.com)).

The patient population of interest was adult patients with RRMS who were treated with high-efficacy infused DMTs, aged 20 to 64 years, and covered by commercial insurance. Three high-efficacy DMTs—NTZ, alemtuzumab, and ocrelizumab—were included in the analysis to represent the technology mix of high-efficacy infused DMTs in the US as recommended by the ISPOR budget impact analysis guideline.<sup>24</sup> The model estimated expected total cost and budget impact on an overall and per-member basis with and without the introduction of biosimilar NTZ onto a formulary. The main model parameters are outlined in Table 1.

The model inputs included estimates of epidemiological data, relapse rates, dosing, utilization rates, and costs. Costs to payers included drug acquisition, administration, monitoring, relapse, and adverse event (AE) management costs. All costs were obtained from literature and adjusted to 2021 US\$. In accordance with recommended practice for short-term budget impact analyses, we did not apply discounting on costs to derive present values.<sup>24</sup>

Base-Case Model Inputs and Data Sources

**Model population.** Although biosimilar NTZ has the same indications as reference NTZ, this model focused on the most common phenotype of MS: RRMS. The population of interest was patients with RRMS (treatment-naïve patients and patients with existing treatment) aged 20 to 65 years who were currently being treated with or newly started on infused high-efficacy DMTs.<sup>25,26</sup>

The annual incidence and prevalence rates of MS were assumed to be constant over the 3-year time horizon of the analysis. RRMS incidence and prevalence were age adjusted by age groups from US census data, age-specific incidence and prevalence of MS, and the proportion of patients with RRMS in the US.<sup>7,8,27-29</sup> These model inputs are presented in eAppendix Table 1.

**Perspective.** The analysis was conducted from a US commercial payer perspective. Analysis of the budget impact from a Medicare perspective is presented separately in eAppendix Section C.

**Dosing.** In the base-case analysis, we assumed dosing frequency derived from published real-world studies.<sup>30,31</sup> The findings from multiple studies indicate that clinicians in the US are prescribing

and administering NTZ less frequently than the FDA-labeled dosing (theoretical setting), which is associated with a reduction in the risk of progressive multifocal leukoencephalopathy.<sup>31,32</sup> In addition, patients receiving ocrelizumab and alemtuzumab in real-world settings were observed to require more doses than on label to control relapses, as highlighted by Nicholas et al.<sup>30</sup> The total number of doses administered in a year are given in [eAppendix Table 2](#).

**Cost.** Drug acquisition costs were derived from wholesale acquisition costs (WACs) from IBM Redbooks (dated July 1, 2021), similar to other recent budget impact analysis studies.<sup>33-35</sup> The base-case WAC price for biosimilar NTZ was assumed to be 15% lower than the cost of reference NTZ based on the historical experience of other biosimilar launches in the US.<sup>36</sup> The WAC drug price for each drug is shown in [eAppendix Table 3](#).

Costs associated with administration, monitoring, and pretreatment for the included DMTs were obtained from a study conducted in 2020 by Kozma et al<sup>37</sup> (given in eAppendix Section B).

AE treatment costs were obtained from a study by Chirikov et al.<sup>38</sup> AE management costs for each DMT are shown in eAppendix Section B and were utilized to obtain the total AE cost for the treatment-naïve and existing patients.

Relapse management costs of \$3116 per episode were derived from literature (shown in eAppendix Section B).<sup>39</sup> The annualized relapse rates for NTZ, ocrelizumab, and alemtuzumab were 0.19, 0.22, and 0.17, respectively, calculated based on relative risks from the Institute for Clinical and Economic Review.<sup>40</sup>

All treatment (non-DMT) costs obtained from literature were adjusted to 2021 US\$ based on US Consumer Price Index inflation statistics.<sup>41</sup>

**Utilization rates.** The overall budget impact was calculated by assuming a 10%, 15%, and 20% uptake of biosimilar NTZ from reference NTZ in years 1, 2, and 3, respectively. Our uptake assumption of biosimilar NTZ is consistent with 3-year market shares of past biosimilar launches in the US since 2013.<sup>42,43</sup> The utilization rates of ocrelizumab and alemtuzumab were assumed to remain constant.

### Analysis: Base-Case Analysis Using Real-World Dosing Pattern

The number of patients continuing and newly starting treatment for each year was estimated using patient-year calculations and stratified by patients who switched to biosimilar NTZ and those who remained on reference NTZ, ocrelizumab, and alemtuzumab. Results with FDA label dosing are presented in eAppendix Section D.

**TABLE 2.** Annual Cost and Budget Impact to Commercial Payer

Scenario 1: World without biosimilar NTZ				
NTZ	Year 1	Year 2	Year 3	Cumulative costs
Drug acquisition cost				
Reference NTZ	\$2,891,396	\$2,948,922	\$3,006,650	\$8,846,968
Ocrelizumab	\$3,255,793	\$3,320,863	\$3,386,162	\$9,962,818
Alemtuzumab	\$455,438	\$464,442	\$473,478	\$1,393,358
Treatment-related costs <sup>a</sup>	\$295,764	\$301,649	\$307,554	\$904,966
Total costs	\$6,898,391	\$7,035,876	\$7,173,843	\$21,108,111
Cost per treated member per year	\$82,865	\$82,861	\$82,856	\$248,582
Cost PMPY	\$6.90	\$7.04	\$7.17	\$21.11
Cost PMPM	\$0.57	\$0.59	\$0.60	\$1.76
Scenario 2: World with biosimilar NTZ				
NTZ	Year 1	Year 2	Year 3	Cumulative costs
Drug acquisition cost				
Biosimilar NTZ <sup>b</sup>	\$556,407	\$851,215	\$1,157,172	\$2,564,794
Reference NTZ	\$2,236,800	\$1,947,492	\$1,645,272	\$5,829,564
Ocrelizumab	\$3,255,793	\$3,320,863	\$3,386,162	\$9,962,818
Alemtuzumab	\$455,438	\$464,442	\$473,478	\$1,393,358
Treatment-related costs <sup>a</sup>	\$295,764	\$301,649	\$307,554	\$904,966
Total costs	\$6,800,201	\$6,885,662	\$6,969,636	\$20,655,500
Cost per treated member per year	\$81,686	\$81,092	\$80,498	\$243,275
Cost PMPY	\$6.80	\$6.89	\$6.97	\$20.66
Cost PMPM	\$0.57	\$0.57	\$0.58	\$1.72
Total budget impact to commercial payer	-\$98,189	-\$150,214	-\$204,207	-\$452,611

NTZ, natalizumab; PMPM, per member per month; PMPY, per member per year.

<sup>a</sup>Treatment-related costs include the cost of drug administration, monitoring, pretreatment, and treatment of adverse events and relapses. See eAppendix Section A for details.

<sup>b</sup>Wholesale acquisition cost price of biosimilar NTZ is assumed to be 15% lower than reference NTZ based on historical biosimilar pricing trends.<sup>33</sup>

A 1-way sensitivity analysis was performed to assess the impact of varying each base-case parameter by  $\pm 25\%$  on the model outcomes. Additional analysis of price sensitivity is reported in eAppendix Section E.

## RESULTS

### Budget Impact for Payers

In the base-case analysis for a hypothetical 1-million-member health plan, 84 patients aged 20 to 64 years with RRMS (2 incident and 82 existing cases) were estimated to require high-efficacy DMT in year 1. Over the 3-year time horizon, it was estimated that 255 patient-years of high-efficacy DMTs would be provided ([eAppendix Table 4](#)).

In base-case analysis assuming real-world dosing patterns, the model estimates that the cumulative total cost of high-efficacy DMT over 3 years from the payer perspective is \$21.1 million and can be reduced to \$20.6 million with the inclusion of biosimilar NTZ. The formulary inclusion of biosimilar NTZ for RRMS could result in cumulative cost savings of \$452,611 over 3 years, starting at \$98,189 in year 1 and rising to \$204,207 in year 3, as shown in [Table 2](#).

**TABLE 3.** Number of Infusions in Real-World Setting and Annual Cost to Payer

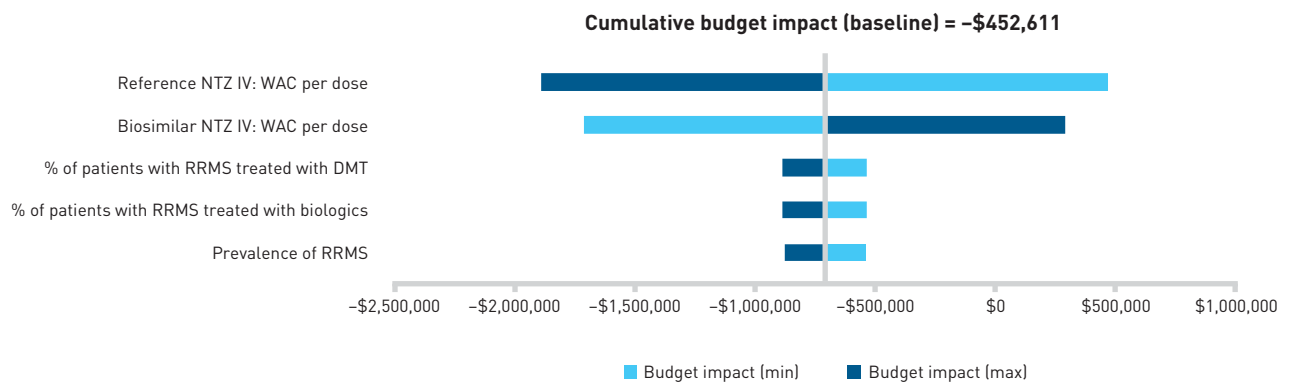
DMT	New patient		Existing patient	
	Mean number of infusions	Annual cost	Mean number of infusions	Annual cost
Biosimilar NTZ <sup>a</sup>	12.71	\$88,977	9.96	\$69,532
Reference NTZ <sup>b</sup>	12.71	\$103,958	9.96	\$81,262
Ocrelizumab <sup>b</sup>	2.24	\$81,832	2.24	\$81,013
Alemtuzumab	5	\$136,580	3	\$81,728

DMT, disease-modifying therapy; NTZ, natalizumab.

<sup>a</sup>Assumed equal dosing to reference NTZ.<sup>34</sup>

<sup>b</sup>Real-world dosing.<sup>30,31</sup>

**FIGURE.** One-Way Sensitivity Analysis of Cumulative Budget Impact<sup>a</sup>



DMT, disease-modifying therapy; IV, intravenous; max, maximum; min, minimum; NTZ, natalizumab; RRMS, relapsing-remitting multiple sclerosis; WAC, wholesale acquisition cost.

<sup>a</sup>Negative budget impact indicates cost savings to the payer. Only the top 5 most impactful parameters are shown in the sensitivity analysis tornado graph.

Within this base-case analysis, payer cost savings were primarily driven by the decrease in drug acquisition costs due to the shift from reference NTZ to biosimilar NTZ, which we assume will have lower drug acquisition costs based on historical biosimilar experience.

Without biosimilar NTZ in the formulary for the commercial plan population, the per-member per-year (PMPY) cost was \$6.90 in year 1 and up to \$7.17 in year 3. The increased PMPY costs were due to the incorporation of annual population growth into the model. With biosimilar NTZ, PMPY costs were reduced to \$6.80 in year 1 and \$6.97 in year 3. The cost savings per treated member per year were \$1179 in year 1, \$1769 in year 2, and \$2359 in year 3. The mean annual total cost per existing patient to the payer was found to be the lowest for biosimilar NTZ (\$69,532) and higher for the other DMTs (reference NTZ [\$81,262], ocrelizumab [\$81,013], and alemtuzumab [\$81,728]) (Table 3).

From a Medicare perspective analysis, 10 patient-years of high-efficacy DMT would be provided over 3 years. The inclusion of biosimilar NTZ into the formulary would generate cost savings of \$18,642 over 3 years, equivalent to a mean cost savings per treated

member per year of \$1192 in year 1, \$1786 in year 2, and \$2380 in year 3. Detailed results for Medicare are provided in eAppendix Section C.

### One-Way Sensitivity Analysis

The base-case results were most sensitive to the drug acquisition cost of reference NTZ and biosimilar NTZ (Figure). Results of price sensitivity analysis are reported in eAppendix Section E.

## DISCUSSION

Biosimilar NTZ from Sandoz is the first biosimilar for the treatment of RRMS to be launched in the US. This budget impact model estimated that, assuming a 15% reduction between the WAC prices of reference NTZ and biosimilar NTZ, switching from the reference to biosimilar NTZ could result in savings of approximately \$452,611 from a commercial payer’s perspective over a 3-year time horizon.

Our model assumed the lowest price differential between biosimilar and reference product from historical experience in the US; cumulative savings could be even higher if the price difference

was at the historical maximum of 37%.<sup>36</sup> Such savings to the US health care system would result in significant economic and social benefit to payers and patients. The 1-way sensitivity analysis revealed that the budget impact was most sensitive to variation in the WAC price of reference NTZ, followed by the predicted WAC price of biosimilar NTZ.

Besides reference and biosimilar NTZ, our model also included alemtuzumab and ocrelizumab as part of the treatment mix to provide additional context in this therapeutic area. In general, there is no uniform approach for DMT selection or sequencing for patients with RRMS, and product selection is influenced by patient preferences for efficacy, safety, tolerability, route of administration, and cost. Moreover, patients and their neurologists can switch from one DMT to another for any one of these reasons. There is, however, growing consensus that early use of higher-efficacy DMTs such as NTZ or ocrelizumab might be advantageous for improving long-term outcomes, and their use has increased.<sup>44</sup> Although ocrelizumab has been demonstrated to be cost saving or more cost-effective vs NTZ, the emergence of a lower-cost, high-efficacy DMT, such as biosimilar NTZ, has the potential to produce significant cost savings for payers. We did not assume that NTZ (reference or biosimilar) would take market share from alemtuzumab or ocrelizumab within the short time frame of our analysis, although changes to the overall treatment mix between these high-efficacy DMTs are possible over the longer term.

Although reference NTZ is a high-efficacy DMT commonly used for the treatment of RRMS, since its approval in 2004, newer and less costly high-efficacy DMTs have been approved; these include ocrelizumab in 2017 and ublituximab in December 2022. Based on our model with lower biosimilar NTZ WAC prices and the use of real-world dosing patterns, our results (Table 3) showed that from the perspective of cost per treated patient per year, biosimilar NTZ would be on par with newer treatments such as ocrelizumab, especially after the first year of treatment. This in turn ensures continued patient access to highly efficacious DMTs and treatment alternatives within the drug class.

Despite the cost-saving advantages of biosimilars, there are many barriers to the entry of biosimilars in the US. The introduction of biosimilars in the US market is essential for increasing patient access and market competition and thus decreasing the overall treatment cost for both the government and payers. In the US, MS is associated with the highest OOP expenditure, including hospital and doctor bills, prescription drugs, and premiums, among the most common diagnoses such as diabetes, injuries, stroke, mental illnesses, and heart disease.<sup>45</sup> With increasing global prevalence of MS, the utilization of DMTs has also increased because DMTs demonstrate high efficacy in reducing relapses, delaying disease progression, reducing disability, and improving the quality of life among patients with MS.<sup>11-14</sup> However, despite the availability and proven efficacy of DMTs in patients with MS, affordability of DMTs remains a major challenge because of increasing costs.<sup>46</sup> A recent cross-sectional study highlighted that nearly 70% of Medicare beneficiaries with MS were using a DMT and that for the patients

who used DMTs consistently throughout the year, OOP costs were high.<sup>47</sup> Although DMTs have been available to patients for more than 25 years, DMT-related costs continue to be high.<sup>48-51</sup> Hence, health care plans should consider including the cost-saving treatments in their drug formulary, which could potentially reduce the financial burden.

This is the first study to assess from a US payer perspective the budget impact of introducing a high-efficacy DMT biosimilar into a formulary for the treatment of patients with RRMS. Our findings, however, should be interpreted with caution, as the estimated cost savings depend on many interrelated factors such as biosimilar price differential relative to the reference product, biosimilar uptake rate, and patient access to biosimilars. Biosimilars have been available in the US since 2015, and they have enabled the health care system to realize significant savings.<sup>52-54</sup> The considerable potential savings on drug spending when patients switch from reference NTZ to biosimilar NTZ as observed in the present study are consistent with previous biosimilar literature ([eAppendix Table 5](#)).

As the promising cost savings due to biosimilars are emerging, a RAND study estimated total biosimilar savings of \$38.4 billion from 2021 to 2025 in the US.<sup>54</sup> Further, a report by IQVIA Institute for Human Data Science on biosimilars in the US projected an increased savings of \$181 billion in 2023-2027, which will be more than 4 times the savings over the past 5 years (\$40 billion), as newly approved biosimilars launch and existing biosimilars see continued uptake and price reduction.<sup>42</sup> However, the potential role of biosimilars and their contribution to the health care system will not be realized until more policy makers and physicians support biosimilar usage by understanding their value proposition. In general, biosimilars are equally efficacious, offer the same dosing approach and schedule as reference medicines, and have potential to increase access while delivering cost savings in the US.

## Limitations

The results of this economic model are meant to provide an estimate of the potential costs that can be incurred and the savings realized from the perspective of a commercial health plan with the inclusion of biosimilar NTZ. Actual savings experienced by health plans will depend on their unique circumstances such as their covered population, treatment utilization rates, and pharmacy and medical costs.

Our analysis did not take OOP maximums into consideration due to the wide variation in plan designs. Patients receiving care out of network are likely to have much higher OOP thresholds. Similarly, patients on original Medicare<sup>35</sup> who have 20% Part B coinsurance without annual patient cost-sharing limits can benefit from the reduced drug price and resulting reduced co-pay for biosimilars. Additionally, we also did not assess the impact of potential deductibles, manufacturers' co-pay assistance, or co-pay cards for commercially insured patients. We excluded these parameters because of the complexity and variety of payer and manufacturer benefit structures across the US.

The model assumed that patients starting alemtuzumab would stay on treatment for the rest of the model's time horizon. However,

this assumption did not have any significant impact on the results because alemtuzumab market share was assumed unchanged in both analysis scenarios. Real-world dosing patterns utilized in the base-case scenario were derived from the included studies but can still vary in other real-world settings. We also did not account for use of ofatumumab (not infused but high efficacy) or off-label rituximab, which is considerably less expensive.

Because biosimilar NTZ had not launched in the US at the time of this analysis, the price is currently an assumption based on historical market trends, and the base case price differential represents the most conservative scenario.<sup>36</sup> The model assumed that the utilization of NTZ remained stable over the 3 years. Utilization rates were based on multiple references describing the proportion of patients treated with various DMTs. Some of the references may not reflect the current treatment population count, and individual payer utilization rates may be different.

## CONCLUSIONS

Based on this 3-year analysis, the use of biosimilar NTZ is economically attractive and can potentially address high spending and access barriers to high-efficacy DMTs. Assuming a reduction in price, the value proposition of NTZ is expected to improve. Future analyses should be continually conducted to assess whether these short-term financial benefits can translate into more cost-effective care, increased access and earlier adoption of NTZ, and improved population-based outcomes. ■

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**Author Disclosures:** Dr Li is employed by Sandoz and owns stock in Novartis. Mr Goh and Ms Gupta are employed by Novartis. Ms Schauf is employed by Sandoz International. Dr Chen is employed by and owns stock in Sandoz. Dr Hartung has consulted for the National Multiple Sclerosis Society and has provided expert testimony in litigation on behalf of Humana and the US Department of Justice.

**Authorship Information:** Concept and design (EL, AG, SG, MS, AC, DMH); acquisition of data (AG, SG); analysis and interpretation of data (EL, AG, SG, AC, DMH); drafting of the manuscript (EL, AC); critical revision of the manuscript for important intellectual content (AG, SG, MS, AC, DMH); statistical analysis (AG, SG); administrative, technical, or logistic support (AC); and supervision (MS).

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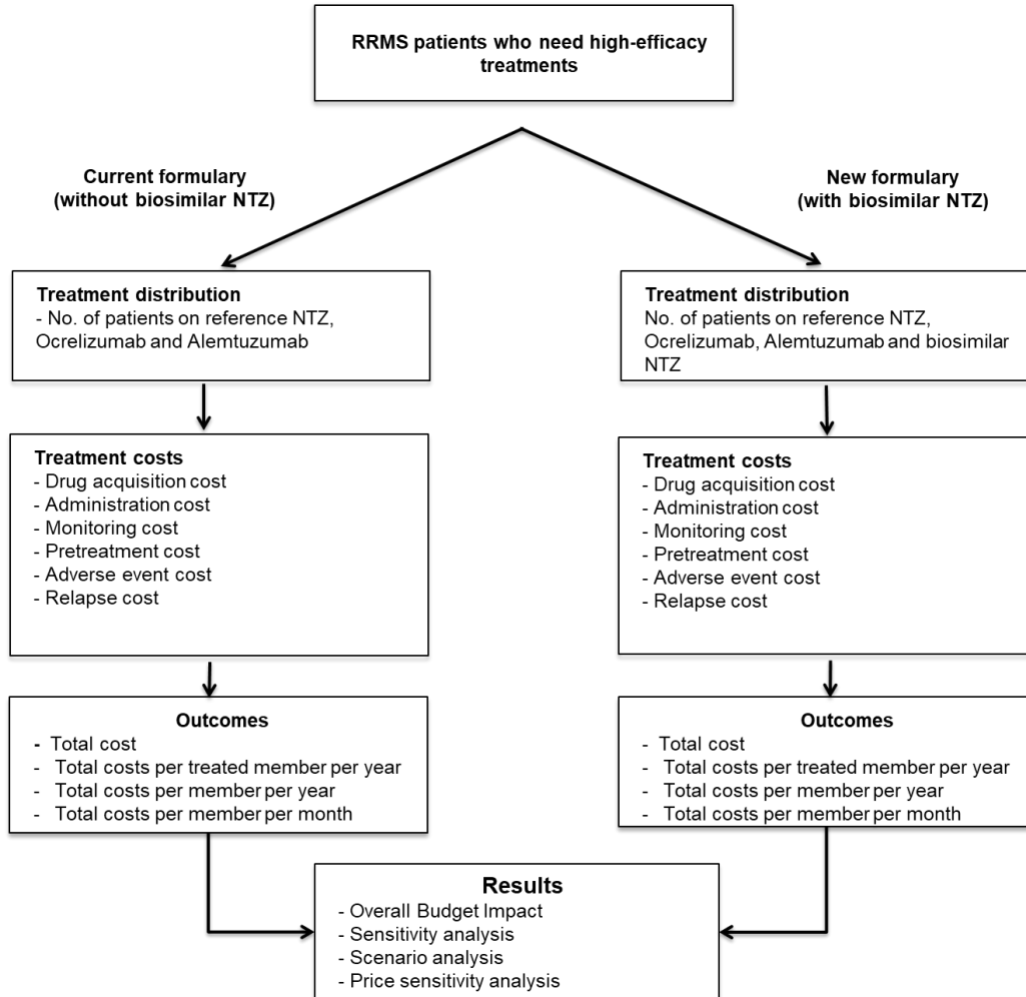
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## eAppendix

### Section A

eAppendix Figure 1. Model Structure



NTZ, natalizumab; RRMS, relapsing-remitting multiple sclerosis.



**eAppendix Table 1. Model Epidemiology Inputs**

<b>Parameter</b>	<b>Commercial (20–65 years)</b>	<b>Source</b>
<b>Initial hypothetical plan population size (Year 1)</b>	1,000,000	Assumption
<b>Population growth rate</b>	0.35%	Data Commons <sup>1</sup>
<b>Prevalence range of MS (based on age)</b>	0.0401–0.3035%	Dilokthornsakul et al., 2016 <sup>2</sup>
<b>Incidence range of MS (based on age)</b>	0.003–0.0117%	Lo et al., 2021 <sup>3</sup>
<b>Proportion of patients with RRMS in an MS population</b>	72.20%	Nazareth <sup>4</sup> 2018
<b>Calculated prevalence range of RRMS (based on age-adjusted)</b>	0.0841%	Calculated using the above inputs and age-adjusted census data
<b>Calculated incidence range of RRMS (based on age-adjusted)</b>	0.0017%	Calculated using the above inputs and age-adjusted census data
<b>Proportion of patients with RRMS treated with DMTs</b>	58.31%	Zhang et al., 2021 <sup>5</sup> ; Kern et al., 2020 <sup>6</sup>
<b>Proportion treated with infused high-efficacy biologics</b>	16.64%	Elsisi et al., 2020 <sup>7</sup>
<b>Natalizumab</b>	7.35%	
<b>Ocrelizumab</b>	8.16%	
<b>Alemtuzumab</b>	1.13%	

DMT, disease-modifying therapy; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.

**eAppendix Table 2.** Total Number of Doses Administered in Real-World Setting and in a Theoretical Setting (Per Year)

DMTs	Real-world setting Number of doses per year			Theoretical setting: FDA-labeled dosing Number of doses per year		
	Year 1	Year 1+	Source	Year 1	Year 1+	Source
Reference NTZ and proposed biosimilar NTZ IV 300 mg	12.71	9.96	Nicholas et al., 2020 <sup>29</sup> ; Zhovtis et al., 2016 <sup>30</sup>	13	13	US FDA label <sup>8</sup>
Ocrelizumab IV 600 mg	2.24 <sup>a</sup>	2.24		2 <sup>a</sup>	2	US FDA label <sup>9</sup>
Alemtuzumab IV 12 mg	5	3		5	3	US FDA label <sup>10</sup>

DMT, disease-modifying therapy; FDA, Food and Drug Administration; IV, intravenous; NTZ, natalizumab; US, Unites States.

<sup>a</sup>One additional infusion was considered in the analysis as the first 600 mg infusion is given in 2 equal doses (i.e., 300 mg) 2 weeks apart

**eAppendix Table 3. WAC Drug Price and Co-insurance Cost Per Dose**

<b>DMTs</b>	<b>WAC price (per dose)<sup>11</sup></b>	
Proposed biosimilar NTZ	\$6677 <sup>a</sup>	
Reference NTZ	\$7855	
Ocrelizumab	\$35,592	
Alemtuzumab	\$26,502	

DMT, disease-modifying therapy; NTZ, natalizumab; WAC, wholesale acquisition cost.

<sup>a</sup>WAC price of proposed biosimilar NTZ is assumed to be 15% lower than that of reference NTZ based on historical biosimilar pricing trends<sup>12</sup>

**eAppendix Table 4.** Target Population Summary (Per Million)

	<b>Year 1</b>	<b>Year 2</b>	<b>Year 3</b>
<b>Hypothetical plan population size</b>	1,000,000	1,003,500	1,007,012
<b>Incidence of RRMS</b>	17	17	17
<b>Prevalence of RRMS</b>	841	858	875
<b>Total number of new patients with RRMS treated with DMTs</b>	10	10	10
<b>Total number of existing patients with RRMS treated with DMTs</b>	490	500	510
<b>Incident patients with RRMS newly starting high-efficacy DMT treatment</b>	2	2	2
<b>Prevalent patients with RRMS currently using high-efficacy DMT treatment</b>	82	83	85
<b>Total number of patients using high-efficacy DMT treatment</b>	84	85	87

DMT, disease-modifying therapy; RRMS, relapsing-remitting multiple sclerosis.

**eAppendix Table 5.** Key Findings of Biosimilar Savings From the Literature

<b>Author-Year</b>	<b>Study type</b>	<b>Biosimilar</b>	<b>Key findings</b>
Yang et al., 2021 <sup>13</sup>	Budget impact analysis	Bevacizumab	<ul style="list-style-type: none"> <li>Cumulative cost savings were \$7,030,924 (\$0.012 PMPM) for a commercial payer and \$4,059,257 (\$0.007 PMPM) for Medicare over 5 years for a hypothetical 10-million-member health plan</li> </ul>
Trautman et al., 2019 <sup>14</sup>	Budget impact analysis	Filgrastim	<ul style="list-style-type: none"> <li>Cost savings totaled \$469,385 (PMPY = \$0.48) for a 1-million-member health plan, with total annual costs decreased by almost \$0.5 million, with per-member cost savings of \$0.04 monthly and \$0.48 annually</li> </ul>
Grewal et al., 2018 <sup>15</sup>	Budget impact analysis	Filgrastim	<ul style="list-style-type: none"> <li>5-year cost savings of \$256 million, of which 34% and 48% were savings for commercial payers and Medicare, respectively, and 18% were from reduced patient OOP costs</li> </ul>
Mullalley et al., 2020 <sup>16</sup>	US center-based cohort study	Pegfilgastrim, bevacizumab, trastuzumab, and rituximab	<ul style="list-style-type: none"> <li>Assuming 70% conversion from reference medicine to biosimilars and 6450 combined doses of pegfilgastrim, bevacizumab, trastuzumab, and rituximab, \$6.3 million estimated to be saved annually</li> </ul>

OOP, out of pocket; PMPM, per member per month; PMPY, per member per year; US, United

States

**Section B: Inputs**

**eAppendix Table 6.** List of AEs Considered for Natalizumab

<b>AE</b>	<b>Description</b>	<b>Unit cost</b>	<b>Annual probability of event</b>	<b>Cost per event</b>	<b>Total cost of AE</b>
PML	Hospitalization for viral meningitis for 14 days	\$36,851.00	0.02%	\$47,148.42	\$ 136.83
	Doctor discharge services (only for last day)	\$214.18			
	Plasma exchange (5 times)	\$2693.75			
	1 John Cunningham virus antibody laboratory test; HIV-1 laboratory test	\$270.97			
	Lumbar puncture; initial doctor consultation in hospital, Level 4 (1 consult); initial doctor visit in hospital, Level 3 (1 consult)	\$705.12			
	Complete Blood Count with Differential (3 times daily for 14 days)	\$1474.62			
	Comprehensive Metabolic Panel (3 times daily for 14 days)	\$2636.76			
	1 MRI of the orbit/face/neck without contrast	\$2302.02			
UTI	1 office visit, established patient, Level 5; 1 office visit, established patient, Level 4	\$450.97	14.56%	\$451.46	
	First line: sulfamethoxazole/trimethoprim (400 mg/80 mg) oral tablet 2 times daily for 3 days (Use cost per unit and #6 units/tabs): WAC, Redbook 2016, Teva Pharmaceuticals, sulfamethoxazole/trimethoprim, oral, tablet, 400 mg/80 mg, pack size 500	\$0.49			
Influenza	1 office visit, established patient, Level 5; 1 office visit, established patient, Level 4	\$450.97	6.19%	\$463.72	
	Azithromycin 250 mg oral tablet (use 6 tablets). WAC Redbook 2016, Apotex Corp, oral, tablet, pack size 500	\$12.75			
Vaginal infection	1 office visit, established patient, Level 4	\$173.45	4.08%	\$179.14	
	Metronidazole 250 mg orally 3 times daily for 7 consecutive days	\$5.69			
Fatigue	1 office visit, established patient, Level 4	\$173.45	14.56%	\$173.45	
Infusion-associated reaction	Cetirizine.HCl 10 mg oral tablet daily for 7 days: Cetirizine.HCl; WAC, Redbook 2016, J&J, Zyrtec, oral, tablet, 10 mg, pack size 70	\$2.79	12.82%	\$3.13	

	Ibuprofen 200 mg 3 times daily for 7 days: Ibuprofen; WAC, Redbook 2016, Perrigo Pharmaceuticals Co, oral, tablet, 200 mg, pack size 500	\$0.34			
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AE, adverse event; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging;

PML, progressive multifocal leukoencephalopathy; UTI, urinary tract infection; WAC,

wholesale acquisition cost.

**eAppendix Table 7.** List of AEs Considered for Ocrelizumab

<b>AE</b>	<b>Description</b>	<b>Unit cost</b>	<b>Annual probability of event</b>	<b>Cost per event</b>	<b>Total cost of AE</b>
Herpes virus	1 office visit, established patient, Level 5; 1 office visit, established patient, Level 4	\$450.97	3.38%	\$466.99	\$ 194.88
	Acyclovir 400 mg oral tablet every 8 hours for 7–14 days. (Use maximum duration for immunocompromized patients - 400 mg and 42 units/pills): WAC, Redbook 2016, Prestium Pharma, ZOVIRAX, oral, tablet, 400 mg, pack size 100	\$16.02			
Upper respiratory tract infection	1 office visit, established patient, Level 5; 1 office visit, established patient, Level 4	\$450.97	24.71%	\$451.31	
	Ibuprofen 200 mg 3 times daily for 7 days: WAC, Redbook 2016, Perrigo Pharmaceuticals Co, oral, tablet, 200 mg, pack size 500	\$0.34			
Infusion-associated reaction	Cetirizine.HCl 10 mg oral tablet daily for 7 days: Cetirizine.HCl; WAC, Redbook 2016, J&J, Zyrtec, oral, tablet, 10 mg, pack size 70	\$2.79	20.61%	\$3.13	
	Ibuprofen 200 mg 3 times daily for 7 days: Ibuprofen; WAC, Redbook 2016, Perrigo Pharmaceuticals Co, oral, tablet, 200 mg, pack size 500	\$0.34			
Depression	4 office visits, established patient, Level 4	\$693.80	4.53%	\$883.74	
	Psychotherapy, 60 minutes with patient and/or family	\$188.40			
	Sertraline 100 mg oral tablet daily for 30 days: WAC, Redbook 2016, Exelan Pharmaceuticals, Inc, oral, tablet, 100 mg, pack size 180	\$1.54			



<b>AE</b>	<b>Description</b>	<b>Unit cost</b>	<b>Annual probability of event</b>	<b>Cost per event</b>	<b>Total cost of AE</b>
Lower respiratory tract infections	1 office visit, established patient, Level 5; 1 office visit, established patient, Level 4	\$450.97	4.53%	\$464.06	
	Ibuprofen 200 mg oral tablet 3 times daily for 7 days: WAC, Redbook 2016, Perrigo Pharmaceuticals Co, oral, tablet, 200 mg, pack size 500	\$0.34			
	Azithromycin 250 mg oral tablet (use 6 tablets). WAC Redbook 2016, Apotex Corp, oral, tablet, pack size 500	\$12.75			
Back pain	1 office visit, established patient, Level 4	\$173.45	3.38%	\$173.79	
	Ibuprofen 200 mg oral tablet 3 times daily for 7 days: WAC, Redbook 2016, Perrigo Pharmaceuticals Co, oral, tablet, 200 mg, pack size 500	\$0.34			

AE, adverse event; WAC, wholesale acquisition cost.

**eAppendix Table 8.** List of AEs Considered for Alemtuzumab

Adverse event	Description	Unit cost	Annual Probability of event	Cost per event	Total cost of AE
Infusion-associated reaction	Cetirizine.HCl 10 mg oral tablet daily for 7 days: Cetirizine.HCl; WAC, Redbook 2016, J&J, Zyrtec, oral, tablet, 10 mg, pack size 70	\$2.79	71.80%	\$3.13	\$218.14
	Ibuprofen 200 mg 3 times daily for 7 days: Ibuprofen; WAC, Redbook 2016, Perrigo Pharmaceuticals Co, oral, tablet, 200mg, pack size 500	\$0.34			
ITP (annualized over 4 years)			0.50%	\$ 51.05	
ITP (observation only)	1 office visit, established patient, Level 5	\$277.52	0.03%	\$635.54	
	1 office visit, new patient, Level 5 (hematology consult)	\$358.02			
ITP (steroids only)	1 office visit, established patient, Level 5	\$277.52	0.18%	\$942.94	
	1 office visit, new patient, Level 5 (hematology consult)	\$358.02			
	IV methylprednisolone 250 mg daily for 3 days with IV administration for 1 hour	\$298.45			
	Prednisone start at 60 mg with taper. (use 20 mg tablet; quantity, 45 tablets).	\$8.95			
ITP (steroids and immunoglobulin)	1 office visit, established patient, Level 5	\$277.52	0.17%	\$20,822.94	
	1 office visit, new patient, Level 5 (hematology consult)	\$358.02			
	IV methylprednisolone 250 mg daily for 3 days with IV administration for 1 hour	\$298.45			
	Prednisone start at 60 mg with taper. (use 20 mg tablet and quantity 45 tablets.)	\$8.95			
	Chemotherapy/biologic infusion (IV), 1 hour infusion for 5 days	\$2110.70			
	6 hours of monitoring for 5 days	\$1370.90			
	IV immunoglobulin 2 g/kg for a 65 kg female adult or 130 g dose 1 time (need 4 vials of IV immunoglobulin)	\$16,398.40			

Adverse event	Description	Unit cost	Annual Probability of event	Cost per event	Total cost of AE
	.WAC Redbook 2016, Grifols Therapeutics Inc, injection, strength 100 mg/mL, pack size 400 mL				
ITP (steroids and rituximab)	2 office visits, established patient, Level 5	\$555.04	0.11%	\$7236.06	
	1 office visit, new patient, Level 5 (hematology consult)	\$358.02			
	IV methylprednisolone 250 mg daily for 3 days with IV administration for 1 hour	\$298.45			
	Prednisone start at 60 mg with taper. (use 20 mg tablet; quantity, 45 tablets.)	\$8.95			
	IV rituximab 375 mg/m <sup>2</sup> once ~650 mg (65 kg female, 5'6"; BSA 1.74 m <sup>2</sup> ), IV administration for 4 hours	\$5741.42			
	4 hours of monitoring	\$274.18			
ITP (steroids and splenectomy)	1 office visit, established patient, Level 5	\$277.52	0.02%	\$28,999.99	
	1 office visit, new patient, Level 5 (hematology consult)	\$358.02			
	Splenectomy (hospitalization, procedure, anesthesia)	\$28,057.05			
	IV methylprednisolone 250 mg daily for 3 days with IV administration for 1 hour	\$298.45			
	Prednisone start at 60 mg with taper. (use 20 mg tablet and quantity 45 tablets.)	\$8.95			
Autoimmune thyroid-related AE/Thyroid disorders (annualized over 4 years)			9.90%	\$ 56.84	
Breakdown of thyroid disorders					
Hypothyroidism	1 office visit, established patient, Level 5; 1 office visit, established patient, Level 4	\$450.97	2.03%	\$ 582.65	
	Thyroid-stimulating hormone direct-to-consumer laboratory test	\$100.40			
	Synthroid 0.05 mg oral tablet daily for 30 days	\$31.28			

Adverse event	Description	Unit cost	Annual Probability of event	Cost per event	Total cost of AE
Hyperthyroidism	1 office visit, established patient, Level 5; 1 office visit, established patient, Level 4	\$450.97	7.87%	\$ 571.98	
	Thyroid-stimulating hormone direct-to-consumer laboratory test	\$100.40			
	Methimazole 15 mg (three 5 mg oral tablets) daily for 30 days.	\$20.61			
Rash	1 office visit, established patient, Level 4	\$173.45	31.44%	\$ 173.45	
Headache	1 office visit, established patient, Level 4; First line: ibuprofen 200 mg 4 times daily for 3 days	\$173.65	30.72%	\$ 173.65	
Pyrexia	1 office visit, established patient, Level 4; First line: acetaminophen 325 mg as needed or ibuprofen 200 mg (4 times daily for 3 days) as needed. Ibuprofen; 4 times daily for 3 days, Perrigo Pharmaceuticals Co, oral, tablet, 200 mg, pack size 500	\$173.65	15.74%	\$ 173.65	
Urticaria	1 office visit, established patient, Level 4	\$173.45	8.35%	\$ 176.24	
	1st line: diphenhydramine 25 mg as needed, or cetirizine.HCl 10 mg oral tablet as needed. Antihistamines (10 mg once daily for 1 week): Cetirizine.HCl; WAC, Redbook 2016, J&J, Zyrtec, oral, tablet, 10 mg, pack size 70	\$2.79			
Herpes infection	1 office visit, established patient, Level 5; 1 office visit, established patient, Level 4	\$450.97	8.35%	\$ 466.99	
	Acyclovir 400 mg oral tablet every 8 hours for 7–14 days. (Use maximum duration for immunocompromized patients - 400 mg and 42 units/pills): WAC, Redbook 2016, Prestium Pharma, ZOVIRAX, oral, tablet, 400 mg, pack size 100	\$16.02			

BSA, body surface area; ITP, immune thrombocytopenia; IV, intravenous; WAC, wholesale acquisition cost;

**eAppendix Table 9.** ARR Calculation (Using ICER Report, 2017)

ICER Table C4							ICER Table 5			
Drug	Treatment arm	N	Person-years	Relapses	Trial ARR	ARR	IFN44 RR	RR	Trial placebo ARR	Average placebo ARR
<b>Natalizumab</b>	Natalizumab 300 mg IV	627	1200	276	0.23	0.23		0.31	0.73	0.61
	Placebo IV	315	578	422	0.73	0.73				
<b>Alemtuzumab</b>	Alemtuzumab 12 mg IV	112	309.09	34	0.11	0.18	0.64	0.27	0.66	0.61
	IFN B1A 44 SC	111	247.22	89	0.36	0.42				
	Alemtuzumab 12 mg IV	376	661.11	119	0.18					
	IFN B1A 44 SC	187	312.82	122	0.39					
	Alemtuzumab 12 mg IV	426	907.69	236	0.26					
	IFN B1A 44 SC	202	386.54	201	0.52					
<b>Ocrelizumab</b>	Ocrelizumab 600 mg IV	410	754.3	121	0.16	0.16	0.64	0.35	0.45	0.61
	IFN B1A 44 SC	411	756.2	219	0.29	0.29				
	Ocrelizumab 600 mg IV	417	767.2	123	0.16					
	IFN B1A 44 SC	418	769.1	223	0.29					

ARR, annualized relapse rate; ICER, The Institute for Clinical and Economic Review; IFN, interferon; IV, intravenous; RR, relapse rate; SC, subcutaneous

Note: Relapses Calculation for Each Drug = Drug RR x Placebo ARR x Person Years = # of Relapses

**eAppendix Table 10.** Treatment-related Costs to Commercial Payers by Cost Type

<b>Treatment-related costs</b>	<b>Year 1</b>	<b>Year 2</b>	<b>Year 3</b>
Relapse costs	\$52,255	\$53,299	\$54,347
Pretreatment costs	\$13,029	\$13,288	\$13,547
Drug administration and monitoring costs	\$215,145	\$219,420	\$223,710
Safety costs	\$15,335	\$15,642	\$15,950

**eAppendix Table 11.** Drug Administration, Monitoring, and Pretreatment Costs (Per Infusion)

<b>DMTs</b>	<b>Drug administration and monitoring costs</b>		<b>Pretreatment costs</b>	
	<b>Year 1</b>	<b>Year 1+</b>	<b>Year 1</b>	<b>Year 1+</b>
Biosimilar NTZ	\$353.15	\$353.15	\$18.37	\$18.37
Reference NTZ	\$353.15	\$353.15	\$18.37	\$18.37
Ocrelizumab	\$765.50	\$765.50	\$53.07	\$53.07
Alemtuzumab	\$844.09	\$844.09	\$79.61	\$79.61

DMT, disease-modifying therapy; NTZ, natalizumab.

**eAppendix Table 12.** Adverse Event Costs Used in the Model (Per Patient Per Year)

<b>DMT</b>	<b>Adverse event costs</b>
	<b>Years 1, 2, and 3</b>
Biosimilar NTZ	\$148
Reference NTZ	\$148
Ocrelizumab	\$210
Alemtuzumab	\$235

Note: Unit costs from Appendix Tables 7,8,9 were inflated to 2021 \$ terms

DMT, disease-modifying therapy; NTZ, natalizumab.



## Section C: Inputs and Results from Medicare Payer Perspective

eAppendix Table 13. Model Epidemiology Inputs

Parameter	Medicare (65+ years)	Source
<b>Initial hypothetical plan population size (Year 1)</b>	1,000,000	Assumption
<b>Population growth rate</b>	0.35%	Data Commons <sup>27</sup>
<b>Prevalence range of MS (based on age)</b>	0.0131–0.0757%	Dilokthornsakul et al., 2016 <sup>7</sup>
<b>Incidence range of MS (based on age)</b>	0.003%	Lo et al., 2021 <sup>8</sup>
<b>Proportion of RRMS in an MS population</b>	72.20%	Nazareth 2018 <sup>26</sup>
<b>Calculated prevalence range of RRMS (based on age)</b>	0.006%	Calculated using the above inputs and age-adjusted Census data
<b>Calculated incidence range of RRMS (based on age)</b>	0.0004%	Calculated using the above inputs and age-adjusted Census data
<b>Proportion of RRMS patients treated with DMTs</b>	30.86%	Zhang et al., 2021; Kern et al., 2020 <sup>23, 28</sup>
<b>Proportion treated with infused high-efficacy biologics</b>	16.64%	Elsisi et al., 2020 <sup>24</sup>
<b>Natalizumab</b>	7.35%	
<b>Ocrelizumab</b>	8.16%	
<b>Alemtuzumab</b>	1.13%	

DMT, disease-modifying therapy; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.

**eAppendix Table 14.** Target Population Summary (Per Million)

	<b>Year 1</b>	<b>Year 2</b>	<b>Year 3</b>
Hypothetical plan population size	1,000,000	1,003,500	1,007,012
Incidence of RRMS	4	4	4
Prevalence of RRMS	60	63	67
Total number of new RRMS patients treated with DMTs	1	1	1
Total number of existing RRMS patients treated with DMTs	18	20	21
Incident patients with RRMS newly starting high-efficacy DMT treatment	0.19	0.19	0.19
Prevalent patients with RRMS currently using high-efficacy DMT treatment	3.06	3.25	3.44
Total patients using high-efficacy DMT treatment	3.25	3.44	3.63

DMT, disease-modifying therapy; RRMS, relapsing-remitting multiple sclerosis.

**eAppendix Table 15.** Annual Cost and Budget Impact to Medicare Payer

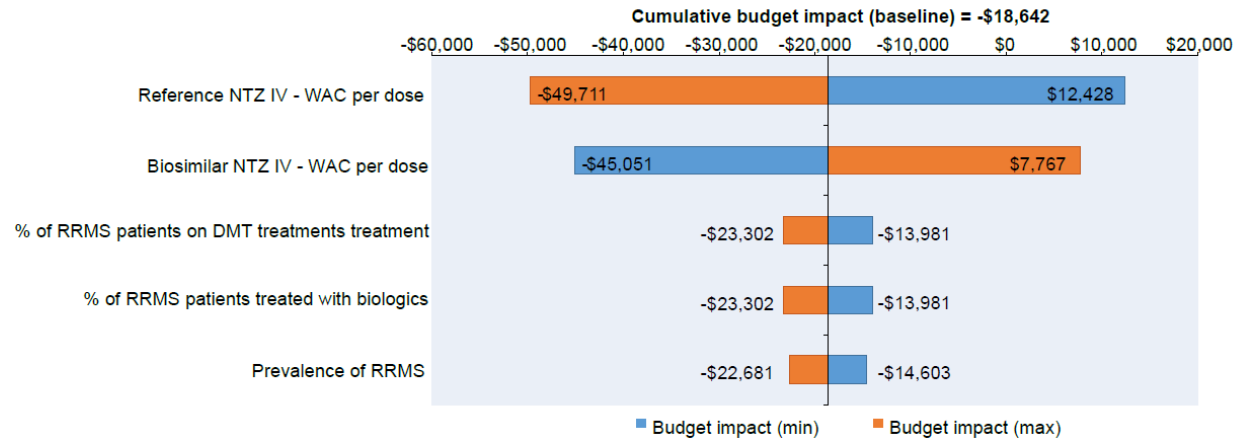
<b>World-without-proposed-biosimilar-NTZ scenario</b>	<b>Year 1</b>	<b>Year 2</b>	<b>Year 3</b>	<b>Cumulative costs</b>
Drug acquisition cost				
Reference NTZ	\$114,008	\$120,528	\$127,070	\$361,607
Ocrelizumab	\$127,049	\$134,423	\$141,824	\$403,296
Alemtuzumab	\$18,216	\$19,236	\$20,260	\$57,712
Treatment-related costs	\$11,662	\$12,329	\$12,998	\$36,989
<b>Total costs</b>	<b>\$270,935</b>	<b>\$286,517</b>	<b>\$302,153</b>	<b>\$859,604</b>
Cost per treated member per year	\$83,402	\$83,360	\$83,322	\$250,083
Cost PMPY	\$0.27	\$0.29	\$0.30	\$ 0.86
Cost PMPM	\$0.02	\$0.02	\$0.03	\$ 0.07
<b>World-with-proposed-biosimilar-NTZ scenario</b>	<b>Year 1</b>	<b>Year 2</b>	<b>Year 3</b>	
Drug acquisition cost				
Biosimilar NTZ	\$21,939	\$34,791	\$48,906	\$105,636
Reference NTZ	\$88,198	\$79,598	\$69,534	\$237,330
Ocrelizumab	\$127,049	\$134,423	\$141,824	\$403,296
Alemtuzumab	\$18,216	\$19,236	\$20,260	\$57,712
Treatment-related costs	\$11,662	\$12,329	\$12,998	\$36,989
<b>Total costs</b>	<b>\$267,063</b>	<b>\$280,377</b>	<b>\$293,522</b>	<b>\$840,963</b>
Cost per treated member per year	\$82,210	\$81,573	\$80,942	\$244,725
Cost PMPY	\$0.27	\$0.28	\$0.29	\$ 0.84
Cost PMPM	\$0.02	\$0.02	\$0.02	\$0.07
<b>Total budget impact to Medicare payer</b>	<b>-\$3,872</b>	<b>-\$6,140</b>	<b>-\$8,630</b>	<b>-\$18,642</b>

Treatment-related costs include the cost of drug administration, monitoring, pretreatment, and treatment of adverse events and relapses.

NTZ, natalizumab; PMPY, per member per year; PMPM, per member per month.

**eAppendix Figure 2. One-Way Sensitivity Analysis of Cumulative Budget Impact to Medicare:**

Tornado Diagram<sup>a</sup>



Parameter	Base Case value	Parameter min Value	Parameter max Value
Reference NTZ IV - WAC per dose	7855	5891	9819
Biosimilar NTZ IV - WAC per dose	6677	5008	8346
% of RRMS patients on DMT treatments treatment	0.30862	0.23147	0.38578
% of RRMS patients treated with biologics	0.16640	0.12480	0.20800
Prevalence of RRMS	0.00006	0.00004	0.00007

Note: Negative budget impact indicates cost savings to the payer

AE, adverse event; DMT, disease-modifying therapy; IV, intravenous; NTZ, natalizumab; RRMS, relapsing remitting multiple sclerosis; WAC, wholesale acquisition cost.

<sup>a</sup>Only the top 5 most impactful parameters are shown in the sensitivity analysis tornado graph.

## **Section D: Scenario Analysis with Utilization Exactly According to FDA Label**

**eAppendix Table 16** summarizes the results of the budget impact analysis using dosing frequencies that exactly match the FDA label instead of real-world dosing patterns for high-efficacy DMTs used in the base-case analysis. The model suggests that inclusion of proposed biosimilar NTZ in the formulary for RRMS would still result in savings to payers of \$127,514 in Year 1, \$195,093 in Year 2, and \$265,239 in Year 3 following the inclusion of proposed biosimilar NTZ into the formulary for a hypothetical commercial plan population of 1 million.

**eAppendix Table 16.** Annual Budget Impact for Commercial Payers: Dosing Scenario Analysis  
That Exactly Matches the FDA Label

	<b>Year 1</b>	<b>Year 2</b>	<b>Year 3</b>
<b>Without biosimilar NTZ</b>	\$ 7,444,905	\$ 7,593,588	\$ 7,742,790
<b>With biosimilar NTZ</b>	\$ 7,317,392	\$ 7,398,494	\$ 7,477,551
<b>Budget impact (annual)</b>	-\$127,514	-\$195,093	-\$265,239

FDA, Food and Drug Administration; NTZ, natalizumab.

## **Section E: Additional Analysis on price sensitivity analysis**

### **Methods**

#### *Price Sensitivity Analysis*

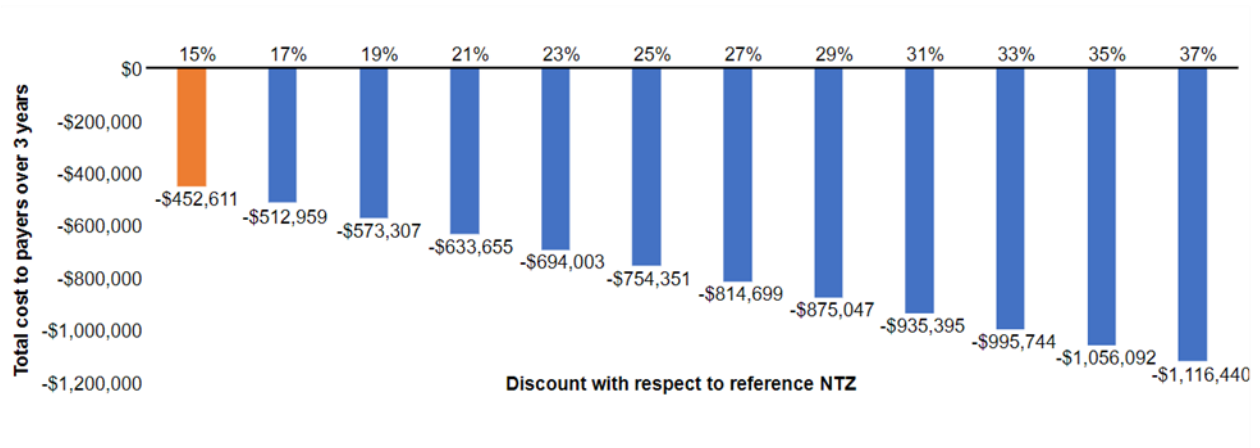
A price sensitivity analysis was conducted by varying the WAC price of proposed biosimilar NTZ based on a range of historical biosimilar pricing experience in the US over the last 8 years.<sup>12</sup> The price of proposed biosimilar NTZ was varied 15–37% lower than the WAC price of reference NTZ.<sup>12</sup>

### **Results**

#### **Price Sensitivity Analysis**

As the one-way sensitivity analysis determined that the model was most sensitive to the acquisition cost of NTZ (biosimilar and reference), it warrants further examination. In the base-case analysis, the cumulative savings to payers were estimated to be \$452,611 over 3 years, assuming a 15% difference between reference NTZ and proposed biosimilar NTZ WAC prices. A 15%-reduced WAC for a biosimilar compared to its reference product is on the lower end of historical biosimilar pricing trends in the US; a recent analysis identified a range of 15–37% lower WAC for biosimilars compared to their reference medications.<sup>12</sup> The price sensitivity analysis shows that with the potential lower WAC price of biosimilar NTZ, payers could potentially gain savings from \$452,611 to \$1,116,440 over 3 years. **eAppendix Figure 3** depicts the potential savings to payers by varying the hypothetical price reduction between biosimilar and reference NTZ.

**eAppendix Figure 3.** Overall Budget Impact to Payers With Varying Price Differential of Proposed Biosimilar NTZ WAC



NTZ, natalizumab; WAC, wholesale acquisition cost

<sup>a</sup>Orange-colored bar of 15% assumed biosimilar price reduction in base-case analysis



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